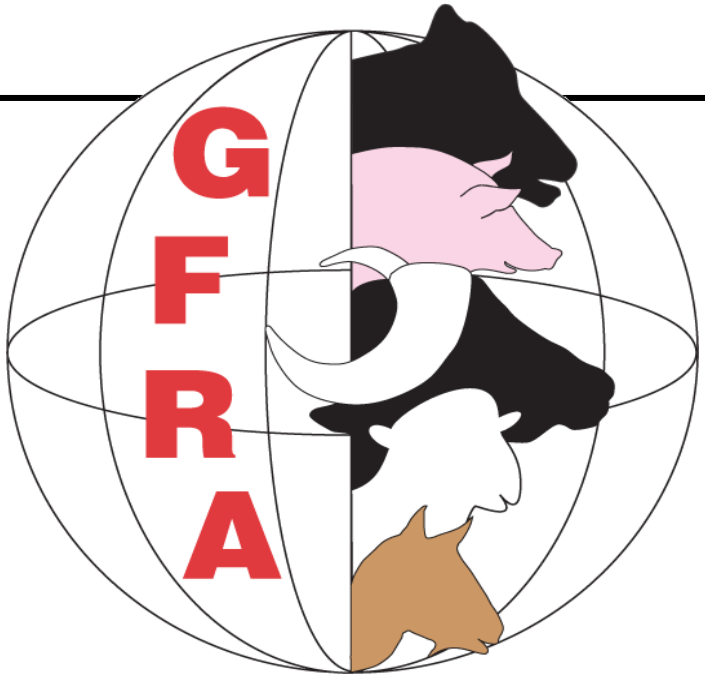
Foot-and-Mouth Disease

Gap Analysis

Workshop Report 2022



Global Foot-and-Mouth Disease
Research Alliance

The Global Foot-and-Mouth Disease Research Alliance (GFRA) aims to expand FMD research collaborations worldwide and maximize the use of resources and expertise to achieve its five strategic goals:

1. To facilitate research collaborations and serve as a communication gateway for the global FMD research community.

2. To conduct strategic research to increase our understanding of FMD.

3. To develop the next generation of control measures and strategies for their application.

4. To determine social and economic impacts of the new generation of improved FMD control

5. To provide evidence to inform development of policies for safe trade of animals and animal products in FMD-endemic areas.

Additional information on the GFRA and the work of the alliance can be found on the following website: http://www.ars.usda.gov/GFRA

The purpose of the FDM Gap Analysis Workshop was to assess current scientific knowledge and the available countermeasures to effectively control and mitigate the impact of an FMD outbreak in the United States, also supporting global control and eradication initiatives in FMD-endemic countries.

The FMD Gap Analysis Workshop was organized by the GFRA with the support of the United States Department of Agriculture USDA) and the Instituto Nacional de Tecnología Agropecuaria (INTA), Argentina.

To cite this report:

Global Foot-and-Mouth Disease Research Alliance (GFRA) Gap Analysis Report. December 2022. https://go.usa.gov/xdrKh

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Additional literature review and comments were provided by Dr Daniel Ackerman, Dr Laura Roden and Dr Lucy Robinson from Insight Editing London, following a commission assigned by the US Department of Agriculture.

Dr Maria Cruz Miraglia and Dr Nancy Cardoso kept records of all the sessions and organized the information and materials generated during the Workshop.

The GFRA wants to acknowledge CRDF for helping with the meeting organization in Buenos Aires.

Glossary

AADIS	Australian Animal Disease Spread modeling framework
amiRNA	Artificial microRNA
APHIS	Animal and Plant Health Inspection Service
ARS	Agricultural Research Service
BHK-21	Baby Hamster Kidney fibroblast cell line
bp	Base pair(s)
BTY	Bovine thyroid
cELISA	Competitive ELISA
CLIA	Chemiluminescence Immunoassay
DC	Dendritic Cell(s)
DIVA	Differentiating Infected from Vaccinated Animals
DNA	Deoxyribonucleic Acid
ELISA	Enzyme-Linked Immunosorbent Assay
EU	European Union
FAO	Food and Agriculture Organization of the United Nations
FDC	Follicular DC
FMD	Foot-and-Mouth Disease
FMDV	Foot-and-Mouth Disease Virus
GDP	Gross Domestic Product
GFRA	Global Foot-and-Mouth Disease Research Alliance
GF-TADs	Global Framework for the Progressive Control of Transboundary Animal Diseases
HPLC	High-Performance Liquid Chromatography
HSP	Heat Shock Protein
IFN	Interferon
Ig	Immunoglobulin
IL	Interleukin
IRES	Internal Ribosome Entry Site

IRF	Interferon Regulatory Factor
IRT	Infrared Thermography
LAMP	Loop-mediated isothermal amplification
LAV	Live Attenuated Vaccine
LFA	Lateral Flow Assay
LMIC	Low- and Middle-Income Country
LPBE	Liquid-Phase Blocking ELISA
mAb	Monoclonal Antibody
MAP	Multiple Antigen Peptide
MAPK	Mitogen-Activated Protein Kinase
MDA	Maternally Derived Antibodies
MDA5	Melanoma Differentiation-Associated gene 5
MHC	Major Histocompatibility Complex (also called SLA in pigs)
miRNA	microRNA
NF-κB	Nuclear factor-κB
NK	Natural Killer
NLR	NOD-Like Receptor
NLRP3	NLR family pyrin domain containing 3
NOD	Nucleotide-binding Oligomerization Domain
NSP	Non-Structural Protein
nt	Nucleotide(s)
OIE	Office International des Epizooties (now the World Organization for Animal Health)
OPF	Oropharyngeal Fluid
ORF	Open Reading Frame
PBMC	Peripheral Blood Mononuclear Cell(s)
PBS	Phosphate-Buffered Saline
PCR	Polymerase Chain Reaction
PEG	Polyethylene Glycol
PK-15	Porcine Kidney 15 cell line
PPR	*Peste des Petits Ruminants*

PRR	Pattern Recognition Receptor
qPCR	Quantitative real-time Polymerase Chain Reaction
R0	Reproductive number
rhAd5	Recombinant Human Adenovirus 5
RIG-I	Retinoic acid-Inducible Gene-I
RLH	RIG-I-like Helicase
RNA	Ribonucleic Acid
RNAi	RNA interference
RPA	Recombinase Polymerase Amplification
rRT-PCR	Real-time RT-PCR
RT-PCR	Reverse Transcription PCR
SBS	Secure Beef Supply
SCD	Synonymous Codon Deoptimization
shRNA	Short hairpin RNA
SPCE	Solid-Phase Competition ELISA
TLR	Toll-Like Receptor
TNF	Tumor Necrosis Factor
UAE	United Arab Emirates
UK	United Kingdom
USA	United States of America
USD	US Dollars
USDA	US Department of Agriculture
UTR	Untranslated Region
VLPs	Virus-Like Particles
VSV	Vesicular Stomatitis Virus
VNT	Virus Neutralization Test
WOAH	World Organization for Animal Health
WRLFMD	World Reference Laboratory for FMD
WT	Wild Type

Executive Summary

A group of international experts on Foot-and-Mouth Disease (FMD) was convened to conduct a gap analysis workshop of our current knowledge of FMD and the available countermeasures to effectively control and mitigate the impact of an outbreak in the FMD-free, and support global control and eradication initiatives in FMD-endemic countries.

The Foot-and-Mouth Disease Gap Analysis Working Group was organized with the support of the GFRA and the Instituto Nacional de Tecnología Agropecuaria (INTA), Argentina. The working group met in Buenos Aires, Argentina, December 5 and 6, 2022.

Session chairs prepared presentations highlighting the advances, accomplishments, and remaining knowledge gaps since 2018 in their corresponding areas of expertise. After each presentation, contents were open to discussion to all workshop attendants. For all sessions, written reports were produced by their corresponding chairs, including relevant bibliography related to the specific area.

This report is based on the presentations, discussions and reports produced during the workshop, combined with a literature review and additional comments provided by Dr Daniel Ackerman, Dr Laura Roden and Dr Lucy Robinson from Insight Editing London, following a commission assigned by the US Department of Agriculture.

The workshop was structured in six separate sessions, corresponding to six research areas, including the following topics:

Session 1: Epidemiology

Chairs: Andres M. Perez, University of Minnesota, USA and Jonathan Arzt, ARS-USDA, USA.

- Global status.
- Economic impact
- Obstacles to Prevention and Control.
- Models.
- Risk-assessment in different scenarios.
- Field trials.

Session 2: Diagnostics

Chairs: Michael Eschbaumer, FLI, Greifswald, Germany and Nagendrakumar Singanallur Balasubramanian, CSIRO, Geelong, Australia.

- Review of available diagnostics
- Criteria for selecting diagnostics.
- Validation of diagnostics
- Assessment of vaccine efficacy and virus circulation

Session 3: Vaccines and Biotherapeutics

Chairs: Elizabeth Rieder, ARS-USDA, USA and Melanie Chitray, OVI-ARC, South Africa.

- Criteria for selecting vaccines.
- Review of available vaccines (available now and in the pipeline).
- Criteria for selecting a biotherapeutic.
- Review list of experimental biotherapeutics.
- Define biotherapeutic targets.

Session 4: Immunology

Chairs: Alejandra Capozzo, IVIT, INTA-CONICET, Argentina and Mariano Perez Filgueira IVIT, INTA-CONICET, Argentina.

- Advances in immune response to infection in different species.
- Advances in immune response to vaccination in different species.
- Immunogenetics.
- Tissue-specific immunology.
- Immunological bases of protection and cross-protection.
- Innate responses.
- Adaptive responses.

Session 5: Virology

Chairs: María Inés Gismondi, IABIMO, INTA-CONICET, Argentina and Tobias J Tuthill, The Pirbright Institute, UK.

- Molecular virology.
- Biological activity of viral proteins.

- Biological activity of viral RNA.
- Capsid stability.
- Virus – cell interaction.
- New technologies.

Session 6: Pathogenesis

Chairs: Carolina Stenfeldt, ARS-USDA, USA and Jonathan Arzt, ARS-USDA, USA.

- Advances in the knowledge of pathology in different species.
- The role of the carriers.
- Transmission.
- Experimental infection methods.
- Transmission in the field.
- Inter-species transmission.

Introduction

The highly contagious disease of ruminants and swine caused by foot-and-mouth disease virus (FMDV) was first described by a Venetian monk in the early 16th century (reviewed in Jamal and Belsham, 2013). The current presentation of FMD remains very similar to the clinical signs he described, including behavioral disruptions and lesions on the feet and mouth. Today, FMD is one of the most significant diseases of ruminants and swine and is circulating in ~77% of the global livestock population (WOAH, 2022a). While the mortality of FMD is generally low in adult animals, its effects on animal productivity (including reduced milk production and herd fertility) have a massive impact on the economic security of livestock farmers, and these costs are felt disproportionately by the rural poor (Casey-Bryars et al., 2018). In Africa, >85% of livestock keepers live in extreme poverty, and subsistence farming plays a vital role in the food security of many communities; however, the complex epidemiology of FMDV, limited surveillance resources, and viral maintenance in wild buffalo make FMD control extremely challenging in these rural areas (Calkins and Scasta, 2020). FMD management and outbreak response are also highly expensive, encompassing surveillance and vaccination programs, loss of access to international trade networks, and culling of infected animals (Knight-Jones and Rushton, 2013).

FMD is currently present in over 100 countries in Africa, Asia, West Eurasia, the Middle East, and South America (WOAH, 2022a), costing an estimated $8.4 to $27.3 billion USD annually ((Knight-Jones and Rushton, 2013), adjusted for inflation). This epidemic is marked by the continuing emergence and re- emergence of viral strains and their transmission across national borders (e.g., the O/ME-SA/Ind-2001 lineage that reappeared in India in 2008 and subsequently spread across Southeast Asia, the Middle East, and North Africa) (reviewed in Brito et al., 2017)). The USA has been free of FMD since 1929, but the threat of reintroduction is ever-present (Walz et al., 2020; WOAH, 2022a).

From a total of 182 member countries of the World Organisation for Animal Health (WHOA), 98 countries have no official status, 68 countries are recognized as FMD-free (67 where vaccination is not practiced, 1 where vaccination is practiced), and 13 countries have zones that are FMD-free, with and without vaccination use. In most FMD-free regions in which virus introduction is reported, outbreaks are usually managed by the slaughter of at least some of the infected and in-contact animals.

Although this restores FMD-free status, such widely publicized culls of livestock are increasingly controversial due to loss of genetically optimized breeding stock, and community, economic and environmental concerns.

The etiological agent is a virus of the family Picornaviridae, genus Aphthovirus (the FMD virus [FMDV]), which has seven immunologically distinct serotypes (O, A, C, SAT1, SAT2, SAT3 and Asia 1). Additionally, many subtypes have evolved within each serotype, with the result that FMD is often considered as at least 7 distinct diseases. FMDV is transmitted by direct or indirect contact from animate and inanimate vectors and may spread over great distances with movement of infected or contaminated animals, products, objects, and people. Airborne spread may occur up to 60 km (40 miles) overland and 300 km (190 miles) by sea, especially in temperate zones.

The World Reference Laboratory for FMD, Pirbright, United Kingdom, has recommended the division of circulating FMD viruses into seven regional pools, based on the observation that genetically distinctive virus strains tend to occur within a defined region. The seven regional pools are 1) Eastern Asia, 2) Southern Asia, 3) Euro-Asia, 4) Eastern Africa, 5) Western Africa, 6) Southern Africa, and 7) South America. Within those pools, FMD viruses circulate and, incidentally, infect regions endemically infected by other pools or free regions of the world.

The cost of FMD outbreaks in endemic regions and the risks of transmission to FMD-free areas necessitate a coordinated research and policy response that incorporates new data as rapidly as possible. Over the past five years, great progress has been made in understanding the fundamental biology of FMDV, its pathogenesis and transmission patterns, and the strategies available for effective FMD management and control.

This report provides updates on many of the advances that have been made since 2018 in key fields of FMD biology and disease control research, aiming to assist scientists and policymakers in establishing the avenues of future investigation that will most effectively advance FMD management and reduce its economic burdens on livestock farmers worldwide.

Research priorities by area

Epidemiology

Literature Review

1. General Aspects

FMD is considered to be one of the most contagious infectious animal diseases in the world and typically inflicts severe and far-reaching economic losses throughout infected countries (Knight-Jones and Rushton 2013, Knight-Jones, McLaws et al. 2016,Tadesse et al. 2019). Since the first description of the disease nearly five centuries ago (Fracastorii H, 1554), the FMDV has been found in more than 70 species, including cattle, buffalo, sheep, goats, pigs, and deer (Arzt et al. 2011, Weaver, Domenech et al. 2013,Stenfeldt et al. 2015,Stenfeldt et al. 2016). FMD viruses are genetically very diverse, with seven immunologically distinct serotypes (A, O, C, SAT1, SAT2, SAT3, and Asia1).

FMDV continues to spread rapidly across six of the seven geographic pools into which the United Nations Food and Agriculture Organization (FAO) divides the FMD-endemic regions (FAO, 2022a). Distinct viral strains tend to circulate within these pools and evolve independently of other regions, but FMDV is capable of "cross-pool" transmission between these regions (Bertram et al., 2018a; Ryoo et al., 2021), with corresponding consequences for biosecurity, surveillance programs, and vaccine development. Since 2018, the growing dominance of the O/ME-SA/Ind-2001e sublineage in South and Southeast Asia has reinforced concerns about the speed with which FMDVs circulate and seed new outbreaks in this geographical zone (Dahiya et al., 2021; FAO, 2021a). Recent events – including the spread of Ind-2001e to Mauritius on at least two separate occasions, the introduction of O/EA-3 and A/AFRICA/G-I from East Africa to Bahrain via imported cattle, the unexpected detection of South American-origin viruses in Egypt, and the introduction of O/EA-2 into Southern Africa and Ind-2001e into Indonesia and Pakistan – illustrate the dynamic global situation, with FMD transmission

remaining poorly controlled in many countries and livestock populations worldwide (FAO, 2021b, 2022a).

FMD epidemiology is complicated by the virus's high mutation rate and corresponding ability to thrive in a variety of host animals and environmental conditions. FMD is currently endemic in regions with very different climates and geographies, from sub-Saharan Africa to Southeast Asia and even island nations like Mauritius. The transmission networks, outbreak patterns, and risk factors associated with FMD depend on many local and regional variables. One constant is the importance of anthropogenic factors (including inadequate on-farm biosecurity and movement of infected animals between farms or across national borders) in FMDV transmission within and between countries.

Since 2018, there have been many new FMD outbreaks and there is evidence of continuous evolution and diversification of the viral landscape. In Southeast, Central, and East Asia, emergent viruses including the O/ME-SA/Ind-2001 sublineages D and E are gaining prevalence and continuing to spread across complex networks of smallholder farmers. Vaccination programs are in use across the region, but their efficacy and compliance rates vary widely. Indonesia lost its FMD-free without vaccination status due to an outbreak of Ind-2001e in May 2022. FMD also remains a major economic burden in India, where the O/ME-SA/PanAsia and Ind-2001 lineages are widespread and cause periodic outbreaks across the country.

Recent studies have begun to clarify the transmission networks that link India with Eurasia and the Middle East, where FMDV serotypes O, A, and Asia 1 are prevalent. This region also sees bidirectional FMDV transmission with Africa, where the disease's epidemiology is particularly complex due to high levels of poverty in rural livestock keepers, lack of access to veterinary care and disease control resources (including vaccines), and viral persistence in wild buffalo populations. Recent studies have begun to close the gaps in FMD surveillance throughout Africa, particularly concerning the widespread SAT 1-3 serotypes, but much work remains to be done.

The past five years have brought an expansion in FMDV vaccine matching studies, which are critical for determining whether widely used vaccine strains are maintaining their efficacy in the face of this rapidly evolving virus. Meanwhile, epidemiologists are gathering region-specific information on the transmission patterns of FMD, including the roles played by wild ruminant and swine species, environmental contamination in different climates, the controversial carrier state of

chronically/subclinically infected animals, and human activities such as legal and illegal livestock trade. The growing power of computational modeling systems has also been brought to bear on the questions facing FMDV epidemiology, with new models constructed for the analysis of FMDV evolution, transmission, and outbreak risks in a multitude of settings.

Reporting of FMD outbreaks, factors related with FMD transmission and spread, and identification and sequencing of FMD virus strains is based on the voluntary submission of information, reports and clinical samples to international organizations, rather than to the active collection of information and application of targeted sampling schemes. There is no global surveillance system for real-time reporting, visualization, analysis, and long distance communication of spatial and temporal distribution and incidence of FMD. Moreover, the informatics technology and analytical tools required for the development and support of a global surveillance system are still at the initial steps of research and development.

To compensate for lack of recent experience with the FMD outbreaks in the U.S, models for FMD spread have been developed to simulate the expected spread of the disease in the U.S. and to identify the most cost-effective combination of control strategies. However, these models are not intended to be used in helping the decision-making process in the face of an epidemic, but to provide more general estimates of how an FMD epidemic would behave under certain conditions or assumptions. The consequences of misusing simulation models were dramatically demonstrated during the FMD epidemic that affected the U.K. in 2001. Attributes of a new generation of simulation ('intelligent') models must include the ability to capture information emerging from the field in the face of an epidemic, to use that information to adapt the model parameters ('learning'), to modify model assumptions, including those related with the characteristic of the strain causing the outbreak, and to produce updates in near-real time that correct previous estimates of the expected evolution of the epidemic.

2. Economic Loss

Potential economic loss is a major driver in an FMD-free country's decision of which control strategy to employ in the case of an outbreak. Porphyre et al. used an epidemiological, spatially explicit, simulation model in combination with a direct cost calculator to assess how vaccine availability constraints impacted the economic benefit of a "vaccination-to-retain" strategy during a FMD outbreak in Scotland (Porphyre et al., 2018). The authors simulated the various scenarios of vaccination using a modified Warwick FMD model to represent the Scottish livestock industry. The data demonstrated that in scenarios in which large outbreaks are possible, all vaccination strategies performed better than the strategy where only culling was implemented, and that the impacts of low vaccine availability were aggravated by delays in the initial decision to vaccinate, or low vaccine efficacy. While their model reaffirmed findings of the epidemiological benefits of vaccinating animals to support culling strategies their findings indicate that these strategies can also be economically beneficial when controlling widespread epidemics (Porphyre et al., 2018).

The eradication of the 2001 FMDV outbreak in the United Kingdom is estimated to have cost U.S $14.5 billion (Anderson, 2001). While the United States is currently FMD-free, the disease poses a significant threat to the sustainability of U.S. animal agriculture. Estimates from several studies indicate far-reaching economic consequences if the U.S. acquires FMD. Direct and indirect costs estimated from a study in 1979 (McCauley E. H., et al, 1979) indicates that FMD would cost more than $37 billion over a 15-year period with values projected in year 2006 dollars. An FMD epidemic in southern California would directly cost an estimated $4.3-$13.5 billion (1999 dollar value) (Ekboir J, 1999). A study done in 2015 concluded that an FMD outbreak in Mid-western USA would account for $188 billion and government cost would be $11 billion (Schroeder et al. 2015). These estimates do not address extensive losses expected by allied livestock industries (e.g. feed, equipment, product development), or indirectly related industries, such as was experienced by the loss of tourism and horse racing in the 2001 U.K epidemic. Other impacts would include reduced availability of animal products throughout various segments of the economy, including bovine fetal serum used in tissue culture and vaccine production and gelatin used in pet foods, nutritional supplements, and cosmetics.

The continued spread and diversification of FMDV place a disproportionately high burden on rural smallholders in low- and middle-income countries (LMICs) that already struggle with substantial socioeconomic burdens (Phillipson et al., 2020), threatening the livelihoods of communities that rely on livestock for food and income (Knight-Jones and Rushton, 2013). The COVID-19 pandemic has placed additional strain on these livestock producers, and pandemic-associated restrictions severely impacted FMD surveillance and outbreak reporting programs (e.g., by increasing the costs of shipping samples to FMD Reference Laboratories) in many countries (FAO, 2021c).

In FMD endemic regions, the calculations are different: how does a country balance the costs of ongoing vaccination with variably effective vaccine, compared to the multi-factorial cost of the disease? Truong et al. analyzed the financial impact of a biannual vaccination strategy to prevent and eradicate FMD in cattle in South Vietnam based on survey responses from farmers (Truong et al., 2018). The study area had high economic dependence on livestock production, was important as a source of animals for other provinces and countries and was in a high-risk area for FMD. Interestingly, cost-benefit analysis of biannual vaccination for FMD prevention showed clear financial advantages for dairy farmers, but this was less certain for those rearing cows for beef. The authors suggest that subsidies may be beneficial in encouraging FMD vaccination in beef farms to boost biosecurity in the region (Truong et al., 2018). The findings of the farm-based study above were mirrored in a cost-benefit analysis of the first phase of Vietnam's national FMD containment and eradication program which involved pro-active vaccination (Do et al., 2022). Do et al. used a spatial and dynamic model to simulate FMD outbreaks in all species and considered factors that affect transmission such as the distance between livestock premises, herd size and composition. Their data show that the vaccination program is economically beneficial with a benefit-cost ratio of 5.7 (Do et al., 2022).

Although the in-country benefits of vaccination-to-retain are clear, there may be little economic incentive for countries reliant on animal and/or meat exports to adopt this policy because of the longer period before the WOAH Scientific Commission FMD-free status can be regained, compared to the vaccinate-and-remove approach. The impact of this policy was explored by Bradhurst et al., who exploited an enhanced AADIS model to compare post-outbreak management strategies for vaccinated animals using two case studies that compared the retention of vaccinated animals with their removal (Bradhurst et al., 2019). The authors demonstrated that while a vaccinate-and-retain strategy incurred lower post-outbreak management costs, there were significantly higher trade losses; however, the

disposal of healthy but vaccinated animals purely to facilitate return to global markets is not desirable from a social nor an animal welfare perspective (Bradhurst et al., 2019). Miller et al. also explored the impacts of alternative responses to a hypothetical FMD outbreak, but this time in the Midwestern United States (Miller et al., 2019). The authors used the Regional Economic Modeling Incorporated Policy Insight (REMI) + computable general equilibrium model to ask about the impact of FMD control decisions on employment and GDP in models with forecasts of a 10-year period and disease outbreak durations of up to 2 years. The strictly depopulation strategy that made no use of vaccination resulted in high job and GDP losses, which could be reduced through control responses that made use of vaccination strategies (Miller et al., 2019). Fewer jobs were lost as vaccination capacities and zone areas increased, with the greatest benefits seen by using a vaccinate-to-retain strategy applied rapidly and over a large area. Their model demonstrated the importance of rapid response and short detection times in achieving the best epidemiological and economic outcomes following an outbreak in a disease free setting (Miller et al., 2019).

The potential trade benefits of FMD-free status are considerable but making the transition from the widespread use of vaccination to a control system based on active surveillance and biosecurity can be a real challenge. Perry et al. explored these two options in the context of Uruguay, finding that the move to no-vaccination may be economically desirable, but will require parallel investment in strengthened veterinary services to ensure sufficient surveillance and generally improved health of farmed livestock (Perry et al., 2020).

Also looking at cost-effectiveness, but this time of local and regional movement controls in the case of an FMD outbreak in the UK, Tildesley et al. used mathematical modeling to identify which of the following factors contributed most to the overall national cost of the outbreak: (i) the number (and type) of animals infected, and their eventual fate; (ii) the number (and type) of animals culled as part of the control; (iii) the duration of the outbreak; (iv) the number of movements prevented by the restriction (Tildesley et al., 2019). Their model found that the optimal strategy for limiting economic impact was the prohibition of movements in a small radius around infected farms (Tildesley et al., 2019). This insight should enable more effective prioritization and decision making in the case of future outbreaks.

3. Computational models for epidemiological predictions

As the power of computational models continues to grow, their applications for predicting the spread of FMDV and associated risk factors have become an increasingly active field of research (reviewed in Andraud and Rose, 2020). FMD transmission networks (incorporating genetic data, epidemiological data, and/or anthropogenic factors such as animal movements) have been modeled to estimate viral spread in many countries where FMD is endemic or threatens to become so, including China (Gao and Ma, 2021; H.-R. Ren et al., 2021; J. Zhang et al., 2019), Japan (Firestone et al., 2020, 2019; Hayama et al., 2019), Cameroon (Pomeroy et al., 2019), Niger (Souley Kouato et al., 2018c), Turkey (Herrera-Diestra et al., 2022), Iran (Ilbeigi et al., 2018), and Ecuador (Vinueza et al., 2022). These studies are too numerous to discuss in detail here – what follows is a brief overview of the current state of FMD computational modeling, and we encourage readers to consult the individual cited papers through the References section for greater detail on the computational methods employed. Additional discussion of FMD computational models, focused specifically on their applications for tracking and predicting disease transmission, can be found in the Surveillance section of this report.

Computational modeling can help to fill the many gaps in our knowledge of viral evolution and transmission in endemic regions of Africa. Studies from Malawi (Chimera et al., 2022), Uganda (Adamchick et al., 2021b; Munsey et al., 2019), and Ethiopia (Belayneh et al., 2020), for instance, have applied various models to identify risk factors and spatiotemporal clustering associated with FMD outbreaks. Souley Kouato et al. reviewed several different FMD epidemiological risk models to identify the best-supported modeling techniques for use in endemic regions of Africa, highlighting the importance of using spatiotemporal models and the need to take region-specific sociocultural variables and animal husbandry practices into account (Souley Kouato et al., 2018a). High-quality data remains an "unavoidable prerequisite" for developing reliable models, and the development of these models must therefore go hand-in-hand with improved disease surveillance programs to ensure the success of both (Souley Kouato et al., 2018a). Incorporating up-to-date virological and epidemiological data can also have a significant impact on the predictive capacity of computational models – Di Nardo et al., for instance, combined VP1 sequence data with geographical, host animal, and epidemiological variables to estimate the evolution and spatial diffusion of FMDV in West Eurasia and the Middle East

(Pool 3) – these authors found evidence that complex viral maintenance and competition patterns in Southern Asia result in the periodic evolution of new viral lineages that subsequently spread west (Di Nardo et al., 2021), in line with previously discussed epidemiological findings (Canini et al., 2022; FAO, 2021b).

In Southeast Asia, Thailand has been the focus of many recent FMD epidemiological modeling studies, particularly at its vulnerable borders with neighboring countries (Arjkumpa et al., 2021). Contact network modeling of markets near the Myanmar border indicated that intra-provincial animal movements may play an unexpectedly important role in FMDV transmission, and focusing disease control measures specifically on highly interconnected markets may be an effective strategy for controlling these movements (Wiratsudakul and Sekiguchi, 2018). Numerous spatial and spatiotemporal models have been used to estimate between-farm transmission rates, anthropogenic factors, and FMD outbreak hotspots and seasonal trends (Arjkumpa et al., 2020a; Chanchaidechachai et al., 2021; Punyapornwithaya et al., 2022b; Sangrat et al., 2020; Sansamur et al., 2020), and a recent study compared different machine learning models for outbreak prediction on Thai cattle farms (Punyapornwithaya et al., 2022a).

Computational modeling has been applied to investigate FMDV transmission by animals in the incubation stage prior to developing clinical signs, predicting significant consequences for the size of a potential FMD outbreak (Arzt et al., 2019a). The authors of this study also modeled FMDV transmission dynamics and estimated exposure doses in contact-exposed pigs (Moreno-Torres et al., 2018) and computed the durations of the incubation, latent, and infectious periods for different FMDV serotypes in cattle and pigs (Moreno-Torres et al., 2022; Yadav et al., 2019). Meanwhile, at the University of Minnesota, researchers are conducting ongoing studies of the spatiotemporal dynamics of FMD spread in endemic regions (K. VanderWaal, 2023, personal communication).

In addition to these endemic regions, mathematical models are also particularly important for predicting FMD dynamics, viral transmission, and outbreak-associated costs in non-endemic regions where empirical data are not available, including New Zealand (Sanson et al., 2021a), Austria, (Marschik et al., 2021b), Belgium (Bianchini et al., 2020), Denmark (Halasa et al., 2020), and North Macedonia (O'Hara et al., 2022). In the USA, a recent study combined a within-herd FMD transmission model with expert opinion to estimate depopulation/disposal-associated variables in the

event of a potential FMDV introduction, reporting that leakage of body fluids from infected carcasses enroute to off-site disposal locations may be a significant source of transmission risk under these circumstances (Walz et al., 2020). An animal movement network analysis of swine in Iowa predicted that biosecurity measures should be focused on sow farms rather than nursery sites in the case of an FMD outbreak (Passafaro et al., 2020). Other recent modeling studies of potential FMDV transmission in the USA include a national-scale disease spread model with emphasis on spatial and demographic heterogeneity (Tsao et al., 2020), a meta-population stochastic model of transmission dynamics within and among cattle feedlots (Cabezas et al., 2020), a simulation of anthropogenic factors (Q. Yang et al., 2021), and a social network analysis of livestock movement networks (Cabezas et al., 2021a). Network analysis has also been applied to estimate the impact of information-sharing techniques on transmission risk due to cattle movements and truck visits in southwest Kansas (Q. Yang et al., 2020; Yi et al., 2022).

Along with virological and epidemiological data, meteorology can also be incorporated into computational modeling to predict the role of climatic factors in potential FMDV transmission. A recent study combining transmission modeling with the National Oceanic and Atmospheric Administration's atmospheric dispersion model indicated that significant risk of airborne spread may extend past the USDA's recommended 10 km minimum control area around a potential FMD outbreak (Coffman et al., 2021). These findings complement an earlier study that investigated the occurrence of airborne transmission-promoting weather patterns in the USA, finding particularly favorable conditions in the upper Midwest (Hagerman et al., 2018).

Australia is also FMD-free but remains at risk of viral introduction. Manyweathers et al. have developed predictive models to improve our understanding of Australian farming practices and on-farm biosecurity vulnerabilities (Manyweathers et al., 2022, 2021a, 2021b, 2020), and the previously published Australian Animal Disease Spread (AADIS) epidemiological model (Bradhurst et al., 2015) has been used to simulate the economic impacts of various FMDV incursion scenarios and governmental responses (Capon et al., 2021; Hafi et al., 2022; Seitzinger et al., 2022). Similar results were reported from a time series analysis in Scotland, where control of a simulated large outbreak via vaccination was estimated to cost less overall compared to a culling-only approach (Barratt et al., 2019). Simulations of the efficacy of different vaccination strategies (combined with stamping out) in

Australia, New Zealand, the USA, the UK, and Canada also indicated that limiting vaccination to high-risk areas may be less effective than unrestricted vaccination programs (Rawdon et al., 2018).

As with all in silico studies, care must be taken to account for each computational model's assumptions and biases, which may cause the accuracy and precision of simulated results to deteriorate depending on epidemiological variables (e.g., epidemic length, presence of super-spreaders, etc.) (Hidano and Gates, 2019). New models have been validated against historical outbreak data (e.g., the 2001 FMD epidemic in the UK) to assess and compare their predictive abilities (Shanafelt et al., 2018; Stockdale et al., 2021; M. A. Ward et al., 2022). Economic modeling studies also require high-quality data and standardization of methods reporting – low-quality analyses can encourage inefficient use of disease control and surveillance resources, and a recent systematic review reported that quality was generally poor among a subset of representative economic analyses of endemic FMD (Compston et al., 2022).

In the context of livestock disease modeling, it is also particularly important to incorporate unique farm structure and demographic variables (e.g., production system, animal populations, and their spatial locations) that significantly impact FMD persistence and transmission patterns (Kinsley et al., 2018). These data are not readily available or necessarily accurate in many countries, limiting the usefulness of computational models applied to them (van Andel et al., 2018).

4. Wildlife

Wild animals play a complex role in FMDV epidemiology, and the degree to which they impact disease transmission varies greatly depending on local wild species and their population levels, the degree of interaction between wildlife and livestock, and local farming practices (reviewed in Rahman et al., 2020; Thomson et al., 2003). A recent review of the importance of wildlife in FMDV and similar transboundary animal diseases highlighted the differences caused by region-specific variables – the role of African buffalo in FMD maintenance is well-known, for example, while the 2010-2011 FMD epidemic in Bulgaria began in wild boar (Sus scrofa) but was resolved despite sporadic cases in wildlife (Gortázar et al., 2022). More research is also needed into the susceptibility of wildlife in non-endemic regions, as these populations may become unexpected reservoirs for FMD (Cripps et al., 2019;

Gortázar et al., 2022). In the UK, for instance, populations of wild boar are increasing, and the size of their home ranges may significantly impact the risk of FMD becoming endemic in a potential FMDV introduction scenario (Croft et al., 2019).

In Africa, buffalo are a maintenance host for the three SAT serotypes of FMDV, which cause mild or asymptomatic infections in these animals. Despite generally high seroprevalence among buffalo, their role in regional FMD epidemiology is usually reported as minimal, with far greater risk coming from livestock movements and anthropogenic activities (Omondi et al., 2019, 2020). However, seroprevalence in domestic livestock has been reported to decrease with greater distance from wild ungulate populations (Nthiwa et al., 2020), and the role of African buffalo in FMD persistence in Eastern Africa remains an active area of research (K. VanderWaal, 2023, personal communication).

Infected wildlife may play a greater role in the epidemiological systems of Southern than in Eastern Africa (Casey-Bryars et al., 2018). High-risk areas for FMD outbreaks were found to cluster near game reserve fences in South Africa (Sirdar et al., 2021), and phylogenetic characterization of SAT 2 outbreak strains suggested that new variants may have emerged at the wildlife-livestock interface in the greater Kruger National Park area (Blignaut et al., 2020). In Botswana, continual circulation of FMDV in the north has been attributed primarily to co-existence between cattle and buffalo (Babayani and Tholoolwane, 2022). This extensive interface was also explored in neighboring Zimbabwe, where spatiotemporal analysis of FMD outbreaks between 1931-2016 showed significant clustering in the Southeast Lowveld near protected conservation areas with high buffalo populations (Guerrini et al., 2019).

FMD endemicity and the high level of livestock-wildlife interactions in Africa have made it the focus of most studies of FMD-infected wildlife. However, several recent reports have emerged from West Eurasia and the Middle East, including the first isolation of FMDV from a wild boar in that region (Karniely et al., 2020) and the first detection of a spillover infection from domestic to wild species in Pakistan (Ijaz et al., 2022). The continual transmission and introduction of new strains to new environments necessitates ongoing study of wild species' susceptibility to infection: in the UAE, for instance, three FMD outbreaks were reported between 2013-2015 in captive scimitar-horned oryx (Oryx dammah; extinct in the wild) near Abu Dhabi, demonstrating that this species is susceptible to locally circulating serotype O and A (Lignereux et al., 2020). Interestingly, a serological study of

dromedaries (Camelus dromedarius) in Oman found no seropositive camels even in herds where the animals grazed together with seropositive ruminants (Body et al., 2020), consistent with previous conclusions that FMDV does not infect dromedary camels (reviewed in Wernery and Kinne, 2012).

5. Anthropogenic factors

As many of these studies indicate, human activity (including legal and illegal livestock trade, inadequate biosecurity on livestock premises, and noncompliance with biosecurity programs) remains one of the most significant drivers of FMDV transmission worldwide (Kedkovid et al., 2020). Movement of animals, animal products, and contaminated fomites through formal trade networks is never free of risk, but informal networks and illegal smuggling are far harder to control and can facilitate unexpected disease transmission events (reviewed in Beltran-Alcrudo et al., 2019; M. Kardjadj, 2018). A recent field serological investigation in Egypt reported 50% FMDV seropositivity among illegally imported small ruminants from neighboring countries (Hosny et al., 2020), and unrestricted cross-province animal movements are a potent driver of FMDV dissemination and subsequent outbreaks in Egypt and the Middle East (Ur Rahman et al., 2018). Many of these movements may be associated with refugee travel and festivals including Eid al-Adha, which was highlighted as a particularly high-risk period for illegal animal introduction in both Pakistan and Afghanistan (Osmani et al., 2019; Ur Rahman et al., 2018). Resource use and overuse can also have significant downstream effects on FMD transmission patterns. In Pakistan, per capita water availability has declined dramatically in recent decades due to overexploitation of groundwater for irrigation; this has forced farmers to use untreated wastewater drainage systems for animal bathing, increasing their risk of contracting FMD (Elahi et al., 2018).

In Africa, phylogenetic analyses of circulating strains indicated that animal movements (as part of pastoralism and/or trade), high cattle and human population densities, and close proximity to livestock markets are primary drivers of intra- and international transmission (Ehizibolo et al., 2020; Munsey et al., 2021). The availability of disease control resources also varies widely across the continent, and the corresponding lack of large-scale national FMD management programs pushes the burden of control

onto the low-income farming communities and smallholders whose livelihoods are already most threatened by FMD's impacts on livestock health and productivity (Knight-Jones et al., 2017; McLachlan et al., 2019). As in many areas of Asia and the Middle East, socioeconomic challenges (e.g., lack of access to vaccines or the ability to pay for them) limit biosecurity in much of Africa, and only ~5.5% of African cattle are thought to be vaccinated against FMD (Knight-Jones et al., 2017).

Differences in livestock farming systems also have a significant effect on the risk of exposing animals to FMD – in Laos, for instance, penned pigs had a significantly lower risk of FMDV seropositivity compared to those kept in traditional scavenger systems or in communal areas (Holt et al., 2019). Similar findings emerged from Niger and Rwanda, where mixed farming was found to significantly associate with FMDV seropositivity (Souley Kouato et al., 2018b; Udahemuka et al., 2020).

Participatory epidemiology is an important tool in establishing the factors driving pastoralists' behavior and decision-making in rural communities where unregulated animal movement is common, and increasing awareness of FMD outbreaks via clear and understandable communication methods could be an effective policy strategy in such environments (Ullah et al., 2021). A recent participatory study highlighted the ease with which goats, the most common livestock species kept by African smallholder farmers, can exit FMD protection zones undetected – such movements are a common occurrence within communal farming regions, with more than half of surveyed farmers unaware of the need for veterinary movement permits for goats (Lazarus et al., 2021). Importantly, the need for increased awareness of and responsiveness to FMD among farmers and veterinarians is not limited to Africa, or indeed to FMD-endemic regions in general – a recent study in France found that some cattle farmers were unaware of the risk of FMD reintroduction to the country, and the speed with which veterinarians reported suspicions of FMD depended on the occurrence of FMD cases in other European countries (Raut et al., 2018).

6. *Current global situation and recent findings*

Pool 1 – Southeast Asia/Central Asia/East Asia

Southeast Asia: Much recent attention has focused on the FMDV strains dominant in South Asia (including O/ME- SA/Ind-2001 sublineages d and e) and the frequency with which these viruses spread into Pool 1 (FAO, 2021a). Despite the ongoing South-East Asia and China Foot-and-Mouth Disease (SEACFMD) campaign and longstanding vaccination programs in individual countries, FMD remains persistently endemic in the region, placing significant burdens on livestock market development and smallholder livelihoods. Local control efforts are hampered by limited international cooperation and financial constraints which, in turn, limit surveillance of critical transboundary livestock movements (reviewed in Blacksell et al., 2019; Patrick et al., 2017).

These circumstances allow FMDV to spread easily across national borders in the smallholder farming systems of South and Southeast Asia. An analysis of the non-structural protein (NSP)-coding sequences of strains endemic to Southeast Asia found evidence for a close phylogenetic relationship between endemic O/SEA/Mya-98 and A/ASIA/Sea-97 viruses and identified several strains hypothesized to have been generated by recombination between these lineages (Brito et al., 2018). The O/ME-SA/Ind- 2001 lineage, not detected in Southeast Asia prior to 2015, was identified as the causative agent of outbreaks in Laos, Vietnam, and Myanmar in that year (Qiu et al., 2018; Vu et al., 2017), and analysis of recent outbreaks in Cambodia indicated that O/ME-SA/Ind-2001e may soon become dominant there following cross-pool transmission (Ryoo et al., 2021); this sublineage has now also been detected in other countries in the region including Malaysia, China, and South Korea. Similarly, in 2018, Ind- 2001d isolates from Laos and Vietnam were found to be closely related to previously circulating strains in India. Isolates from Myanmar, however, were more similar to Bangladeshi strains, indicating that this sublineage may have reached Southeast Asia via at least two independent introduction events (Qiu et al., 2018).

Numerous recent studies have explored the circulation and control of FMD in these Southeast Asian countries and their closely interconnected animal movement networks. Myanmar reported an outbreak of serotype Asia 1 in 2017, the first detection of this serotype in the country since 2005 (Bo et al.,

2019). In Laos, researchers reported mixed results from the risk-based partial vaccination that has been implemented on a region-by-region basis (Han et al., 2022; Nampanya et al., 2018). Socioeconomic analysis in three provinces identified a general improvement in livestock production in villages included in the vaccination campaign (Wada et al., 2022), but vaccination rates, disease reporting, and farmer participation remain generally low (Lormaisim et al., 2021; MacPhillamy et al., 2022b; Souriya et al., 2020; Xaydalasouk et al., 2021). A participatory study of farmers in Laos and neighboring Cambodia found that their average level of knowledge about animal health and biosecurity increased between 2015-2018, with resource scarcity playing a major role in their decision- making (MacPhillamy et al., 2022a). Lack of access to vaccines in this region also limits the ability of many village animal health workers to protect their animals against FMD (Sieng et al., 2022a; van Andel et al., 2020a; Win et al., 2021), while unrestricted animals movements facilitate long-distance disease spread (Subharat et al., 2022).

Similar epidemiological conditions prevail in Thailand, where modernization and increasing demand for livestock products is introducing new dynamics into farming and meat production systems (Bunmee et al., 2018). The country reported 1,209 FMD outbreaks between 2008-2019, and current control measures may not be sufficient to control the disease (Arjkumpa et al., 2021). As in many other countries, underreporting is a significant concern (Arjkumpa et al., 2020b), and the capture-recapture method has been tested as a tool for estimating true FMD prevalence in the country (Sansamur et al., 2021). Alongside these surveillance-focused studies, phylogenetic research in Thailand has highlighted the rapid diversification and generation of VP1 sequence diversity in circulating serotype A strains, with many coding region substitutions observed compared to widely used vaccine strains (Bae et al., 2021; Seeyo et al., 2020).

Central Asia: The major role of China in global livestock production and food supply networks make its FMD status a cause for international concern. The high demand for livestock and their products in China spurs illegal movement of large numbers of animals into the country from Southeast Asia, presenting an important source of FMDV introduction risk each year (Blacksell et al., 2019; Smith et al., 2015). Retrospective risk analyses have identified spatiotemporal outbreak hotspots and a northwest- southeast directional trend in FMD transmission (J. Chen et al., 2020; Ma et al., 2017). FMD is classified as a disease requiring compulsory vaccination in China, leading to much higher reported vaccination coverage (nearly 100% of cattle and yak farms) compared to other livestock

diseases such as brucellosis, bovine viral diarrhea, and bovine ephemeral fever (Chen et al., 2021). Serotype O remains dominant in the country, particularly within its pig populations (H.-R. Ren et al., 2021), and the Ind- 2001d sublineage was first reported there in 2018 (Z. Zhu et al., 2018). Promisingly, the corresponding vaccine strain O/XJ/CHA/2017 appears to provide broad protection against this sublineage in livestock (Cao et al., 2021).

In neighboring Mongolia, a spate of FMD outbreaks in 2017 cost the country ~0.65% of its GDP and significantly impacted the livelihood of subsistence farmers (Limon et al., 2020). A study of imported vaccines found them able to induce satisfactory protection against circulating FMDV lineages, but vaccine availability issues may limit their use (Ulziibat et al., 2020).

East Asia: In South Korea, where FMD vaccination and continual serosurveillance have been mandatory for domestic cattle and small ruminants since 2011, a recent assessment of post-vaccination immunity levels reported 80-100% population immunity and seroprevalence in livestock, indicating that this vaccination campaign has been broadly successful (M.-Y. Park et al., 2021). However, a major 2014- 2015 outbreak of a lineage O/SEA/Mya-98 virus (O/Jincheon/SKR/2014) necessitated the development and validation of new vaccines against this strain, which exhibited a unique partial deletion in its 5' non-coding region compared to other South Korean O/SEA isolates (Park et al., 2018). Continuing FMD outbreaks mainly impact cattle and pig farms with relatively lower seroprevalence, particularly in the densely populated Gyeonggi and North/South Chungcheong Provinces (Lee et al., 2021).

Finally, Indonesia had been considered FMD-free without vaccination since at least 1990 (Blacksell et al., 2019; FAO, 2022b), but a recent outbreak of O/ME-SA/Ind-2001e in the Jawa Timur province caused this status to be suspended in April 2022, and the virus has since spread rapidly across the country (FAO, 2022b; WOAH, 2022a). Illegal importation of animals is suspected to have been the source of this outbreak (R. Chen et al., 2022).

Pool 2 – South Asia

FMD is considered among the most economically important livestock diseases in India, with outbreaks of serotypes O, A, and Asia 1 causing significant losses to smallholders throughout the country (Ali et al., 2020; Dahiya et al., 2022; Govindaraj et al., 2020; Kakker et al., 2022; Sinha et al., 2017). India

began implementing a mass FMD vaccination campaign in 2003, and a retrospective study of pre- and post-vaccination monitoring data revealed a notable but region-dependent increase in immunological protection across the country (Gunasekera et al., 2022). The authors of this study used a Bayesian spatiotemporal model to correlate these data with reported FMD outbreaks, finding ~50% reduced outbreak risk in states participating in the vaccination campaign (Gunasekera et al., 2022). Unsurprisingly, states where the country's FMD vaccination program was not implemented were more vulnerable to outbreaks (Govindaraj et al., 2021) and tended to conduct vaccinations reactively rather than proactively (Hopker et al., 2020). Many farmers in India avoid vaccinating cattle due to anticipating a post-vaccination reduction in milk yield (Krishnaswamy et al., 2021), while limited access to vaccination services and poor communication from vaccinators have been identified as significant factors negatively affecting uptake (Hopker et al., 2021).

Topotype O/ME-SA is particularly widespread in India and transmits to nearby countries and beyond (Dahiya et al., 2021; Rout et al., 2018). The PanAsia lineage escaped the Indian subcontinent between 1998-2001 and caused widespread outbreaks in the Middle East, Southeast Asia, Africa, and Europe (Hemadri et al., 2002), and Ind-2001 appears to be following a similar course. Phylogeographic studies of the Ind-2001d sublineage (and Ind-2001e, first reported in India in 2015) found evidence of 15+ escape events from the subcontinent between 2013-2017, causing outbreaks in regions as far- separated as Russia, South Korea, and Mauritius (Bachanek-Bankowska et al., 2018b; Jamal and Belsham, 2018). Notably, a genetic characterization study of circulating Indian strains indicated that Ind-2001e exhibits a faster apparent mean evolution rate compared to Ind-2001d (Dahiya et al., 2021), with potential consequences for vaccine development. Ind-2001d has also caused massive outbreaks in Sri Lanka, where phylodynamic analysis revealed that this sublineage followed a similar pattern of transboundary spread and evolution compared to the historical C/ASIA, (introduction from India followed by outbreaks the following year and subsequent evolution independent of the ancestral viral populations) (Ranaweera et al., 2019).

In 2020, lineage Asia1/ASIA/G-IX was identified for the first time in India, with in situ evolution and introduction from neighboring Bangladesh both considered possible origins (Subramaniam et al., 2020). Serotype O currently dominates in Bangladesh, and recent studies have identified the country's first occurrence of the PanAsia-2 lineage (Hossen et al., 2020) and the emergence of two novel Ind-2001 sublineages (BD1 and BD2) (Ali and Giasuddin, 2020; Siddique et al., 2018) and the country's

first occurrence of the O/ME-SA/PanAsia-2 lineage. Overall FMDV seroprevalence among cattle in the region remains high against serotypes O and A (Hoor-E-Jannat et al., 2018; Jannat et al., 2020).

Pool 3 – West Eurasia and the Middle East

Pool 3 comprises a wide range of farming systems, geological/climatological conditions, and FMD transmission patterns, and phylogenetic studies have revealed inter-serotype recombination events between circulating viruses in this region (Jamal et al., 2020). In Pakistan, serotypes O and Asia 1 have supplanted A as the predominant serotypes since 2014 (Ali et al., 2022; Ali and Habib, 2018; Rafique et al., 2020), and an analysis of field samples from serotype O outbreaks revealed two new distinct sublineages of O/PanAsia-2 (Ur Rahman et al., 2018). O/ME-SA/Ind-2001 was first detected in this country in 2019 (Hicks et al., 2020) and spread rapidly, becoming widely established by the following year (FAO, 2020). Ind-2001e isolates from 2019-2020 outbreaks in northern Pakistan appear to be closely related to strains circulating in Bhutan, Nepal, and India; promisingly, vaccine matching studies suggested that current vaccine strains are likely suitable for controlling field outbreaks of this sublineage (Jamal et al., 2021).

In neighboring Afghanistan, decades of ongoing conflict have greatly damaged diagnostic and surveillance capabilities, with significant consequences for the country's susceptibility to FMD (Wajid et al., 2020). Among these consequences is the inherent challenge of conducting epidemiological studies in volatile areas where researchers may face danger to their own safety (Osmani et al., 2021b). Serotypes O, A, and Asia 1 continue to circulate widely and cause regular outbreaks (Osmani et al., 2019), and a participatory study assessing Afghan farmers' self-reported knowledge of and behaviors toward FMD reported low levels of livestock vaccination due primarily to a lack of vaccine availability (Osmani et al., 2021a). A similar study in Pakistan reported generally limited understanding of FMDV transmission routes and outbreak risks among farmers, indicating that both socioeconomic (e.g., more easily accessible vaccines) and cultural efforts (e.g., increased educational outreach) will be needed to control FMD at the Pakistan-Afghanistan border (Ghafar et al., 2020). Similar issues face Iran, where surveillance data indicate middling protection levels and low vaccination coverage despite the country-level adoption of mass vaccination of domestic ruminants (Emami et al., 2022). In 2021, the first detected FMDV infection of domestic dogs was observed in Iran, when a sublineage O/ME-

SA/PanAsia-2QOM-15 virus caused high mortality in young dogs fed infected lamb carcasses (Waters et al., 2021).

In neighboring Iraq, serotype A appears to be dominant (Mansour et al., 2018), but other serotypes (including O/ME-SA/PanAsia-2 strains) regularly circulate in the region and contribute to high seroprevalence in cattle, buffalo, and small ruminants (Al-Salihi, 2019; Baba Sheikh et al., 2021). Topotype Asia1/G-VII strains have been isolated from the Iraq-Iran border and caused an outbreak in Iraq's Basne district after potentially being introduced via illegal animal movement from Balochistan province in Pakistan (Abdul Aziz et al., 2019).

Similar FMDV transmission events, between noncontiguous countries via under-surveilled animal movement networks, have been hypothesized in response to recent developments in the Arabian Peninsula. In Saudi Arabia, isolates from a 2016 Ind-2001 outbreak displayed 99% VP1 nucleotide identity with Bangladeshi FMDV strains (Hemida et al., 2018). Relatively high seroprevalence was also reported among domestic small ruminants in Medina, raising concerns that frequent movement of pilgrims to and from the city could promote FMDV transmission (Shabana and Krimly, 2020). FMD seroprevalence is similarly high in neighboring Oman (Hussain et al., 2019).

Epidemiological links between Pools 2 and 3 have also been suggested in the UAE, where a new FMDV lineage (O/ME-SA/SA-2018, previously detected in India and Sri Lanka) was identified for the first time (FAO, 2022b), and outbreaks of topotype O/EA-3 in Bahrain in 2021 were linked to strains previously detected in Ethiopia and Yemen (Canini et al., 2022; FAO, 2021b). These findings indicate an expansion of viral transmission alongside improvements in transcontinental movement networks linking Asia, Africa, and the Middle East.

In the Eastern Mediterranean, the Ind-2001e sublineage was first detected in Jordan in 2017, causing an outbreak with high mortality in young lambs and goats. (Ababneh et al., 2020). Later FMD outbreaks in Jordan and Palestine were linked to sublineage O/ME-SA/PanAsia-2ANT-10 viruses that closely matched isolates identified in Pakistan in 2019, raising the possibility of unexpected transmission networks within Pool 3 (FAO, 2022c). Serotype O remains dominant in Israel and Palestine; numerous reported cases include a 2017 outbreak of O/EA-3 that affected vaccinated animals despite closely matching the O3039 vaccine strain (Shmeiger et al., 2021) and a 2021 outbreak of PanAsia-2 in the northern Galilee region (Etinger et al., 2022).

Turkey, where FMD outbreaks occur annually with particularly high incidence in the East and Central Anatolia regions (Bayir and Gürcan, 2022), is another major player in the animal movement networks that connect Pool 3 with Asia and Africa. FMD is controlled via biannual mass vaccination of cattle in this country (Knight-Jones et al., 2016), but numerous outbreaks of the A/ASIA/G-VII lineage have necessitated annual updates to these vaccines (Tuncer-Göktuna et al., 2021). This lineage is believed to have originated in Pool 2 before spreading to Pool 3 (Bachanek-Bankowska et al., 2018a).

Finally, in Kazakhstan, ring vaccination efforts beginning in 1970 significantly reduced disease transmission and outbreaks, leading to the country's declaration as FMD-free with partial vaccination in 2015 (Abdrakhmanov et al., 2018). Unfortunately, a recent outbreak of Ind-2001e in the Shetskiy District prompted the suspension of this status in June 2022 (Tyulegenov et al., 2022).

Pool 4 – North and Eastern Africa

FMD remains widespread in Africa, where viral persistence in domesticated species and wild African buffalo (Syncerus caffer) and complex geographic, political, and socioeconomic factors combine to make epidemiology, surveillance, and outbreak reporting a difficult task (Calkins and Scasta, 2020). Livestock production plays a central role in the economy, food security, and rural livelihood of many African nations, but resource limitations and a lack of reliable data hamper the tracking and prediction of FMDV transmission and evolution in these animal husbandry networks. The misapplication of epidemiological findings from regions with different socioeconomic circumstances can lead to poor understanding of viral transmission, ineffective disease control, and underestimation of FMD's impact on smallholders (Casey-Bryars et al., 2018). Increasing our ability to collect surveillance and epidemiological information in these regions – e.g., through the joint FAO/WOAH Global Framework for the Progressive Control of Transboundary Animal Diseases (GF-TADs) regional roadmaps, which provide an important forum for gathering data from different countries – will likely be an important component of future strategies for managing FMD in Africa.

North Africa: Numerous instances of international transmission have been reported in North Africa over the past decade (reviewed in Kardjadj, 2018), with frequent animal movements between Tunisia, Algeria, and Libya considered a high-risk factor (Squarzoni-Diaw et al., 2021). Algeria saw an FMD outbreak in 2014 that was apparently controlled via vaccination, but the disease recurred in subsequent years (Baazizi et al., 2019). Cases of serotype A were recently detected in this country for the first time

since 1977, with isolates classified as a A/AFRICA/G-IV lineage closely related to strains circulating in Nigeria (Pezzoni et al., 2019). The authors of this report later characterized the genomes of 22 serotype O (Ind-2001d) isolates from recent outbreaks in Algeria and Tunisia, finding that they had likely originated in Libya and subsequently spread to Morocco (Pezzoni et al., 2022). Topotype O/EA-3 viruses also continue to cause outbreaks in Algeria and Tunisia, posing a threat to nearby nations across the Mediterranean in southern Europe (Canini et al., 2022; FAO, 2022b).

Egypt, where numerous serotype O, A, and SAT 2 lineages are currently circulating (El-Bagoury et al., 2022; Ismael et al., 2021; Shahen et al., 2020; Soltan et al., 2019a, 2019b), has been the subject of many recent studies of FMD epidemiology and control. Case numbers in the country have fallen due to an ongoing FMD control program using locally produced inactivated polyvalent vaccines, but severe annual outbreaks continue, with particularly high circulation during the winter season (El Bahgy and Moustafa, 2018). Divergence from vaccine strains has been detected within some circulating viruses, including SAT 2 (El Damaty et al., 2021; El Nahas and Salem, 2020) and topotype O/EA-3 isolates (Diab et al., 2019), and standard primers used for FMDV molecular serotyping in Egypt were unable to subtype some new strains (Abdulrahman D. et al., 2020; Hassan et al., 2022b). This poor antigenic matching may be attributable to viral evolution under pressure from vaccines, though issues with vaccine quality control, storage, and potency have also been theorized (Abdulrahman D. et al., 2020). Abd El Rahman et al. reported a recombination event between an Egyptian serotype A and an African serotype O isolate that evidenced poor biosecurity and accidental release of virulent virus from a laboratory or vaccine production facility (Abd El Rahman et al., 2020), though these conclusions were disputed by private vaccine development stakeholders in the Middle East (Wasfy, 2021). Several studies have also reported co-infections by multiple serotypes in Egyptian cattle, and inter-serotype recombination is another potential cause of vaccination failure in the country (Al-Hosary et al., 2019; Refaei et al., 2020).

Intriguingly, two recent studies have reported the unexpected identification in Egypt of South American-origin viruses belonging to topotypes O/EURO-SA and A/EURO-SA (Hagag et al., 2022; Soltan et al., 2022). The route of transmission remains unconfirmed, and many questions remain surrounding the introduction, circulation, and establishment of these lineages in Egypt (FAO, 2022a).

Eastern Africa: FMDV serotypes O, A, and SAT 2 also continue to circulate in Sudan, through their prevalence (particularly in small ruminants and wildlife) remains poorly understood (Raouf et al., 2022). The country's Northern state may be nearly FMD-free (Ahmed et al., 2021; Alfouz et al., 2021), but live animal trade facilitates transmission across the Egyptian border, and FMDV seroprevalence is high among imported cattle (Abu-Elnaga et al., 2020; Hekal et al., 2019). Genotyping of Sudanese FMDV isolates from 2009-2018 demonstrated both intra- and international circulation; many serotype O strains appeared to be maintained without requiring transboundary introduction, while sequences from serotype A and SAT 2 isolates indicated connections with neighboring countries and the Middle East (Raouf et al., 2022). Experimental and surveillance data on Sudanese SAT 2 viruses also indicate a failure of ongoing vaccination programs, with monovalent vaccines unable to provide adequate protection in the face of growing viral diversity (Raouf and Ibrahim, 2022).

To the south, FMD control efforts in Uganda have also had limited success despite widespread vaccination; wildlife reservoirs, uncontrolled animal movements, and poorly performing vaccines allow diverse lineages from five serotypes (O, A, and SAT 1-3) to remain endemic (Velazquez-Salinas et al., 2020). Outbreaks in Uganda appear to be particularly concentrated near the border with Tanzania (Kerfua et al., 2018), where the cost and limited availability of vaccines have led to low vaccination rates among smallholder farmers (Häsler et al., 2021; Williams et al., 2022). Recent studies have begun to clarify viral transmission patterns, phylogenetics, and evolution rates in Uganda and Tanzania (Kerfua et al., 2020, 2019), but further research is needed to solidify our understanding of FMDV epidemiology in this region. Similar conditions are present in densely populated Burundi, where underreporting and inadequate surveillance are common within the country's subsistence-oriented livestock systems. An investigation of a March 2016 outbreak in that country found >80% seroprevalence against serotypes O, A, and SAT 1-3 in representative provinces, with phylogenetics indicating a transboundary origin for lineage A/AFRICA/G-I and SAT2/IV viruses (Estevez Garcia et al., 2022).

As these reports indicate, transboundary animal movements alongside limited surveillance and vaccination rates are major sources of FMDV transmission risk within Eastern Africa (Abegaz, 2022; Kefle et al., 2018; Niyokwishimira et al., 2018; Yousif et al., 2018). Where traditional disease reporting and surveillance resources are lacking, participatory epidemiology can be an important tool for generating qualitative epidemiological data and involving local stakeholders in FMD control efforts

(Cameron et al., 2020). Socioeconomics, cultural factors, and local knowledge and experience are primary influences on the behavior of smallholder farmers and are therefore closely tied to the success or failure of FMD response strategies (Campbell et al., 2021; Masole et al., 2019; Penrith et al., 2021). Participatory epidemiology is particularly valuable in rural regions, including those in East Africa, where resource limitations and diverse livestock systems create a challenging environment for conventional veterinary science (Adamchick et al., 2021a). In Kenya, where information on the epidemiology of circulating FMDV strains remains severely limited (Chepkwony et al., 2021), several participatory methods have been applied to study FMD prevalence, risk factors, and associated smallholder perceptions (Kerfua et al., 2021; Nthiwa et al., 2019; Nyaguthii et al., 2019; Onono et al., 2019).

Similar strategies have also shown promise for disease prioritization in Ethiopia (Bahiru and Assefa, 2022; Duguma, 2020; S. Gizaw et al., 2020), which is home to the largest reported livestock population on the continent. At least seven viral clades from serotypes O, A, and SAT 2 have been identified in this country, with molecular characterization supporting the hypothesis that FMDV circulates in two distinct niches (northerly and southerly) in the broader Eastern Africa region (D. Gizaw et al., 2020; Sulayeman et al., 2018).

The average seroprevalence of FMD in cattle varies widely across the country, with rates between ~3-97% reported in different states (Awel et al., 2021; Bahiru and Assefa, 2022; Mesfine et al., 2019). A spate of recent serological and molecular investigations have begun to close some of the gaps in our knowledge of FMD dynamics in Ethiopia, including new analyses of understudied northern and central regions (Ahmed et al., 2020; Dubie and Amare, 2020; Dubie and Negash, 2021; Mohammed et al., 2022; Tadesse et al., 2019, 2020; Tesfaye et al., 2020a), but many studies are hampered by complex regional livestock networks and low data availability (Woldemariyam et al., 2022). Governmental FMD control programs (e.g., vaccination and animal movement control) are severely limited in Ethiopia (CSA, 2020; Shurbe et al., 2022), and poor disease reporting and animal husbandry problems contribute to FMD maintenance (Woldemariyam et al., 2021). While farmers are generally enthusiastic about vaccinating their livestock against FMD (Jemberu et al., 2020a), studies on the efficacy of locally produced vaccines have returned mixed results (Jemberu et al., 2020b; Tesfaye et al., 2022, 2020b).

Pool 5 – West/Central Africa

As in East Africa, FMD control and surveillance programs are limited in much of the center and west of the continent (Brito et al., 2016; Pezzoni et al., 2022). Participatory epidemiology can be a particularly useful strategy for assessing FMD dynamics, socioeconomic factors impacting disease control, and farmer perceptions and activities within the complex smallholder community networks of Western Africa (Alhaji et al., 2020; Kaltungo et al., 2018; Majekodunmi et al., 2018; Wungak et al., 2019a).

A recent study from southwestern Niger illustrated the epidemiological challenges facing the region: many FMD outbreaks go unreported, vaccination is rare, susceptible wildlife populations are widespread, and transboundary movement of animals is common and unrestricted, creating a melting pot of viral transmission and evolution that remains critically under-surveilled (Souley Kouato et al., 2018b). Lack of disease control resources and effective communication with pastoralists in sub-Saharan Africa make FMD outbreaks a constant, unpredictable threat to these farmers – some resort to deliberate infection of livestock to reduce this uncertainty and lower overall disease duration, though this practice likely increases disease burden without substantially affecting outbreak length (McLachlan et al., 2019).

This complex epidemiological situation is exemplified by Nigeria, where molecular epidemiology studies have described a complex network of circulating serotype O, A, and SAT 1-3 viruses including strains genetically close to isolates from Cameroon, Sudan, and even North Africa (Ehizibolo et al., 2019; Fomenky et al., 2021; Ularamu et al., 2021). An analysis of cattle outbreaks between 2012-2017 revealed that half were caused by sublineages of topotype O/EA-3, but topotypes A/AFRICA, SAT1/X, SAT2/VII, and O/WA were also observed throughout the country (Ularamu et al., 2020).

Evidence for international FMDV transmission has also been collected in nearby Ghana (Teye et al., 2019) and Chad, where serotypes O, A, SAT 1, and SAT 2 continue to circulate (Ouagal et al., 2018). Transboundary transmission between Chad, Nigeria, and Cameroon has been reported as well (Abdel-Aziz et al., 2020; Ehizibolo et al., 2020). Sequence analysis of viruses isolated from traded cattle at border checkpoints also indicated continuous trade-associated introductions in the region (Bertram et al., 2018a).

Pool 6 – Southern Africa

In Zambia, following the first outbreak of SAT 3 in domestic cattle in 2015, characterization of circulating strains revealed outbreaks of SAT 2 in the Western Province and a new topotype SAT3/II isolate that likely emerged from illegal cross-boundary livestock movement and/or transmission from infected water buffalo in the Sioma Ngwezi National Park (Banda et al., 2021). New epidemiological patterns may also be emerging in South Africa, where characterization of the SAT 2 viruses responsible for major outbreaks in 2013/2014 found them genetically closer to isolates from Mozambique and Zimbabwe than to previous South African strains (Blignaut et al., 2020). In neighboring Botswana, most of the land area has been declared FMD-free without vaccination, though this status was recently suspended for part of the country's North-East District following an outbreak of serotype SAT 2 (WOAH, 2022a).

As elsewhere on the continent, control of FMD in Southern Africa will likely remain a significant challenge for some time. Vaccine matching studies have provided varying estimates of protective efficacy against circulating SAT 1-3 strains (Fana et al., 2021; Sirdar et al., 2019), and the recent identification of serotype O in Namibia – its first detection in Southern Africa – poses a risk to nearby countries that do not currently use serotype O vaccines (Banda et al., 2022).

Pool 7 – South America

In South America, recent studies of FMD epidemiology give reason for considerable optimism. Efforts to eradicate the disease are ongoing following its effective elimination from Ecuador and the Southern Cone subregion (Rivera et al., 2023), and overall cattle vaccination coverage across the continent has been estimated at 146.1% (reflecting vaccinations of the same animals more than once per year) (Knight-Jones and Rushton, 2013). Fresh outbreaks of serotype O in Colombia between 2017-2018 were successfully controlled (PANAFTOSA-OPS/OMS, 2020), and serotype C, responsible for widespread outbreaks in South America in the 1970s and '80s, has decreased dramatically and is now likely extinct (reviewed in Paton et al., 2021; Sanchez-Vazquez et al., 2019).

Brazil was declared FMD-free with vaccination in 2018 and is slowly withdrawing FMD vaccination throughout the country, though a recent social network analysis study emphasized the need for investments in sanitation/biosecurity education and efficient FMD diagnostics to reduce the risk of

rapid disease spread in the event of a reoccurrence (de Menezes et al., 2020). Venezuela is currently the only South American country not considered FMD-free (with or without vaccination), remaining an outlier in the broadly positive outlook for FMD control on the continent (WOAH, 2022a). The country's vaccination program recently deteriorated, with a drop in coverage from >90% to <50% of bovines from 2015 to 2020, and surveillance and serological monitoring studies are severely lacking (Rivera et al., 2023).

Research Knowledge Gaps

The GFRA Gap Analysis Working Group identified the following research knowledge gaps that may represent obstacles to effectively prevent and control FMDV.

- ✓ Poor and inadequate education and training of veterinarians and livestock producers in detecting early signs of FMD.
- ✓ Lack of validated commercial pen-side test kits for disease control (Portable or field-based tests).
- ✓ Failure of serologic methods to determine status (infected, uninfected) in some vaccinated animals.
- ✓ Absence of a surveillance system for early recognition of signs, or to find evidence using antigen detection, antibody, or virus detection.
- ✓ Lack of reliable comprehensive international surveillance systems to collect and analyze information, e.g., data on animal and animal products movement, FMD incidence and risk, and molecular epidemiology surveillance to provide estimates of international situation awareness in near-real time.
- ✓ Current epidemiological models do not provide answers to certain questions that will emerge in the face of an FMD epidemic. Current models have not been designed to evaluate in real-time the cost-effectiveness of alternative control, surveillance, and sampling strategies, so that the results of the evaluation can be used to implement specific measures in the face of the introduction of specific FMD virus strains into the U.S.

- ✓ Several aspects of FMD epidemiology and transmission still must be uncovered, including the influence of viral factors that affect viral persistence, emergence, competition, transmission, and spread of FMD virus strains.
- ✓ While several commercial vaccines are available internationally, their efficacy and safety profiles need evaluation.
- ✓ At present, there is no rapid pen-side or field-based diagnostic test for FMD control during a disease outbreak that has been validated in the field as "fit for purpose."
- ✓ There is a need for analytical tools to support the decision-making process in endemic settings.

Recommendations

- ✓ A global FMD surveillance system that provides high quality, accurate, and real-time information on FMD risk is needed to cover critical gaps of information of the FMD situation worldwide and to support FMD control and eradication on a global scale.
- ✓ Epidemiological models (e.g. spread, spatial, temporal, phylogenetic, and risk analysis models and analytical approaches) should be applied to identify key areas of the world to be targeted for active collection of samples and information, for intervention, and for monitoring the evolution of the disease as part of the global FMD surveillance system in critical regions of the world.
- ✓ Training on epidemiological analysis and translation of research results into policy has to be promoted in endemic regions of the world to pursue the progressive mitigation of risk in endemic settings and, ultimately, the control of the disease at a global scale.
- ✓ Analytical tools to support the decision-making process must be developed, including:
    - o Anomaly detection methods to identify outlier events.
    - o Prediction models for identification of genetic variants of viruses, to predict severity, duration, and likelihood of transmission of disease, and to evaluate the degree of success of control and prevention interventions.

- Epidemiological models that project spread of disease in a defined region under various control strategies and that can be used in developing disease control programs and for active surveillance sampling.
- Models to evaluate the degree of success of control and prevention interventions.
- Models that project spread of disease in a defined region under various control strategies and that can be used in developing disease control programs.
- Models for surveillance sampling identify optimal combination of sampling size, frequency, and targeting to maximize the probability of detecting virus circulation rather than disease.

✓ Sensitivity and specificity of diagnostic tests and surveillance systems have to be evaluated at global, regional, and national scales.

✓ Evaluate the mechanisms for dissemination and evolution of established and emergent FMDV strains.

✓ Development and standardization of tools to enable utilization of NGS-derived sub consensus sequence data for enhanced tracing.

✓ Continued investigation of the relevance of sub clinically infected animals in the propagation of contagion, including carriers and acute (neoteric) subclinical infections.

✓ Epidemiological patterns of disease transmission and spread in species other than cattle (e.g., sheep, goats, pigs).

✓ Understanding the social and economic determinants for disease spread, the impact of the disease in human populations, and how social sciences can help modify negative behaviors.

Diagnostics

Literature Review

1. General Aspects

Rapid and accurate diagnosis of FMD is a keystone of successful disease epidemiology, surveillance, and control. Diagnostic assays allow farmers to properly manage and care for their animals, provide researchers with data on the occurrence and transmission of viral strains, and give policymakers the necessary information to construct effective biosecurity strategies and limit losses due to outbreaks. The WOAH requires FMD diagnosis by virus isolation or the detection of viral RNA, viral antigen, or anti-FMDV antibodies in tissue or fluids samples from an infected animal, followed by confirmatory testing (WOAH, 2022b). Unfortunately, positive identification of FMD can be particularly challenging due to its clinical presentation (which is indistinguishable from several other vesicular diseases of ruminants and swine) and the great diversity of FMDV strains.

FMD diagnosis is a well-developed field despite these difficulties, with numerous validated tests available for the detection of viral RNA, viral antigens, and FMDV-specific antibodies. Real-time reverse transcription PCR (rRT-PCR) is generally considered the gold standard for nucleic acid-based diagnosis, while antigens and antibodies are usually detected via ELISAs (reviewed in Longjam et al., 2011; Wong et al., 2020). However, while our current standard FMD diagnostics do not lack sensitivity and specificity, they have technical requirements that limit their applicability in the field. FMD is endemic in many resource-limited regions where diagnostic equipment, laboratory staff and training, diagnostic supplies/reagents, and cold storage are unavailable or extremely difficult to access (Vudriko et al., 2021).

The optimal characteristics for an FMDV diagnostic test depend on the local epidemiological variables at play in each region – speed and ease-of-use are vital in some cases (e.g., field diagnosis of suspected FMD cases in remote areas), while the highest possible positive and negative predictive rates are required for outbreak verification and laboratory diagnosis. Foglia et al. tested a range of FMDV diagnostic tests (comprising pan-FMDV and serotype-specific rRT-PCRs, a mAb-based antigen-

detection ELISA, and in vitro virus isolation) on field samples from East Africa, comparing their relative strengths and weaknesses while highlighting the need to use all four approaches to reach ~100% diagnostic and serotyping performance (Foglia et al., 2021). Accordingly, much of the FMD diagnosis research conducted over the past five years has focused on the development of assays that retain high sensitivity and specificity while reducing cost and technical requirements, allowing pen-side diagnosis and removing an important barrier to rapid disease detection and reporting.

At a global scale, commercially produced diagnostic kits are essential for FMD surveillance and outbreak response, because the cottage industry production of tests in laboratories cannot meet the increasing demand. The replacement of traditional components such as inactivated whole-virus antigen and polyclonal sera by virus-like particles (Ran X et al., 2019, Zhang Y et al., 2020, Zhang Y et al., 2020, Zhang Y et al., 2022), monoclonals (Nguyen QT et al., 2019, Grazioli S et al., 2020) or recombinant antibodies (Shimmon G et al., 2018, Salem R et al., 2019, Jeong et al, 2019) promotes the standardization of reagents, improves biosafety, and facilitates international shipment of diagnostic products. At the same time, the sale and use of diagnostic tests for foreign animal diseases are often tightly regulated by national governments, which can be at odds with the business interests of manufacturers. The fitness for purpose of these tests must be ensured and their performance measured against appropriate benchmarks, including internationally harmonized reference panels (Ludi AB et al., 2021).

2. Validation of diagnostic tests

Technologies for rapid diagnosis of disease agents, such as rapid antigen tests (RATs), loop-mediated isothermal amplification (LAMP) PCR assays, CRISPR-based assays and many more, have flooded the market, most notably during the recent SARS-CoV-2 pandemic. Such technologies may also be under various stages of development across multiple research facilities for detecting FMDV antigen or genome. The Manual of Diagnostic Tests and Vaccines for Terrestrial Animals of the World Organisation for Animal Health (WOAH) lists specific tests that are considered “gold standard tests” (GSTs) for FMD (WOAH, 2022). These traditional methods (culture, isolation, identification, and biochemical tests) were developed during the early phase of understanding diseases and diagnostic

methods, and they have slowly but steadily been replaced by molecular methods. During the development of these new assays, their performance characteristics are established by comparing them with the WOAH-prescribed assays. On most occasions, in direct comparisons, the candidate/new test turns out to be the second best to the WOAH-approved GST. The inherent limitations of the GST are not considered when comparing it to the new test that is potentially more sensitive or specific.

To understand the science behind diagnostic test development and validation, the specific terminology must be clear. A 'diagnostic' test is used to diagnose a condition/disease and identify the causative agent(s). In contrast, a 'reference' test is often an approved method routinely used as a diagnostic test. An 'index' test is a new test developed with diagnostic characteristics that must be established before a routine test, either replacing or used as an adjunct to the existing diagnostic test. 'Validation' is the stepwise development of an assay into a diagnostic test to establish its characteristics in identifying a specific analyte in the sample to a sufficient concentration and with confidence. 'Verification' is the exercise of a stepwise comparison of a validated test if any components are changed, modified, or improved. In publications and reports, these terms are often used incorrectly to report the developmental stages of diagnostic tests.

The WOAH manual describes the stepwise pathway to develop and validate a 'fit-for-purpose' assay for diagnostic purposes (WOAH, 2013). The chapter in the manual has three major sections: Assay Development Pathway, Assay Validation Pathway and Validation Status Retention. As of today, very few diagnostic tests have been validated using this pathway and approved by the Secretariat for Registration of Diagnostic Kits of WOAH. While WOAH has encouraged test developers and kit manufacturers to adopt this process, many have failed to follow this pathway in diagnostic test development, validation, and reporting. One of the constraints they indicated is the non-availability of GSTs prescribed by the WOAH Terrestrial and Aquatic Manuals. Since most GSTs are limited to reference or national laboratories, they are not accessible in most research facilities. The second reason is that these tests did not undergo the same rigors of validation that the current tests are expected to have. This raises a simple but pertinent question, are these GSTs "golden"? Will they stand up to the same scrutiny with today's standards and expectations? Unfortunately, the answer is no.

Halpin and colleagues (Halpin K et al., 2021) added a new dimension to test validation with the advent of point-of-care tests (POCT) such as lateral flow devices (LFDs), LAMP PCRs, and other assays,

where an additional stage 5 is proposed to consider the robustness and ruggedness of the tests, cost implications and broader impacts like feasibility, distribution, and service.

Currently, the WOAH pathway for assay development and validation to emergency or provisional recognition has steps 1 and 2. These can be achieved by meticulous sample selection and employing relevant statistical procedures. Once the true meaning of these steps is understood, it becomes easy to devise protocols, arrange samples and record the results. Information on the samples used for achieving the diagnostic test characteristics in the publications or kit inserts is often limited. In most cases, the sample selection is biased, and samples are not ideal to arrive at the desired results. In 2003, two papers were published based on a WHO initiative to address the sampling issue (Bossuyt PM et al., 2003a, Bossuyt PM et al., 2003b). The objective was to comprehend the results of diagnostic accuracy studies and help users to understand the design, conduct, analysis, and results of diagnostic test development studies. They also identified that the quality of reporting of diagnostic accuracy studies could be better. Complete and accurate reporting is necessary to enable readers to assess the potential for bias in the research and to evaluate the generalizability of the results. It became mandatory for any new tests to follow the principles and guidelines of the STARD Initiative (Bossuyt PM et al., 2003a).

Following the footsteps of the STARD initiative, similar standards were proposed for diagnostic tests intended for use in terrestrial mammals in 2011 (Gardner IA et al., 2011) and aquatic species in 2016 (Gardner IA et al., 2016). A current study that developed a DIVA test for detecting horses infected with the Hendra virus shows how these principles can be applied (Balkema-Buschmann A et al., 2022). The manuscript follows the STARD principle and defines the samples used to estimate the different test parameters (analytical sensitivity (ASe), analytical specificity (ASp), diagnostic sensitivity (DSe) and diagnostic specificity (DSp)) and the methods used to arrive at them.

Generally, the uptake of these recommendations amongst researchers who develop diagnostic tests is still lacking, but they are nevertheless published as ‘validated tests. Scrutiny of such publications shows that they fall behind the required WOAH standards. The crucial common denominator is the non-availability of reference standards and the failure to collect samples from animals or herds that are ‘fit-for-purpose’. Major hurdles are the reluctance to reach out to laboratories that have such samples and the unwillingness by the laboratories to part with them.

The terms ‘sensitivity’ and ‘specificity’ are often used very loosely and vaguely, and the criterion for reporting needs to be revised. The difference between analytical and diagnostic parameters needs to be better understood, considering that they are often being used interchangeably. ASe is the lowest detection limit in each matrix from where the analyte could be detected or will be detected. The limit of detection (LOD) is sometimes shown as the ASe of a test and is often determined using dilutions of the analyte prepared in a diluent. ASe must be demonstrated using at least three samples with different but known analyte concentrations (high, moderate, and low) as triplicates carried out at least with three runs on three different days (the so-called ‘multiples-of-3 concept’).

DSe, on the other hand, is the identification of test positives in disease-positive individuals. If a GST is used as a reference test, then a direct comparison using a 2×2 table can be used to estimate DSe. However, as mentioned above, most GSTs are imperfect reference tests, so the estimate of DSe is relative to the imperfect reference test. The DSe estimate can be ‘fit-for-purpose’ based on the sample types used to arrive at the value. Using latent class models, the DSe can be determined even if the true disease status is unknown.

ASp is the detection of a specific analyte in the presence of closely related conditions. It must be established for diseases with similar clinical presentation and closely related causative agents. The choice of discriminants can be based on prevalent diseases in the geographical area where the test will be used. DSp is the identification of test negatives in disease-negative individuals and is relative to the imperfect reference test. It can be decided based on ‘fit-for-purpose’, and latent class models can be used to arrive at this estimate.

Similarly, the terms ‘repeatability’ and ‘reproducibility’ are often used interchangeably even though they are not synonymous. While repeatability is established within one laboratory under identical conditions, reproducibility is confirmed between laboratories where the personnel, equipment and other conditions may differ. It is advised to follow the ‘multiples-of-3 concept’ (see above). For repeatability, a test validation must identify the variability between wells/plates/days/personnel and for reproducibility, it must identify the variability between laboratories.

Finally, the terms ‘diagnostic accuracy’ and ‘precision’ are used vaguely and interchangeably. These terms are derived from the controls used in the assay for quality assurance. These parameters can be measured and visualized while performing the repeatability and reproducibility assessment of the tests.

These measures will provide us with estimates to calculate the coefficient of variation and arrive at the region of uncertainty of test results around the cut-off.

The presence of the analyte depends on the duration of exposure, the pathogen phase, and the host response phase. Selecting the right diagnostic target is essential, be it antigen or antibody or any host- or pathogen-driven metabolite. This depends on the stage of infection, namely exposed, infected, infectious or diseased. Therefore, for the diagnostic test to be perfect, it must match the ideal analytical target, be it the genetic material, protein, metabolite, or antibodies. The diagnostic target is also dependent on the nature of the infection. In a systemic infection, the analyte can be measured from different sites within the host so that a variety of samples may be acceptable. However, if it were a focal infection, the sample collection must be specific. The sample viability also depends on the speed with which it reaches the laboratory where the test is deployed. POCT can circumvent this issue if the stability of the reagents in the test is adequately validated for use under different conditions.

An imperfect correlation between diagnostic and analytical targets will not be able to give positive discrimination between disease and no disease. Most operators choose samples with perfect discrimination resulting in an overestimation of parameters. In the same sense, imperfect discrimination will lead to false-positive and false-negative results, making the test imperfect. There needs to be a balance. An imperfect test with flawed sampling will overestimate the DSe and DSp, and the test will appear perfect. This is a common finding in most publications and kit inserts. However, an appropriate estimate of DSe and DSp can be obtained for an imperfect test if the sampling methods follow the principles of random sampling of a population or populations with appropriate stratification to remove effects of age, sex, breed, geographical area etc.

If samples are collected using the random sampling method described earlier, there is every chance of results overlapping, giving rise to conditional probabilities where there are disease-negative individuals in test-positive results and disease-positive individuals in test-negative results. If the analyte has true discriminatory power, these overlaps will be minimal.

False positive and false negative results induce a latent class, especially when comparing two diagnostic tests without known disease prevalence in the population. This condition can be modelled using latent class analysis, making the validation process robust. The absence of knowledge about true infection/disease status leads to latent class analysis (LCA) terminology. This terminology represents

that diagnostic outcome data are modelled as a mixture from a source population where animals are either infected or not. Still, it is generally unknown due to the absence of a perfect reference test. The prevalence of infection defines the mixing parameter in the mixture.

In contrast to studies designed to evaluate the accuracy of tests when the disease status is known, the latent class methods are characterized by the absence of a reference test, the incorporation of properly justified prior information, the need for an explicit definition of the condition that the tests under evaluation are targeting, and the complexity of the statistical models (Johnson WO et al., 2019). The reporting requirements for these critical elements are addressed herein and are termed under the modified STARD-BLCM guidelines (Kostoulas P et al., 2017).

Considering these factors, random sampling of populations with different disease prevalence is recommended. Two recent publications describe how to tackle this issue and have gained prominence (Johnson WO et al., 2019, Kostoulas P et al., 2017). These publications lay down certain assumptions to consider while validating diagnostic tests without any information on the disease in the population.

Each method is flawed, as they all are based on assumptions. However, our actions based on the test results based on some assumptions have consequences. In contrast, the frequentist approach considers that the data is assumed to be random and establishes the likelihood function with fixed estimates, i.e., a mean for parameters with a 95% confidence interval. However, a latent class approach assumes the data is considered fixed and defines a likelihood function. Without true knowledge of disease prevalence in the population, a prior distribution of estimates can be assumed and leads to a posterior distribution based on probabilities. Here the estimates are random with 95% posterior probabilities. The median values are essential when compared to the mean.

Three critical assumptions the latent class model considers are that the target populations must have different disease prevalence, the diagnostic characteristics must be constant across the populations selected and consideration must be given to the conditionality between the index and reference test. If the two tests measure the same analyte, they are conditionally dependent and require additional modelling for conditional probability measuring the co-variance between the tests (Cheung A et al., 2021). However, if the two tests measure different analytes, they are conditionally independent, and the model becomes simple. These are some fundamental assumptions in the standard model form. In complex situations where some of these assumptions may not apply, it is recommended to seek expert

guidance. Some recent publications have considered complexities in their models (Balkema-Buschmann A et al., 2022; Dreumel AK et al., 2015, Moody NJG et al., 2022, Bath C et al., 2020).

Any new test must be fit-for-purpose with clear identification of the analyte and diagnostic target matching the stage of the disease. The reagents must be prepared in the best possible manner, and with consistent yields. Consulting a biostatistician during the developmental stage and following the principles of the STARD initiative is very important. A clear validation pathway must be drawn, results must be tabulated and matched to the models. Then, the test can be launched or published with confidence, but the door must be left open for continuous improvement and total quality management.

3. Assays for virus detection and characterization

Some aspects of FMDV diagnosis have seen remarkable progress since previous gap analysis exercises (Knight-Jones TJD et al., 2016), while others received little or no attention from the research community. A lot of attention continues to be focused on pen-side testing, since reliable field tests can have applications in free regions as well as in areas where FMD is enzootic.

LFDs for FMD antigen detection and even serotype differentiation have great potential for use in enzootic situations, but the availability of the products in the market is often a problem, as is the diagnostic sensitivity of the method overall. Some existing products have issues with the detection of SAT 2 serotype viruses, which is being addressed with new monoclonal antibodies (Cavalera S et al., 2022, Yang M et al., 2021; Yang M et al., 2019) or universal capture ligands (Yang M et al., 2022). Chemical signal amplification techniques may increase sensitivity across the board (Morioka K et al., 2020). Development work in this area is ongoing and laboratory results are promising, but so far validation data from the field is lacking.

The LFD format can be particularly useful to increase FMD surveillance in enzootic settings when it is combined with simple but effective (and validated!) on-site inactivation protocols (Romey A et al., 2018). This allows the targeted collection and submission of viral genetic material for molecular characterization. Similar protocols can be used to improve biosafety when collecting vesicular material on infected premises during an outbreak response in a free region (van Jansen Vuren P et al., 2022; Horsington J et al., 2020), in contrast with the long-standing recommendation (e.g., in the WOAH manual) to use neutral-buffered media for sample collection and shipment. This has been made

possible by the increasing use of sensitive and robust molecular methods, particularly real-time RT-PCR, which has generally replaced virus isolation and antigen ELISA as the primary diagnostic test for FMD. Real-time RT-PCR can be employed for a wider variety of sample matrices than virus isolation (Fontél KS et al., 2019). Furthermore, it has been shown that reliable PCR and sequencing results can be obtained, and virus can be recovered by transfection even when vesicular samples are severely degraded (Dill V, Eschbaumer M, 2019), but more comprehensive validation with different virus strains and sample matrices is called for. The biological risk associated with sample shipments is greatly reduced by inactivation treatment or the use of biosample collection cards (Keck H et al., 2022a), even if the viral genome in the inactivated samples is not entirely without risk either (Keck H et al., 2022b). More research may be warranted to better quantify the residual risk of contagion in different exposure scenarios.

In general, shipping samples from areas where FMD is enzootic to international laboratories in free countries is becoming more difficult every year and had been virtually impossible during the height of the COVID-19 pandemic. This can be mitigated by local capacity building, e.g., with portable sequencing platforms such as MinION (Brown E et al., 2021; Hansen S et al., 2019) and on-line dashboards to visualize and share data in real-time.

(Note: All participants in the international sharing of biological samples or digital sequence information should familiarize themselves with access and benefit sharing requirements as laid out in the Nagoya Protocol and national legislation).

The standardization of reagents is also beneficial for applications where nucleic-acid-based techniques cannot fully replace cell culture, such as in the amplification of new virus isolates for in-vitro vaccine matching. Adequately sensitive permanent cell lines (Kabelo T et al., 2020; Gray AR et al., 2020) that grow quickly and remain stable over many passages are a cheaper and less demanding alternative to primary cultures. However, more work remains to be done to ensure proper identification (LaRocco M et al., 2015) and freedom of adventitious agents (Gray AR et al., 2021, LaRocco M et al., 2021) for all cell lines used in FMD research and diagnosis.

In the area of portable nucleic acid detection, good results are being obtained with reverse transcription (RT) LAMP. Due to primer design constraints, the assays often have a local epidemiological focus [45, 46], but pan-FMDV tests have been developed as well (Lim D-R et al., 2020). Additives such as

graphene oxide gold nanoparticles and carboxamides are being tested to increase the specificity of pen-side nucleic acid detection (Kim J-W et al., 2020; Ghaith DM, Abu Ghazaleh R, 2021). Crucially, most published assays have not (yet) been tested under actual field conditions. Published results are generally obtained on sophisticated and expensive laboratory equipment rather than low-cost portable devices (Lim D-R et al., 2020). Efforts are being made to reduce the need for specialized equipment, e.g. by using indicator chemistry with color changes that are discernible by eye (Zhang J et al., 2022), and a mostly equipment-free setup, based on reverse transcription recombinase polymerase amplification (RT-RPA) using body heat and a visual read-out, has been proposed (Liu L et al., 2018). However, this assay and other RPA-based tests require lateral-flow dipsticks for product detection (Wang H et al., 2018; Wang H-M et al., 2018), making amplicon contamination a major concern.

An alternative to inherently more portable assay formats like LAMP and RPA is the adaptation of regular real-time RT-PCR to portable equipment, which often only requires a change of reagents (Hole K, Nfon C, 2019; Edge D et al., 2022). Overall, there is constant innovation in this sector, but the biggest hurdle appears to be the transition from a proof-of-concept study (often done in the laboratory) to a sustainable, commercially viable portable platform. Reliance on equipment and/or chemistry by one specific manufacturer can be problematic, since many players in this field are start-ups that often fail (Goller KV et al., 2018). Even when the companies themselves endure, their platforms can become obsolete and are replaced in quick succession (Hole K, Nfon C, 2019). So far, only two products – by OptiGene (ath C et al., 2020) and Tetracore (Howson ELA et al., 2018) – have persisted long enough to be thoroughly validated under field conditions and can be considered sufficiently mature to be used by veterinary services, but more must follow.

Recent work has shown that the high sensitivity of real-time RT-PCR allows the reliable detection of FMDV in non-conventional samples, such as oropharyngeal fluids, meat juice (Yeo S et al., 2020), (pooled) milk (Armson B et al., 2020; Armson B et al., 2018; Armson B et al., 2019), airborne particulates and environmental swabs (Colenutt C et al., 2018; Brown E et al., 2021; Colenutt C et al., 2022). Multiplex assays that can detect several (exotic and enzootic) pathogens at the same time (Xu X et al., 2019; Wang Y et al., 2020; Das A et al., 2022; Erickson A et al., 2018; Chen W et al., 2022) can provide additional value. However, it will not be possible to realize the full potential of these important innovations in enzootic regions if collected samples must be transported to central laboratories and tested there, causing days or weeks of delay. In this environment, the development,

validation, and deployment of mobile diagnostic capability (be it simple handheld devices, “suitcase labs” or even larger setups mounted on vehicles) are essential for rapid testing and informed decision-making on the spot. Conversely, in FMD-free countries with good transport infrastructure and sophisticated veterinary services, often significantly more time is lost by a delayed decision to initiate testing than by the diagnostic tests themselves. Exclusion testing schemes, which promote laboratory testing to rule out foreign animal diseases in cases that do not rise to the level of a formal suspicion, are used successfully in several countries, and should be considered for adoption in other FMD-free areas (Eschbaumer M et al., 2020).

In enzootic settings with several co-circulating FMDV strains, the utility of both centralized and pen-side detection of viral nucleic acid can be greatly increased with the growing range of serotype- or lineage-specific assays (Saduakassova MA et al., 2018; El Bagoury GF et al., 2022; Lim D-R et al., 2022; Liu Y-L et al., 2018). The design of assays that are intentionally geographically restricted is the most viable method to use RT-PCR for FMDV serotyping, but the dynamic evolution of the circulating strains requires constant updating of genomic databases and recurrent validation of these assays with representative panels of contemporary viruses (Chestley T et al., 2022). Specific assays are not yet available for all relevant virus lineages and more development in this area is encouraged. Going forward, the design of PCR primers and probes may be facilitated by predictive in-silico models (Chestley T et al., 2022; Howson ELA et al., 2020).

The diversity of research on FMDV antigen detection is remarkable. In addition to nucleic acid amplification and immunological detection of antigens, recently published work included DNA aptamers (Sousa Lacerda CM de et al., 2022) and biosensors (Hamdy ME et al., 2018; Hussein HA et al., 2019). It has even been shown that the biochemical activity of the virus itself can be used for its detection (Malik S et al., 2020; Swatek KN et al., 2018). In general, combining multiple assays (traditional and novel) can dramatically increase diagnostic performance and resolution (Foglia EA et al., 2021; Khan S et al., 2021; Rios L et al., 2018).

4. *Serology-based assays*

Antibody responses to FMDV structural proteins

Antibody responses against FMDV's external structural proteins (SP) can be used to measure humoral immunity induced after vaccination or infection. Consequently, serology is widely applied to assess quality in FMD vaccines and herd immunity in vaccination campaigns.

The virus neutralization test (VNT) is the current gold standard for detecting neutralizing antibodies against FMDV, but it is time-consuming and requires biocontainment capabilities that make it unsuitable for field testing (Cao et al., 2022). The enzyme-linked immunosorbent assays (ELISA) are therefore the test of choice for rapid serological diagnosis of FMDV owing primarily to its reliability, cost-effectiveness, and ease of use (reviewed in Ma et al., 2011 and Wong et al., 2020).

Among different types of ELISA, the liquid-phase blocking ELISA (LPBE) developed by Hamblin et al is widely utilized (Hamblin et al, 1986). The LPBE may keep a very good correlation with the homologous protection, as demonstrated for viral strains previously circulating in South America (Maradei et al, 2008). The assay can be used in multiple animal species to assess herd immunity during vaccination campaigns as well as to evaluate vaccine potency. However, as a downside, it requires the availability of strain-specific monoclonal or polyclonal sera, and should be performed under controlled conditions, especially regarding the viral antigen integrity.

In this regard, a study by Mansilla and Turco et al. showed that the disassembly of viral capsids in expired inactivated FMD vaccines can cause the production of antibodies against capsid fragments in immunized animals, negatively impacting the concordance between standard LPBEs and the VNT (Mansilla et al., 2020). Ludi et al. published similar findings in their recent study of cross-serotype reactivity in anti-NSP antibody-detecting ELISAs, reporting that stabilized recombinant capsid antigens that did not expose internal epitopes facilitated reduced cross-reactivity (Ludi et al., 2022b).

At present, the best correlates of protection are homologous and heterologous VNT titers (Paton DJ et al., 2019). However, as mentioned above, VNTs are only available in a small (and decreasing) number of laboratories and inter-laboratory variability is high.

As an alternative to these problems, other immunoassays that can be used to predict homologous and heterologous protection are available (e.g., avidity ELISAs) (Lavoria et al, 2021). There are ongoing efforts within GFRA to refine these tests and transfer them to more laboratories, particularly in enzootic settings where effective post-vaccination monitoring (PVM) is critical for the success of FMD control programs. At the same time, other possible replacements for the VNT in both vaccine matching and PVM should continue to be explored and refined (Kang Y-L et al., 2018; Cao Y et al., 2022; Karabassova AS et al., 2022; Mansilla FC et al., 2020).

ELISAs against FMDV capsid protein-specific antibodies are often used to complement and confirm anti-NSP serological diagnostics, but the variability of capsid epitopes necessitates the use of multiple serotype-specific ELISAs in parallel (Biswal et al., 2015). Wong et al. identified two highly conserved regions of the VP1 functional epitope (residues 145-152 and 159-170); they reported that a phage T7 displaying the VP1159-170 epitope may be a useful diagnostic for identifying anti-FMDV antibodies in vaccinated animals, as this short C-terminal epitope displayed higher antigenicity compared to the complete immunodominant region (Wong et al., 2018). A later in silico analysis found that VP2 is significantly more conserved among serotypes compared to VP1, particularly in its N-terminal domain (Mishu et al., 2020). Asfor et al. uncovered a pan-serotype epitope in this highly conserved VP2 N-terminal region, with a subsequent VP2-ELISA displaying 99% sensitivity and 93% diagnostic specificity for detection of antibodies against strains from all seven FMDV serotypes (Asfor et al., 2020), and Salem et al. used recombinant VP2 capsid protein as a capture antigen for a universal indirect ELISA with results comparable to standard LPBEs (Salem et al., 2019).

FMDV serotype characterization

Antibodies against FMDV's SP can also be used to detect and identify the specific serotypes of the virus circulating in the field. Recent studies have focused on identifying new targets, reagents, and protocols for enhancing our repertoire of ELISAs.

Sandwich ELISAs generally require consistent production of mAbs from hybridomas, which can suffer from unpredictable genetic instability and other reproducibility and contamination concerns (reviewed in Moraes et al., 2021). Shimmon et al. published a workflow for circumventing these issues by generating serotype-specific mouse/rabbit D9 chimeric antibodies, which can be produced in stable recombinant systems (Shimmon et al., 2018). Meanwhile, Chitray et al. used a single chain variable

fragment (scFv) phage display library to identify new epitopes downstream of the RGD domain in the VP1 gene, validating one SAT 1- and two SAT 3-specific scFvs as capture/detection reagents for the development of an improved diagnostic ELISA (Chitray et al., 2020). Following a different approach, Morioka et al. applied silver amplification immunochromatography to FMDV antigen detection, reporting higher sensitivity relative to commercially available kits in multiple sample types including saliva (Morioka et al., 2020).

Ran et al. developed a cELISA based on bacterium-origin FMDV VLPs for detection of FMDV serotype O while avoiding the biosafety risks associated with the use of live virus (Ran et al., 2019). VLP-based solid-phase competition ELISAs (SPCEs) have been validated for detecting serotypes O and/or A (Y. Zhang et al., 2022, 2020a, 2020b).

Dromedary camels mount a unique humoral immune response dominated by single-domain heavy-chain antibodies that are better able to bind clefts on protein surfaces compared to conventional antibodies (De Genst et al., 2006). The diagnostic potential of these camelid antibodies has been tested for numerous diseases including FMDV, where antibodies against serotype O, A, and Asia 1 capsid epitopes were successfully used as capture agents in a diagnostic liquid-phase blocking ELISAs (LPBEs) (Dash et al., 2019).

Venerable in-house assays and commercial products for the detection and quantification of SP antibodies in serum are available, but all suffer from cross-serotype reactivity (Ludi AB et al., 2022). This is not problematic or maybe even beneficial if SP antibody testing is only used to confirm infection, e.g. by corroborating an NSP antibody ELISA result. In enzootic settings, however, extreme caution is needed when using serological assays to evaluate the prior exposure of animals to multiple FMDV serotypes or dissect the immune response to polyvalent vaccination (Ludi AB et al., 2022). Currently, only VNT offers reliably low levels of inter-serotypic cross-reactivity, and more work is required to identify truly serotype-specific epitopes that can be used for improved SP antibody tests. Conversely, the characterization of cross-reactive and potentially cross-protective epitopes has great potential for the development of new vaccines (Marrero Diaz de Villegas R et al., 2021). All antigenic variation is the consequence of genetic evolution leading to amino acid substitution. There has been incremental progress in the prediction of epitopes and antigenic relationships based on sequence data (Qiu J et al., 2021; Upadhyaya S et al., 2021; Xu W, Yang M, 2021; Xu W et al., 2018; Islam MR et

al., 2021), but traditional empirical methods of vaccine matching by VNT (and ultimately, in-vivo potency tests) remain the gold standard. It is expected that the pace of innovation in this field will increase using machine learning and artificial intelligence (AI).

Detection of FMDV circulation and persistence

Antibodies against viral non-structural proteins (NSP), which do not normally exhibit serotype specificity, are commonly utilized to detect infected animals, and assess virus circulation in the field.

Commercial ELISAs for detecting anti-NSP antibodies have demonstrated high performance and reproducibility (Browning et al., 2020; Fukai et al., 2018). However, serological diagnosis of FMDV infection and/or vaccination can also benefit from a combination of assays targeting different moieties (Kang Y-L et al., 2018).

All commercially available non-structural protein (NSP) antibody assays are 3ABC tests, but tests for antibodies against 2B or other NSPs have been developed that could be used for cross-confirmation e.g., in post-vaccination DIVA applications (Tewari A et al., 2021; Jain B et al., 2019). Hosamani et al produced a new competitive ELISA (cELISA) that maintained the sensitivity and diagnostic specificity of commercial kits while allowing detection of antibodies against the 3B NSP in a wider range of host animals (Hosamani et al., 2022). Camelid antibodies have also been deployed in a nanobody-based cELISA for detecting anti-3ABC antibodies in cattle in Uganda, designed to provide high sensitivity and specificity while facilitating low-cost production (Gelkop et al., 2018).

In addition to the concerns already discussed in this section, there is room for improvement in many aspects of existing tests, e.g., to lower the cost of production or prolong the shelf life without refrigeration. As for nucleic acid detection methods, there is a cornucopia of entirely novel or improved serological tests at the early experimental stage – universal SP antibody assays (Asfor AS et al., 2020; Salem R et al., 2019), multiplex (Nfon C et al., 2018) chemiluminescence assays (Liu Z-Z et al., 2018; Liu W et al., 2021), tests using camelid-derived single-domain antibodies (Dash L et al., 2019; Gelkop S et al., 2018) or gold nanoparticles (Jain B et al., 2018) and many more. It will be interesting to see which of these technologies will ultimately prove useful for FMD diagnostics at large.

Further validation and potentially commercialization of such tests would be beneficial. The same applies to structural protein (SP) antibody assays that can be used to detect carrier animals based on

their high levels of FMDV-specific immunoglobulins in nasal secretions (Jain B et al., 2019; Biswal JK et al., 2021).

While the epidemiological significance of the FMD carrier state remains controversial, the difficulty of detecting these asymptomatic animals is a significant hurdle for field studies of its prevalence and potential role in viral persistence. FMDV-specific mucosal IgA is produced in acutely and persistently infected cattle, but not in vaccinated animals (Pacheco et al., 2010; Parida et al., 2006). Biswal et al. took advantage of this phenomenon to produce a mucosal IgA ELISA for detecting FMDV carrier animals using nasal, saliva, or OPF samples, reporting 99% diagnostic specificity and 76.5% sensitivity (which increased to 96.9% when combined with an NSP-ELISA) (Biswal et al., 2021), and Jain et al. reported a highly sensitive IgA ELISA against the 3AB3 NSP (Jain et al., 2019).

DIVA testing

Our ability to monitor the efficacy of FMDV vaccines depends on reliably identifying vaccinated animals, requiring diagnostic tests suitable for Differentiating Infected from Vaccinated Animals (DIVA). As viral NSPs are typically depleted in traditional inactivated vaccines or not present in recombinant vaccines, the nonstructural polyprotein 3ABC and its individual component proteins (or antibodies against these proteins) are commonly used as a negative markers for DIVA testing (Hardham et al., 2020; Moghaddam et al., 2021; Tewari et al., 2021; Zia et al., 2022). Wang et al. identified a conserved linear epitope (126ERTLP130) in the NSP 3A and validated a mAb against this epitope for DIVA testing of sera from FMDV-infected pigs and cattle (M. Wang et al., 2019), and a similar study from Liu et al. found three linear B cell epitopes in the 3ABC polyprotein (W. Liu et al., 2019). Chitray et al. developed the first 3ABC antibody ELISA specifically for the SAT serotypes, reporting sensitivity and specificity comparable to commercial assays when tested on field sera samples (Chitray et al., 2018).

Interestingly, removing the 3C sequence from 3ABC resulted in a recombinant 3AB with similar antigenic properties but reduced degradation and insolubility (Salem et al., 2021). Bhatt et al. conducted a mutational analysis of the FMDV 3AB-coding region to identify functionally silent mutations that could be targeted for new DIVA tests – deletion of the C-terminal residues 87-144 did not reduce infectivity in BHK-21 cells, and an indirect ELISA targeting the deleted region showed good sensitivity and specificity (Bhatt et al., 2018). Chung et al. produced a rapid DIVA-compatible

cELISA utilizing a blocking mAb against a highly conserved 3B epitope, reporting 100% pan-serotypic analytical and diagnostic specificity and high reproducibility (Chung et al., 2018). Finally, Diez et al. used recombinant occlusion bodies of baculovirus to carry the 3AB1-3 NSP and included them in a DIVA- compatible FMD ELISA (Diez et al., 2018).

While ELISAs against NSPs are commonly used for FMDV DIVA testing, repeated application of insufficiently purified vaccines can induce an anti-NSP antibody response that confounds these assays (Hardham et al., 2020). Multiplexed DIVA assays that test for multiple negative markers are a potential solution to this problem (reviewed in Tewari et al., 2020).

5. Other diagnostic tools

Infrared thermography (IRT) has been used as a screening tool for humans during the COVID-19 pandemic (e.g., at airports and border crossings).

IRT has also been studied as a rapid screening tool for identifying diseased animals via detection of changes in blood flow (and subsequent heat radiation) due to inflammation (reviewed in Choudhury et al., 2020 and Mota-Rojas et al., 2022, 2021). It remains to be seen whether AI can be used to overcome the problems in image interpretation that have so far prevented IRT from becoming widely adopted. AI may also benefit behavioral analysis as a disease screening tool (Wolf TE et al., 2020).

IRT was first demonstrated for FMD screening in cattle in 2009, when foot temperatures were used to detect FMDV-infected animals with ~61% sensitivity and 88% specificity (Rainwater-Lovett et al., 2009). Nevertheless, there have been very few reports of its application for FMD surveillance and early detection (Nishi T et al., 2021) in the last decade. Chiu and Hsu recently combined IRT with accelerometer-based behavior logging to identify hoof lesions in dairy cows under subtropical climates. These authors used a lower cutoff hoof temperature for defining pathology compared to Rainwater-Lovett et al. (32.05°C vs. 34.4°C) and reported 75% agreement with clinical diagnosis (Chiu and Hsu, 2022). IRT has also been deployed in Indonesia to monitor signs of mastitis and FMD (Bansi, 2018). Finally, a comparison of low-cost LCD devices vs. host-cost devices in diagnosing lameness via IRT found no significant differences between the two captured datasets, suggesting that

on-farm IRT-based detection systems could be deployed more cost-effectively than previously thought (Coe and Blackie, 2022).

Recommendations

The GFRA Gap Analysis Working Group recommends the following research priorities for diagnostics:

- ✓ Promote the replacement of diagnostic reagents that are hard to standardize, suffer from batch-to-batch variation or require biological containment for their production (primary cell lines, polyclonal sera, inactivated whole-virus preparations) with suitable alternatives (permanent cell lines, monoclonal and recombinant antibodies, virus-like particles, recombinant proteins)
- ✓ Validation of diagnostic assays (pen-side tests) using harmonized procedures, benchmarks, and reference panels; for pen-side tests, demonstration of fitness-for-purpose under field conditions is essential.
- ✓ Build local diagnostic capacity in enzootic regions (antigen detection and characterization, serological assays for post-vaccination monitoring) and promote data sharing in real time.
- ✓ Identify and address the impact of access and benefit sharing regulations for biological resources and digital sequence information on FMD diagnosis and research.
- ✓ Standardization and commercialization of isothermal amplification-based diagnostic tests
- ✓ Improved stability of reagents in commercial diagnostic kits
- ✓ Validate and promote the adoption of inactivation protocols that increase biosafety during sample transport without compromising diagnostic utility of samples.
- ✓ Development of new reference reagents for FMDV diagnostics and inter-laboratory standardization
- ✓ Standardization of low-cost, easy-to-use sample collection and transport methods
- ✓ Investigation of artificial intelligence for the development of algorithms to recognize FMD signatures in domestic animal species (cattle, pigs)

- ✓ Continue the development, validation, and deployment (particularly in enzootic regions) of alternatives to virus neutralization tests for vaccine matching and post-vaccination monitoring.
- ✓ Pursue the characterization of cross-reactive and potentially cross-protective epitopes and the prediction of epitopes and antigenic relationships based on sequence data; explore the use of artificial intelligence and machine learning for this application.

Vaccines and Biotherapeutics

Vaccines

Literature Review

1. General Aspects

Vaccines to protect animals against FMDV infection are a much-needed tool in both outbreak settings and in endemic regions. At present, the only type of vaccine that is commercially available to end-users comprises inactivated virus (of one or more serotypes) adjuvanted with mineral oil or aluminum hydroxide: the same type of vaccine that has been used against FMDV for almost the past 50 years. However, currently available vaccines offer variable levels of protection in the field, require high-containment production facilities for the culture of large amounts of live virus for inactivation, and necessitate cold-chain storage prior to use. Although use of this type of vaccine undoubtedly reduces the clinical severity of the infection and decreases transmission by lowering viral load in infected animals, it has shortfalls across its immunological effects, its practical application, and the challenges of its manufacture. In short, there is much scope for innovation and improvement, and the research field evidences numerous publications towards these aims.

Among these shortfalls, the largest is probably the vaccines' inability to rapidly induce long-lasting, cross-protective immunity. The antigenic diversity of FMDV across serotypes and strains means that, at present, a farmer may only see protection of his vaccinated herd against the same or very similar strains of FMDV as are incorporated in the vaccine (though some exceptions to this have been informally reported). As vaccine-induced antibody titers decrease with time, so this protection will wane, unless regular boosters are given. Partly, these problems likely relate to the weak T cell response induced by conventional vaccines, which fail to support the level/type of immunity needed for long-lasting sterile protection from FMDV. However, yet, we have an incomplete picture of what the "optimal" T cell response looks like, though several studies are beginning to shed light on this phenomenon.

Despite the improvements on the transfer of recombinant new technologies to industry, no new vaccines have reached the shelf or been widely distributed in international markets since the last gap analysis in 2018. Since 2018, hundreds of studies have been published that cover attempts to improve upon currently available vaccines against FMDV, including improved formulations of inactivated vaccine antigen with novel adjuvants, and/or better delivery systems, as well as numerous trials of novel vaccines based on viral or bacterial vectors, virus-like particles, dendrimers/multi-antigen vaccines, and recombinant proteins or peptides. Many of these vaccines exhibit superior performance – either immunologically or in DIVA– to the conventional vaccine, yet, as far as we are aware, there are few reports of successful commercial development. Notable successes in this regard include the granting of a license to MSD Animal Health by The Pirbright Institute to develop their virus-like particle vaccine platform towards production (The Pirbright Institute, 2019); and the application by Zoetis to the Animal and Plant Health Inspection Service (APHIS) to allow the manufacture of the leaderless FMDV DIVA-compatible live- attenuated virus originally described by Uddowla et al. (Uddowla et al., 2012) and more recently tested by Eschbaumer et al. (Eschbaumer et al., 2020) for use as an inactivated vaccine in the USA (APHIS, 2020). These are important steps forward. Overall progress in the field has led to the emergence of several promising candidates that are at varying stages of development, but variable vaccine study design, lack of follow-up studies in natural target species, and failure to integrate key findings from other groups into a progressive vaccine development plan, are some of the obstacles to the widespread production and adoption of better vaccines against FMDV.

The new additional tools currently under advanced development (marker protein vaccine platforms) provide solutions to gaps identified on current inactivated vaccines. These new tools will facilitate dealing with FMD incursions more rapidly, safely and to manage the disease with higher confidence to regain a disease-free status following outbreak incursions, in non-endemic regions.

2. Inactivated FMDV vaccines

Selection of adequate viral strain within the vaccine formulation is paramount to respond during the emergency of field outbreaks. Current FMDV vaccines have insufficient immunological breadth and

are often unable to control some lineages arising in these regions, arguing for the use of custom-made vaccines. For vaccination to be effective, it requires therefore the incorporation of vaccine strains representative of strains prevalent in the locality in question. Matching of vaccines to field outbreak isolates is therefore required, and this imposes substantial delays in outbreak responses (Cox et al 2007). In case of an outbreak, an appropriate high potency vaccine of sufficient quantity (homologous potency of 6PD50) has been proposed and put in practice (Brehm KE et al 2008).

Other experimental studies examined the protection against clinical disease conferred by higher potency FMD commercial vaccines and the extent to which these vaccines could prevent the spread of disease. High potency vaccines of A22/IRQ/64 or A/MAY/97 proved to be useful to induce intra serotype heterologous cross protection against newly emerged A/Asia/G-VII lineages (Dekker et al Vaccines 2020, 8, 24). Efficacy of high quality, high pay load O1Campos vaccine was demonstrated in swine against heterologous challenge with Korean O/Mya 98 lineage (Galdo Novo et al Vaccine, 2018). Studies have also included additional susceptible species and assessed the responses of diverse FMDV target species to commercially available vaccines. For instance, the immune response to commercially available oil-adjuvanted and aqueous-adjuvanted multivalent vaccines against O/ME-SA/PanAsia and A/ASIA/Sea-97 lineages, demonstrated significantly higher antibody responses elicited in the presence of oil-based adjuvant in cattle, sheep, and camels, but that in all cases the responses of camels were significantly lower than in the other two species (Ulziibat et al., 2020). Recent study from Bangladesh described levels of antibody consistent with 100% protection on cattle following immunization with a trivalent inactivated vaccine comprising full doses (6μg antigen) of O, A, and Asia-1 isolates of FMDV (Al Amin et al., 2020b). An important knowledge gap concerns the effectiveness of high potency vaccines in reducing virus shedding, the number of animals that become persistently infected, the incidence of carrier animals among those challenged, and their capacity to respond against a broad range of heterologous viral strains.

Much of the recent work on commercially available inactivated FMDV vaccines has focused on measuring the cross-protective immunity that can be elicited by multi-valent vaccines. Such protection against heterologous FMDV strains is particularly important in regions where multiple serotypes of the virus are in circulation. For example, a study in Bangladesh showed levels of antibody consistent with 100% protection of cattle following immunization with a trivalent inactivated vaccine comprising full doses (6 μg antigen) of O, A, and Asia 1 isolates of FMDV (Al Amin et al., 2020b). Several studies

have similarly aimed to define the utility of inactivated multivalent vaccines in eliciting cross-protective immunity in goats (Lazarus et al., 2020). Alongside, studies of emergency (high payload) vaccines in sheep indicate efficacy at a useful level in outbreak situations, with significant protection from clinical disease but more variable protection from viremia (Horsington et al., 2018a, 2018b).

An important ongoing initiative, based on conventional FMDV inactivated formulations and aiming to decrease the FMDV vaccine resource gap between developed and less-developed countries, is the AgResults FMD challenge project. Launched in 2021, this scheme aims to financially support and incentivize the development of effective vaccines to protect against currently circulating FMDV strains in Eastern Africa, thereby increasing the relevant vaccine pool and increasing uptake in the region. The Project is being run in two phases: a development phase, which will encourage the production of regionally relevant vaccines, and a cost-share phase, designed to help to reduce the price of these vaccines in the marketplace to the end users, which is hoped will encourage broader uptake (Hammond et al., 2021).

In a recent study, Di Giacomo et al. tested the performance of different vaccine formulations and immunization schedules in cattle, working with a vaccine-matching model for serotype A strains. This work assessed all the previously mentioned parameters in an *in-vivo* challenge experiment, showing that antigenic payload, multivalency, and revaccination may improve the clinical outcome after heterologous challenge with FMDV These results suggest that protection to the experimental heterologous infection was related to qualitative traits of the elicited antibodies, such as avidity, IgG isotype composition, and specificity diversity, as indications of the vaccine-induced maturation of the humoral response. (Di Giacomo et al. 2022).

FMDV's rapid evolution has resulted in the obsolescence of some existing vaccines (reviewed in Mahapatra and Parida, 2018). Large-scale vaccine matching studies found that, while the O1/BFS vaccine strain still provided adequate protection against most circulating serotype O strains, the relatively higher apparent rate of evolution among serotype A strains rendered their corresponding vaccines substantially less effective (Xu et al., 2018; Xu and Yang, 2021). Many new candidate vaccines have recently been developed to keep pace with this viral diversity, with numerous studies targeting specific strains that have newly emerged within particular regional pools (reviewed in Ludi

et al., 2022a). A more detailed discussion of the different vaccine technologies and their recent development can be found in the Vaccines section of this report.

The A/ASIA/G-IX/SEA-97 sublineage circulating in South and Southeast Asia has been found to match poorly with existing vaccine strains, though strains A22/IRQ/64 and A/MAY/97 reportedly provided effective protection against it (Singanallur et al., 2020). A/MAY/97 also provided cross-protection against a representative A/ASIA/G-VII strain (Dekker et al., 2020a) but lacked efficacy against the co- circulating A/ASIA/Iran-05 lineage (Singanallur et al., 2022). In India, antigenic drift in circulating serotype A strains has reduced the efficacy of the A/IND/40/2000 vaccine strain, but a new vaccine based on the A/IND/27/2011 isolate has demonstrated increased protection in cattle (Mohapatra et al., 2018; Sreenivasa et al., 2022).

Several new vaccine candidates have been reported from East and Southeast Asia, aiming to control circulating serotype O, A, and Asia 1 strains and mitigate introductions of other serotypes (Bo et al., 2019; Horsington et al., 2018b; Jo et al., 2019b; G. Lee et al., 2020; S.-H. Park et al., 2021; Shin et al., 2020). A major outbreak of O/Jincheon/SKR/2014 in South Korea prompted many studies of effective countermeasures: the commercial O1/Campos and O/Primorsky/2014 strains (Choi et al., 2021; Galdo Novo et al., 2018), a bivalent O1/Manisa + O3039 vaccine (T. Kim et al., 2019), an O/Jincheon/SKR/2014 variant dubbed O JC-R (Jo et al., 2019a), and a strain expressing the P1 structural protein from the O/CATHAY isolate Taiwan/97 (Choi et al., 2019) were all found to provide good protection against the new virus, and an O/ME-SA/PanAsia-2-based vaccine was effective against both O/Jincheon/SKR/2014 and the Ind-2001 lineage (Ko et al., 2020). The O1/Manisa and O3039 vaccine strains were later tested against an Ind-2001d sublineage virus from Algeria (O/ALG/3/2014). In line with previously published data (Fishbourne et al., 2017), the O3039 strain alone or in combination with O1/Manisa elicited protective immunity as early as 7 days post-vaccination (Singanallur et al., 2021).

In keeping with the increasing focus on international surveillance and biosecurity programs to control the transboundary spread of FMDV, it is important to note that inter-laboratory differences (e.g., varying liquid-phase blocking ELISA protocols, antibody titer-protection correlation curves, etc.) can generate inconsistencies among vaccine matching studies, making it more difficult to select optimal vaccine strains (Willems et al., 2020). Standardization of vaccine matching techniques and validation

of in vitro methods (e.g., r1 values) in field scenarios will be important for harmonizing vaccine efficacy and protection studies among different regions (Bergmann et al., 2021). Simple and efficient alternatives to the laborious virus neutralization test (VNT), such as the avidity ELISA (Lavoria et al., 2012), may enhance the ability of geographically disparate laboratories to generate directly comparable data on vaccine efficacy (Jain et al., 2022). Improvements to vaccine production capacity are also vital for ensuring a steady supply to countries struggling with low vaccine availability (X.-R. Li et al., 2019).

Alongside, some researchers have started the important task of examining the responses of diverse FMDV target species to commercially available vaccines. One such study measured the immune response to commercially available oil-adjuvanted and aqueous-adjuvanted multivalent vaccines that aim to cover the O/ME-SA/PanAsia and A/ASIA/Sea-97 lineages and found significantly higher antibody responses were elicited in the presence of oil-based adjuvant in cattle, sheep and camels, but that in all cases the responses of camels were significantly lower than in the other two species (Ulziibat et al., 2020). The authors noted that there is not the available information to predict likely protection levels in camels from these vaccines, illustrating the need for further basic studies in non- classical FMDV target species.

Looking to improve the design of current vaccines against serotype A FMDV, which often fail to provide protection against circulating field strains, Hwang et al. developed an A/SKR/Yeoncheon/2017 vaccine strain with a lower-than-usual number of P1 mutations (typically induced by adaptation to cell culture) and immunized pigs, cattle and mice with the experimental vaccine (Ulziibat et al., 2020). Both pigs and cattle mounted antibody responses that could neutralize the homologous virus and several heterologous A serotype field strains in vitro, and the vaccine also provided dose-dependent protection from FMD in mice (J.-H. Hwang et al., 2021). Understanding the impact of the vaccine on protection from clinical disease and virus shedding in natural target species, and the establishment of the carrier state in ruminants, would be an interesting topic for future investigation.

Other engineered FMDV strains have also been produced, inactivated, and used to elicit superior immune responses compared to conventional inactivated vaccines. Among the most successful of these is a modified FMDV A24 strain that lacks the leader sequence and contains marker modifications in 3B and 3D that enable DIVA, which was first described by Uddowla et al. (Uddowla et al., 2012) with

further characterization by Eschbaumer et al. (Eschbaumer et al., 2020). These studies showed that the modified virus was highly attenuated in pigs and cattle (Eschbaumer et al., 2020; Uddowla et al., 2012), and that, once inactivated, a single dose elicited complete protection of cattle from challenge with the parental virus (Uddowla et al., 2012). The excellent safety profile and high efficacy of the vaccine led to Zoetis petitioning APHIS, part of the USDA, for permission to manufacture a new inactivated vaccine based on a leaderless live-attenuated virus against FMDV in the USA (APHIS, 2020).

Other potential candidates for new inactivated vaccines based on modified FMDV have also been investigated. For example, Lee et al. added the T cell epitope from 3A and the immunostimulatory HSP- 70 into the VP1 sequence of an O1/Manisa-A22 chimera and showed high levels of antibody production in pigs and mice, and complete clinical protection in mice (M. J. Lee et al., 2020). Most recently, specifically aiming to overcome the limiting effect of maternal antibodies on FMD vaccine responses in young animals (Bucafusco et al., 2014), Lee et al. inserted a T cell independent B cell stimulatory epitope (C3d) into the VP1 of O and A serotype FMDV and used the inactivated recombinant viruses to vaccinate 8-9-week-old piglets either having or lacking maternal antibodies (M. J. Lee et al., 2022). The researchers found that the novel vaccine induced greater cell mediated immune responses in pigs than did the same vaccine constructs lacking C3d and suggested that this would be an effective strategy for the generation of subunit vaccines that were not subject to inhibition by maternal antibodies (M. J. Lee et al., 2022).

Another reason to explore capsid engineering is to improve stability under conditions of higher temperature and/or across a range of pH conditions. If achieved, this would facilitate more efficient production of inactivated vaccines by reducing the amount of capsid disassembly during manufacture and storage and would increase ease of use by reducing the need for a continuous cold chain, without which, immunogenicity can be significantly adversely affected (Sieng et al., 2018). One way of achieving these aims is by the addition of novel stabilizer solutions such as sucrose alone, in the case of live vaccine seed stocks (Hwang et al., 2020), or in combination with lactalbumin hydrolysate for purified vaccine antigen (Kim et al., 2021). Mutation of the virus itself can also be used to affect the physiochemical properties of the capsid: targeting acid-stability specifically, Yuan et al. reported that a recombinant O serotype FMDV bearing the D86H substitution in VP2 was as infective as WT virus in vitro and in vivo in suckling mice, while exhibiting increased stability over a broader range of pH values, as well as higher thermal stability, compared to WT (Yuan et al., 2020). Similarly, in a

screening study of several FMDV mutants bearing single or multiple mutations, Gao et al. showed that the VP1 Y2098F mutant strain exhibited high immunogenicity in pigs with significantly increased thermostability (Gao et al., 2021). Moreover, Kotecha et al. produced a chimeric SAT 2-01K infectious clone bearing alterations in VP4 that led to increased thermostability, without compromising known antigenic sites, growth characteristics in vitro or immunogenicity in vivo in calves (Kotecha et al., 2018); while a high- temperature selection experiment led to the identification of the A1013T substitution in VP1 of O serotype FMDV as a thermostable mutant with high immunogenicity in guinea pigs (Dong et al., 2021). A thermostable FMDV vaccine is also currently under development at the ICAR-Directorate of FMD in India (J. K. Biswal, 2023, personal communication).

3. Live-attenuated vaccines

Live attenuated vaccines (LAVs) are attractive candidates for next-generation FMDV control tools, with several recent studies reporting progress towards this goal. For example, Medina et al. identified an Lpro mutant FMDV exhibiting reduced deISGylase activity, which prevented its inhibitory interaction with host antiviral protein ISG15, and thereby limited its replication ability in mice (Medina et al., 2020a). In natural host species, Yang et al. showed that C351G mutation in the IRES rendered FMDV attenuated in swine, whilst retailing high immunogenicity that induced complete protection from disease and viremia and showing no evidence of reversion to virulence either during 20 in vitro passages in BHK-21 cells, or three passages through pigs (D. Yang et al., 2020). The authors also described a parallel approach with a different mutant, effective in cattle (D. Yang et al., 2020). An interesting study took a more systematic approach and looked at the potential for synonymous codon deoptimization (SCD) – where mutations are introduced into the capsid-coding-sequence that do not change the amino acid encoded but lead to viral attenuation – for generating LAV against FMDV (Diaz- San Segundo et al., 2021b). Building on their previous work applying SCD to P1 of FMDV to generate a safe and effective LAV candidate in swine (Diaz-San Segundo et al., 2016), Diaz-San Segundo et al. used SCD on the highly-conserved NSP-coding regions, P2 and P3, to produce a LAV with the potential to induce cross-reactive immunity; however, while the resultant viruses were somewhat attenuated and could induce high levels of immune response, the study highlighted the

difficulty in balancing a level of virulence that is immunogenic, and yet does not cause overt disease (Diaz-San Segundo et al., 2021b). Meanwhile, researchers at the ICAR-Directorate of FMD are developing next-generation FMDV vaccines including a DIVA-compatible LAV (J. K. Biswal, 2023, personal communication).

4. Bacterial-vectored vaccines

Bacterial-vectored vectors are innately immunogenic, easily modified, rapidly produced, and may lend themselves to alternative administration routes. Zhi et al. developed an oral FMDV vaccine comprising attenuated Salmonella enterica Typhimurium expressing VP1 from FMDV serotype A and showed that the vaccine induced mucosal IgA in the intestine that recognized FMDV, as well as systemic CD4+ and CD8+ T cell responses in mice vaccinated twice (Zhi et al., 2021). Similarly, Zhang et al. used Lactococcus lactis as a vaccine vehicle, expressing a novel Co1-FMDV VP1 multiepitope fusion protein, designed to target the viral protein to intestinal M cells and so induce strong mucosal responses (F. Zhang et al., 2021). The researchers found compelling evidence not only of intestinal responses to the vaccine, but also of IgA production in the lungs of orally vaccinated mice (F. Zhang et al., 2021). These promising initial findings warrant further investigation in natural host species of FMDV, specifically assessing IgA production in the respiratory and oral mucosa, and directly measuring protection from FMDV challenge.

Other bacteria have also been preliminarily investigated as FMDV vaccine vectors, including Listeria ivanovii (Mahdy et al., 2019b) and mutant Listeria monocytogenes (Mahdy et al., 2019a), both of which were engineered to express FMDV VP1, and showed encouraging immunogenicity after being injected into mice.

5. Viral-vectored vaccines

The use of adenoviruses as vectors for FMD vaccines has been explored over the past 25 years, with early studies in swine (Mayr et al., 2001, 1999) driving continued interest, and leading to the

development and conditional approval of an adenovirus-vector vaccine for use against FMDV serotype A in case of an outbreak in the USA, in 2012. Adenoviruses encoding FMDV proteins hold great promise as vaccines, with potential advantages of reduced side-effects, safe manufacture, potentially rapid induction of protective immunity and suitability for DIVA; however, there are risks too, including reversion to virulence, shedding of replication-competent virus to other animals, excretion of live virus in feces/milk, and the limiting factor of anti-vector antibody formation by the host (reviewed in McCann et al., 2022).

Although the recombinant human adenovirus 5 (rhAd5) -vectored FMDV vaccine has been licensed in the USA for ten years, ongoing research is still deepening our understanding of the vaccine and how it might be leveraged most effectively for broader control of FMDV. Building on the group's previous study (Schutta et al., 2016), Neilan et al. assessed the efficacy of a rhAd5 vector-based vaccine (similar to the licensed product) expressing FMDV A24 P1 and FMDV A12 3C in cattle, showing that a single high dose had the potential to provide complete clinical protection after 7 days, but, with some groups only showing 50% protection, highlighting the impact of potential inter-vaccine-batch differences and/or heterogeneous responses to vaccination (Neilan et al., 2018). Further studies on this vaccine indicated that the addition of adjuvant might help to increase responses, particularly to low doses of vaccine (Barrera et al., 2018b), and that the vaccine could be readily adapted to cover different serotypes/topotypes, with high efficacy in cattle challenge experiments (Barrera et al., 2018a). Focusing on duration of immunity, Sitt et al. showed that protection of cattle wanes between six and nine months after a single immunization of adjuvanted Ad5-based vaccine, with the degree of protection at these times also influenced by the route of immunization: the transdermal route performed best, with intramuscular and sub-cutaneous performing less well in challenge studies (Sitt et al., 2019).

An enduring challenge in the development of broadly effective adenoviral-vectored FMD vaccines is the high variability in individual animals' vaccine responses. Towards a better understanding of this phenomenon, Jouneau et al. conducted an important study looking at immune correlates of vaccine responses in sheep and found different results depending on vaccine type (Jouneau et al., 2020). Transcriptomic analysis of blood samples at 24 hours post-immunization revealed activation of distinct gene modules involved in cell cycle by Ad5-vectored and conventional vaccine, while the addition of adjuvant to the Ad5-vectored vaccine reduced this difference, and added activation of modules relating to dendritic cells, monocytes and inflammation; moreover, comparing high- and low/non- responding

individuals showed that early downregulation of peripheral T cell responses was associated with later high antibody titers in response to conventional vaccine and to the Ad5-vectored vaccine with adjuvant, but not to the Ad5-vectored vaccine alone (Jouneau et al., 2020). The authors propose that rapid T cell recruitment to the lymph nodes, where they act to support B cell activation, could account for the negative correlation between T cell module expression in peripheral blood and later antibody responses; however, it is yet unclear which factors drive differential T cell recruitment strength/speed in these animals. This topic will be interesting to dissect further, and to extend to research in other target species. One could envisage such work leading to a significant advance in rational adjuvant design, targeting T cell recruitment to lymph nodes as a primary outcome.

As well as adenoviral vectors, researchers have also explored the use of alternative viruses to carry FMDV antigens into the host. Steigerwald et al. constructed a modified Vaccinia virus encoding FMDV A24 P1 and a mutated 3C (to lower toxicity to target cells) and showed moderate immunogenicity that resulted in 100% protection against both clinical FMD and viremia after one or two doses (Steigerwald et al., 2020).

6. Virus-like particles (VLPs)

VLPs are promising vaccine candidates able to stimulate both antibody- and cell-mediated immunity but having a lower risk profile than live-attenuated viruses (reviewed in Nooraei et al., 2021). They also have the advantages of not requiring the growth of infectious virus for production, ease of modification for field-strain matching, and rapid production; however, the low immunogenicity due to lack of genetic material and challenges of expressing VLPs with native epitope display means that their full potential has yet to be realized in the field.

VLPs are generated by the introduction of FMDV coding sequence into a host cell type, which may be either prokaryotic (bacteria or yeast) or eukaryotic (insect, mammalian, or plant), with each having their own advantages and drawbacks (reviewed in Nooraei et al., 2021). A recent study using Escherichia coli as the FMDV VLP expression system, reported that the incorporation of small ubiquitin-like modifier into the capsid-protein-encoding plasmid allowed superior control of the relative ratios of their production, as well as resulting in highly immunogenic VLPs with multiple

natural epitopes exposed (Xiao et al., 2021). Alongside, point mutations can be introduced to confer desirable physiochemical properties, such as increased acid resistance (Deepak et al., 2019; Xie et al., 2019); or the VLPs can be formulated with liposomes to increase the level of cellular immunity that is induced (W. S. Kim et al., 2020), though this strategy has yet to be trialed in natural target species of FMDV.

The use of transfected mammalian cell cultures to produce FMDV VLPs has faced the additional challenge of overcoming FMDV 3C toxicity to the transfected cells. Recently, Puckette et al. described the combination of P1-2A of target WT FMDV strains, with L127P attenuated mutant derived from FMDV Asia 1 as suitable for production in HEK-293T/17 cells (Puckette et al., 2022). The resulting VLPs were adjuvanted with Montanide and administered to swine and cattle, eliciting complete protection of cattle after a single immunization, and in pig after two immunizations (Puckette et al., 2022). The authors noted the significant improvement in immunogenicity relative to previous approaches to FMDV VLP production using baculovirus vectors (Mohana Subramanian et al., 2012; Porta et al., 2013), speculating that it was due to the use of the L127P mutated 3C which is likely to have increased transgene expression. Meanwhile, Primavera et al. evaluated the effects of viral 2B viroporin on VLP production in HEK-293T cells; they reported an enhancement of transgene expression when 2B was incorporated into an FMDV molecular vaccine construct with a wildtype 3C protease, though this enhancement was lost when using the L127P mutant (Primavera et al., 2022).

Alongside, building on their initial work showing protective immunogenicity in mice of FMDV A serotype VLPs generated in transiently transfected mammalian cells (Mignaqui et al., 2013), and the high immunogenicity of a single immunization of the same VLPs in cattle (Quattrocchi et al., 2020), Mignaqui et al. most recently performed a rare and highly valuable follow-up study, aiming to provide much of the information needed to render industrial-scale production of the VLP-based vaccine possible. The researchers compared multiple strategies to increase VLP yield in their system, as well as experimenting with different VLP-production approaches, and assaying VLP stability in various vaccine formulations (Mignaqui et al., 2020). As a result of the stepwise and logical progression of the group's work, this promising vaccine candidate is well-poised for adoption by the field.

The use of VLPs derived from other viruses but expressing one or several FMDV proteins (chimeric VLPs) has also been explored and may represent a useful strategy for generating multivalent vaccines.

Rangel et al. constructed a chimeric VLP comprising rabbit hemorrhagic disease virus expressing a B cell epitope from FMDV VP1 and a T cell epitope from FMDV 3A, in a variety of conformations, and used the novel vaccines to immunize mice and pigs (Rangel et al., 2021). The researchers showed that the VLPs induced the production of FMDV-neutralizing antibodies but afforded only partial clinical protection when animals were challenged with virulent FMDV (Rangel et al., 2021). Another study reported potent immune responses induced in mice by a chimeric truncated hepatitis B virus core VLP expressing B cell epitopes from type O and A FMDVs, and a T cell epitope from FMDV 3A (Lei et al., 2019); while Liu et al. generated a chimeric hepatitis b core antigen/FMDV VP1-4 VLP, and showed that this vaccine was able to induce high frequencies of long-lived plasma cells, which was associated with prolonged antibody responses in mice (Liu et al., 2022). Bovine parvovirus VLPs expressing a conserved FMDV neutralizing B cell epitope were also immunogenic in mice, with the level of immunogenicity being affected by the insertion position of the epitope into the VLP capsid (Chang et al., 2019). Testing these novel vaccines alongside conventional vaccines in natural host species challenged with FMDV will be critical to understand their true potential.

VLPs can also be used as delivery systems for DNA vaccines, which may increase their potency by enhancing innate immune stimulation and broadening the immune response to the target virus (reviewed in He et al., 2022). FMDV VLPs loaded with a pcDNA3.1/P12A3C plasmid induced similar levels of FMDV-specific antibody and IFN-γ production as did VLPs without the plasmid, but significantly higher levels of neutralizing antibodies and lymphocyte proliferation in immunized guinea pigs (Lu et al., 2020). The VLP containing the plasmid also rendered significantly better clinical protection compared to either component alone, or extended the duration of the serological response (Lu et al., 2020). Assessment of the immunological parameters and protective efficacy of this promising vaccine candidate in natural host species would be an interesting topic for future research.

7. Recombinant proteins, peptides, and dendrimers

Peptide vaccines are easy and inexpensive to produce, safe, and defined, but can lack sufficient immunogenicity in vivo. However, their potential advantages have led researchers to persist in their search for ways to render these candidates as immunogenic as the conventional inactivated FMDV

vaccine. Cui et al. constructed a set of novel peptide vaccines comprising various combinations of FMDV B cell epitopes, a truncated form of VP1, and a universal T cell epitope, with bacterial flagellin as an integral adjuvant; the vaccines all induced neutralizing FMDV antibodies and cytokine responses in immunized guinea pigs, which were associated with varying levels of protection from challenge (B. Cui et al., 2019). Lee et al. also reported some progress in this area, showing that a novel recombinant protein vaccine comprising the FMDV VP1 GH loop epitope linked to VSV glycoprotein elicited higher titers of specific antibody compared to conventional vaccine, in outbred pigs under field conditions (H.-S. Lee et al., 2020). However, it was not clear from this study whether the adjuvants used for the conventional vaccine and novel peptide were identical, and therefore there is the potential for difficulties in interpreting the results.

Dendrimers, or multiple antigen peptide (MAP) based vaccines, have been under investigation for over a decade for use against FMD, with recent studies looking to advance the rational design of these synthetic peptides. Dendrimer design typically incorporates B and T cell epitopes, arranged as a branching macromolecule, with or without small molecule immunostimulators to act as adjuvants (reviewed in Heegaard et al., 2010).

In 2020, five papers from the same group reported promising results of FMDV dendrimer vaccine studies in pigs. Building on their previous work (Blanco et al., 2016), Cañas-Arranz et al. reported that a single dose of a dendrimer vaccine comprising two copies of a B cell epitope from FMDV VP1 linked through maleimide units to a single T cell epitope from FMDV 3A, induced potent B and T cell responses that partially protected pigs from challenge with serotype O FMDV (Cañas-Arranz et al., 2020b), with protection lasting up to five months after one or two immunizations (Cañas-Arranz et al., 2020). The researchers then went on to experiment with using a different T cell epitope – this time derived from FMDV 3D – and found that this elicited comparable immune responses in outbred pigs (Cañas-Arranz et al., 2020a), though their protection from challenge was not assayed in this study. Alongside, Defaus et al. explored the impact of different MAP architectures on the ensuing immune response, finding that the same epitopes presented differently had markedly different outcomes in mice, and that the lead candidate – a homodimer of B and T cell epitopes – also induced levels of FMDV-specific antibodies consistent with protection from challenge in outbred pigs (Defaus et al., 2020). Lastly, adding to our knowledge of the application of MAP vaccines to pigs, León et al. studied the relationship between SLA haplotype and response to immunization with either of the above

dendrimer vaccines (de León et al., 2020). The strongest association was between SLA class-II Lr haplotypes and the T cell response, but other, less strong associations were also revealed (de León et al., 2020), providing key insights for future rational design of MAPs for use in swine. For example, these data could be incorporated into approaches seeking to build on a recent study that applied bioinformatics to modeling the design of optimal MAP vaccines against FMDV (Riaz et al., 2021). More recently, Cañas-Arranz et al. demonstrated the high immunogenicity of a bivalent vaccine, comprising a mixture of dendrimers carrying serotype-specific B cell epitopes with the 3A T cell epitope, which elicited high titers of neutralizing antibodies to both serotypes of virus in mice immunized twice (Cañas-Arranz et al., 2021).

8. Adjuvants

Adjuvants play a major role in shaping both the quantitative and qualitative aspects of an immune response to a vaccine but can also be used to decrease the amount of antigen needed, thus making commercial vaccine production more efficient. Commercially available FMD vaccines are formulated with mineral oil- or aluminum hydroxide-based adjuvants, but the immunity induced is not optimal and the side-effects profile could be improved. Furthermore, the composition of the adjuvant can have profound effects on the long-term stability of the stored vaccine (Song et al., 2020). These effects are important in the field, illustrated by a comparative study of inactivated vaccines with different adjuvant formulations, showing a two-month difference in duration of humoral immunity in sheep (Hassan et al., 2018). Accordingly, studies on new adjuvants, or modified applications of existing adjuvants, abound.

Multiple studies show moderate enhancements to vaccine performance in mice by the addition of various agents to the virus/viral proteins, including: aqueous extracts of the succulent plant Artemisia rupestris, which enhanced activation of DCs and reduced the activity of T regulatory cells (D. Wang et al., 2019), as well as enhancing the CD8+ T cell response following immunization with inactivated FMDV vaccine (D. Wang et al., 2021); covalently linked Mycobacterium tuberculosis heparin-binding hemagglutinin to a multi-epitope subunit vaccine (Lei et al., 2020); polysaccharides derived

from the parasitic succulent Cistanche deserticola (Quanxiao Li et al., 2021; A. Zhang et al., 2021); soybean oil combined with vitamin E and ginseng saponins, which interestingly out-performed ISA 206 in inducing a higher antibody titer significantly more rapidly (X. Cui et al., 2019); a plasmid encoding the CCL20 chemokine, which enhanced the performance of ISA206-adjuvanted inactivated vaccine (Jayeshbhai et al., 2018).

In pigs, the immunopotentiator CVC1302 added to conventional vaccine induced stronger cytokine responses and higher specific antibody production compared to vaccine alone, which were associated with complete protection from clinical signs and significantly lower viremia upon challenge with a homologous mouse-passaged FMDV strain (Chen et al., 2018). Importantly, the same group went on to ask about the mechanisms responsible for the enhancing effect of CVC1302, finding that the intramuscular injection site expressed high levels of monocyte chemoattractants, leading to higher numbers of monocytes recruited to the site, compared to inactivated vaccine alone. The researchers followed the response to the draining lymph nodes, revealing significantly enhanced expression of proteins involved in signal transduction, apoptosis, endocytosis and innate immune responses, with the main involved pathways being AMPK, phospholipase D, cAMP, Rap1, and MAPK (L. Du et al., 2019). These types of follow-up mechanistic studies are rare in the adjuvant field but are key to advancing our understanding of how to drive the immune response in the direction of optimal protection from FMDV.

In cattle and pigs, Lee et al. screened multiple PRR ligands and cytokines for their adjuvant properties when combined with conventional inactivated vaccine. Their study identified the combination of ligands for Mincle and STING as driving long-lasting humoral responses in both species and warranting further investigation as conventional vaccine adjuvants (M. J. Lee et al., 2019). Sunflower and peanut oils supplemented with ginseng saponin also showed potential as replacements for conventional mineral oil-based adjuvants, performing as well as Montanide ISA206 in calf immunization studies using a polyvalent inactivated FMDV vaccine (Gamil and Soliman, 2021); similarly, vegetable oil-based adjuvants performed well in sheep immunized with inactivated FMDV (Cui et al., 2020). Alongside, an initial trial of a lipid and saponin-based cage-like particle adjuvant showed encouraging improvements to T cell responses in cattle immunized with inactivated FMDV but elicited antibody levels consistent with only 80% predicted protection (Bidart et al., 2020), and therefore requires some refinement in future studies.

A recent illustration of rational adjuvant design came from Jo et al. who built on their group's previous work on recombinant FMDV vaccines incorporating heat-shock protein 70 (HSP-70) (M. J. Lee et al., 2020), and developed a recombinant protein vaccine adjuvant comprising seven linked components: HSP-70 to help connect innate and adaptive immunity; a universal FMDV 3A T cell epitope; an exogenous T cell epitope; two B cell epitopes, one from FMDV type O and another from type A; the VP1 region of FMDV O; a transdermal delivery molecule (astrotactin 1-derived peptide); the immune-enhancing peptide, Pan HLA-DR reactive epitope; a linker amino acid sequence, and a His tag to allow easy purification (Jo et al., 2021). Utilizing the protein in place of conventional oil-in-water adjuvant for inactivated FMDV vaccine, elicited significantly superior immune responses and rendered pigs completely protected from challenge with either serotype (Jo et al., 2021). Linking up the use of systems biology and experiments on rationally designed adjuvants (and vaccines) would rapidly advance our understanding of FMDV target species' responses to vaccines and expedite the selection of next-generation novel vaccines.

Other novel types of adjuvants have also been explored, including the use of several different types of nanoparticles. Wu et al. trialed layered double hydroxide clay, which was previously proven effective as an adjuvant for vaccines against pathogenic E. Coli (Chen et al., 2017, 2016), as an FMDV vaccine adjuvant in mice and pigs (Wu et al., 2020). The researchers found that the clay nanoparticles performed as well as conventional adjuvant in stimulating IFN-γ production in pigs and showed advantages in maintaining the duration of antibody response in mice (Wu et al., 2020); however, in the absence of challenge studies, the overall performance of the adjuvant could not be assessed. Similarly, the performance of ferritin nanoparticles as an FMDV subunit vaccine adjuvant showed only moderate protection in mice (Y. Chen et al., 2020), and has yet to be tested in natural host species. Although also yet-untested in a natural host species, poly (lactic-co-glycolic acid) showed somewhat more potential when tested as a delivery system for an FMDV DNA vaccine including porcine IL-18, which induced significantly greater lymphocyte proliferation responses in guinea pigs to the virus than did conventional inactivated vaccine (Y. Yang et al., 2021). Similarly, Li et al. found that cationic solid lipid nanoparticles could stimulate comparable levels and isotypes of specific antibody as conventional inactivated vaccine, but significantly greater effector- and central- memory T cell responses in mice (S. Li et al., 2020). The use of gold-star nanoparticles showed promising enhancement of FMDV VLP immune responses, compared to conventional ISA206 adjuvant (Teng et

al., 2018). Although many questions remain around the potential of this strategy, not least its efficacy in natural hosts, given that T cell responses are critical for long-term vaccine-induced immunity to FMDV, the preliminary results reported by Li et al. and Yang et al. warrant further investigation.

Dietary adjuvants have also been explored: although this is a less conventional approach to increasing or shaping vaccine responses, the profound impact of the intestinal microbiota on systemic immunity, the often-low cost of these dietary additions (especially when plant-based), and the ease of administration, combine to render this an attractive opportunity for advances in the field. Recently, Zhao et al. showed increased responses to an inactivated FMDV vaccine administered twice to mice that had been orally dosed with the immunostimulatory Purslane polysaccharide P3b for the prior four days, linking the enhanced response to greater intestinal DC activation and the production of mucosal IgA in these animals (Zhao et al., 2019). Whether the enhanced mucosal response extended to the airways of these animals, the extent to which the results are replicated in natural target species, and the potential for combination with an orally administered FMDV vaccine, warrant further investigation. Other dietary adjuvants trialed with some evidence of increased responses include silicate supplementation in weaning-to-finishing pigs (J. H. Lee et al., 2020); resveratrol in piglets (Fu et al., 2018); a mixture of herbal extracts including Astragalus membranaceus and Codonopsis pilosula in growing-finishing pigs (Cheng et al., 2020).

9. Delivery devices: needle free and micro needle

Many currently marketed vaccines for humans and animals are administered through needle-based injections through intramuscular, subcutaneous, or intradermal routes. Despite their success in reducing disease burden, needle-based immunizations have limitations. Needle-free strategies offer numerous advantages such as reduced pain and stress, decreased injury at the injection site, lowered risk of disease transmission among animals due to shared needles, lower vaccine volume requirement compared to needle-based injection, prevention of accidental self-injections, and broken needle fragments in meat from vaccinated livestock (Dalmau, et al. 2021). However, the scarcity of marketed needle-free immunization strategies has led to the misconception that they're less effective than traditional methods. Contrarily, recent studies using needle-free strategies demonstrate comparable or

superior efficacy to needle-based vaccination, emphasizing the need for more development in needle-free vaccines for human and animal diseases.

Needle-free immunization options are categorized into cutaneous and mucosal, depending on the route of administration. Cutaneous needle-free methods include liquid-jet injection, ballistic methods such as epidermal powder immunization, and topical administration such as microneedle patches. These methods can induce more potent immune responses as they achieve greater antigen dispersal compared to traditional needle-based injections and can result in the induction of potent systemic and mucosal immunity by targeting Langerhans cells, important professional antigen presenting cells that are enriched in the skin (Mitragotri, 2006, Gockel, et al., 2000, Glenn, et al, 1998). Furthermore, microneedle patches offer a pain-free alternative to needle-based vaccination, are scalable and useful for mass vaccinations due to ease of administration and can be engineered to release vaccine payloads at predetermined time intervals, avoiding the need for booster and repeat injections (Tran et al., 2021, 2022, Caudill et al., 2021).

Intradermal administration may also be vaccine-sparing, which could be particularly important in outbreak or low- resource settings: a recent study conducted in Thailand showed that, compared to needle-based sub- cutaneous injection, the same vaccine administered at the same dose subcutaneously, or at a half- dose intra-dermally, using a needle-free system elicited comparable levels of FMDV-neutralizing antibody in outbred heifers under field conditions (Wataradee et al., 2021). A similar study in an Indian cattle breed gave comparable results (Rashmi et al., 2021a). A more recent study confirmed the vaccine-sparing ability of needle-free administration, showing that intra-dermal administration could be as immunogenic with just one quarter of the dose needed for intramuscular injection of cattle, plus no risk of local reactions in the muscle (Çokçalışkan et al., 2022). Similar observations have been made in a guinea pig model of FMDV intradermal immunization (Rashmi et al., 2021b), and in pigs (Hwang et al., 2019). Transdermal needle-free immunization also significantly reduced the incidence of immunization site lesions in pigs vaccinated with inactivated FMDV vaccine, from just under 20% in the control intra- muscularly vaccinated pigs, to just over four percent in the transdermally immunized group, with the lesions in the transdermal group being subcutaneous and not resulting in loss of muscle mass accepted at slaughter (Ko et al., 2018). However, the immune response to the vaccine administered by the different routes was not monitored in this study.

Mucosal vaccines are another attractive needle-free vaccination strategy that involves the delivery of the vaccine payload at mucosal sites such as the oral or nasal cavities. Mucosal vaccination is thought to be superior to parenteral needle-based vaccination owing to its ability to elicit both systemic and mucosal immune responses, which are difficult to achieve with parenteral vaccination. Orally delivered vaccines such as the oral polio vaccine and the vaccinia virus vectored rabies RABORAL V-RG vaccine have demonstrated the potential of mucosal vaccines for mass vaccination and their efficacy in controlling the spread of viral diseases in both humans and animals (Aylward, et al. 2011, Maki, et al., 2017). While previously thought to only be an effective route of vaccination for live vaccines, the use of potent mucosal adjuvants such as the B subunit of cholera toxin (CTX-B), inactive mutants of E. coli heat labile toxin, CpG DNA, α-Galactosylceramide, and polymer nanoparticles (PLGA, gamma-PGA, and chitosan) has extremely improved the potency of mucosal subunit vaccine candidates (Mansoor, et al., 2015, Dhakal, et al., 2017, Okamoto, et al., 2009, Gallichan et al., 2001, Porgador, et al., 1997, Ko, et al., 2005, Peppoloni, et al., 2003). Coupled with novel needle-free injection devices such as MucoJet, and oral microjet vaccination system, mucosal vaccines can provide a scalable, pain-free, safe, and efficacious alternative to traditional needle-based vaccination for both humans and animals (Aran, et al., 2017).

Several needle-free vaccine delivery devices are currently on the market, including the PulseTM Micro Dose Injection System (Pulse Needle Free Systems), DERMA-VAC™ NF Transdermal Vaccination System (Merial), IDAL® Vaccinator (Intervet), and Agro-Jet® (MIT, Canada).

Taken together, the adoption of needle-free administration appears safe, practicable, and effective across a range of species and settings, and should be encouraged.

Recommendations

The GFRA Gap Analysis task work group advocates actions in research priorities areas to advance scientific knowledge and translational research that are still pending from 2018 gap analysis.

- ✓ Research is needed to investigate the safety and efficacy characteristics of novel attenuated FMD vaccine platforms.

- ✓ Understand and overcome the barrier of serotype- and subtype-specific vaccine protection.
- ✓ Continue efforts to understand the onset and duration of immunity of current and next generation FMD vaccines. Investigate and develop vaccines inducing long-lasting immunity against FMD.
- ✓ Improve FMD vaccine quality control
- ✓ Continue efforts to develop next generation FMD vaccines that prevent FMDV persistence.
- ✓ Invest more resources for the discovery of new adjutants to improve the efficacy and safety of current inactivated FMD vaccines.
- ✓ Develop vaccine formulations and delivery systems to target the mucosal immune responses.
- ✓ Develop vaccine delivery strategies to induce mucosal as well as systemic responses in susceptible species. Current needle inoculation methods present a challenge to effectively deliver vaccine in the face of an outbreak.
- ✓ Increase understanding and development of vaccine formulations effective in neonatal animals with or without maternal immunity.

Biotherapeutics

Literature Review

1. General Aspects

Vaccines may have limited effectiveness in a severe outbreak as they are slow to offer immunity and are relatively short acting. Even after vaccination, animals can become FMDV carriers and there are currently limitations with our ability to reliably distinguish infected from vaccinated animals. Furthermore, there are no licensed therapeutic options available and so there is urgent need to improve the range of products available to manage FMD. Antivirals and biotherapeutics that act quickly prior to vaccine-induced immunity to supplement or substitute for vaccination protocols are still required

for FMDV. The most substantial amount of research to this end has been on interferon (IFN) based therapies. This includes over 20 years of research on IFNs type I, II and III.

The table below (Table 1) (adapted from Medina et al., 2020) and provides a summary of the research done on IFN based therapies against FMDV and the milestones achieved. IFNs have been called the "pillar molecules" of the innate immune system. It mediates early protection against viral infection and rapid production helps to limit viral replication while modulating other immune functions.

Table 1: Use of IFN-based therapies against FMDV (Medina et al 2020. Front Vet Sci.7:465)

Type	Recept.	Signal	Sub-type	Species	Milestone
Type I	*IFNAR1/IFNAR2*	*JAK1, TYK2*	*IFN-α/β*	Porcine/bovine	• Recombinant bacterial expressed IFN-α/β is a potent biotherapeutic against FMDV *in vitro* (17)
			IFN-α	Porcine	• Ad5 delivered poIFN-α protects swine against different serotypes of FMDV (18–20)
					• poIFN-α-protection correlates with enhanced tissue-specific innate immune cell infiltration in swine (21, 22)
					• poIFN-α protection correlates with upregulation of essential ISGs *in vitro* (23, 24)
			IFN-β	Porcine	• Ad5 delivered porcine poIFN-β protects swine against FMDV (20)
			IFN-δ	Porcine	• Bacterially expressed poIFN-δ8 significantly inhibits FMDV replication *in vitro* (25)
			IFN-ω7	Porcine	• *E. coli* produced poIFN-ω7 protects cells against FMDV (26)
			IFN-αω	Porcine	• Bacterially expressed IFN-αω added prior to infection resulted in a significant reduction in FMDV replication *in vitro* (27)
			IFN-τ	Ovine	• Ovine IFN-τ has antiviral effect against FMDV *in vitro* (28)
Type II	*IFNγR1 IFNγR2*	*JAK1, JAK2*	*IFN-γ*	Bovine	• Recombinant bovine IFN-γ reduced FMDV replication in BTY cell culture (29)
			IFN-γ	Porcine	• High dose of Ad5-poIFN-γ protects swine against FMD (30)
Type III	*IFN-λR1/IL-10R2*	*JAK2, TYK2*	*IFN-λ1*	Porcine	• Replication of FMDV in IBRS-2 cells is inhibited by treatment with the purified recombinant poIFN-λ1 (31)
			IFN-λ3	Bovine	• Inoculation with Ad5-boIFN-λ3 resulted in the induction of several ISGs in tissues of the upper respiratory tract (32) and protected cattle against challenge with FMDV (33)
				Porcine	• Ad5-poIFN-λ3 protects swine against challenge with FMDV (34)
IFN Combos			*IFN-α* *IFN-γ*	Porcine	• Use of a combination of Ad5-poIFN-γ and Ad5-poIFN-α (30) or Ad5-poIFN-αγ (35) showed an enhancement of the antiviral activity against FMDV in swine
Other			*Poly IC*	Porcine	• Double stranded (ds) RNA poly ICLC, in combination with Ad5-poIFN-α protected swine against FMDV (36)
			siRNA	Porcine	• Combination of Ad5-poIFN-αγ with Ad-3siRNA targeting FMDV NS coding regions blocked replication of all serotypes of FMDV *in vitro* (37)
			IRF7/3	Porcine	• Inoculation with Ad5-IRF7/3(5D) resulted in induction of IFN-α and fully protected mice and swine challenged with FMDV 1 day after treatment (38, 39)
			IRES	Porcine	• Use of synthetic IRES in combination with adjuvanted type-O FMD, improved immune response and protection against FMDV challenge (40)
IFN/vaccine combos			*IFN-α*	Porcine	• Use of a combination of Ad5-po-IFN-α and Ad5-A24 in swine resulted in complete protection after challenge (19)
			IFNα/γ	Porcine	• Ad5-poIFNα/γ co-administered with Ad5-siRNA targeting NS regions of FMDV, and a commercial inactivated FMD vaccine partially protected swine (41)
			IFN-λ3	Bovine	• Use of a combination of Ad5-bov-IFN-γ3 and Adt-O1M in cattle resulted in complete protection after aerosol challenge (42)

Previous reports and studies have shown that FMDV is very sensitive to IFNs in vitro and in vivo when tested individually or in combos. Treatment with Ad5-IFNs or combinations with Ad5 FMD vaccine can fully protect swine (Moraes et al., 2003) whilst IFN PEGylation prolongs duration of antiviral activity and protects swine against FMD (Diaz-San Segundo et al., 2021). An added advantage of pegylated molecules may offer cheaper molecules with sustained antiviral activity and reduced toxicity. A further advantage of IFN against FMDV is the high likelihood for viral clearance regardless of the specific serotype. Recent work has shown that Ad5 boIFN λ 3 and Ad5 FMD protects cattle at 3dpv (Diaz-San Segundo et al 2016 and 2017, Yoh et al., 2017).

There have been recent developments regarding antiviral drugs against FMDV, showing hopeful results. RNA interference (RNAi) appears as a promising strategy to control virus replication. Short/small-interfering RNAs (siRNA) and micro-RNAs (miRNAs) have shown some potential. Sahu et al., 2020 used silico methods to identify the Bos taurus miRNAs that have targets in FMDV, and 431 miRNA sequences were identified. In this study, miRNA mimics of 8 miRNAs were expressed transiently in BHK-21 cells and infected with FMDV and the results showed variable antiviral effect. Currá et al., 2021 assessed the efficacy of amiRNAs against FMDV and shRNAs targeting the same viral regions in BHK cells. Here, BHK-21 cells transiently expressing shRNAs or amiRNAs proved 70 to >95% inhibition of FMDV growth.

Interestingly, dual expression of amiRNAs did not improve FMDV silencing. Other studies showed that simultaneous expression of multiple siRNAs directed against different regions of the same target RNA can increase silencing efficacy. To generate genetically modified FMDV resistant animals, Zhang et al., 2015 constructed a combinatorial expression cassette producing three siRNAs using the lentivirus vector: LV 3shRNA. The results indicated that LV 3shRNA reduced viral growth 3-fold (24hpi) in BHK-21 cells infected with 107 TCID50/ml of serotype O. Additionally, suckling mice pretreated with LV 3shRNA showed that 75% of the mice challenged with 20 LD50 FMDV survived.

Other antiviral drug research in the early stages of development include:

- ✓ *Mizoribine:* Li et al., 2019 showed antiviral activity against FMDV replication in IBRS-2 cells using mizoribine. This drug functions at the early stage of virus replication. The results revealed antiviral effect on FMDV in vivo for suckling mice.

- ✓ *Ribavirin:* Soumajit et al., 2019 showed that ribavirin inhibited the in vitro replication of FMDV O, A and Asia 1. Furthermore, inhibition was confirmed by serotype specific sandwich ELISA, PCR and real-time PCR assays.
- ✓ *Phytochemicals:* Theerawatanasirikul et al., 2021 used in silico methods to identify potential anti-FMDV agents. Two flavonoids i.e., luteolin and isoginkgetin showed high potent negative effect on the FMDV life cycle by blocking the 3Cpro activity in vitro.
- ✓ *Inhibitors of FMDV 3Dpol:* Sarafianos et al., 2011; Durk R.C. et al 2010; Rai et al 2013 identified an effective inhibitor molecule targeting a novel pocket of the RNA-dependant RNA polymerase (3Dpol) as potential anti-FMDV agents. There is a US PCT/US2011/06219 filled on 11/17/2011. Repeated exposure to 5D9, an inhibitor of 3D polymerase, was shown to effectively limit the replication of FMDV in host cells.
- ✓ *Antisense Morpholino Oligomers (PMO):* Vagnozzi et al., 2007 showed high potent inhibition of foot-and-mouth disease virus infections in cell cultures with antisense morpholino oligomers targeting the first first AUG. Rieder et al 2006 has a US Patent 11/418,904 US 2006/02932268.

2. Interferon therapy

Although FMD can be controlled to some extent with vaccination, the development of a protective adaptive immune response takes five to seven days, during which time the outbreak can spread rapidly through and between herds. To better manage FMD outbreaks, administration of antivirals that suppress virus replication and transmission while the vaccine-stimulated adaptive immune response develops, is desirable. Initial detection of FMDV by host cells occurs through the binding of viral RNA by PRRs in the cytoplasm and/or by membrane bound TLRs. This activates signal transduction cascades that result in the production of antiviral IFNs and inflammatory cytokines. IFN proteins activate cellular signal transduction pathways to induce the expression of antiviral proteins that control the viral infection and modulate other immune functions. There are multiple type I IFN (α/β) subtypes, particularly in bovine and porcine genomes. Recombinant porcine IFN-α/β delivered using a replication-defective human Adenovirus 5 vector (Ad5-poIFN-α/β) has demonstrated potential as a biotherapeutic against FMDV in swine (Medina et al., 2020b).

While the Ad5 delivery method has improved the applicability of the IFN approach to control FMDV in animals, the relatively short half-life of IFN protein in vivo presents a challenge. Accordingly, approaches to alter the pharmacokinetic profile of therapeutic IFN to extend the longevity of the delivered protein have been explored. These include the covalent modification of IFN with PEG molecules (PEGylation):in this small-scale study, the authors demonstrated that PEGylated recombinant porcine IFN-α (PEGpoIFNα) displayed strong and long-lasting antiviral activity against FMDV A24/Cruzeiro/55 (A24Cru) strain in vitro in porcine IB-RS2 cells and in vivo in pigs (Diaz-San Segundo et al., 2021a). The pharmacokinetics of PEGpoIFNα were similar regardless of whether it was administered intravenously or intramuscularly, with a harmonic mean half-life (t1/2) of 59.7 hours and equivalent plasma concentrations of IFN after 72 hours (Diaz-San Segundo et al., 2021a). The agent's efficacy was tested in groups of six pigs, comparing 200 μg/kg of PEGpoIFNα administered 1 or 5 days before challenge, with 1010 PFU/animal of Ad5-poIFNα administered 5 days before challenge, and a control inoculated subcutaneously with phosphate buffered saline 1 day before challenge. While animals in the control group and animals treated with Ad5-poIFNα showed disease symptoms and detectable viral RNA in serum and nasal swabs, infectious virus could not be isolated from any of the animals treated with PEGpoIFNα, and viral RNA was only detected in one out of eight, and two out of eight, sera and nasal swab samples respectively. Although this was a small-scale study, it demonstrates that treatment with PEGpoIFNα is effective against FMDV replication and shedding in pigs (Diaz-San Segundo et al., 2021a), and should be explored further as part of the rapid-response anti-FMDV strategy during an outbreak.

An alternative IFN delivery method using a recombinant baculovirus (BacMam) expressing consensus porcine IFN-α driven by a cytomegalovirus immediate early promoter (Bac-Con3N IFN-α) has also shown some promise: Kim et al. evaluated the antiviral effects of Bac-Con3N IFN-α in the LFBK porcine kidney cell line, in mice and as a vaccine adjuvant in groups of crossbred pigs, finding enhanced expression of interferon-stimulated genes in vitro, and significantly improved protection of mice from virulent challenge (A. Kim et al., 2022). Importantly, those pigs injected with a combination of Bac- Con3N IFN-α and the inactivated FMD vaccine exhibited complete protection from FMDV infection from day one post-immunization, significantly higher cytokine responses from day three post- immunization and higher antibody titers in response to the vaccine, compared to those pigs administered the vaccine alone (A. Kim et al., 2022). Using the baculovirus IFN platform to confer

rapid protection against several FMD serotypes and subtypes during an outbreak should be considered as part of the development of effective control strategies globally, particularly as inoculation with baculovirus per se has immunostimulatory properties, including the induction of endogenous IFN (Molina et al., 2020).

3. Immunostimulants

Baculoviruses are a family of insect viruses with a variety of applications in biotechnology including their use as vectors for gene delivery in vertebrate cells. Baculovirus inoculation has strong immunostimulatory properties and can induce adaptive immune responses that provide rapid nonspecific antiviral status against heterologous viral antigens. Inoculation of mice with the baculovirus Autographa californica multiple nucleopolyhedrovirus (AcMNPV) induced a nonspecific antiviral status from 3 hours to 3 days post-inoculation, which protected mice against a lethal challenge with FMDV A/Arg/01 (Molina et al., 2020). The authors demonstrated that type I IFNs and NK and NKT cells were the main mediators of the antiviral state. Following on from this work, the same group demonstrated that AcMNPV treatment of porcine PBMCs induced IFN-α-mediated antiviral activity in a dose-dependent manner, and that the supernatants of AcMNPV-infected PBMCs protected swine cells from infection with FMDV O1/Campos in vitro (Molina et al., 2021). Furthermore, inoculation of piglets with AcMNPV induced the production of IFN-α and IFN-γ, with peaks detectable in sera in the first 6 hours post-inoculation; lastly, the sera from these piglets demonstrated in vitro antiviral activities against both VSV and FMDV (Molina et al., 2021).

4. Antiviral compounds

The identification of novel antiviral agents derived from plants that are used in traditional therapies is a widely used strategy in drug discovery. Andrographis paniculata is widely used in ancient Asian and ayurvedic medicine for the treatment of a multitude of ailments and diseases, with proven efficacy

against upper respiratory tract infections, and enough evidence of activity against severe acute respiratory syndrome coronavirus 2 that is was licensed by the Health Ministry of Thailand as a pilot therapeutic for treating early stage COVID-19 (reviewed in Kuchta et al., 2022). Two diterpenoids derived from A. paniculata – andrographolide and deoxyandrographolide – effectively inhibited FMDV serotype A replication in vitro in BHK-21 cells by decreasing the protease activity of FMDV 3C and "derepressing" inhibition of interferon-stimulated gene expression, but did not block infection prophylactically (Theerawatanasirikul et al., 2022). Nevertheless, the 3C protease is an essential protein in the FMDV life cycle, and it remains an attractive antiviral target. One particularly interesting study reported using computer-aided virtual screening of natural phytochemical compound libraries to find potential anti-FMDV compounds based on the structure of the FMDV 3C protease. Theerawatanasirikul et al. identified 23 candidate compounds (from 5789 initially screened) and assessed their anti-FMDV activities in a cell-based assay, finding that two flavonoids (luteolin, which is present in variety of fruits and vegetables, and isoginkgetin, a biflavone from Ginkgo biloba) both blocked viral growth and reduced viral load in BHK-21 cells more effectively than the anti-viral drug ribavirin (Theerawatanasirikul et al., 2021). A fluorescence resonance energy transfer assay demonstrated that isoginkgetin was a potent 3C protease inhibitor. This study demonstrates the advantages of virtual screening in terms of time and cost and illustrates its potential to "short-list" promising compounds for further in vitro and in vivo testing.

A different type of antiviral compound targets the cellular metabolism required for viruses to complete their multiplication cycle. De Leon et al. investigated the effectiveness of cell-targeting drugs affecting lipid metabolism and/or membrane rearrangements, against viruses including FMDV (de León et al., 2019). They found that lauryl gallate, an ester derivative of the natural plant phenol gallic acid, has antiviral action against FMDV O and C isolates in BHK-21 cells, and was effective at significantly reducing mortality and viral load in mice when administered 24 hours prior to virulent challenge (but not if co-administered with the challenge virus) (de León et al., 2019). It will be interesting to see whether these promising results can be translated to natural host species of FMDV.

Additional cellular targets for the development of antiviral drugs include enzymes involved in nucleotide biosynthesis or nucleic acid replication. Compounds that inhibit inosine monophosphate dehydrogenase (AVN-944 and mycophenolate mofetil) and dihydroorotate dehydrogenase (teriflunomide) effectively suppressed FMDV O and A replication both in vitro and in vivo in mice,

when used in the early stages of infection (0–8 h) (Loustaud-Ratti et al., 2016). Similarly, brequinar, an inhibitor of dihydroorotate dehydrogenase that is currently used as an immunosuppressive and antiproliferative drug, blocked FMDV replication at the early stages of infection, and prolonged survival of a quarter FMDV-injected suckling mice when injected 2 hours prior to challenge (S. Li et al., 2019a). These results of these studies indicate that inosine monophosphate dehydrogenase and dihydroorotate dehydrogenase could be promising targets for anti-FMDV drug development.

Ribavirin is a synthetic purine nucleoside analogue that inhibits replication of several viruses and is a licensed prescription medicine for the treatment of respiratory syncytial virus, hepatis C, and a handful of viral hemorrhagic fever viruses (reviewed in Loustaud-Ratti et al., 2016). Administering ribavirin intraperitoneally to mice twice a day for 3 days prior to, or 24 hours post, challenge with FMDV prevented disease in 86.6% and 66.6% of mice, respectively, and both shortened the course and severity of the disease (Nikunjkumar et al., 2021). In an earlier study, Choi et al. tested the combination.

of ribavirin and vaccination in a small-scale experiment in mice and specific pathogen-free minipigs: in mice, oral or injected ribavirin alone provided protection against FMDV challenge; pigs that were injected with ribavirin at the same time as commercial vaccine were completely clinically protected from FMDV and excreted only small amounts of virus (Choi et al., 2018). Together, these studies indicate the potential of ribavirin as an antiviral agent for use against FMDV, but future studies should focus on field-like conditions and the potential for mass-administration by inhalation of the drug.

Lastly, epinecidin-1, a synthetic form of an anti-microbial peptide from the orange-spotted grouper (Epinephelus coioides), demonstrated potent virucidal and antiviral activity against FMDV in BHK-21 cells (Huang et al., 2018). FMDV infection was most impaired when epinecidin-1 was administered at the time of viral adsorption to the cells. Anti-microbial peptides such as epinicidin can be easily synthesized and chemically modified to alter their properties including half-life, and so represent an exciting potential for the discovery of new anti-viral drugs.

5. RNAi

RNA interference (RNAi) is a conserved post-transcriptional gene silencing mechanism elicited in response to the detection of double stranded RNA and is directed via small RNA molecules, regulating the expression of endogenous and exogenous pathogenic genes. FMD therapeutic strategies that make use of the antiviral effects of RNAi have been explored, and efforts have been made to identify and develop suitable artificial microRNAs (amiRNAs) or miRNA-like agents. An in vitro study demonstrated that BHK-21 cells stably expressing an artificial miRNA targeting the 3Dpol-coding sequence of the FMDV genome had a 99% lower virus titer at 24 hours post infection (Basagoudanavar et al., 2019). Similarly, Currá et al. showed that a set of other short-hairpin RNAs (shRNAs) and amiRNAs targeting the FMDV 3D polymerase sequence inhibited FMDV A serotype growth in BHK-21 cells by greater or lesser extents at 5 hours post infection, with inhibition of 70 to >95% by some of the most promising candidates (Currá et al., 2021). Interestingly, both of the above studies (Basagoudanavar et al., 2019) (Currá et al., 2021) found that simultaneous expression of multiple miRNAs in a cell did not achieve an additive antiviral effect.

Identifying amiRNAs or miRNA-like agents through bioinformatic approaches may provide novel insights into FMD therapeutics. Researchers at the ICAR-Indian Agricultural Statistics Research Institute, New Delhi, India have curated a repository of information on anti-FMDV miRNAs, putative targetable regions on FMDV genes, and miRNA-like simulated nucleotide sequences with their targets in FMDV (Sahu et al., 2020). This has a user-friendly web interface for searching RNAi related information which may be of use to researchers seeking to pursue this area of knowledge.

Recommendations

Before IFNs could be used as a gold standard therapeutic agent against FMD, several investigations must be conducted:

- ✓ Metabolic rate of absorption and toxicity should be carefully evaluated.
- ✓ Optimize therapeutic doses for each animal species of interest.
- ✓ Better characterize innate immune responses during FMDV infection in vitro and in vivo: refine our understanding of the anti-FMDV properties of IFN and hopefully develop improved therapeutics.

There is still a lot more research required to verify the advantages of siRNA and miRNAs:

- ✓ More research is needed to confirm 100% antiviral effect against FMDV.
- ✓ Complete antiviral seems possible when multiple siRNAs are utilized in combination.
- ✓ Testing in vivo is required & in host species.
- ✓ Application of RNAi therapeutics in combination with potential vaccine candidates need to be explored.

Other antiviral drugs:

- ✓ More substantial research in vitro is required.
- ✓ Studies on host species.
- ✓ Research on various FMDV serotypes

Immunology

Literature Review

1. General Aspects

The host immune response to FMDV is mediated by innate and adaptive immune cells and is shaped by the crosstalk between them. Following infection of a target cell, components of the viral capsid and its genome will be recognized by pattern-recognition receptors, which initiate complex and interlinked signaling pathways with three aims: to restrict viral replication within the cell; to warn other cells nearby of the presence of the infection; and to recruit innate immune cells whose cytokines and interactions will support and guide the development of adaptive immunity. In response, FMDV has evolved mechanisms aiming to interfere with every step of this pathway to ensure its own survival.

2. Innate immunity to FMDV

The innate immune response to FMDV is a double-edged sword: the inflammation caused is linked with the pathogenesis of disease, whilst the mechanisms involved can be critical to clearance of the virus. While our knowledge in this area remains incomplete, there are several areas of new investigation in recent years that are beginning to fill important gaps in knowledge and highlight avenues for future research.

Inflammasomes are multi-protein intracellular platforms with a suite of functions in innate immunity, including driving anti-viral responses but also contributing to immunopathology (reviewed in Spel and Martinon, 2021). Recent data indicate that FMDV 2B (Zhi et al., 2019) and Lpro (Choudhury et al., 2021) can activate the NLR family pyrin domain containing 3 (NLRP3) inflammasome, and that this is important for driving IL1-β-mediated inflammatory responses by porcine bone-marrow-derived

macrophages in vitro (Choudhury et al., 2021). While these studies describe early findings in the field, the importance of the NLRP3 inflammasome in other viral infections and it's prominent targeting by viruses for immune evasion (reviewed in Zhao and Zhao, 2020), in addition to inflammasome activation as an aspect of rational vaccine design (reviewed in Ivanov et al., 2020), render this area ripe for further investigation.

Similarly, exosomes have become a topic of interest within the field. These nano-sized secreted vesicles have prominent roles during viral infection, where their biogenesis machinery may be exploited to enhance replication or infectivity, or for host cells to communicate with one another and initiate effective innate immune responses (reviewed in Chaudhari et al., 2022). Although their previous study showed that FMDV can be transmitted by exosomes between PK-15 cells in vitro (K. Zhang et al., 2019), Xu et al. more recently found that FMDV-infected PK-15 cells secrete fewer exosomes than phosphate-buffered saline (PBS)-treated controls, due to the degradation of Rab27a - which is involved in exosome secretion (Ostrowski et al., 2010) - by FMDV 2C (Xu et al., 2020). To understand why the virus would want to decrease secretion of potentially pro-transmission exosomes, the authors looked at the exosome contents. They found high levels of miRNAs in exosomes from FMDV-infected cells, compared to PBS-treated controls: among these miRNAs, miRNA-136 exhibited potent anti-FMDV activity (Xu et al., 2020). The authors concluded that FMDV degraded Rab27a to limit secretion of exosomes containing the innate immune stimulatory miRNA-136, as a novel method of immune evasion. The role of this miRNA during innate immune responses to the virus in vivo remains to be elucidated.

Another non-protein-coding transcript with potentially important anti-FMDV effects is miRNA-1307. During in vitro infection of PK-15 cells, Qi et al. detected significant increase in levels of this miRNA, which overexpression studies in BHK-21 cells showed was associated with increased proteasomal degradation of FMDV VP3 and induction of innate immune signaling via the type I (IFN) pathway (Qi et al., 2019). Again, whether and how this miRNA contributes to the innate immune response in primary host cells and infected animals should be the topic of future investigations.

Extending our molecular knowledge into non-canonical FMD host species, one study also identified antiviral ncRNAs with broad activity against FMDV, African swine fever virus, vesicular stomatitis virus (VSV) and swine vesicular disease virus in a wild boar lung cell-derived cell line (Rodríguez

Pulido et al., 2020). Such studies in potential FMDV reservoir species should be similarly encouraged to assist with management strategies and outbreak risk assessment (Croft et al., 2019).

Lastly, several studies have noted molecular interactions between FMDV proteins and components of the host cell antiviral machinery. For example, FMDV NSP 3D was shown to interact with DEAD-box RNA helicase 1 in PK-15 cells, leading to induction of IFN-β and reduced viral replication (Xue et al., 2019). Moreover, recombinant FMDV capsid proteins VP1 and VP3 interact with TLR2, TLR6 and CD14 in murine macrophages, and TLR2 in porcine macrophages, leading to IL-6 induction in vitro (Lin et al., 2020). This is the first demonstration of FMDV proteins acting as direct TLR ligands and could prove a useful starting point for better understanding the innate immune response to the virus, as well as to improved design of inactivated, subunit, or virus-like particle (VLP)-based vaccines.

3. Adaptive immunity to FMDV

The induction of FMDV-specific immunity differs in infected or vaccinated animals, showing significant disparities in the involvement of antigen-specific CD 4+ T lymphocytes.

Early studies by Borca et al. showed that FMDV infection in the murine model of can elicit rapid primary antibody responses by B cells as well as a short-term immunological memory, in both cases in a T-independent manner. (Borca et al, 1986). More than a decade later, experiments in cattle showed that depletion of CD4(+) T cells had no adverse effect on the magnitude or duration of clinical signs or clearance of virus from the circulation, thus indicating that CD4(+) T-cell-independent antibody responses play a major role in the resolution of FMDV infection in cattle (Juleff et al, 2009). The development of new protocols enabling FMDV aerogenous infection in bovines by controlled aerosol exposure (Pacheco et al., 2010), also allowed the study of the induction of the adaptive immunity along the respiratory tract, the main entry portal of the virus in the field. Studies on the time-course of FMDV-specific antibody-secreting cells (ASC) induced in lymphoid organs following aerogenous challenge, established for the first time that cattle effectively develop a rapid and vigorous genuine local antibody response throughout the respiratory tract (Pega et al., 2013). The early induction,

starting at 4 dpi, as well as the progress of the Ig isotype profiles indicated the development of a T cell-independent antibody response which drove the IgM-mediated virus clearance in cattle infected by FMDV aerosol exposure.

Following acute infection, previous studies showed that the lymph nodes of cattle (Juleff et al., 2008) and African buffalo (Maree et al., 2016) retain FMDV proteins and genetic material in germinal centers of lymphoid tissue, localized on follicular DC (FDC). The molecules mediating this retention were, until recently, unknown. Studies using a mouse model of persistent FMDV infection, in which a parallel retention of FMDV antigen occurs on FDC in the spleen, have demonstrated a key role of complement receptors 1 & 2 in enabling FDC antigen retention and thereby the production of high-affinity neutralizing antibodies following infection (Gordon et al., 2022). Studies such as these are beginning to shed light on the mechanisms underlying the ability of cattle to develop long-lasting protective antibody responses to FMDV and are highlighting possible paths towards the development of vaccines able to do the same.

The requirement of antigen-specific CD4(+) T-cell responses for the induction of FMDV-specific humoral responses was also analyzed in vaccinated cattle (Carr et al., 2013). Contrarily to the results obtained for the immune response developed after infection in naïve animals (Juleff et al., 2009), virus neutralizing antibody titers in cattle vaccinated with an inactivated FMD commercial formulation were significantly reduced and class switching delayed following *in vivo* CD4(+) T-cell depletion. Moreover, PBMC cultures from these vaccinated animals in vitro stimulated with inactivated FMDV antigens were found to induce antigen-specific CD4(+) T-cell proliferative and IFN-γ production responses. However, neither the magnitude of T-cell proliferative responses nor the extent of the IFN-γ production showed a clear correlation with the antibody responses (Carr et al., 2013).

Following the same strategy applied in infected steers, Pega et al. also studied the generation of FMDV-specific ASC along the respiratory tract after parenteral FMD vaccination and subsequent aerogenous infection of the vaccinated animals (Pega et al., 2015). FMDV-specific ASC, predominantly IgM, were detected from 7 dpv to 29 dpv in lymph nodes all along the whole respiratory tract and distant from the vaccination site. Oronasal infection with the homologous virus strain of these animals resulted in complete protection and triggered a local anamnestic response upon contact with the replicating FMDV, suggesting that FMD vaccination also induces the circulation of virus-specific

B lymphocytes, including memory B cells that differentiate into ASC soon after contact with the infective virus (Pega et al., 2015).

The induction of FMDV-specific cellular immunity was further analyzed in vaccinated bovines. In this study, homologous and heterologous responses were evaluated in groups of animals immunized with monovalent or tetravalent FMD vaccine formulations comprising O1/Campos, A24/Cruzeiro, A/Arg/2001 and/or C3/Indaial strains (Bucafusco et al., 2015). Unlike antibody responses, FMDV-specific cell-mediated responses measured by in vitro IFN-γ production demonstrated extensive intra- and inter-serotypic cross-reactivity in whole blood samples from FMD-vaccinated cattle. Furthermore, viral strains differed in their ability to elicit FMDV-specific IFN-γ responses, both in vivo and ex-vivo, in close relation to the stability of their corresponding whole capsid particles (140S) (Bucafusco et al., 2015).

More recently, BoLA class II tetramers and FMDV antigen-stimulated PBMCs from vaccinated cattle were used to identify CD4 +T-cell epitopes in the FMDV capsid, previously unreported. In vitro IFN-γ production also indicted a long-lasting Th1 cell phenotype after FMD vaccination, suggesting an important role in maintaining cell adaptive immunity after FMD vaccination (Mitoma el al., 2021).

The actual ability of virus-specific antibodies in preventing the development of FMD in cattle infected by the aerogenous route was studied in animals passively immunized with homologous immune sera from FMD-vaccinated bovines extracted at different times post-vaccination (7 and 26 dpv) (Barrionuevo et al., 2018). This report demonstrates that circulating antibodies, in the absence of other active immune mechanisms, may prevent generalization of the infection only when present in sufficient titers (titers > 1.8 $\log_{10}$). Interestingly, animals vaccinated and challenged with the homologous strain as soon as 7 days after vaccination, developed a potent booster response soon after challenge, characterized by a rapid rise in total and neutralizing antibody titers, a clear change in the isotype profile and a fast increase in the avidity of the immune serum, which were detected at both systemic and mucosal levels. These results highlighted the relevance of the induction of memory B-cell antigen-specific responses in the protective immunity against FMDV in cattle (Barrionuevo et al., 2018).

A passive immunization strategy was also successfully deployed in a field trial during an FMD outbreak in Egypt in 2016-2017 (Soliman et al., 2021). Blood was collected from calves that had been

hyper- immunized three times with a polyvalent FMD virus vaccine against serotypes A, O, and SAT 2, and FMDV-specific bovine polyvalent immunoglobulins were concentrated from the serum, purified, sterilized, and administered to over 450 calves with FMD and 300 adjacent apparently healthy calves (Soliman et al., 2021). The authors reported a significant reduction in morbidity and zero mortality in the affected group, and crucially, none of the apparently healthy calves developed FMD (Soliman et al., 2021).

4. Effects of maternal immunity

Following on from their earlier studies showing that the presence of maternal antibodies delays the onset of primary IgM responses in immunized calves (Bucafusco et al., 2014), Bucafusco et al. went on to investigate the impact of maternal immune cells, contained in colostrum, on calves' ability to mount an immune response following immunization with a commercially available tetravalent inactivated FMDV vaccine (Bucafusco et al., 2019). The researchers found that the presence of maternal immune cells did not affect the rate at which maternal antibodies waned, nor did it modify the kinetics of the calves' cell-mediated immune response to vaccination; thus, they concluded that consumption of colostrum in the field should not be considered a factor when selecting the optimal age for first immunization against FMD (Bucafusco et al., 2019). In a recent study, the effect of maternal antibodies on the primary vaccination was also analyzed in buffaloes. As observed in cattle, neutralizing antibodies are not elicited after primary vaccination in calves with maternally- derived antibodies. Assays measuring total antibodies (LPBE) cannot identify this lack of novel vaccine-induced humoral immune response. In contrast, avidity of antibodies and neutralizing antibody titers produced similar antibody decay curves when calves were vaccinated in the presence of maternal antibodies. It is worth noting that three months after primo-vaccination, calves antibody levels were below the EPP75% cut-off value for VNT titers for both viruses and might therefore be susceptible to FMDV infection. Based on these data, re-vaccination of young buffaloes when Mat -Abs have weaned should be considered (Alejandra Capozzo, personal communication).

Shin et al. investigated the kinetics of maternal antibody decline in pigs, showing that by approximately 50 days after birth, antibody levels were low enough to consider vaccination, while also uncovering evidence of a potential role of T regulatory cells in suppressing the response to vaccination in these young piglets (Shin et al., 2022).

Sareyyüpoğlu et al. asked how maternal antibody titer and/or timing of the last immunization during pregnancy affected the level of maternally derived antibodies (MDAs) in calves, and the duration of the MDAs. They found that late gestation immunization (6.5 months) resulted in significantly higher and longer-lasting (up to 120 days compared to 60 days in calves whose mothers were last immunized during the third month of gestation) MDAs in the calves, and likely protected them from FMD for longer (Sareyyüpoğlu et al., 2019).

5. Study of the immunity against FMDV at single-cell and molecular levels

Studies of the innate and adaptive immune responses to FMDV infection in natural target species remain important, not only for our understanding of immunity and immune pathology during infection, but as a necessary foundation for the design of improved vaccines that are able to induce the type of durable and broad protection more often seen after natural infection. For example, though B cell analysis remains somewhat hampered by the ongoing lack of reagents and tools for detailed research (reviewed in Barroso et al., 2020), studies of the bovine immunoglobulin repertoire revealed that approximately one tenth possesses a heavy chain complementarity-determining region 3 (HCDR3) that is three times longer than unusual, which enables the generation of both high-affinity and broadly neutralizing antibodies in response to viral infection, including, potentially, to FMDV (K. Li et al., 2019). These findings have profound implications for our understanding of antibody-mediated immunity in these species, as well as for rationale vaccine design, but at the same time call into question the relevance of murine models for such studies.

Understanding the determinants of antibody-mediated cross-protective immunity to FMDV is a high-priority research area and requires a thorough knowledge of the mechanisms of antibody neutralization, and those which are, or could be modified to be, operative against diverse strains and

serotypes of the virus. Some progress has been made in this area. For example, He et al. isolated a single B cell clone producing serotype O/A cross-neutralizing monoclonal antibody, from the blood of a recovered cow that had been sequentially infected with FMDV serotype O and A viruses under laboratory conditions, and used cryo-electron microscopy to define the antibody's binding sites on the capsids (He et al., 2021). The authors found that this antibody bound a previously unidentified antigenic site between the 2- and 5- fold axes of the capsids, touching both VP1 and VP3, which was conserved between three O serotype strains and the inoculating A serotype isolate. The study did not assess whether the same binding site was present in other FMDV serotypes, or whether the antibody could protect from infection in vivo; nevertheless, the identification of a new neutralization site shared by O and A serotype FMDV is a notable step forward.

Li et al. also aimed to identify cross-neutralization antigen sites across O serotype FMDV isolates, using monoclonal antibodies derived from cattle sequentially inoculated with thee topotypes of FMDV serotype O (K. Li et al., 2019; Kun Li et al., 2021a). They discovered one novel site on VP3 and another on VP2, which comprised two known epitopes on this capsid protein; interestingly, one of the monoclonal antibodies biding the VP3 site appeared to neutralize the virus by inducing rapid release of viral RNA, which the authors suggested could indicate the presence of a structural "trigger point" for capsid disassembly (Kun Li et al., 2021a).

Work on identifying antigenic sites on FMDV that are recognized by neutralizing monoclonal antibodies from pigs is also underway, enabled by the development of fluorescence-based single cell analysis. Li et al. used this approach and characterized three porcine antibodies that recognized an antigenic site on VP2 that is conserved between serotype O and A FMDV (Kun Li et al., 2021b). Antibodies from cattle have also been used to identify two novel neutralizing epitopes on VP3 from O serotype FMDV, which could serve as additional targets for rationally designed vaccines (Mahapatra et al., 2019).

Alongside, several studies have characterized the structure of FMDV peptides bound to SLA-2. Gao et al. successfully crystallized and characterized SLA-2*HB01 with β2-microglobulin and an epitope generated from VP1 of FMDV serotype A (Gao et al., 2018), while Feng et al. utilized the O serotype Hu64 CTL epitope in their study of SLA-2*HB01 (Feng et al., 2018), and most-recently, Ning et al. added knowledge of the crystal structure of SLA-2*04:02:02 bound to a peptide from VP2 of FMDV

A serotype (Ning et al., 2020). Together, these studies represent an important advance in knowledge for the design of vaccines aiming to elicit CD8+ T cell responses to FMDV.

Measuring the cytokine profiles of infected animals can also provide useful indications of key immune mediators and pathways that warrant further investigation for their roles in infection and influence on mounting effective responses. El-Nahas et al. collected samples of vesicular fluid and epithelium from small groups of cattle infected in the field during three different outbreaks, and analyzed host gene expression (El Nahas et al., 2021). The researchers detected high levels of expression of immune-related genes and noted an association between high expression of CD48 and expression of genes encoding IL-10, TNF-α, IFN-γ and TLR-2 (El Nahas et al., 2021). Sharma et al. conducted a timecourse analysis of IFN-γ and IL-21 protein levels in sera of infected animals, revealing a correlation between the peak cytokine level, around day 28 post-infection, and increased antibody titer, leading the authors to speculate on the role of these cytokines in antibody-mediated protection from disease (Sharma et al., 2018). While the role of IL-21 in FMDV infection has not yet been defined, it is known to be a key player in the regulation of both innate and adaptive immunity to viral infections, and especially in chronic viral infection (reviewed in Asao, 2021), and thus warrants further investigation. In swine, ten days after infection, bulk RNA analysis of whole blood revealed interesting differences compared to uninfected controls, and to previous studies (Zhao et al., 2017), including the identification of the ribosome signaling pathway, as well as the expected immune signaling pathways, as being triggered by FMDV infection (Lv et al., 2018). While such studies can provide useful indications of operative pathways, the application of single-cell transcriptomic techniques should be encouraged, and with the recent definition of reference transcriptomes for porcine peripheral immune cells (Herrera-Uribe et al., 2021), and some progress towards the same in cattle (Wu et al., 2021), the ability to dissect the averaged transcriptional response of the tissue into the heterogeneous responses of individual cells/cell types is now coming within reach of veterinary research teams.

6. Immune evasion

FMDV immune evasion occurs on both the micro (individual cell) and macro (whole immune system/long-term persistence) level: efforts to understand these dual aspects, and their interrelationship, are ongoing.

For many years, researchers have attempted to understand why some ruminant animals become long-term carriers of FMDV following acute infection, and others do not. One possibility is that the carrier state represents a balance between FMDV immune evasion strategies and host innate immunity (reviewed in Sarry et al., 2022). However, a study by Zhu et al. identified additional factors that could be involved (J. J. Zhu et al., 2020). The authors analyzed a previously published transcriptomic dataset (Stenfeldt et al., 2017) of samples of nasopharyngeal epithelium gathered from carrier and non-carrier cattle, which led them to propose three non-exclusive immunological hypotheses for factors underlying the carrier state: first, low expression of genes encoding chemokines that attract neutrophils, antigen-experienced T cells, and dendritic cells; second, reduced NK cell cytotoxicity due to lower binding to infected cells; and third, reduced apoptosis in the tissue, leading to incomplete viral clearance (J. J. Zhu et al., 2020). Developing their analysis further, the same group went on to examine in detail the period during which cattle either clear the virus or become long-term carriers, known as the "transitional phase" of infection: this revealed a likely key role for Th17 responses as well as the aryl hydrocarbon receptor pathway during the establishment of the carrier state (Zhu et al., 2022).

Alongside, Hägglund et al. developed (Hägglund et al., 2020) and molecularly characterized (Pfaff et al., 2019) an important new ex vivo model of the bovine dorsal soft palate – a key site in FMDV persistence – based on multilayer culture at an air-liquid interface. These studies revealed profound changes in gene and protein expression during both acute and persistent FMDV infection: accompanying the expected activation of innate immune pathways, notably, the researchers found that persistently infected samples had returned to control levels of transcription of molecules involved in the IL-1, IL-10 and MHC I pathways, whilst still exhibiting signs of profound transcriptional responses to the virus (Pfaff et al., 2019). These studies represent important steps forward in our understanding of the persistent state at the cellular level; whether/the extent to which the ex vivo model recapitulates the findings made in naturally infected primary tissue, remains to be seen. The possibility of using a

thoroughly validated ex vivo model to test the hypotheses generated by analysis of primary tissue is an exciting opportunity for future research. Further discussion of the carrier state can be found in the Epidemiology and Pathogenesis sections of this report.

Studies aiming to understand the molecular basis of FMDV immune evasion have also proven productive. For example, G3BP1 has emerged as a key potential molecular target of FMDV, at least in vitro. This multi-functional protein is targeted by FMDV Lpro (Visser et al., 2019) and 3Cpro (Ye et al., 2018) to inhibit the formation of stress granules, which exhibit a plethora of anti-viral actions (reviewed in McCormick and Khaperskyy, 2017). Furthermore, Yan et al. found that FMDV 3A also interacts with G3BP1 to increase its autophagic degradation and so inhibit RIG-I-like helicase signaling, which is otherwise promoted by G3BP1, in a series of co/over-expression studies in HEK-293T cells in vitro (W. Yang et al., 2020).

FMDV Lpro also disrupts several cellular pathways linked to the host innate immune response (reviewed in B. Yang et al., 2020), with recent studies increasing the resolution of our understanding of key mechanisms and target molecules. A particular area of focus has been Lpro's de-ubiquitination and deISGlyase activity, and how this contributes to FMDV immune evasion strategies. Swatek et al. showed that FMDV Lpro employs a novel mechanism to target host ISG15 (Swatek et al., 2018), a protein with known anti-viral roles including interference with virus assembly and promotion of the immune response (reviewed in Freitas et al., 2020). The researchers characterized the interaction between Lpro and ISG15, revealing that the viral protein cleaves a peptide bond in the C terminus of ISG15, preventing its normal use as a host-protein modifier, which was a previously unknown mechanism of interference with initiation of immunity (Swatek et al., 2018). More recently, Medina et al. introduced a W105A mutation into Lpro which revealed that its ability to inhibit the type I IFN response could be decoupled from its deISGlyase activity targeting ISG15 for cleavage (Medina et al., 2020a). Importantly, FMDV engineered to express the mutated Lpro exhibited attenuation both in vitro in porcine cells, and in vivo in mice, even in the presence of intact type-I IFN inhibiting capabilities (Medina et al., 2020a). Thus, Lpro targeting of ISG15 appears to be a key contributor to optimal viral growth in these models.

Cellular pattern recognition receptors (PRRs) are a major player in the infected cell's ability to initiate anti-viral processes and to alert neighboring cells to the presence of infection. Although nucleotide-

binding oligomerization domain (NOD) 2 has known roles in infection with other viruses (reviewed in Godkowicz and Druszczyńska, 2022), until recently, whether this PRR was involved in FMDV infection was not known. Liu et al. reported that NOD2 expression was induced by FMDV infection of PK-15 cells in vitro, leading to activation of anti-viral IFN-β and NF-κB pathways, but that FMDV 2B, 2C and 3C proteinases targeted this cytoplasmic PRR as a novel mechanism of immune evasion (H. Liu et al., 2019). FMDV 2B further suppresses the host cell IFN-β response, in vitro, by interacting with the viral RNA-sensor RIG-I, inhibiting its signaling and leading to decreased expression of IFN-β, ISGs and pro- inflammatory cytokines (X. Zhang et al., 2020). The importance of FMDV-targeting of RIG-I may also be emerging in in vivo, where a study by Ekanayaka et al. showed that FMDV 3C mutants, with decreased RIG-I and MDA5 degradation capacity in vitro, were somewhat attenuated compared to the WT virus in a porcine infection model (Ekanayaka et al., 2021). These interesting findings warrant further investigation in a larger cohort of animals to enable robust statistical analysis.

VP1 is another well-known inhibitor of the host type I IFN pathway in FMDV-infected cells, but it appears that its actions might be more diverse than initially anticipated. Li et al. compared gene expression profiles between PK-15 cells transfected with VP1 or empty vector and found approximately five and a half thousand significantly differentially expressed genes (L. Yang et al., 2022). Further analysis indicated a profound rearrangement of cellular functions by VP1, notably including the suppression of expression of the ISG GBP1 and increased expression of chemokines that support FMDV replication (L. Yang et al., 2022). Understanding the implications of these changes of gene expression during infection of primary cells and/or natural host organisms will be a challenge; nevertheless, the data from such studies represent a valuable resource for interrogating pathways and understanding mechanisms of action of FMDV proteins.

Alongside, several recent studies have shed fresh light on the likely mechanisms of action of VP1 during suppression of host cell type-I IFN responses. For example, in a study exploiting several mammalian cell lines, Zhang et al. showed that VP1 suppressed the host IFN-β pathway by inhibiting the function of IRF3, but that this process was counteracted in cells by the action of the DnaJ heat shock protein family member A3 (W. Zhang et al., 2019). More recently, Ekanayaka et al. showed that FMDV VP1 inhibits type-I IFN signaling in HEK293T cells by binding cellular mitochondrial antiviral signaling protein, thereby preventing its association with TREM3, and so effective induction of key innate immune molecules, including IFN-β (Ekanayaka et al., 2020). In groups of three pigs challenged

either with FMDV bearing WT VP1 or mutated VP1 (which was unable to restrain IFN-β expression in vitro), the authors reported decreased virulence of the virus lacking WT VP1 (Ekanayaka et al., 2020); however, as levels of cytokines/IFN induction were not measured in these animals, the observations remain correlative at this stage.

Several other in vitro studies have proposed additional targets of FMDV immune suppression, including p53 (Zhang et al., 2019), PRDX6 (C. Wang et al., 2021), annexin-A1 (Ma et al., 2022), Sec62/IRE1α (Han et al., 2019), ID1 (T. Ren et al., 2021), and CypA (H. Liu et al., 2018). However, there are not yet any studies looking at whether or not FMDV targets the newly described bovine type I, IFN-χ (Guo et al., 2020), or the recently characterized porcine type I IFN, IFN-αω (S. Li et al., 2019b).

7. Host immunogenetics

Understanding the relationship between the genetic makeup of an animal's immune compartment, and that individual's response to FMDV infection, holds the promise of both breeding in favor or resistance, and of better designing effective vaccines. With FMDV outbreaks also having a potentially profound effect on reducing genetic diversity across pedigree herds, in particular (R.-S. Wu et al., 2022), it has never been more important to understand immunogenetics both on the individual animal and on the herd level.

Several different approaches to studying host immunogenetics to FMD have been applied in the past five years. For example, applying RNA-seq to samples of soft-palate from experimentally infected cattle and controls of three different breeds has led to important clues as to the pathways and proteins potentially involved in the relatively high FMD resistance of the Indian Malnad Gitta and Hallikar breeds compared to Holstein Friesian crossbred animals (Saravanan et al., 2021). Saravanan et al. found that the lower viral load of the Indian breeds – most marked for the resistant Malnad Gitta breed – was associated with greater induction of innate immune genes, early antibody responses, and high levels of expression IFN-γ (Saravanan et al., 2021). More recently, Gowda et al. examined the relationship between the high resistance of Malnad Gidda cattle to FMD, their MHC alleles and their

immune response to immunization with an inactivated polyvalent FMDV vaccine (Gowda et al., 2022). The researchers found that Malnad Gidda cattle increased the frequency of CD4+ T cells at 30 days after vaccination by more than double the amount that the more FMD-susceptible Holstein Fresian/Hallikar crossbred animals did, although the starting level of this cell population in Malnad Gitta animals was also markedly lower (Gowda et al., 2022). Furthermore, Gowda et al. identified two allelic variants – MHC DRB3.2*117 and *219 – that were significantly more frequent among Malnad Gidda cattle, leading them to postulate a relationship between these alleles and the stronger T cell response to vaccination. Taken together, the above studies have generated valuable data and given clues as to the mechanisms underpinning the increased resistance of the Indian cattle breeds to FMD.

In cattle, Yang et al. took a highly pragmatic approach to immunogenetics, seeking to identify simple immune correlates of high-responders to FMDV vaccination among a group of young sires for use in breeding selection to favor FMDV resistance, finding that the level of IFN-γ produced by PBMC stimulated in vitro with lipopolysaccharide correlated well with the extent of T cell response to the vaccine (Yang et al., 2018). Whether this characteristic would prove to be stably heritable and to confer increased protection to infection with FMDV, remains to be tested.

In pigs, some progress has also been made. Hammer et al. conducted low-resolution SLA haplotyping of 549 pigs from commercial farms in Europe, defining the relative frequencies of each haplotype in the study population and identifying several novel allele-group combinations (Hammer et al., 2021). These data form a useful basis for understanding the broader implications of the link between SLA haplotype and response to FMDV vaccination (de León et al., 2020), and provide an invaluable resource for the design of vaccines that are effective across the most common SLA haplotypes in Europe. Similar region-specific studies would enable the potential benefits of this approach to be more widely realized.

8. Novel approaches for the study of the immunity against FMDV

Migrating the cutting-edge tools available for human and murine immunology research across into the veterinary field is an important and ongoing challenge. Towards this aim, several studies report significant advances relevant to the study of immunity against FMDV in natural host species.

Studies of the bovine immunoglobulin repertoire revealed that approximately one tenth possesses a heavy chain complementarity-determining region 3 (HCDR3) that is three times longer than unusual, which enables the generation of both high-affinity and broadly neutralizing antibodies in response to viral infection, including, potentially, to FMDV (K. Li et al., 2019). These findings have profound implications for our understanding of antibody-mediated immunity in these species, as well as for rationale vaccine design, but at the same time call into question the relevance of murine models for such studies.

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another on VP2, which comprised two known epitopes on this capsid protein; interestingly, one of the monoclonal antibodies biding the VP3 site appeared to neutralize the virus by inducing rapid release of viral RNA, which the authors suggested could indicate the presence of a structural “trigger point” for capsid disassembly (Kun Li et al., 2021a).

Work on identifying antigenic sites on FMDV that are recognized by neutralizing monoclonal antibodies from pigs is also underway, enabled by the development of fluorescence-based single cell analysis. Li et al. used this approach and characterized three porcine antibodies that recognized an antigenic site on VP2 that is conserved between serotype O and A FMDV (Kun Li et al., 2021b). Antibodies from cattle have also been used to identify two novel neutralizing epitopes on VP3 from O serotype FMDV, which could serve as additional targets for rationally designed vaccines (Mahapatra et al., 2019).

We have also advanced our knowledge of T cell epitopes within FMDV proteins, which are important for activation of the adaptive immune response both independently and in support of antibody production. Mitoma et al. generated bovine leukocyte antigen class II tetramers and used them to screen PBMC from MHC-II-matched vaccinated cattle, allowing the identification of CD4+ T cells specific for FMDV peptides, and subsequently, the characterization of the epitopes they recognized and the T cells that recognized them (Mitoma et al., 2021). This approach revealed three novel peptide epitopes across VP1, VP3 and VP4, which were recognized by rare populations of IFN-γ Th1 polarized memory T cells in vaccinated animals (Mitoma et al., 2021). Replicating this approach in more diverse situations – including in challenge models – and in field samples promises to be a valuable avenue of future investigation.

Alongside, several studies have characterized the structure of FMDV peptides bound to SLA-2. Gao et al. successfully crystallized and characterized SLA-2*HB01 with β2-microglobulin and an epitope generated from VP1 of FMDV serotype A (Gao et al., 2018), while Feng et al. utilized the O serotype Hu64 CTL epitope in their study of SLA-2*HB01 (Feng et al., 2018), and most-recently, Ning et al. added knowledge of the crystal structure of SLA-2*04:02:02 bound to a peptide from VP2 of FMDV A serotype (Ning et al., 2020). Together, these studies represent an important advance in knowledge for the design of vaccines aiming to elicit CD8+ T cell responses to FMDV.

Measuring the cytokine profiles of infected animals can also provide useful indications of key immune mediators and pathways that warrant further investigation for their roles in infection and influence on mounting effective responses. El-Nahas et al. collected samples of vesicular fluid and epithelium from small groups of cattle infected in the field during three different outbreaks, and analyzed host gene expression (El Nahas et al., 2021). The researchers detected high levels of expression of immune-related genes and noted an association between high expression of CD48 and expression of genes encoding IL-10, TNF-α, IFN-γ and TLR-2 (El Nahas et al., 2021). Sharma et al. conducted a timecourse analysis of IFN-γ and IL-21 protein levels in sera of infected animals, revealing a correlation between the peak cytokine level, around day 28 post-infection, and increased antibody titer, leading the authors to speculate on the role of these cytokines in antibody-mediated protection from disease (Sharma et al., 2018). While the role of IL-21 in FMDV infection has not yet been defined, it is known to be a key player in the regulation of both innate and adaptive immunity to viral infections, and especially in chronic viral infection (reviewed in Asao, 2021), and thus warrants further investigation. In swine, ten days after infection, bulk RNA analysis of whole blood revealed interesting differences compared to uninfected controls, and to previous studies (Zhao et al., 2017), including the identification of the ribosome signaling pathway, as well as the expected immune signaling pathways, as being triggered by FMDV infection (Lv et al., 2018). While such studies can provide useful indications of operative pathways, the application of single-cell transcriptomic techniques should be encouraged, and with the recent definition of reference transcriptomes for porcine peripheral immune cells (Herrera-Uribe et al., 2021), and some progress towards the same in cattle (Wu et al., 2021), the ability to dissect the averaged transcriptional response of the tissue into the heterogeneous responses of individual cells/cell types is now coming within reach of veterinary research teams.

Aiming to enable productive studies into the nature of FMDV persistence, Hägglund et al. developed (Hägglund et al., 2020) and proteomically characterized (Pfaff et al., 2019) an important new ex vivo model of the bovine dorsal soft palate. Alongside, Shaw et al. focused on advancing our ability to understand the bovine antibody response, by developing a novel assay based on bio-layer interferometry and validating its use in measuring the avidity of mono- and poly- clonal antibodies from cattle to both FMDV capsids and peptides (Shaw et al., 2022). This assay could be important in advancing our understanding of the nature of the anti-FMDV antibody response, past the level of

traditional ELISA-based avidity assays, which can underestimate the contribution of antibodies recognizing conformational epitopes.

Similarly concerning the antibody response, but this time in pigs, Puckette et al. developed a set of eleven porcine/murine heterohybridoma cell lines, each stably producing a different FMDV-specific porcine monoclonal antibody (Puckette et al., 2020). This marks a significant methodological advance, relevant not only to the FMD field, but to studies of the porcine antibody repertoire and the basis of antibody recognition of viral epitopes.

Braun et al. translated the concept of blood transcriptional modules – networks of genes that interact to execute immune responses detectable in peripheral blood – from humans, into sheep vaccinated against FMD using either inactivated virus alone or formulated with liposomes or TLR ligands as adjuvants (Braun et al., 2018). The researchers identified important correlations between an early optimal response to the vaccines, and certain modules operative in the sheep: key findings included the deleterious effect of early (presumably inappropriate) T and NK cell responses upon later antibody response; and the link between specific adjuvants and increased/decreased activation of specific modules (Braun et al., 2018). It is of note that the detection of these modules was enhanced by the study design including pre-immunization blood samples, which enabled the researchers to examine pre-immunization differences between individual animals, and thereby account for them in their analysis. This strategy should be adopted in future vaccine and adjuvant studies. Such systems approach to studying vaccination responses may have the potential to reveal ways for improving vaccines through the stimulation of parts of the immune system not activated by the current vaccines.

Modeling studies are also increasingly important. Marrero et al. developed computational methods with which to model the interaction between neutralizing antibodies and FMDV. The researchers used previously published x-ray diffraction structures of a major antigenic site in serotype C bound by a monoclonal antibody and applied their algorithm to model the interaction between neutralizing antibodies and VP1 from a serotype A capsid, and to predict the effect of point mutations (Marrero Diaz de Villegas et al., 2021).

As it was mentioned before, in terms of T cell analysis, Mitoma et al. reported a significant advance by generating bovine leukocyte antigen class II tetramers and demonstrating their utility to both identify novel FMDV epitopes recognized by CD4+ T cells in vaccinated animals, and to measure the

frequency of those cells long after vaccination and well beyond the limits of detection of conventional methods (Mitoma et al., 2021).

In the past ten years, single-cell transcriptional analysis has revolutionized the field of biomedical immunology, allowing researchers to appreciate functionally relevant differences in gene transcription within a population of cells, leading to the definition of new cell subtypes and novel molecular targets (reviewed in Aldridge and Teichmann, 2020). However, the success of this approach relies on the definition of reference transcriptomes for the cell types of interest, which had previously been lacking in FMDV target species. Two important studies have recently begun to remove this research bottle-neck, one defining reference transcriptomes for porcine peripheral immune cells (Herrera-Uribe et al., 2021), and another describing some progress towards the same in cattle (Wu et al., 2021). Further developments in this area will bring the ability to dissect the averaged transcriptional response of the tissue into the heterogeneous responses of individual cells/cell types within the reach of veterinary research teams.

Lastly, ongoing projects continuously lead to the generation of new reagents with which to study immune responses in animals. Many of these are listed in the regularly updated Veterinary Immunological Toolbox, hosted by the Roslin Institute at the University of Edinburgh, in Scotland. The toolbox can be consulted here: https://www.immunologicaltoolbox.co.uk/

Recommendations

The GFRA Gap Analysis Working Group identified the following research knowledge gaps in the Immunology area:

- ✓ Tissue immunology, principally applied on primary sites of infection.
- ✓ Study immunological features of the carrier state at the mucosal level.
- ✓ Epigenetics: study the role of metabolism on FMDV infection development. Studies to understand physiology and to improve long immunity.

- ✓ Trained immunity on epithelial cells.
- ✓ Duration of immunity - mechanisms underlying memory cell maintenance in FMD susceptible species. Memory. Long live plasma cell studies to better understanding.
- ✓ Role of DC and macrophages in shaping high avidity immune response is still a gap.
- ✓ Role of innate immunity in controlling the disease and promoting vaccine-induced protective responses.
- ✓ Immune mechanisms behind the development of carrier vs non-carrier animals.
- ✓ Impact of other concomitant infectious diseases in the development and maintenance of FMD protective immunity
- ✓ The immunological bases of cross-protection and strategies to promote cross-protective immune responses.
- ✓ Indirect correlates of protection: what to assess. Deploy avidity and isotype assays to be applied with different strains in challenge trials.

Virology

Literature Review

1. General Aspects

FMDV is the prototype virus of the Aphthovirus genus in the picornavirus family. It comprises a single stranded positive sense RNA genome of approximately 8500 nucleotides inside a non-enveloped capsid of approximately 28nm diameter. The capsid is formed from 60 copies of four viral proteins (VP1, VP2, VP3 and VP4) arranged with icosahedral symmetry. In natural conditions, the virus binds to integrin receptors on the cell surface, is endocytosed into acidified vesicles where uncoating is triggered to deliver the genome into the cytoplasm. FMDV also possesses redundant cell entry pathways, with integrin-dependent, heparan sulfate (HS)- dependent, and integrin/HS-independent pathways identified under various conditions (reviewed in Kangli Li et al., 2021).

Translation of a single ORF is driven by an IRES element in the 5' UTR to produce a polyprotein which is co- and post-translationally processed into precursors and mature proteins required for replication of the genome and assembly of new viruses. Different host properties and epidemiological conditions generate intra- and inter-host genetic bottlenecks that shape FMDV evolution in ways that are difficult to measure and predict (Orton et al., 2020).

The massive genetic diversity and broad host tropism of FMDV complicate studies of its virology, as viral mechanisms (e.g., of cell attachment and entry, immune evasion, etc.) observed in one strain and/or host animal may not apply to another strain in a different host. FMDV initially infects epithelial cells in pigs and cattle, but the specific tissues that host primary infection and subsequently maintain acute and/or persistent infection vary between these species (reviewed in Stenfeldt et al., 2016a).

Many functions for FMDV's structural and non-structural proteins have been identified in intra- and extracellular environments, but large gaps remain in our understanding of critical interactions (e.g.,

determinants of tropism, mechanisms of viral genome translation and recombination between strains, etc.) at the virus-host interface. Knowledge of FMDV genome sequences, protein structures and functions, and interactions with host proteins is critical for understanding viral evolution, predicting transmission and diversification, and developing successful diagnostics and vaccines for emerging strains. Recent research has substantially advanced our understanding of FMDV virology, with many studies newly identifying the functions of viral components, their interactions with host factors, and pathways for applying this knowledge to inform disease control and vaccine development (reviewed in Belsham et al., 2020; Kangli Li et al., 2021; Medina et al., 2018). Simultaneously, improvements in next-generation sequencing technologies are allowing us to generate near-complete FMDV genome sequences faster than previously possible and to expand our genomic coverage of circulating strains in remote regions.

2. Receptors and cell entry

Recent structures of the FMDV-αvβ6 integrin interaction showed interaction of an extended VP1 GH loop with the open form of the integrin along with additional contacts between an N-linked sugar of the integrin and the viral heparin sulfate (HS) binding site. This unexpected sugar-protein interaction might explain the rapid ability of FMDV to adapt to cell culture via HS attachment (Kotecha et al, 2017). However, the integrin may not be the major determinant of tropism at the species level, since both human and equine integrins have been shown to be used by FMDV in vitro albeit neither species is susceptible to infection in vivo. In addition to integrins and HS, a third receptor for FMDV was previously identified as Jumonji C-domain containing protein 6 (JMJD6), however no recent publications further describing this receptor have been identified (Lawrence P, et al, 2016).

Adaptation of an O/CATHAY strain (O/HN/CHA/93tc) to CHO-K1 cells involved a mutation of VP1's E83 residue, which surrounds a pore at the viral capsid's icosahedral fivefold symmetry axis, to positively charged lysine, allowing the virus to undergo integrin-independent entry via heparan sulfate (Gong et al., 2020). FMDV endocytosis and subsequent endosomal internalization into CHO-677 cells were reported to follow an unknown mechanism that required clathrin, caveolin, dynamin,

Rab5, and Rab7, but not integrin or heparan sulfate (HS) receptors (S. Chen et al., 2022). Sarangi et al. adapted three serotype O lineages (O/IND/R2/1975, O/IND/271/2001, and O/IND/120/2002) to BHK-21 cells in the absence of any immune pressure, observing surprisingly low mutation rates (12 substitutions in 13 different passage regimens). Sequence analysis indicated that the net positive charge of the HS- binding pocket (or elsewhere on the capsid) may be more important than site-specific positive charge acquisition for alternative receptor binding (Sarangi et al., 2019). Finally, Zhang and Xu et al. isolated full-length FMDV genomic RNA and partial viral proteins from exosomes produced by infected cells in vitro and in vivo, indicating that these exosomes may facilitate immune evasion and viral entry (K. Zhang et al., 2019).

Genome release by FMDV is often described as being via a mechanism of capsid dissociation. However, by analogy with other picornaviruses, including the acid-sensitive aphthovirus equine rhinitis A virus, FMDV genome release may occur from an intact particle, but which is only transiently stable and rapidly dissociates after genome release (Tuthill et al. 2009).

3. Capsid assembly and stability

In the last years several papers have demonstrated that capsid precursor processing followed by capsid assembly is a highly regulated process involving cellular chaperones (Newman et al. 2018; Kristensen and Belsham 2019). Fundamental studies on capsid assembly and stability are critical for VLP engineering and optimization of VLP-based vaccines and new diagnostic tools. In this sense, recent unpublished evidence suggests that the structure of the FMDV capsid is dynamic, like that of other picornaviruses and in addition to being capable of dissociating into its pentamer components (Malik et al 2017), may in a dynamic state also be capable of exposing additional epitopes (e.g., VP4 and internal VP2 epitopes) that could be tracked in new tests for evaluation of vaccine integrity and antigenicity. This was the first report showing the molecular structure of dissociated FMDV pentamers. Malik et al. published low- resolution (8 Å) structures of pentamers composed of structural proteins VP1-3 (lacking VP4) after acid treatment of native virus particles. These authors observed that the

dissociated pentamers unexpectedly reassembled into an icosahedrally symmetric assembly at neutral pH, and the structure of this assembly (composed of "inside out" pentamers) was solved at 5.2 Å.

Recent evidence supports the conclusion that replication of FMDV, like other RNA viruses, involves interactions between capsid proteins and secondary structures in the viral genome itself. Logan et al. conducted deep sequencing of FMDV to investigate its genome packaging mechanisms, identifying conserved stem-loops in the viral genome that were required for optimal virion assembly in vitro (Logan et al., 2017); meanwhile, mutagenesis mapping of 46 predicted conserved RNA structures in the NSP-encoding genome regions revealed three structures in particular (all at the 3' termini of the viral ORF) that were required for viral replication (Lasecka-Dykes et al., 2021). The secondary structure of the long 5' untranslated region (5' UTR) of FMDV genomic RNA contains 2-4 putative pseudoknots which are also essential for the production of infectious virus, suggesting a role in virion assembly (J. C. Ward et al., 2022). Finally, like other picornaviruses in the Cardiovirus and Aphthovirus genera, FMDV also possesses a long polycytidine tract in the genomic 5'-noncoding region (Black et al., 1979), but our understanding of its function remains limited (reviewed in Penza et al., 2021).

The initial processing of the FMDV polypeptide into its constituent proteins also involves multiple steps that could be targeted for antiviral therapeutic development or inactivated vaccine production. Kjær and Belsham investigated the co-translational cleavage of the initial FMDV polyprotein at the 2A/2B junction, finding that single amino acid substitutions (at the E14, S15, N16, and P19 positions) inhibited this event and subsequently limited viral replication (Kjær and Belsham, 2018). Kristensen et al. identified critical residues within the viral capsid precursor protein P1-2A that are required for cleavage at different junctions (VP0/VP3, VP3/VP1, and VP1/2A) and demonstrated that these junctions are processed independently of each other (Kristensen et al., 2018); this group later identified a highly conserved five-residue motif (YCPRP) in the C-terminal region of VP1 that was required for proper processing of the FMDV capsid precursor in BHK cells, and single amino acid substitutions in this region significantly reduced cleavage and viral infectivity (Kristensen and Belsham, 2019).

Regarding FMDV engineering for stable vaccine production, current efforts are focused on the selection of natural or cell culture-adapted viral strains with increased acid and thermal stability. In addition, the use of reverse genetics systems to engineer stable vaccine strains is being promoted.

In the last decade, extensive research on empty capsids and VLP-based vaccines has been performed, and FMDV VLPs have reached industry. Computational approaches have been applied for the development of thermostable VLPs. Moreover, it has been recently shown that 2B protein improves VLP expression in transfected mammalian cells expressing wild type 3C protease (Primavera et al, 2022). However, there might not be a universal way to stabilize capsids of all serotypes, highlighting the need of further research in this area. Multidisciplinary approaches including computational and artificial intelligence prediction methods, alternative expression technologies and the use of exogenous capsid stabilizing factors such as new adjuvants may help optimization of VLP-based vaccines.

4. Role of RNA structure and composition in FMDV replication

Although the role of FMDV RNA elements has been extensively interrogated, new studies have shown novel structure and functions of the viral genome involved in replication and interaction with the host. For example, the IRES element has been shown to interact with several cellular factors for modulation of translation. Indeed, new IRES-trans-acting factors (ITAFs) have been described in recent years. Moreover, in turn, other structural elements such as the pseudoknots (PK) in the 5'UTR and stem loops predicted within the 3D-coding region have been shown to be required for viral replication (Lasecka-Dykes et al 2021). In addition, both the S fragment, a highly stable stem-loop in the 5'UTR, and the PK have been shown to play a role in viral evasion of the cellular antiviral response. In the same direction, a role of viral RNA structures in shielding viral sensing by Zinc Finger Antiviral Protein (ZAP) has been postulated. Also, an adjuvant effect of the IRES when added to inactivated vaccines has been demonstrated. More recently, some RNA packaging signals have been identified by means of next-generation sequencing of encapsidated RNA (Logan et al 2017).

Regarding FMDV genomics, it is well established that picornaviruses (including FMDV) engineered with fidelity mutations in the polymerase are not able to generate normal levels of viral population diversity and are attenuated *in vivo* and this represents a strategy which could contribute to future live attenuated FMD vaccines. Recent research suggests that viral RNA diversity is required to overcome the cellular antiviral response and further understanding of how viral diversity influences infection is

required. A role for genomic recombination has been well established at the global and regional epidemiological level, and new research has also developed in vitro approaches to study recombination and further research is needed to understand the underlying mechanisms and its role during infection.

It is established for other picornaviruses that aspects of genome composition can influence viral phenotype, providing additional strategies for virus attenuation and these approaches are beginning to be applied to FMDV. Ongoing research is exploring how alterations in RNA composition can be engineered to 'deoptimize' codon usage, codon pair bias, dinucleotide frequency and genome scale RNA structure in order to attenuate FMDV. Further research is required to understand the mechanisms and extent of attenuation in multiple FMD susceptible species.

5. Virus-host interactions

Over the past five years, new data have been published on the roles of viral proteins (including both capsid and non-structural proteins) in virulence and clinical presentation. Numerous host-virus interactions have been mapped in vitro, revealing pathways by which FMDV promotes IRES-dependent translation, shifts cellular resources toward viral replication, and modulates post-transcriptional events. Other studies have focused on the pro- and antiviral roles played by various host proteins and microRNAs, providing new targets for molecular studies and therapeutic development. The determinants of persistent infection have also been explored *in vitro* and *in vivo,* allowing the mechanisms of this complicated phenomenon to be explored in increasing detail.

The leader protease (Lpro) is the most well studied virulence factor of FMDV. In the last years, many fundamental studies have revealed new significant mechanisms involved in Lpro function. These fundamental data support the use of the leaderless vaccine production platform and suggest that modulation of Lpro could contribute to strategies for a live attenuated vaccine against FMD.

The extensive search done for this Gap Analysis revealed a high number of papers describing virus host-interactions, in particular new mechanisms of subversion of antiviral responses (reviewed in Peng

et. al. 2020), new virus cell-interactions promoting virus replication and molecular determinants that might explain pathogenicity in vivo.

FMDV interacts with a complex network of host cell factors during infection, and recent studies have uncovered a number of cellular signaling pathways and specific proteins that can promote or inhibit viral replication at different stages of the cell infection process. The cellular chaperone heat shock protein 90 (HSP-90) is required for optimal processing of P1-2A and its subsequent formation into capsid pentamers (Newman et al., 2018). Zhu et al. found that the mitogen-activated protein kinase (MAPK) signaling pathway was required for FMDV replication, and the viral VP1 capsid protein interacted with host ribosomal protein SA (RPSA) to block its inhibitory effect on this pathway (Z. Zhu et al., 2020). VP1 was also shown to bind the host protein DNAJA3, which promotes its lysosomal degradation (W. Zhang et al., 2019), and to interact with the mitogen-activated protein kinase TPL2 to inhibit interferon regulatory factors 3 (IRF3)/IFN-β signaling and promote viral replication (Hao et al., 2021). Transcriptomic analysis of FMDV-infected PK-15 porcine kidney cells found that VP1 expression upregulated certain chemokines (including CCL5, CXCL8, and CXCL10) to promote viral replication, while the interferon-stimulated gene GBP1 was heavily downregulated (L. Yang et al., 2022). The EGR1 transcription factor is significantly upregulated by FMDV infection and subsequently inhibits viral replication by inducing type I IFN signaling independently of its transcriptional activity (Zixiang Zhu et al., 2018). Several viral proteins (2B, 2C, 3Cpro, and Lpro) promote viral replication by downregulating expression of RIP2 in the NOD2 signaling pathway (H. Liu et al., 2019, 2021). Molecular characterization of FMDV 2B protein showed that this NSP, as in other picornaviruses, forms ion channels in host cells via two pore domains (residues 60-78 and 119-147); mutations in either of these structures resulted in the production of nonviable viruses in infected cells (Gladue et al., 2018). The NSP 2B was also found to interact with the porcine host protein cyclophilin A, suppressing the latter's inhibitory activity toward viral Lpro and 3A and promoting viral replication at the expense of host protein synthesis (H. Liu et al., 2018).

Translation of FMDV's RNA genome requires viral components to manipulate many components of the cellular translational machinery, presenting a wide interface at which many virus/host interactions occur during infection. The primary eukaryotic translation initiation pathway depends on recognition of the 5' cap on an mRNA, and cellular stresses such as viral infection can severely compromise this cap-dependent mechanism (reviewed in Martinez-Salas et al., 2018). Internal ribosome entry sites

(IRESs), cis-acting RNA regions that allow ribosomes to begin translation without cap recognition, can circumvent this pathway. IRES-dependent translation allows protein synthesis to continue when canonical cap-dependent translation initiation is inhibited, and many viruses have evolved to benefit from this mechanism (reviewed in Jaafar and Kieft, 2019). FMDV harnesses numerous host cellular factors to promote IRES-dependent translation, including polycystic kidney disease 1-like 3 (PKD1L3) and ubiquitin-specific peptidase 31 (USP31) (Ide et al., 2022). Host cell nucleolin promotes IRES-driven translation by recruiting translation initiation complexes to IRESs in the viral genome (S. Han et al., 2021). The host ribonucleoprotein hnRNP K binds the FMDV IRES, inhibiting IRES-dependent translation by blocking the binding of another host ITAF, polypyrimidine tract-binding protein – hnRNP K is in turn degraded by the viral protease 3C, and the resulting C-terminal product was found to enhance FMDV replication (Liu et al., 2020). hnRNP L also binds FMDV IRESs and inhibits viral growth – interestingly, however, this effect was attributable to interference with viral RNA synthesis via binding between hnRNP L and the viral RNA-dependent RNA polymerase 3Dpol (Sun et al., 2020).

The stress granule assembly factor G3BP1 was previously shown to negatively regulate viral translation by binding directly to IRES sequences (Galan et al., 2017). Ye and Pan et al. found that FMDV infection triggers dephosphorylation and proteolytic cleavage (via 3Cpro) of G3BP1, blocking both its regulation of viral translation and its activation of innate immune pathways (Ye et al., 2018). G3BP1 is one of several critical host proteins that are processed by wild-type 3Cpro, leading to cytotoxicity in vitro. The L127P mutant (which restricts host protein processing while permitting the P1 processing required for virion formation) is commonly used to circumvent this in FMDV vaccine production platforms, though recent findings indicate that I22P, T100P, and V124P mutations may be superior alternatives (Martel et al., 2019). The FMDV leader protease Lpro also cleaves G3BP1, its fellow stress granule scaffolding protein G3BP2, and RIG-I-like receptors, suppressing the stress response and innate immunity during viral infection (Visser et al., 2020, 2019). Additionally, this protease was recently shown to cleave peptide bonds in immune-associated linkages of ubiquitin and the ubiquitin-like protein ISG15. Importantly, the cleavage products produced by this activity were detectable by anti-GlyGly antibodies during viral infection, presenting a new diagnostic option that relies on an epitope that is host derived.

Wang and Feng et al. reported that the porcine antioxidant enzyme PRDX6 inhibits FMDV replication and is degraded by the viral protease 3Cpro during infection in vitro (C. Wang et al., 2021). The porcine host cell nucleases DEAD-box RNA helicase 21 (DDX21) and DDX23 inhibit FMDV IRES-dependent translation and are in turn degraded via viral proteases (Abdullah et al., 2021, 2020), and DDX1 also reduces viral replication and stimulates IFN-β activation (Xue et al., 2019). Conversely, DDX56 positively regulates FMDV replication, interacting with the FMDV NSP 3A to inhibit IRF3 phosphorylation and subsequent production of IFN-β (Fu et al., 2019). DDX3 also functions in FMDV IRES-dependent translation, interacting with ribosomal protein L13 and eukaryotic initiation factor 3 (eIF3) subunits e and f to facilitate IRES binding and promote initiation of viral mRNA translation (Han et al., 2020).

The NSP 3A is known to play important roles in FMDV infectivity, tropism, and replication (Pacheco et al., 2003). In addition to its DDX56-binding capability, 3A was recently shown to remodel the cellular ER to form vesicle-like structures in a COPII-independent manner, coopting the COPII factors Sec12 (a guanine nucleotide exchange factor) and its target Sar1 to initiate this step of replication organelle formation (H.-W. Lee et al., 2022). 3A also interacts with host annexin-A1 in vitro to block its immune-stimulating activities (Ma et al., 2022). Other recently reported functions for 3A include binding to cellular vimentin, which appears to be required for viral replication (Ma et al., 2020), and inhibiting IFN signaling by blocking the RLH signaling pathway mediated by G3BP1 (W. Yang et al., 2020). Meanwhile, Lotufo et al. determined that 3A's hydrophobic tract (between residues 59-76) and the sequence around its putatively exposed hydrophilic E20 residue are essential for its promotion of viral gene expression (Lotufo et al., 2018).

Host cell variables including cell size, number of inclusions, and cell cycle stage also significantly impact FMDV replication and the levels of FMDV integrin receptor expression, leading to changes in viral adsorption (Xin et al., 2018).

Transcriptomic analysis of porcine whole blood cells during infection with FMDV identified 120 differentially expressed genes which were primarily involved in ribosome signaling and immune-related pathways (Lv et al., 2018). Numerous cellular noncoding circular RNAs (circRNAs) were found to be differentially regulated in FMDV-infected PK-15 cells, with their biological functions

(including ubiquitination, cell cycle regulation, RNA transport, and autophagy) also suggesting a role in immune response (J. Yang et al., 2022).

Many host microRNAs (miRNAs) are differentially regulated during FMDV infection as well (Basagoudanavar et al., 2018), and specific miRNAs have been found to play competing roles in the FMDV infection process. miR-1307 is upregulated by FMDV infection in PK-15 cells, where it enhances host immune response and degrades of viral VP3, and treatment of suckling mice with miR-1307 agomir delayed mortality after infection with mouse-adapted O/BY/CHA/2010 virus (Qi et al., 2019). FMDV infection of PK-15 cells also upregulates miR-4331-5p and -4334-5p, which inhibit IFN pathways to promote viral replication (Ren et al., 2020; Yanxue Wang et al., 2020).

Protein modification events also modulate FMDV activity in infected cells. SUMOylation of four lysine residues in the viral 3C protease inhibited this enzyme via multiple mechanisms, decreasing its stability and inhibiting FMDV replication (X. Wu et al., 2022). The NSP 3B (also called VPg), present as three non-identical copies (3B1, 3B2, and 3B3) linked to the 5' end of the viral genome, primes RNA replication in a process dependent on uridylylation via the viral 3Dpol enzyme (Nayak et al., 2005). de Castro et al. recently conducted x-ray crystallography on 3B1 in complex with 3Dpol to demonstrate that 5- fluorouridine triphosphate acts as a potent competitive inhibitor of this uridylylation (de Castro et al., 2019).

Lastly, new functions have been identified for capsid proteins, which can interact with components of the cellular innate immune response to enhance viral replication. A site-directed mutagenesis study of O/ME-SA/PanAsia-1 described interactions between VP1-3 and VP4 during viral assembly and revealed that the Y2079 residue of VP0 (which undergoes "maturation cleavage" into VP4 and VP2 during encapsidation) is important for FMDV plaque size, pathogenicity, and acid sensitivity correlated with ammonium chloride resistance (Bai et al., 2019).

6. Coinfection and recombination

Recombination can occur between distinct viruses co-infecting the same cell, allowing the exchange of genetic material and subsequent generation of new variants. Coinfections with different sublineages or serotypes have been observed in field samples (Al-Hosary et al., 2019; Ullah et al., 2017), and superinfection with a heterologous strain during the post-acute/subclinical stage of FMDV infection has been proposed as a conducive environment for recombination events (Brito et al., 2018). Although recombination is an important determinant of FMDV diversity, it is challenging to study in controlled experimental settings: previous in vivo studies were unable to observe recombination events in superinfected animals (Cottral and Bachrach, 1968; Maree et al., 2016), and competitive exclusion leads to a single strain achieving dominance in cell culture models of coinfection (Mahajan et al., 2021; Saldaña et al., 2003).

Alternative *in vitro* approaches were designed to circumvent these limitations in the study of virus-host recombination events. Childs et al. used FMDVs encoding epitope-tagged VP1 capsid protein to monitor coinfection products in vitro, reporting the first demonstration of trans-encapsidation (incorporation of one FMDV's genome into a capsid composed of proteins from the coinfecting heterologous strain) (Childs et al., 2021) Analysis of BHK-21 cells infected with an Asia-1 FMDV strain revealed a 12-nt insertion, identical to a highly expressed host cell sequence, at the 3' end of the viral VP1 coding sequence, and resultant progeny viruses displayed a new integrin/HS-independent cell-binding capability (Zou et al., 2019).

Results from Bachanek-Bankowska & Di Nardo et al.'s evolutionary analysis of the O/ME-SA/Ind-2001 lineage indicated recombination by exchange of capsid-coding sequences between two co-evolving sublineages, leading the authors to conclude that only outer capsid protein-encoding sequences should be used for wide-scale phylogeographical reconstructions (Bachanek-Bankowska et al., 2018b).

7. In vitro strategies for virological studies

In vitro models are an important tool for investigating specific aspects of FMDV virology and/or infection pathways under a strictly controlled experimental setting and without the additional challenges of in vivo studies.

Bovine nasopharyngeal mucosal epithelial cells are the primary infection site of FMDV in cattle. Primary bovine thyroid (BTY) cells have long been considered the most sensitive system for FMDV isolation (Snowdon, 1966), the difficulty of obtaining thyroids from FMD-negative calves and the inherent challenges of primary cell culture have spurred the search for alternative in vitro systems. Bai et al. isolated and cultured these cells for an in vitro model of acute FMDV infection (Bai et al., 2018). An immortalized cell line (dubbed hTERT-BTY) was also established from primary bovine thyroid cells, with preliminary results indicating their effectiveness as a model of immune pathway signaling in response to FMDV infection (Mao et al., 2018).

Gray et al. validated the ZZ-R 127 fetal goat tongue and LFBK-αVβ6 fetal porcine kidney cell lines. Both lines were equivalently sensitive for FMDV isolation compared to BTY, while the LFBK-αVβ6 cells were also susceptible to infection with the swine-tropic O/CATHAY strain (Gray et al., 2020). The ZZ-R 127 cell line was used by Wungak et al. for isolation of serotype O, A, SAT 1, and SAT 2 viruses in Nigeria prior to antigen capture ELISA, yielding rapid results while providing greater ease-of-use and cost- effectiveness (Wungak et al., 2019b).

Hägglund et al. developed an *in vitro* model of persistent FMDV infection in cell multilayers derived from bovine dorsal soft palate, reporting a promising capability of mimicking the carrier state phenotype in a controlled experimental setting (Hägglund et al., 2020). LaRocco et al. experimented with highly FMDV-susceptible fetal porcine kidney (LFBK) cells expressing bovine αVβ6 integrin, eliminating the bovine viral diarrhea virus contamination that had previously affected that cell line (LaRocco et al., 2021), and King et al. established a protocol for measuring the effects of antibodies on FMDV evolution by culturing αVβ6-expressing LFBKs in the presence of sub-neutralizing levels of sera from FMDV-exposed animals (King et al., 2022).

Meanwhile, a new three-stage PEG-salt aqueous two-phase extraction system was developed for isolating high-purity FMDV (P. Du et al., 2019) and Newman et al. published a recombinant system for studying differences in viral capsid proteins before and after the maturation cleavage event, using this system to show that the FMDV assembly and disassembly pentamers were not antigenically distinct (Newman et al., 2021). Finally, a recent study by Spinard et al. established a new method for measuring FMDV recombination in vitro, demonstrating that recombination between two genetically engineering non-infectious RNA templates could produce infectious FMDV (Spinard et al., 2023).

8. Generation of complete FMDV sequences since 2018

The proliferation of next-generation sequencing methods has facilitated a significant expansion in the number of sequenced FMDV genomes, and studies continue to report new protocols for efficient, high-accuracy sequencing from different sample matrices – for instance, the scalable probe capture enrichment technique published by Singanallur et al. in 2019, which was effective in identifying single nucleotide polymorphisms in FMDV serotype O- and A-infected pigs (Singanallur et al., 2019). However, sampling difficulties and limited instrumentation availability have continued to bias current genomic datasets against rural and/or remote FMD-endemic regions (Brown et al., 2021a; - Dykes et al., 2018). The increasing focus on portability in emerging third-generation sequencing technologies offers promising alternatives to existing laboratory-based pipelines – for instance, Oxford Nanopore Technologies' MinION portable sequencer was able to rapidly generate high-quality FMDV serotype A, O, and Asia 1 sequence data from samples including tongue epithelial suspensions and oral swabs (Brown et al., 2021a), and new simple Sanger sequencing-based workflows can provide valuable information on the protein-coding region of the FMDV genome (Hassan et al., 2022a). Researchers at the Pirbright Institute WRLFMD are conducting a UK government-funded project aimed at sequencing contemporary samples from FMD cases in endemic countries and producing FMDV- specific protocols for the Oxford Nanopore platform, developing probe enrichment methods that can be used to sequence samples with low viral loads (D. King, 2023, personal communication).

Najafi et al. reported the first full genome characterization of an Iranian FMDV isolate (Asia1/Shimi/2017) – phylogenetic analysis indicated that the virus had likely spread from India to Iran and then on to Turkey (Najafi et al., 2020), in line with the general westward transmission pattern observed in later epidemiological studies of the South/Southeast Asia/Middle East region (Di Nardo et al., 2021).

Vandenbussche et al. reported five complete genome sequences from Nigerian lineage A/AFRICA/G-IV isolates collected between 2013-2015 (Vandenbussche et al., 2018). Obtaining samples and performing next-generation sequencing can be extremely challenging in endemic areas of sub- Saharan Africa, and sequences of serotype SAT 1, 2, and 3 are particularly underrepresented among FMDV sequence data (Lycett et al., 2019; Woodburn et al., 2021). Recent studies have begun to close this gap. An analysis of 34 SAT isolates from East and Southern Africa found evidence of recombination events and identified two novel genotypes harboring atypical 5' UTR and non-structural encoding regions (Lasecka-Dykes et al., 2018). Fish et al. reported the first near-full-length SAT 2 genome sequence from West Africa in 2019 (Fish et al., 2019), while Palinski et al. published complete or near-complete sequences from Kenyan serotype A, SAT 1, SAT 2, and O isolates (Palinski et al., 2019d, 2019b, 2019c). This research group also published sequences of topotype SAT1/X viruses from Cameroon (Bertram et al., 2019a), O/ME-SA/Ind-2001d viruses from India (Bertram et al., 2019b), O/CATHAY viruses from Vietnam (Vierra et al., 2020), and a total of 71 Asia 1 viruses from cattle and water buffalo (including subclinically infected animals) in Pakistan (Bertram et al., 2022; Stenfeldt et al., 2022a).

Bertram et al. used an Illumina NextSeq system to sequence seven FMDV isolates collected between 1997-2009 in India, matching them to the four sublineages (a-d) of O/ME-SA/Ind-2001 (Bertram et al., 2020a). Bachanek-Bankowska et al. utilized MiSeq to sequence three sublineage O/ME-SA/PanAsia- 2ANT-10 viruses from Pakistan in 2016-2017, finding that two of them displayed distinct antigenic phenotypes against commonly used vaccines despite their genetic closeness (Bachanek-Bankowska et al., 2019), and sequencing of two serotype O viruses from a 2019 outbreak revealed the first known introduction of the O/ME-SA/Ind-2001 lineage in the country (Hicks et al., 2020). Sequences of several Pakistani serotype A viruses (specifically the A/ASIA/Iran-05SIS-13 sublineage) were also recently reported as part of a larger study of FMDV recombination patterns, evolutionary pressures, and transmission routes within the country (Naqvi et al., 2022).

Finally, recently announced sequences from Southeast Asia are helping to fill the gaps in our understanding of viral introduction, transmission, and evolution in these complex smallholder-driven agricultural systems. Collected complete or near-complete sequences include O/SEA/Mya-98 isolates, O/ME-SA/Ind-2001e isolates, and recombinant viruses (containing A/ASIA/Sea-97 capsid and O/ME-SA/PanAsia nonstructural regions) from Vietnam (Bertram et al., 2021; H. Lee et al., 2019; Palinski et al., 2019a); O/ME-SA/Ind-2001BD1 and -BD2 and A/ASIA/G-VII isolates from Bangladesh (Al Amin et al., 2019, 2020a; Ul Alam et al., 2019); and O/ME-SA/Ind-2001e viruses from the 2022 outbreak in Indonesia that ended the country's long-held FMD-free status (Zainuddin et al., 2023).

Recommendations

The GFRA Gap Analysis Working Group identified the following research knowledge gaps in the Virology area:

Role of exosomes/extracellular vesicles in FMDV cell exit (non-lytic release): This mechanism of viral dissemination has been previously shown for other picornaviruses like hepatitis A virus (HAV). However, it is not clear for FMDV whether exosomes or other extracellular vesicles are involved in non-lytic virus release. Interestingly, this type of cell exit allows for the transmission of whole viral populations within single vesicles, thus the impact on FMDV genetic diversity and its role in virus evolution is evident. Moreover, it should be noticed that mammalian exosomes contain cellular microRNAs that carry the potential of modulating the transcriptome of the recipient cell. Fundamental studies on composition of extracellular vesicles derived from infected cells and their role in cell-to-cell spread, evasion of the host immune response and quasispecies evolution are needed.

Lack of integrated genomics and interactome databases and curated genomic/transcriptomic database for target species, including small ruminants and African buffalo: In the area of viral genomics, The Pirbright Institute has recently launched a new curated and annotated FMDV genomic database (fmdbase.org) containing >12000 sequences. In the area of virus-host interactions, the need of an integrated database that includes multiple types of data (transcriptomic, RNA and protein structure, functional genomics, interactomics, etc) has been suggested as a research gap. The goal of this database

would be to present a global picture of the FMDV infected cell in a species-specific manner. In the area of host genomics, the lack of genomic information (no full genome or only poorly annotated genomes) for many FMD susceptible species (e.g., small ruminants and wildlife such as buffalo) was highlighted.

Determinants of host range at the species and cellular level: As mentioned before, integrins may not be the determinants of species-level tropism. Indeed, post-receptor intracellular restriction factors (e.g. ISGs) that define mammalian susceptibility may exist, also promoting the research on the molecular mechanisms defining the host range (at the species and cellular level).

Lack of complex cell culture systems to study virus-host interactions in vitro: To translate in vitro results obtained with cultured cells to pathogenesis in vivo, there is a need of developing additional complex cell culture systems (primary cells, ex vivo cultures, 3D cultures, organoids) that may better correlate with *in vivo* conditions. More relevant *in vitro* systems may also reduce the number of animals used in research.

Molecular mechanisms of attenuation: Modifications in the 5'UTR RNA structure, large scale alterations to RNA composition (deoptimization) and polymerase fidelity mutations are the three elements present in the successfully developed 2nd generation live attenuated poliovirus vaccine. The recent development of deoptimized viruses as FMD vaccine candidates has raised the question of how attenuation is achieved in this kind of strategies and linking with the poliovirus research community may be valuable. For FMDV, in vitro studies in relevant systems (primary cells, ex vivo samples, cell culture systems competent for antiviral responses) to better understand mechansims of attenuation and to predict levels of attenuation in a range of natural hosts was identified as a major gap.

Gene editing to produce disease resistant livestock: Although challenging, this topic needs further fundamental research on cellular receptors and virus-host interactions to identify and characterize gene editing targets prior to gene editing of livestock itself being considered as a research gap.

Role of genetics in infection (recombination, virus fitness, diversity): The molecular mechanisms of recombination within an infected cell are not clearly understood. Also, in vitro studies on quasispecies diversity and viral fitness are needed to understand the impact of these processes in the natural host.

Pathogenesis

Literature Review

1. General Aspects

FMDV infects a wide range of animals critical for food production, including cattle, buffalo, sheep, pigs, and goats. Viral host tropism and virulence vary between strains, and the high mutation rate of FMDV facilitates the evolution of new variants with differing transmission patterns and clinical presentations. Even closely related FMDV strains can vary in pathogenicity, and the mechanisms of infection depend on the host. In cattle, FMD begins with infection of the nasopharyngeal epithelium, and subsequent spread to the lower respiratory tract facilitates viremia and generalized disease (reviewed in Kangli Li et al., 2021; Stenfeldt et al., 2015), whereas infection of pigs likely begins in the oropharyngeal tonsil epithelium before spreading to peripheral sites (reviewed in Stenfeldt et al., 2016a). FMDV infection can persist in the epithelium of cattle long after acute infection (Stenfeldt et al., 2018b), creating the controversial "carrier state" that presents an uncertain risk of transmission. A recent study in African buffalo indicated that the palatine tonsil may also be an important site of early and continuing viral replication during FMDV infection (Perez-Martin et al., 2022); persistent tonsil localization in the epithelial crypts of the palatine tonsil had also previously been reported in sheep (Stenfeldt et al., 2019), and further research will be needed to determine whether these findings are applicable to cattle as well.

Although FMDV is rarely fatal in adult animals, mortality can be high in young animals, and the impacts of FMD on animal productivity are a major drain on animal production systems in endemic areas (particularly in rural and/or remote regions in LMICs). Identifying the mechanisms and viral components responsible for various aspects of infection (tropism, replication, etc.) is critical for a deeper understanding of FMDV biology and potential routes of control, treatment, and vaccination. Accordingly, much recent research has focused on uncovering the functions of viral proteins

(especially those that could be targeted to block viral infection or replication), mapping the interactions between FMDV and its host cells, and identifying the molecular determinants of viral transmission, tropism, and persistent infection.

Recent work has elucidated many aspects of virus-host interactions; yet important gaps remain. Enduring gaps in our understanding of the molecular events of early pathogenesis still limit the design and development of completely effective countermeasures which may induce sterile immunity. It remains clear that in naïve hosts (outbreak scenarios), the rapid systemic dissemination with high titer viral replication is the most critical event for viral success at the individual host level and onward transmission. However, recent works have also suggested a potentially critical role of subclinical neoteric (early) infection in FMDV evolution and dissemination. An important overarching knowledge gap is lack of understanding of differences between endemic and epidemic scenarios regarding population-level maintenance and transmission.

2. FMDV transmission and primary infection sites

FMDV is spread primarily via direct contact between infected and naïve animals. Both farm and livestock density are primary risk factors for FMD outbreaks in many regions (Munsey et al., 2019), and the trend toward increasing concentrated commercial livestock premises in industrialized countries may facilitate larger outbreaks (Meadows et al., 2018). While less common than direct infection, airborne transmission is considered a "low probability-high consequence event" influenced by regional climate variables (Brown et al., 2022) and high-density farming systems (Björnham et al., 2020). FMDV may possibly travel up to 500 km by air under the right conditions, as in a 1974 outbreak on the island of Jersey thought to have originated in Brittany, France (Brown et al., 2022; Donaldson et al., 1982).

Understanding of primary infection processes in different species is critical to development of next generation countermeasures which may ultimately prevent infection, not just prevent clinical disease. Recent works have highlighted critical differences in anatomic localization of primary and persistent infection amongst susceptible host species. In cattle, it is well established that primary infection occurs

in specialized regions of the nasopharyngeal mucosa (Burrows et al. 1981; Brown et al. 1996; Arzt, Pacheco, and Rodriguez 2010; Stenfeldt, Eschbaumer, et al. 2015; Stenfeldt, Eschbaumer, et al. 2016; Stenfeldt et al. 2018). The first cells to become infected are cytokeratin-containing epithelial cells overlaying regions of the mucosa-associated lymphoid tissue (MALT). These cells slough, leaving areas of erosion, from which the virus moves into the underlying lymphoid tissue. It is suspected that viremia is established in this process (Arzt, Pacheco, and Rodriguez 2010). These initial experiments also proposed that viremia may be established in the lungs, especially following aerosol exposure (Arzt, Pacheco, and Rodriguez 2010). However, further experimental studies using contact exposure have suggested that infection of the lungs may not be a critical step in establishment of viremia under such conditions (Stenfeldt et al. 2018).

Primary infection is quite similar in pigs, except the critical regions of primary infection are epithelial crypts in the oropharyngeal tonsils (para-epiglotic tonsil and the tonsil of the soft palate) rather than the nasopharynx (Stenfeldt et al. 2014). Despite the distinct anatomic site, the morphologic and mechanistic features are exquisitely similar to cattle. Sheep seem to share some attributes of primary infection of both cattle and pigs (Stenfeldt, Pacheco, et al. 2015; Stenfeldt et al. 2019); however, less work has been done in small ruminants.

Recent work has suggested that the palatine tonsil may be a critical site of early and sustained viral replication during FMDV infection in the African buffalo (Syncerus caffer) (Perez-Martin et al. 2022). Overall, this improved understanding of primary sites of infection should be viewed as a potential target to exploit with novel countermeasures. Specifically, enhancement of mucosal immunity is likely to produce a substantially improved prophylactic effect.

3. Establishment of viremia

In clinically susceptible hosts, primary infection is followed by establishment of viremia, coincidently with further viral amplification at peripheral lesion (vesicle) predilection sites, thereby defining the clinical phase. By contrast, neoteric subclinical infection may occur in some hosts due to pre-existing immunity because of prior exposure or vaccination. During such neoteric subclinical infection, viral

replication may be restricted to the primary infection site with resultant viral shedding in oronasal secretions, and thus risk of viral transmission in absence of clinical disease. In ruminants, neoteric subclinical infection may progress to persistent infection. In the context of countermeasures development, it should be noted that it is critical that prophylactic products target these pre-viremic events in the upper respiratory or upper gastrointestinal tracts. Thus, enhancement of mucosal immunity has a high probability of improving protection. Additionally, incomplete understanding of virus-host interactions during early phases of infection is a substantial knowledge gap; elucidation of such events will ultimately contribute to the development of effective tools to block viral infection.

The clinical phase of disease is characterized by fever and rapid dissemination of FMDV to secondary sites of infection, most significantly in the skin and other stratified squamous epithelia, where virus is greatly amplified; the classic vesicular lesions develop only at specific and consistent sites of friction (coronary bands, oral cavity, snout, tongue, prepuce and teat skin) despite widespread virus dissemination (Alexandersen et al. 2003; Arzt et al. 2009; Burrows et al. 1981).

4. FMDV persistence

Clearance of virus from blood occurs 2 to 5 days after viremia is first detected, followed by the appearance of circulating antibodies (Stenfeldt et al. 2011; Pega et al, 2013; Eschbaumer et al. 2016). Elimination of virus at secondary sites of infection usually takes 10 to 14 days (Oliver et al. 1988). Pigs are efficient in complete clearance of infectious FMDV within 28 days after infection (Stenfeldt, Pacheco, et al. 2016). However, in domestic and wild ruminants, FMDV may persist (i.e., carrier state) with intermittent viral shedding in the oropharyngeal fluid for extended periods of time (Sutmoller and Gaggero 1965; Burrows 1966; McVicar 1969; Hedger and Condy 1985; Moonen and Schrijver 2000; Stenfeldt and Arzt 2020). Persistence may occur after symptomatic or asymptomatic infection of naïve, convalescent, or vaccinated animals. Recent evidence has confirmed that the sites of viral persistence in cattle are in the nasopharyngeal region; specifically in epithelium of the nasopharyngeal MALT, or associated lymphoid tissue (Stenfeldt, Eschbaumer, et al. 2016; Juleff et al. 2008). Studies of experimental FMDV infection in African buffalo suggest that, in contrast to cattle, sustained FMDV

replication in the palatine tonsil may be a feature of FMDV persistence in this host species (Perez-Martin et al. 2022). Interestingly, recent studies of FMDV tissue distribution in sheep have localized persistent FMDV infection to epithelial crypts of the palatine tonsil in this species too (Stenfeldt et al. 2019), further emphasizing critical host-dependent differences in FMDV pathogenesis.

Substantial effort has been invested in recent years to elucidate viral and host mechanisms of establishment and maintenance of persistence (Eschbaumer et al. 2016; Stenfeldt et al. 2016; Stenfeldt et al. 2017; Parthiban et al. 2015; Maree et al. 2016; Zhu et al. 2020). Complete elucidation remains elusive, but much has been learned.

It is particularly noteworthy that both primary and persistent FMDV infection in cattle have been associated with the same regions of epithelium of the nasopharyngeal mucosa (Arzt, Pacheco, and Rodriguez 2010; Stenfeldt, Eschbaumer, et al. 2015; Stenfeldt, Eschbaumer, et al. 2016), suggesting unique virus-host relationship at that site. Recent investigations based on transcriptomic analyses of nasopharyngeal tissues from FMDV carriers and animals that had cleared infection suggests that FMDV persistence is associated with an impaired cellular immune response, inhibition of apoptotic pathways, increased Th17 activity and potentially upregulated aryl hydrocarbon (AHR) signaling (Eschbaumer, Stenfeldt, Smoliga, et al. 2016; Stenfeldt et al. 2017; Zhu et al. 2022).

Experiments on laboratory animal models and *in vitro* studies are also contributing to revealing some of the features of the carrier state. Persistence of the FMDV in cattle and buffalo was associated to the detection of viral capsid proteins and/or genome in the light zone of germinal centers and follicular dendritic cells (FDC) in the nasopharyngeal lymphoid tissue (Juleff et al. 2008; Cortey et al, 2019). Following these results, Gordon et al. used a mouse model to investigate FMDV retention in the spleen. These authors observed a similar pattern of FMDV binding in mouse spleen, as well as the association of FMDV particles to spleen FDC. This study also indicated that this pattern, together with sustained induction of neutralizing antibodies, were dependent on viral binding to complement receptors type 2 and 1 (Gordon et al., 2022).

Li et al. investigated the mechanisms of persistent subclinical FMDV infection by establishing a persistently infected cell line based on BHK-21 cells (BHK-Op), with transcriptomic analysis revealing many differentially expressed immune-related genes and significant downregulation of ribosome- and translation-related genes in persistently vs. acutely infected cells (J. Li et al., 2020).

This group later reported that the host genes Cav1 and Ccnd1 were associated with promotion and inhibition, respectively, of persistent infection (L. Han et al., 2021), and that upregulation of the MAPK/ERK signaling pathway and its downstream Fos transcription factor may also play a role in maintaining FMDV infection (Yuan et al., 2022).

Finally, major transcriptomic alterations have been observed in host cells undergoing persistent infection; Han et al. identified a subset of persistently infected BHK-21 cells that displayed thousands of differentially expressed genes and alternative splicing events and a weaker MAPK signaling pathway compared to parental cells (Han et al., 2018).

5. In vivo recombination and within-host evolution

During the las few years, several studies have focused the attention in the within-host recombination processes as additional sources of virus variability and potential evolutionary drivers.

Palinski et al performed phylogenetic analyses using virus isolates from buffaloes co-infected with SAT1 and SAT2 viral strains. The results suggested the existence of interserotypic recombination in the non-structural protein-coding regions P2 and P3, thus indicating that recombination may represent an additional factor contributing to broad viral diversity in wildlife reservoirs (Palinski et al 2022).

The same research group, coinfected cattle with serotypes O (O1/Manisa) and A (A24/Cruzeiro), reporting different infection outcomes depending on whether the two viruses were administered simultaneously or after a 21-day gap. Importantly, dominant interserotypic recombinants (with serotype O capsid-coding and serotype A NSP-coding regions) were isolated from the upper respiratory tracts of five animals out of 12 that received staggered superinfection, indicating that superinfection during the subclinical stage does indeed promote recombination events (Arzt et al., 2021). Further characterization of these viruses found no penalties to growth rate or packaging. All recombinants were also found to incorporate capsid from the superinfecting virus (to which the host lacked neutralizing antibodies), indicating a significant impact by host immune pressure on the generation of recombinants (Fish et al., 2022).

Ferretti et al. published the first genome-wide study of within-host FMDV recombination rates, with the observed distribution of recombination events indicating that the within-host evolutionary pressures that drive recombination differ from the larger-scale pressures that shape phylogenetic-/population-scale divergence (Ferretti et al., 2018). This group later studied recombination in African buffalo experimentally infected with two SAT 1 FMDV subpopulations with different capsid sequences, finding an unexpectedly high recombination rate in VP1 during acute infection of ~0.1/base/year, comparable to the mutation/substitution rate (Ferretti et al., 2020).

A long-term study of naturally infected water buffalo found <2.5% sequence divergence at the consensus level in persistently infected animals yielding more than one virus of the same serotype, indicating an unexpectedly low level of intra-host genetic diversity in these animals (Ramirez-Carvajal et al., 2018). Cortey and Ferretti et al. reported similar results in African buffalo, where SAT 1 isolates from persistently infected animals showed limited sequence divergence and no evidence of immune escape from antibody neutralization in vivo (Cortey et al., 2019). Researchers at the University of Minnesota are conducting studies of within-host viral evolution during the carrier state, aiming to shed additional light on this poorly understood aspect of FMDV variant generation (K. VanderWaal, 2023, personal communication).

6. Chronic disease and long-term carriers

FMD is known to persist in a prolonged, subclinical state in a significant proportion of infected animals, with localized infection in the nasopharyngeal epithelium persisting for months to years after the initial disease (Bertram et al., 2020b; Stenfeldt et al., 2016b; Stenfeldt and Arzt, 2020). The reported dynamics of this "carrier state" vary among studies and host species, and establishment of the carrier state does not appear to depend on specific determinants in the viral genome (Arzt et al., 2019b). In India, a study of dairy cattle farms reported a ~13-month mean extinction rate for the carrier state that was significantly shorter in adult than in younger animals (Hayer et al., 2018).

FMDV RNA and infectious virus can be isolated from the milk and oropharyngeal fluid (OPF) of persistently infected animals (Arzt et al., 2018; Buckle et al., 2021; Nawaz et al., 2019; Ranjan et al.,

2018), including vaccinated animals that become subclinically infected (Farooq et al., 2018; Navid et al., 2018). However, as the carrier state lacks obvious signs of disease, it is difficult to accurately measure its prevalence and epidemiology under field conditions. The potential role of carrier animals in FMDV maintenance and transmission therefore remains an active and controversial field of research. Experimental intranasopharyngeal inoculation with untreated OPF from persistently infected carrier cattle has been shown to cause clinical FMD in naïve cattle, indicating the presence of infection-capable viruses in carrier animals, but natural disease transmission remains to be observed (Arzt et al., 2018; Stenfeldt and Arzt, 2020). A recent study of naïve cattle in direct contact with persistently infected cattle observed no evidence of transmission to the naïve animals and no FMDV infection or seroconversion in three calves born to carrier animals (Bertram et al., 2018b).

Given the difficulty of field studies of the carrier state, mathematical models may prove a valuable tool for filling these research gaps. A stochastic model was recently applied to determine the minimum rate of transmission from carrier animals required to maintain FMD in each region. The study authors estimated that even very rare events, if undetected, could theoretically support FMD persistence, though movement-related transmission remained a more likely hypothesis (Guyver- Fletcher et al., 2022). Similar studies applied to Africa have produced differing results, with the potential importance of carrier transmission depending on herd dynamics and regional variables (McLachlan et al., 2019; Schnell et al., 2019).

These recent studies ultimately conclude that the risk of FMDV transmission from carriers is likely to be low. Notably, however, significant antigenic variation has been observed in FMDV isolated from subclinically infected animals, indicating continuing evolution and divergence from vaccine strains (Biswal et al., 2019). The risks of undetected viral gain-of-function mutations and the difficulty of recreating and modeling low-probability transmission events mean that the epidemiology of the FMD carrier state will likely remain an open question and an active field of research in the future (Paton et al., 2018).

Despite an allegedly low risk of contagion associated with persistently infected FMDV carriers, recent studies have demonstrated a potentially critical role of these animals in FMDV ecology. Specifically, it was demonstrated that heterologous superinfection of FMDV carrier cattle with an antigenically distant strain led to rapid development of dominant inter-serotypic recombinant viruses in the upper

respiratory tract of exposed animals (Arzt et al. 2021; Fish et al. 2022). In most animals, these inter-serotypic recombinants were eventually outcompeted by non- recombinant parental viruses. However, the recombinants were dominant through the neoteric phase of infection during which virus shedding is most substantial, thus creating a potential opportunity for dissemination (Arzt et al. 2021).

The true role of FMDV carriers in the transmission of FMDV is poorly understood, although some evidence indicates that persistently infected African buffaloes (Syncerus caffer) can serve as a source of infection to cattle (Hedger and Condy 1985). Additionally, experimental studies have confirmed that intranasopharyngeal inoculation of naïve cattle with oropharyngeal fluid from persistently infected cattle leads to fulminant FMD, despite the presence of secreted antibody (Arzt et al. 2018). Despite the uncertainty surrounding the true threat posed by FMDV carriers, it is clear that the perception of threat from these animals is one of the main driving forces dictating FMD-associated trade regulation and outbreak response in free regions. Thus, one of the long-term goals of novel FMD countermeasures must be prevention or cure of the carrier state.

7. Impact of the genomic divergence in the FMDV pathogenesis

Selective pressures (e.g., from immune pressure, host adaptation, competition between viral strains, etc.) generate divergent FMDV strains with varying virulence and other phenotypic/virological properties. A study of the pathogenesis of serotype SAT 2 FMDV strains in southern Africa, for instance, found that the analyzed viruses (including ZIM/5/83, ZIM/7/83, and EGY/09/12) varied not only in virulence but also in pH stability and thermolability (Ramulongo et al., 2020). FMDV virulence also depends on the species of host animal. One of the most dramatic examples of this is the topotype O/CATHAY isolate O/HKN/1/2015 – the high morbidity and mortality of this strain in pigs has caused severe economic losses in swine production systems in Southeast Asia, while in cattle, the virus presents little risk of viral transmission or persistence (Nishi et al., 2021). Identifying the molecular-level determinants of such differences is critical for our ability to predict the properties and risks associated with emerging strains of FMDV.

Japan experienced two FMD outbreaks with vastly different severity in 2000 (O/JPN/2000) and 2010 (O/JPN/2010); the former was limited to four cattle farms, while the second spread to 292 farms and necessitated the culling of ~290,000 animals (Muroga et al., 2012). Nishi et al. generated recombinant viruses to investigate this difference, finding that replacing either the VP1 or 3Dpol gene of O/JPN/2010 with that of O/JPN/2000 reduced mortality in experimentally infected suckling mice from 100% to 0% (Nishi et al., 2019b). In contrast to the typical FMDV infection pathway, the O/JPN/2010 strain was not observed to infect basal epithelial cells in pigs, raising additional questions on the mechanisms of skin lesion development in these animals (Yamada et al., 2018).

The error-prone 3Dpol RNA-dependent RNA polymerase is a vital source of genetic diversity for FMDV – high-fidelity mutagen-resistant variants of FMDV Asia1/YS/CHA/05 were previously shown to be attenuated in vivo (Zeng et al., 2013), and recent studies from this group demonstrated similar attenuation and reduced transmissibility in high-fidelity mutants of the O/YS/CHA/05 strain (Li et al., 2018; C. Li et al., 2020). The M16, T19, and L21 residues in the N-terminal nuclear localization sequence of 3Dpol have also been shown to play important roles in mediating polymerase fidelity (de la Higuera et al., 2018; Kloc et al., 2020).

The 3Cpro protease directly degrades BP180, an anchoring protein that connects the skin's dermal and epidermal layers, leading to skin loosening and contributing to blister formation (Ekanayaka et al., 2022). Expression of the viral NSP 3A upregulated autophagy- and immune response-related genes in BHK cells (Lalzampuia et al., 2021). Partial deletion of the 3A-coding region in the FMDV genome was found to significantly attenuate the virus's virulence in cattle but did not prevent subclinical infection (Stenfeldt et al., 2018a). Finally, the viral capsid protein VP3 promoted FMD's inflammatory symptoms (e.g., fever, lesions, and myocarditis) by inhibiting Rab7b, leading to activation of the lipopolysaccharide-responsive toll-like receptor (TLR)4 (J. Zhang et al., 2021).

While FMDV is primarily an epithelial-tropic virus, its high mortality rates in neonatal animals are attributable to infection of the myocardium, causing muscle-associated lesions and myocarditis (reviewed in Z. Zhang et al., 2021). Recent studies in Eastern Africa and the Middle East identified ventricular tachycardia, polymorphic ventricular premature complexes, and atrial fibrillation events in young sheep and cattle, and serum analysis and histology revealed elevated cardiac troponin I and

Purkinje cell pathology (Chalmeh et al., 2020; Mahadappa et al., 2021; Sobhy et al., 2018). These cardiac events are also associated with increased levels of other cardiac biomarkers such as creatine kinase-MB, lactate dehydrogenase, urea, and potassium (Alsaad et al., 2020; Hashem et al., 2018; Hefnawy et al., 2018; Nikvand et al., 2018). Rhyan et al. compared FMD pathogenesis in cattle and mule deer (Odocoileus hemionus), which harbored the only known outbreak of FMD in wildlife in the USA, nearly 100 years ago. Mule deer were found to exhibit a high prevalence of myocarditis and high mortality after experimental infection with FMDV O1/Manisa, with deer-to-deer, cattle-to-deer, and deer-to-cattle transmission all found to occur (Rhyan et al., 2020).

The typical progression of FMD in ruminants and pigs (including fever, lesions on the mouth and feet, lameness, and behavior changes) is well-understood (Wolf et al., 2020), but unusual clinical signs are occasionally reported under different circumstances. In Thailand, Satsook et al. reported impaired ovarian activity in naturally infected goats (Satsook et al., 2021), and studies in infected Awassi sheep in Poland and calves in Turkey reported oxidative cell damage (Deveci et al., 2018; Özkan et al., 2018). A series of serotype O FMD outbreaks in Egypt between 2015-2018 caused neurodegeneration and subsequent dysautonomia in many buffalo calves, and postmortem examinations have detected FMDV antigens in brain tissue samples of deceased FMD-infected calves (Bayoumi et al., 2021; Sahoo et al., 2022).

The pseudoknot region in FMDV's 5' UTR has been implicated in viral tropism and virulence – an O/ME- SA/PanAsia strain (O/GD/CHA/2015) was found to contain an 86-nt deletion in this region that significantly attenuated its tropism for bovine cells and cattle without affecting swine tropism, while a 43-nt deletion observed in the O/CATHAY topotype decreased viral pathogenicity in cattle (Zhu et al., 2019). The small fragment (S fragment) region of the 5' UTR has also been linked to virulence in serotype O virus – a 70-nt deletion in this region, observed in several naturally occurring Chinese isolates, reduced viral pathogenicity in cattle and pigs, and a coinciding amino acid insertion to the viral leader protein (Lpro) restricted tropism to pigs (F. Yang et al., 2020).

Recommendations

The GFRA Gap Analysis Working Group recommends the implementation of the following research, education, and extension objectives to advance our ability to rapidly detect, control and respond to an FMD outbreak.

- ✓ Continued investigation of virus-host interactions at the primary sites of infection in ruminants and pigs with focus on factors defining tropism, generalization, and early host responses.
- ✓ Continued investigation of determinants of virulence for different serotypes and strains of FMDV in cattle, sheep, pigs, Asian buffalo, and African buffalo.
- ✓ Identifying mechanisms which may be subverted through vaccines, countermeasures, or post-exposure therapy.
- ✓ Investigate innate immune pathways (including trained immunity) that may influence establishment of persistent FMDV infection.
- ✓ Elucidate viral and host mechanisms of FMDV persistence in ruminants with goal of
- ✓ Determine characteristics and mechanisms of FMDV within-host evolution over distinct phases of infection.
- ✓ Determine the critical differences in FMDV infection in pigs as compared to ruminants that enable complete clearance of infection (i.e., no viral persistence).
- ✓ Investigate host genomics to gain understanding of species-specific and breed-specific continuum of permissiveness/tolerance/resistance to clinical and sub-clinical infection.
- ✓ Improved understanding of onset and duration of infectiousness from clinically and sub-clinically infected animals.
- ✓ Elucidate viral and/or host mechanistic determinants of highly successful emergent lineages (PanAsia, Ind2001a-e).

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