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Fighting Foot-and-Mouth Disease together

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Photo courtesy of M.Atkinson

A Consortium of Anses (France) and Sciensano (Belgium) will become the next European Union Reference Laboratory for foot-and-mouth disease (EU RL FMD)

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After the "Brexit" vote in 2016, the European Commission (EC) has published a tender to appoint a new mandate for the European Union Reference Laboratory (EU RL) for foot-and-mouth disease (FMD), which until December 31st 2018 is held by the Pirbright Institute in the UK. A joint candidacy of Anses (France) and Sciensano (Belgium) has been selected by the EC and this consortium will become the EU RL for FMD from January 1st 2019 onwards.

In this consortium, Anses takes the lead and Dr Labib Bakkali-Kassimi from Anses is the Director, with two Deputy Directors, Dr Kris De Clercq from Sciensano and Dr Stéphan Zientara from Anses. Anses and Sciensano have a long history of collaboration on viral diseases in animals such as FMD, Bluetongue disease, West Nile virus disease etc.

Anses is a public administrative organisation accountable to the French Ministries of Health, Agriculture, Environment, Labour and Consumer Affairs. Sciensano is a Federal scientific research establishment under the wardship of the Minister for Small and Medium-sized Enterprises, the Self-Employed, Agriculture and Social Integration and it is administratively connected to the Federal Public Service for Public Health, Food Chain Safety and Environment. Both organisations are designed by their respective competent authority as National Reference Laboratory (NRL) for several infectious animal diseases including FMD and other vesicular diseases.

The Anses Laboratory for Animal Health is located in Maisons-Alfort on the campus of the National Veterinary School of Alfort (ENVA). Founded in 1901, it was the first laboratory created in the world to fight against infectious animal diseases, with a focus on FMD. It has approximately 150 staff members spread across four main units covering all aspects of animal health and infectiology (Joint Research Unit for Virology (JRU), JRU for Parasitic and Fungal Molecular Biology and Immunology, Bacterial Zoonoses Unit, Epidemiology Unit).

The Maisons-Alfort Laboratory for Animal Health (Director: Dr. Pascal Boireau, Deputy Director: Dr Stéphan Zientara) is characterised by extensive reference laboratory activities at the national, European and international levels (NRL, NRC, EU RL, OIE, FAO, etc.) and sustain research activities in partnership with other organisations in France and abroad (INRA, CIRAD, ENVA, Pasteur Institute, universities, the Pirbright Institute, Sciensano, FLI, IZSLER, etc.), and has been accredited by the French Ministry of Research for its Joint Research Units and Contracted Units.

The laboratory's work focuses on controlling (i) major animal epidemics (FMD, bluetongue disease, etc.), (ii) bacterial, viral and parasitic zoonoses, and (iii) emerging multi-species infectious animal diseases namely vector -borne diseases and opportunistic mycoses.

The laboratory's joint research virology unit 1161 (UMR1161), headed by Dr. Stéphan Zientara, has been in charge for decades of the NRL mandate for FMD and related vesicular diseases (swine vesicular disease, vesicular stomatitis) and since 2015, he also heads the OIE Reference Laboratory for FMD. It has been nominated as a FAO Reference Centre for FMD and other vesicular diseases. The unit has also been holding the mandate of EU RL for equine diseases including vesicular stomatitis since 2008 [Commission Regulation (EU) No 208/2011] which plays a part in the differential diagnosis of FMD. This mandate was renewed in May 2017 [Commission implementing Regulation (EU) 2017/793]. The JRU for Virology is composed of five teams dealing with orbiviruses (BIOR team), hepatitis E and coronaviruses (VEBE team), flaviviruses (ZEN team), adenoviruses (THAI team) and FMD (Biopic team).

The BioPic team is headed by Dr. Labib Bakkali-Kassimi. Its activities include the diagnosis of FMD, particularly emergency diagnosis in case of suspected infection, in addition to expertise and scientific and epidemiological monitoring. It provides scientific and technical support for the control of FMD and carries out research to improve tools for detecting and characterising the virus, and to study the mechanisms of viral persistence. It coordinates a network of four departmental laboratories in France, all accredited for the FMD serological diagnosis and for which it organises annual inter-laboratory proficiency tests. Lastly, it participates in the annual simulation exercises organised in France.

The Virology Unit of ANSES Maisons-Alfort Animal Health Laboratory has all necessary scientific infrastructures and equipment that enable it to perform its missions. The Virology Unit operates in a highly controlled biosafety level 3 facility that meets the minimum standards for laboratories working with live FMD virus (Council Directive 2003/85/EC, Art. 65, Annex XII). The Virology Unit has a 200 m2 containment facility dedicated to handling FMD virus and complies with the OIE and EuFMD biosafety standards in force. The laboratory inaugurated in October 2016, a new level-3 infectiology platform of ca. 600 m2 (iCube), is made up of one containment facility for handling FMD virus and a second one for handling zoonotic pathogens.

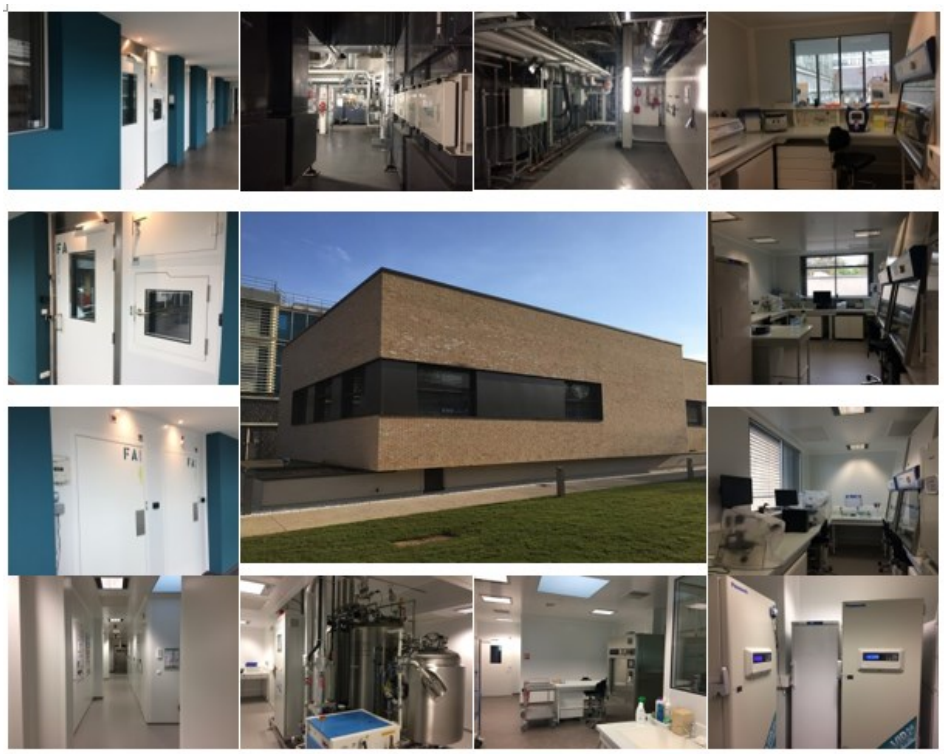

Figure 1: iCube BSL-3 infectiology platform at Anses.

Sciensano is the result of the merger of two sister institutions, the ISP (Scientific Institute of Public Health) and the CODA-CERVA (Veterinary and Agrochemical Research Centre). Founded in 1904, the ISP brought together at the time the Pasteur Institute of Brabant and the Institute of Hygiene and Epidemiology. For over a century it has served as a reference in the field of public health. The Belgian Veterinary Laboratory was founded in 1924 as predecessor of CODA-CERVA that focused on the safety of food production, veterinary health and public health. Sciensano is based on the 'One Health' concept whereby human health, animal health and environmental management are intrinsically linked. Sciensano seeks to decipher the mechanisms governing interactions between humans, animals and the environment to prevent, assess and minimise threats to public health. The Directorate of Infectious Diseases in Animals is located in Uccle (Brussels) while the experimental animal facilities are located in Machelen, near Brussels.

Sciensano has 700 staff members and its organisation consists of 5 directorates overseeing Sciensano's core functions and 2 supportive offices. The activities of Sciensano that include infectious diseases in animals rely on more than 200 scientists, technicians and administrative personnel, spread over six scientific Services and the experimental animal facilities in Machelen. These scientific Services are 1) Veterinary bacteriology, 2) Enzootic, vector-borne and bee diseases, 3) Exotic viruses and particular diseases, 4) Avian virology and immunology, 5) Veterinary epidemiology and 6/ Coordination of veterinary activities.

Sciensano's activities are accredited according to the European and International ISO 17025, ISO 17043, ISO 15189, ISO 14001 and ISO 9001 quality standards. Sciensano hosts more than 80 NRLs recognised by the Belgian federal government and the European Union. These include NRLs for the identification of the epizootic and enzootic pathogens listed by the World Organisation for Animal Health (OIE) (FMD, African and classical swine fever, Avian Influenza, Newcastle disease, etc.) and for zoonotic organisms that are a danger to humans (Salmonella, anthrax, tularaemia, brucellosis, tuberculosis, EHEC, MRSA, etc.).

The Directorate of infectious diseases in animals (Director: Dr. Thierry van den Berg) ensures quick identification and characterisation of infectious agents, including next-generation sequencing supported by bioinformatics, provides expert advice as part of the control policy, performs veterinary vaccine control and develops and validates the tools required to put control strategies in place for the main known and newly-emerging pathogenic animal viruses and pathogenic zoonotic viruses, as a privileged federal partner and a major international interlocutor.

The Service for Exotic viruses and particular diseases, i.e. the consortium partner of the BioPic team of ANSES in the EU RL for FMD, is headed by Dr. Kris De Clercq. It serves as an NRL for FMD, swine vesicular disease, vesicular stomatitis, bluetongue, sheep and goat pox, lumpy skin disease and Rift Valley fever. The Service is recognised as a OIE Collaborating Centre for validation, quality assessment and quality control of diagnostic assays and vaccine testing for vesicular diseases in Europe, and as a FAO Reference Centre for vesicular diseases. Since January 1st 2017, the Service is the EU RL for diseases caused by capripox viruses (lumpy skin disease, sheep pox and goat pox viruses). The Service has over 20 years of expertise in international standardisation, techniques and practices in the field of vesicular and exotic animal diseases, striving for the harmonisation of international surveillance and control of animal diseases.

To perform its tasks, the Directorate of infectious diseases in animals in Uccle has a surface of 10.200 m² including BSL-1, BSL-2 and BSL-3 laboratories and BSL-2 and BSL-3 facilities for rodents and poultry. The experimental animal facilities in Machelen have 8.000 m² of ABSL-1, -2 and -3 facilities for large animals, suited for vaccination and/or infection experiments with relevant vesicular or exotic viruses. The experimental Centre works following the Good Clinical Practice (GCP) guidelines.

Figure 2: The Sciensano facilities in Uccle.

Figure 3: The experimental animal facilities of Sciensano in Machelen.

Conclusion:

This new mandate for an EU RL for FMD will complement the current mandates of Anses and Sciensano as NRLs and OIE and FAO reference centres for FMD. The collaborations that our laboratories have initiated for many years with many partners in Europe (not at least the World Reference Laboratory at the Pirbright Institute in the UK) and worldwide will be reinforced. This new responsibility is an exciting challenge that we will meet as an actor for the control of FMD in Europe and elsewhere.

Overview: Research and Development of Countermeasures to Support the Control of Foot and Mouth Disease in Uganda (2014-2018)

Lauro Velazquez-Salinas [1,6], Frank Norbert Mwiine[2], Zaheer Ahmed[6], Sylvester Ochwo[2], Anna Munsey[1], Mary Kenney[6], Julius J. Lutwama[3], Francois F. Maree[4], Katherine Scott[4], Leslie Lobel[5], Ariel Sobarzo[5], Andres M. Perez[1], Luis L. Rodriguez[6], Kimberly Van der Waal[1], and Elizabeth Rieder[6*]

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Introduction

Since foot and mouth disease (FMD) was first recorded in Uganda back in 1953 (Ayebazibwe et al., 2010), all serotypes with exception of Asia 1 and C have caused outbreaks on a regular basis (Thomson et al., 2003; Tekleghiorghis et al., 2016). According to the Food and Agricultural Organization (FAO), Uganda is in stage one of the FMD progressive control pathway (Namatovu et al., 2013). The main goal at this stage, is to gain a better understanding about the epidemiological status of FMD in Uganda, and develop a risk-based approach to reduce the impact of FMD in this country.

In this report, we present a summary of the results from an international collaborative foot and mouth disease research project funded by the Cooperative Biological Engagement Program of the U.S. Department of Defense Threat Reduction Agency, and conducted in Uganda between 2014-2018. This research project included scientists from the United States Department of Agriculture (USDA), the University of Minnesota, the Agricultural Research Council (ARC) of South Africa, Makerere University and the Uganda Virus Research Institute (UVRI) in Uganda, Ben Gurion University in Israel and the Uganda Ministry of Agriculture. The main goal of this research was to characterize the distribution of foot and mouth disease virus (FMDV) strains in various regions of Uganda by analyzing samples collected from livestock with and without clinical signs, history of FMD or vaccination status. Surveillance of FMDV in Uganda was evaluated by a cross sectional study regardless of outbreak occurrence (project I), and by a longitudinal study collecting samples from a subset of cattle-herds over time (project II). Additional objectives to project II included: the development of new and inexpensive tools for the diagnosis of FMDV in Uganda, increasing training of diagnostic technical personnel, and increasing diagnostic capacities for FMD in Uganda.

The analysis of a large number of serum (> 13,000) and oropharyngeal fluid (>2,000) samples collected from more than 200 cattle herds located in 40 districts representing different geographical regions, showed the active circulation of FMDV. Our results indicated a high sero-prevalence of antibodies to non-structural proteins (NSPs) of FMDV, which correlated with the circulation of multiple serotypes (O, A, SAT 1 and SAT 2) and multiple topotypes of FMDV in Uganda between 2014 and 2018 (Mwiine et al, manuscript submitted). Collectively, the results of this project demonstrate the complexity of controlling and eradicating FMDV in Uganda for the short term. Our results highlight the importance of

conducting further research to understand the role of wildlife in the maintenance of FMDV in Uganda, and to improve selection of vaccines to increase coverage in this country. Additionally, this project resulted in more than 300 novel viral sequences that has been deposited in the GenBank database. These sequences will support future genomic analyses to understand the phylodynamics of FMDV in Uganda.

Project II: Longitudinal study in Uganda (2014-2017).

For this project, four districts with different ecological; management systems and incidence rates were chosen and assessed by the UVRI team led by Dr. Julius J. Lutwama. This included the Nakaseke and Gomba (central Uganda), and Isingiro and Mbale districts (western and eastern Uganda,). A total of 100 samples per district including sera and oropharyngeal fluids collected from specific animals (cattle) four times a year. Serum samples were tested for the presence of antibodies to NSPs, while oropharyngeal fluids samples were tested by real time PCR, viral isolation and sequencing analysis. Preliminary results indicate a high sequence identity between some viral isolates recovered from this study and a specific viral lineage of the FMDV O serotype identified during the project I cross-sectional study. Currently, additional analyses are ongoing to elucidate the transmission dynamics of this lineage in specific herds.

Development of new diagnostic tools for FMDV in Uganda.

During this project, the research team from Ben Gurion University in Israel, led by Dr. Leslie Lobel, developed a novel Nanobody-based FMD 3ABC competitive ELISA for the detection of FMD NSP antibodies in sera of cattle herds in Uganda. This novel technology includes camelid-derived single-domain nanobody fragments with great efficacy for serological diagnostics development. Results from assay validation, demonstrated that this novel NSP ELISA is in high concordance when compared with the commercial prioCHECK FMDV NSP-FMD test (Gelkop et al 2018). This design represents a low -cost and effective alternative detection method for FMD NSP antibodies in cattle in Uganda. An extensive validation will be conducted to implement this novel technology routinely for the FMDV diagnosis in Uganda.

Unfortunately, Dr. Leslie Lobel, an important member of this project, passed away on May 01, 2018.

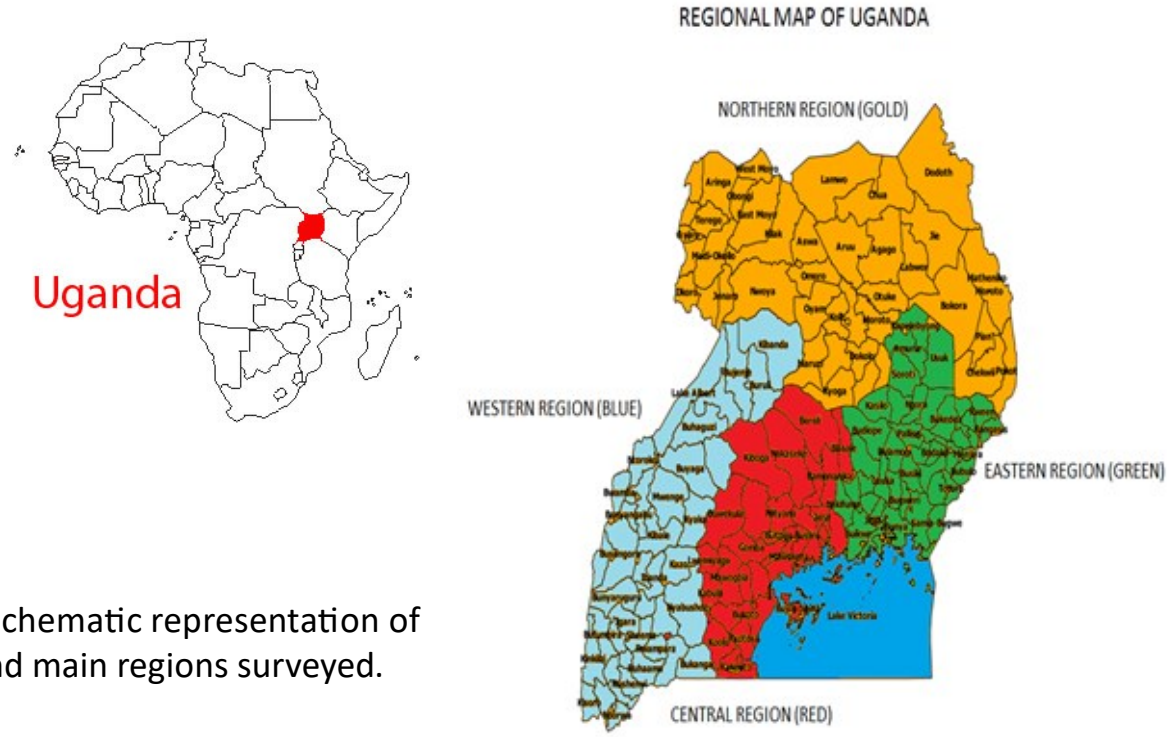

Figure 1: Schematic representation of Uganda and main regions surveyed.

Improving training and building FMDV diagnostic capacities in Uganda.

Diagnosis is an essential component in a control and eradication plan for FMDV. To improve diagnostic capabilities in Uganda, diagnostic technical personnel were trained in the following:

A. Field sample collection and laboratory diagnostic procedures including real-time PCR and ELISA (July, 2014).
B. Training on new technologies: Recombinant protein expression purification and analysis (May, 2015).
C. Competitive ELISA development and evaluation for FMDV field diagnostics in Uganda (2015, 2016).
D. Molecular diagnostic tools for FMDV (PCR and sequencing) (June, 2015, June 2017).
E. Foot-and-mouth disease virus (FMDV) serotyping serology (Dec 2017).

Finally, during this project the UVRI laboratory was refurbished and upgraded by providing Biosafety cabinet, PCR machines, an ELISA reader and washer, a deep freezer and a refrigerator. Several staff for laboratory and field workers were hired and trained for the diagnosis of FMDV.

In conclusion, the results of this project are valuable to improve vaccine-mediated FMD control programs in Uganda, provides new assays for the detection of FMDV and contribute to gradually increase the progressive control pathway for FMD status in the region.

Figure 2: Field sample collection in Uganda in 2014.

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Figure 3: Project participants on the first meeting in Uganda in 2014.

Research Funded by:

DEFENSE THREAT REDUCTION AGENCY

"Development and application of a European foot-and-mouth disease spread model" – EuFMDiS

Maria DelaPuente, Koen Mintiens, Sally Gaynor, Keith Sumption

Emergency preparedness for foot-and-mouth disease (FMD) remains a core issue for European veterinary services, as entry of FMD continues to be a risk for the region, and the consequences would be devastating.

The majority of European countries have not faced an FMD incursion, for many decades, and therefore lack direct experience in dealing with such a situation. As cattle, small ruminants, pigs and even wildlife may be involved in an epidemic, there are no direct comparator diseases and therefore we need to be able to simulate what may happen in an epidemic to improve understanding of the consequences as well as for improved plans and appropriate training, equipping and exercising.

Decision support tools, such as disease models can help us to do a better job in preparing for FMD, as we can simulate the spread of the disease, select various control measures, allocate resources for control, test decisions we would make, and explore the range of likely consequences.

In this sense, the European Commission for the Control of Foot-and-Mouth Disease (EuFMD) has managed the EuFMD-iS project with the objective to provide a robust, flexible training and decision support tool to support FMD planning, training and exercises in European countries.

Seven countries have been involved in the pilot phase of the project: Italy, Austria, Croatia, Hungary, Romania, Bulgaria and Slovenia; and it is foreseen that at least two more EU countries will join EuFMD-iS in the following months.

EuFMD-iS overview

EuFMD-iS is based on the Australian FMD model (AADIS), which is a hybrid model created by R. Bradhurst and G. Garner. The European model hybrid structure combines:

- Equation-based modelling to simulate within -herd spread.
- Agent-based modelling to simulate between -herd spread.
- Animal movement networks (between regions and countries) based on data from The European Trade Control and Expert System (TRACES) .

EuFMD-iS allows simulating different FMD spread pathways:

1. Local spread, covering the short-range transmission of disease from an infected herd to neighbouring susceptible herds (Sanson, 1994).
2. Direct spread, when a susceptible animal comes into direct contact with an infectious animal.
3. Indirect spread, related to the movement between herds of contaminated animal products, by-products, and fomites such as equipment, people and vehicles.
4. Airborne spread, which is the infection of susceptible animals by virus conveyed on the wind.
5. Spread via Assembly Centres. Assembly centres are places where consignments of animals are prepared to be moved to other locations (predominantly to other countries).

Making EuFMD-iS possible

During a first workshop held in Vienna, Austria, in December 2017, the seven involved countries defined a common herd classification (9 herd types that would fit all the countries) and 25 livestock production regions that represent different livestock production characteristics and disease risk.

In order to adapt the Australian model to the European context, each country collected and provided the required data in order to:

* Set up the livestock populations
* Represent FMD spread
* Model disease control

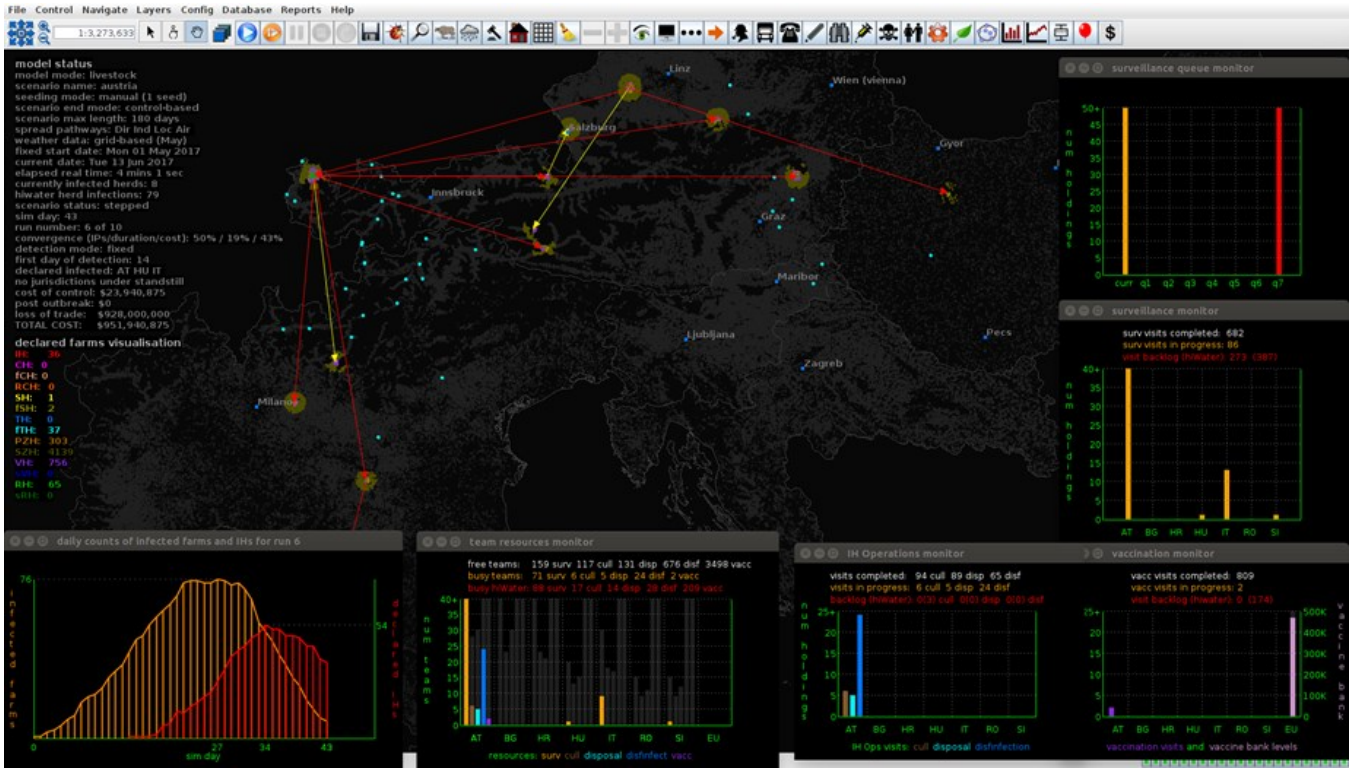

Figure 1: Screen capture of EuFMD-iS running .

Modifications to the software and incorporation of European farm population and each country data to parameterize FMD transmission and control were made in order to make create EuFMD-iS.

Once the first version of the model was ready, a second workshop was held in Budapest, Hungary, in July 2018. The aim of this workshop was to install the EUFMD-iS software and train experts from the seven countries on the use and application of the model.

Using EuFMD-iS

During the EuFMD Open Session, held in Puglia, Italy, in October 2018, a case study using EuFMD-iS was presented, in order to:

1. Demonstrate how the model can assist planning and disease preparedness.
2. Compare response strategies involving various approaches using vaccination.
3. Assess potential vaccine requirements in plausible multi-country FMD outbreak in central Europe.

Setting up a hypothetical outbreak scenario, stamping out only strategy was compared with four other scenarios where in addition to stamping out, vaccination was applied: two stamping out plus suppressive ring vaccination strategies (vaccinating only cattle; vaccinating all susceptible species) and two stamping out plus protective ring vaccination strategies (vaccinating only cattle; vaccinating all susceptible species).

Suppressive ring vaccination was set in the model as vaccination applied around each infected holding in a 3 km radius; Protective ring vaccination was set in the model as an annulus around each infected holding whose inner radius was 3 km and outer radius 8 km.

Although the model was still a prototype at the time of the conference, interesting results were presented, showing how new generation tools, such as EuFMD-iS can be used by epidemiologists and disease managers to explore different outbreak scenarios and test alternate approaches to control.

Links: Video https://youtu.be/PeTTs2lOPk4
website: http://www.fao.org/ag/againfo/commissions/eufmd/commissions/eufmd-home/en/

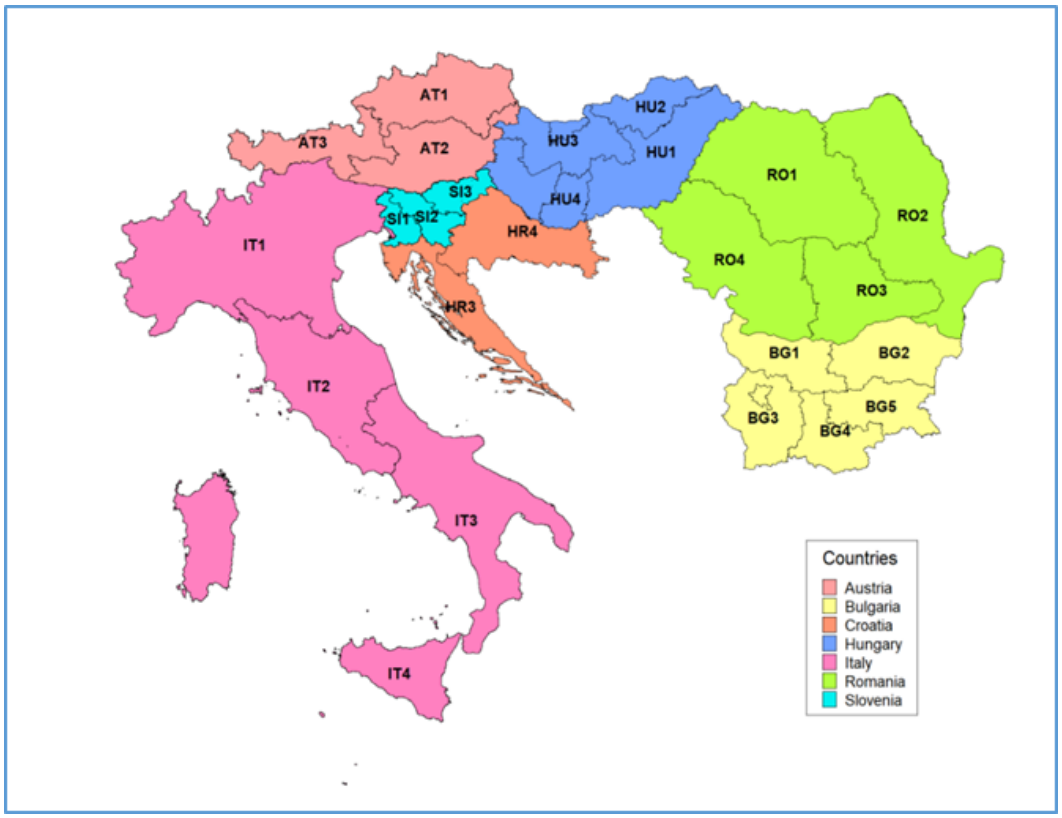

Figure 2: Regions defined in EuFMD-iS by the participating countries.

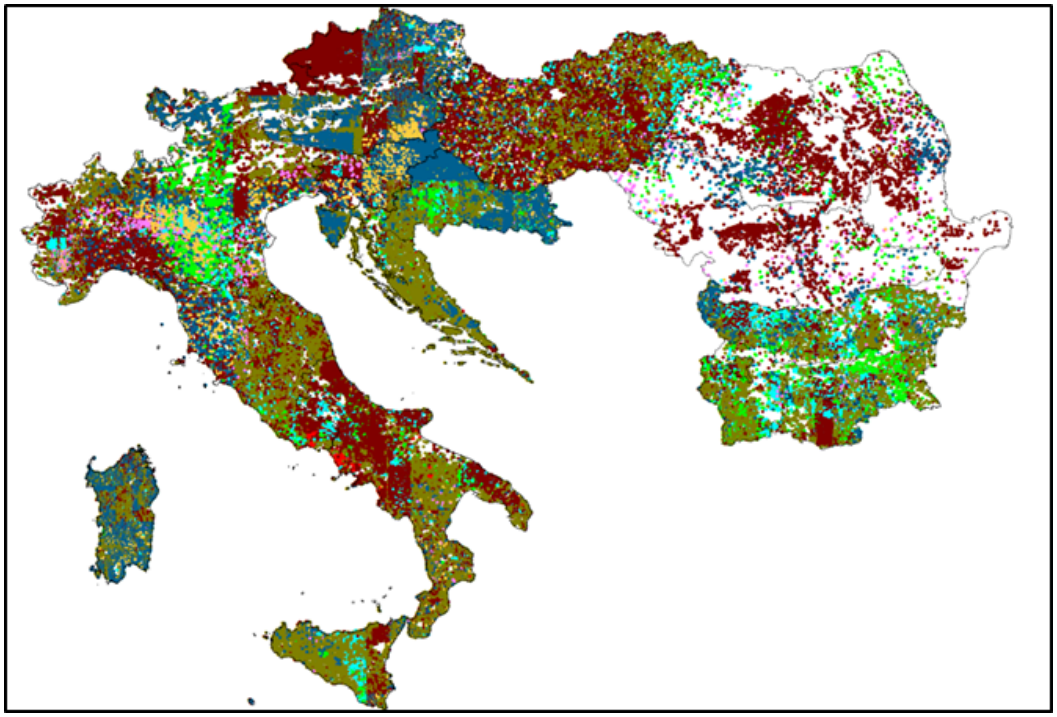

Figure 3: Distribution of the defined herd types in the different participating countries .

The complexities of subclinical foot-and-mouth disease

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Introduction

Long-term, post-acute, subclinical FMDV infection has been recognized for over 50 years and is referred to as virus persistence or "the carrier state". However a more insidious and substantial problem for FMD control may exist in the form of early (neoteric) subclinical infection. This less recognized form of infection occurs when animals become newly infected, never manifest signs of disease, yet shed substantially greater quantities of infectious virus than carriers.

The carrier state remains a political and regulatory impediment despite multiple demonstrations that carrier cattle are unlikely to transmit infection under most circumstances. By contrast, neoteric subclinical infection is poorly understood and minimally investigated. In the field, the situation is further complicated by the fact that neoteric and persistent subclinical infections may be occurring in the same herds at the same time, particularly in hyper-endemic settings. Furthermore, neoteric superinfection of carrier animals may lead to recombination across viral serotypes and strains leading to emergence of new strains. Thus, in many ways, the tools and approach to investigation of neoteric and persistent infection are intertwined.

The aim of this short review is to clarify distinct definitions of subclinical FMDV infection and to summarize current knowledge and future directions for research within this area.

Subclinical FMDV infection under experimental versus field conditions

Experimental studies investigating FMDV pathogenesis in naïve cattle have provided distinct definitions of successive phases of infection (Figure 1). Specifically, an animal becomes sub-clinically (pre-clinically) infected, followed by systemic dissemination of virus, which is accompanied by clinical signs of disease thereby defining the end of the incubation phase (5). After resolution of the clinical, or acute phase of disease, cattle will either completely clear infection or progress into the carrier state (3), which has historically been defined in relation to an arbitrary threshold of 28 days post infection (1). However, these distinct phases are less apparent in vaccinated cattle, which generally become sub-clinically infected following virus exposure. In these vaccinated animals the new subclinical infection may be referred to as "neoteric subclinical infection" to distinguish it from the carrier state. Recent experimental studies have confirmed earlier findings that moderate levels of FMDV shedding in oral and nasal fluids can be detected in standard swab samples during the early stages of subclinical infection of vaccinated cattle (2,3). By contrast, during persistent infection, infectious virus can only be recovered from oropharyngeal fluid sampled using a probang cup (3,4). With regards to the localization of FMDV in bovine tissues, the restriction of infection to the nasopharynx during primary (pre-clinical/pre-viremic), and persistent phases of infection is similar in vaccinated and naïve cattle (3,5). The striking difference between these cohorts being that while the non-vaccinated animals traverse a phase of systemic generalization and clinical disease, vaccinated animals that fail to clear infection progress into the persistent phase without any apparent signs of disease.

Similarly, bovids with natural or adaptation-based resistance to clinical FMD may progress through the neoteric and persistent phases of subclinical infection following virus exposure. The most commonly cited example of naturally occurring neoteric subclinical FMDV infection pertains to African buffalo (*Syncerus caffer*), in which clinical signs of FMD are rarely observed despite widespread infection.

This is typically attributed to the co-adaptation of specific strains of virus and this host species over the course of considerable quantities of time. Similar reports exist of subclinical circulation of FMDV in domestic herds of Asian buffalo (Bubalus bubalis) in the presence or absence of vaccination (6-8). Less well-documented examples of this same phenomenon have been described in Asia and Africa when FMDV outbreaks occur in European breeds of cattle, but seemingly spare the sympatric domestic breeds.

Evidence from field and laboratory studies indicate that a large proportion of ruminants maintain persistent infection after resolution of FMD outbreaks, including both clinically affected and asymptomatic animals. Many carrier animals clear the infection over time, and the rate of decrease in the proportion of persistently infected cattle has been estimated at 0.03 – 0.11 per month (9-11). However, under natural conditions, a substantial proportion of cattle maintain persistent infection for at least 12 months, and a small proportion of animals maintain persistent infection for more than 24 months (9,10,12). Under hyperendemic FMD conditions, these carriers are susceptible to superinfection with distinct strains while they are persistently infected with an earlier circulating virus (Figure 2) (6,13).

Subclinical persistent infection is a concern primarily because of the perceived potential for these animals to transmit FMDV to naïve animals. However, transmission has only been demonstrated from persistently infected African buffalo (11), while persistently infected cattle failed to transmit the virus when housed with naïve cattle for up to 6 months under experimental and natural conditions (2,9). In contrast, subclinical neoteric infection may be a greater risk for transmission, and simultaneous circulation of multiple FMD viruses has been demonstrated within herds of vaccinated Asian buffalo in the absence of any signs of clinical FMD (6,7).

Implications of subclinical FMDV infection in relation to disease control

Subclinical infection with multiple FMDV serotypes or strains has been demonstrated in African and Asian buffalo, either sequentially or simultaneously. Simultaneous infection may lead to emergence of new strains as a result of viral recombination, potentially leading to increased virulence and outbreaks of clinical disease (14). Distinct lineages of FMDV are known to recombine in the field although the conditions

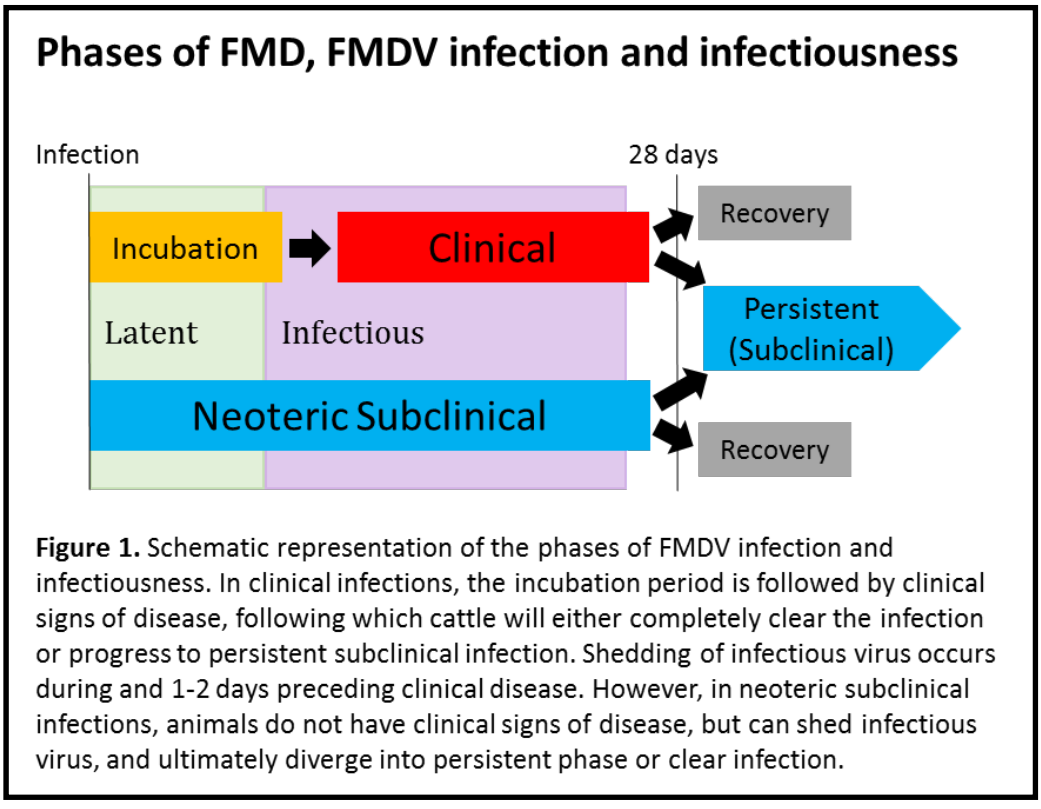

Figure 1. Schematic representation of the phases of FMDV infection and infectiousness. In clinical infections, the incubation period is followed by clinical signs of disease, following which cattle will either completely clear the infection or progress to persistent subclinical infection. Shedding of infectious virus occurs during and 1-2 days preceding clinical disease. However, in neoteric subclinical infections, animals do not have clinical signs of disease, but can shed infectious virus, and ultimately diverge into persistent phase or clear infection.

under which this recombination occurs are not well understood. Most importantly, all stages of subclinical FMDV infection include the presence of infectious virus in the absence of clinical disease, which increases the risk of dissemination through animal movements. Even though the contagiousness and thereby the risk of onward transmission likely varies between neoteric and persistent phases of infection, it is not practically feasible to clearly differentiate between these two concepts in endemic settings. Therefore, it is critical to monitor FMDV infection in clinically healthy animals in endemic regions to gain information on currently circulating virus strains and inform FMD control efforts. Over time this information will complement knowledge gained from passive surveillance of outbreak strains to generate more comprehensive understanding of regional FMDV circulation.

Current vaccines are effective in preventing clinical FMD when appropriately applied. However, vaccination does not prevent widespread subclinical neoteric infection; monitoring of subclinical infection will become increasingly important as more countries implement vaccination as part of their FMD control and eradication programs.

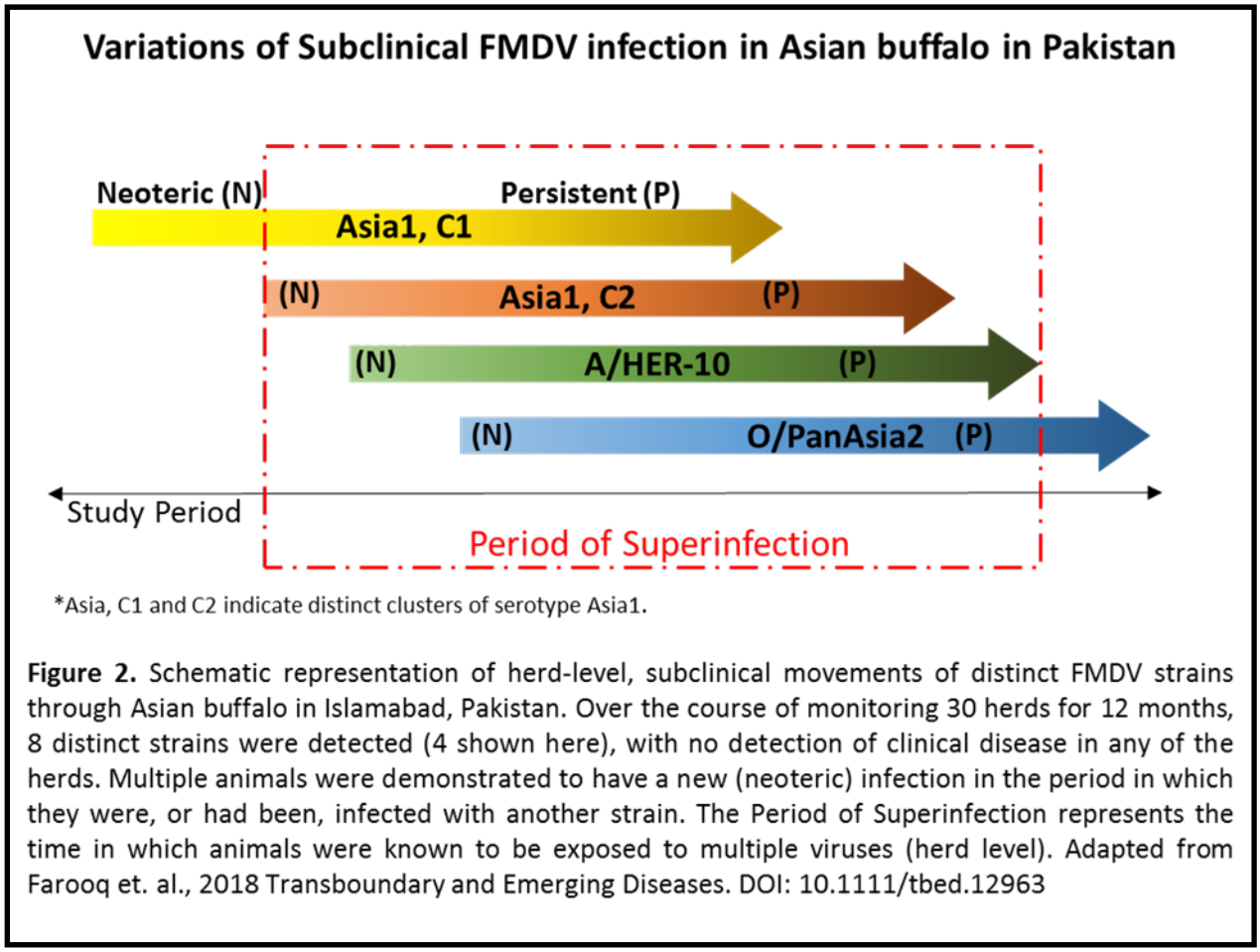

Figure 2. Schematic representation of herd-level, subclinical movements of distinct FMDV strains through Asian buffalo in Islamabad, Pakistan. Over the course of monitoring 30 herds for 12 months, 8 distinct strains were detected (4 shown here), with no detection of clinical disease in any of the herds. Multiple animals were demonstrated to have a new (neoteric) infection in the period in which they were, or had been, infected with another strain. The Period of Superinfection represents the time in which animals were known to be exposed to multiple viruses (herd level). Adapted from Farooq et. al., 2018 Transboundary and Emerging Diseases. DOI: 10.1111/tbed.12963

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FMD Research Gap Analysis Workshop 2018 – INTA, Buenos Aires, Argentina

Consuelo Carrillo, Wilna Vosloo, Mariano Perez-Filgueira

BACKGROUND

The third USDA-GFRA gap analysis workshop was held 12–14 June 2018 with the purpose of bringing together more than 30 international FMD experts from various countries, regulatory and government officials and vaccine manufacturers to assess gaps in the scientific information and veterinary medical countermeasures needed to control FMD on a global scale. The goal was to update the previous gap analysis that was published in 2010. The new gap analysis will be available by the end of the year on the GFRA website (https://www.ars.usda.gov/GFRA) and will be for public access to:

1) serve as a comprehensive source of scientific information;
2) identify gaps and research priorities; and
3) inform researchers, funders, regulatory authorities, and the private sector.

The workshop was organized into themes related to vaccines, immunity, diagnostics, epidemiology, virology and pathogenicity. Each session was introduced with a summary of what is new in the thematic area and possible impact on the 2010 gaps, whilst existing or newly identified gaps were highlighted.

A. VIROLOGY

1. VIRAL EVOLUTION and DISCOVERY OF DETERMINANTS OF VIRULENCE

(Elizabeth Rieder / Teresa De Los Santos)

New molecules found to be involved in the FMDV life cycle have been published, of which some have a role in virulence. However, it is still not clear which of these host factors are critical for virulence, an important issue to help in controlling the disease. Virulence determinants that play a role in the field are also important to study. There is a need to understand persistent infection and carriers, and its role in transmission as well as the correlation between the cell cultures and animal models.

2. HOST RANGE and ADAPTATION

The factors that played a role in the possible global eradication of C serotype, the localization of Asia 1 serotype to certain geographical areas or the explosive spread of certain lineages of serotypes A and O need to be further studied.

B. HOST-PATHOGEN INTERACTIONS: PATHOGENESIS

(Jonathan Arzt / Francois Maree)

Newly published work determined early pathogenic events in cattle, swine and small ruminants as well as describing a reproducible challenge method in sheep and swine using intra nasopharyngeal inoculation. However, the results are descriptive and do not add to the previously identified gaps in knowledge of FMD pathology and transmission. Knowing if the carrier status is significant in transmission and eradication is critical to define policies such as “vaccination to live” and trade agreements. We need to better understand the bases for viral processes, functional genomics, and predictive genomics, define tropism, analyze multiple infections in wild species and persistence, demonstrate if persistence is a dead-end infection or find definitive evidence of the role of persistent infection and carriers in FMD perpetuation in natural environments, explain the mechanisms that govern permissiveness to infection of distinct species/breeds), and how these factors apply to variability of virulence across cattle breeds.

C. IMMUNITY

(Alejandra Capozzo / Mariano Perez-Filgueira)

Important advances have been made in understanding adaptive immune responses against infection and vaccination, such as:

- Immune response against FMDV is T-independent after infection (B-cell response).
- FMDV infection does not compromise immune competence in cattle.
- Aerogenous infection promotes genuine local responses.
- IFN gamma and CD4-T cell responses in vaccinated cattle are cross-reactive and depend on the whole-capsid integrity.
- Parental vaccination induces mucosal adaptive responses as well as secondary responses upon aerosol infection.
- CD4-T cell responses are required for inducing protection after vaccination.
- IgM drives the clearance of viremia.
- Protection can be achieved with low Ab titers (memory cells), is the quality of the antibodies what determine cross-reactive responses (avidity), and other cytokines (IFN, IL-12, IL-15).
- Polyvalent vaccines are more effective than high load monovalent vaccines.
- The quality of antibodies is important for cross-reactive responses.
- In buffalo the kinetic of neutralizing antibodies is similar to the kinetic in cattle, but the T-cell response is lower.
- High payload vaccines have not coverage for new viral variants, while multivalent vaccines and multiple vaccination programs are more efficient protecting against the wide spectrum of variants during the outbreaks.

The remaining gaps are understanding the longevity of immune responses after infection vs. vaccination, the immunity during carrier and persistent infection, and most importantly, consistent ways to measure and evaluate protection.

D. VACCINES

1.NEW VACCINES TECHNOLOGIES AND BIOTHERAPEUTICS / ANTIVIRALS

(Teresa De Los Santos / Elizabeth Rieder)

The significant differences between the vaccines distributed in endemic vs. free regions/ countries, the need to develop molecular FMD vaccine platforms toward broader coverage, DIVA compatibility and long lasting protection were discussed. Recent advances in new marker vaccines, the use of vectors to deliver complete empty capsids of FMD and peptide based vaccines were highlighted. Modified live attenuated vaccines such as an improved leaderless virus, Sap mutants, chimeric infectious clones, and de-optimized virus were mentioned. The development of bio-therapeutics such as characterization of cell transcription factors was also discussed. However, current vaccines still require 4 to 7 days to induce protection against FMDV infection.

2.COMMERCIAL VACCINES: PROTECTION ACCORDING TO THE TARGET SPECIES, CHALLENGES IN GLOBAL SUPPLIES OF FMD VACCINES

(Wilna Vosloo / Eliana Smitsaart)

New routes for vaccination such as oronasal and intra-nasal inoculation as well as intradermal delivery (ID) have been published. There have not been much progress in new adjuvants and vaccine formulations. The challenges in technological transfer pipelines between research and industry, and how to make the collaboration between researchers and pharmaceuticals possible to ensure market success, development, and experimentation of better adjuvants were discussed.

Vaccines need to be fit for purpose, and thermal stability will play an important role in disease control in hot climates where a cold chain cannot be guaranteed. In addition, knowledge on when a new vaccine strain is required would play an important role in decisions regarding vaccine manufacture.

E. DIAGNOSTICS

1.IN VITRO ASSAYS FOR ASSESSING VACCINE SELECTION – MATCHING AND POTENCY

(Alejandra Capozzo / Consuelo Carrillo)

Focus has been to improve in vitro methods to measure protection in vivo leading to tests such as the avidity ELISA, isotype ELISA, IFN gamma re -stimulation tests and other new serological tests. The disadvantages of relying only on r values to evaluate vaccine matching are clear. The proposed solution was to use an algorithm integrating different tests. In addition, a large number of in vivo and in vitro tests use high payload monovalent vaccines which does not reflect most endemic settings. We need to understand the epitope repertoire which contributes to protection, if and how this can be modulated to improve cross-protection and how we can better use sequence data.

2.DETECTION, FREEDOM FROM INFECTION (WITH OR WITHOUT VACCINATION) AND HERD IMMUNITY

(Zhidong Zhang / Charles Nfon)

New developments to detect infections have been nanopore sequencing technologies, new isothermal amplification (RPA), serological test with new detection systems, QRT-PCR-VNT in less than 24hs, etc.

F. EPIDEMIOLOGY

1.GLOBAL SURVEILLANCE, VIRAL-POOLS GEOGRAPHICAL DISTRIBUTION, AND OIE/FAO REFERENCE LABORATORY NETWORK

(Donald King)

There are gaps in surveillance data from West, Central and East Africa and GFRA partners are encouraged to set up research links in those areas to enhance our understanding of the global FMD epidemiology. In addition, research labs should share their data with laboratory networks.

There has been advances in developing livestock movement maps showing how differences in market prices and changes in acquisition power of some regions influence long distance movements of specific genetic variants of FMDV. Recent studies of seroprevalence, vaccine matching and long-term follow-ups have improved knowledge of co-circulation of viral strains, transmission and vaccine matching.

2.MOLECULAR EPIDEMIOLOGY AND TRANSMISSION MODELING
(Guido Konig / Andres Perez)

Molecular epidemiology can be used to help model countermeasures in anticipation of an outbreak in FMD free areas. The goal would be to develop models for cost-effective recovery of status after an outbreak, continuity of business, and efficient surveillance strategies. The main obstacles are our poor understanding of FMD ecology, and the lack of predictive tools.

Recently there have been advances identifying low scale genetic tracking of outbreaks, application of NGS to epidemiological studies, estimation of unbiased prevalence for better control of FMD, including virus recombination in phylogenetic analysis, managing meta-data to facilitate understanding of endemic settings, and integrating molecular epidemiology with vaccine matching and serology.

GFRA Gap Analysis Workshop 2018, INTA, Buenos Aires, Argentina.

EuFMD Open Session – Borgo Egnazia, Italy (29 – 31 October, 2018)

EuFMD, Corissa Miller

Increasing global security in the supply of effective foot-and-mouth disease (FMD) vaccines: can we really manage the risks and achieve progressive control without it?

The Open Session of the European Commission for the control of Foot-and-Mouth Disease (EuFMD) is held every two years and has become the largest technical and scientific meeting on FMD to be convened on a regular basis. Set amongst the olive groves of Puglia and with the Adriatic Sea as a backdrop, the 2018 Open Session (OS18) marked the largest meeting yet, drawing 270 participants from around the world, and an additional 290 through the OS18 online platform.

OS18 brought together colleagues from the public sector, scientific institutions, academia and the private sector to champion the concept of Global Vaccine Security; recognizing the need for an increased supply of, and access to, effective and affordable vaccines for both FMD-free and endemic settings. A total of 23 technical sessions were held in plenary and parallel streams, along with panel discussions, poster sessions and post-meeting workshops. A dedicated mobile application enabled participants to keep track of events, plan their meeting timetables and provide feedback on session conclusions. The meeting provided a forum for participants not only to listen, but to engage, identify challenges and generate innovative solutions.

The meeting highlighted the significant progress made in the progressive control of FMD in recent decades, with almost all of Europe and South America now officially recognized as FMD-free. The role that quality vaccines have played in this progress was acknowledged. A central message generated from OS18 is that investors and regulators are key partners in the network of stakeholders that contribute to FMD control, and engagement with them is valued and necessary to resolve the barriers surrounding Global Vaccine Security.

Lack of global FMD vaccine security affects all nations, regardless of FMD status. Addressing this issue requires innovative thinking to create an enabling environment between public and private sectors to increase access to quality vaccines. To move forward, a shift in the vaccine stewardship paradigm is required, from the traditional top-down public sector oversight of vaccine stocks to one of public-private collaboration for enhanced end-user access to vaccines.

OS18 Group Photo, Borgo Egnazia, Italy (29 – 30 October, 2018)

Celebrating the 60-year history of the World Reference Laboratory for Foot-and-Mouth Disease (WRLFMD)

During November, the Pirbright Institute hosted a two-day symposium attended by over 100 FMD scientists to celebrate the 60-year anniversary of the establishment of the World Reference Laboratory for Foot-and-Mouth Disease (WRLFMD). The meeting was opened by Christine Middlemiss (UK, Chief Veterinary Officer), Matthew Stone (Deputy Director General of the OIE) and Keith Sumption (from FAO/EuFMD). Subsequent scientific sessions reviewed the current activities of the WRLFMD (and OIE/FAO FMD Laboratory Network: https://www.foot-and-mouth.org), and discussed new opportunities to monitor, diagnose and control FMD by applying knowledge from fundamental research projects that aim to understand the pathogenesis, host responses and epidemiology of the disease. Talks from invited speakers and WRLFMD staff were within four themes of:
(i) Risks & Threats,
(ii) Diagnostic Innovation,
(iii) Pathogenesis & Immunity and
(iv) FMD Control with a Focus on Vaccination.

These presentations showcased the synergy between fundamental/basic science and the on-going global surveillance activities undertaken by FMD Reference Laboratories. In the evening, the meeting delegates (including past and present members of the WRLFMD) were royally entertained at a local hotel by after-dinner "trips down memory lane" talks from Nick Knowles and Dave Rowlands that highlighted key events and personalities that

Awards for the Chairs, Speakers and Organisers of the symposium

For those of you who are interested to learn more, some key "official" events in the history of the WRLFMD are highlighted in the timeline picture below, and further details of this event including .pdfs of the talks can be found on the recently re-launched WRLFMD website (http://wrlfmd.org/60th-anniversary).

WRLFMD takes this opportunity to thank commercial sponsors (ThermoFisher Scientific, Zoetis, MSD and Boehringer Ingelheim), and BBSRC who supported the meeting and all of the international speakers, chairs and delegates who travelled to Pirbright from across the world share in the celebrations with us.


60 YEARS
of CONTROL and SURVEILLANCE
of FOOT-and-MOUTH DISEASE
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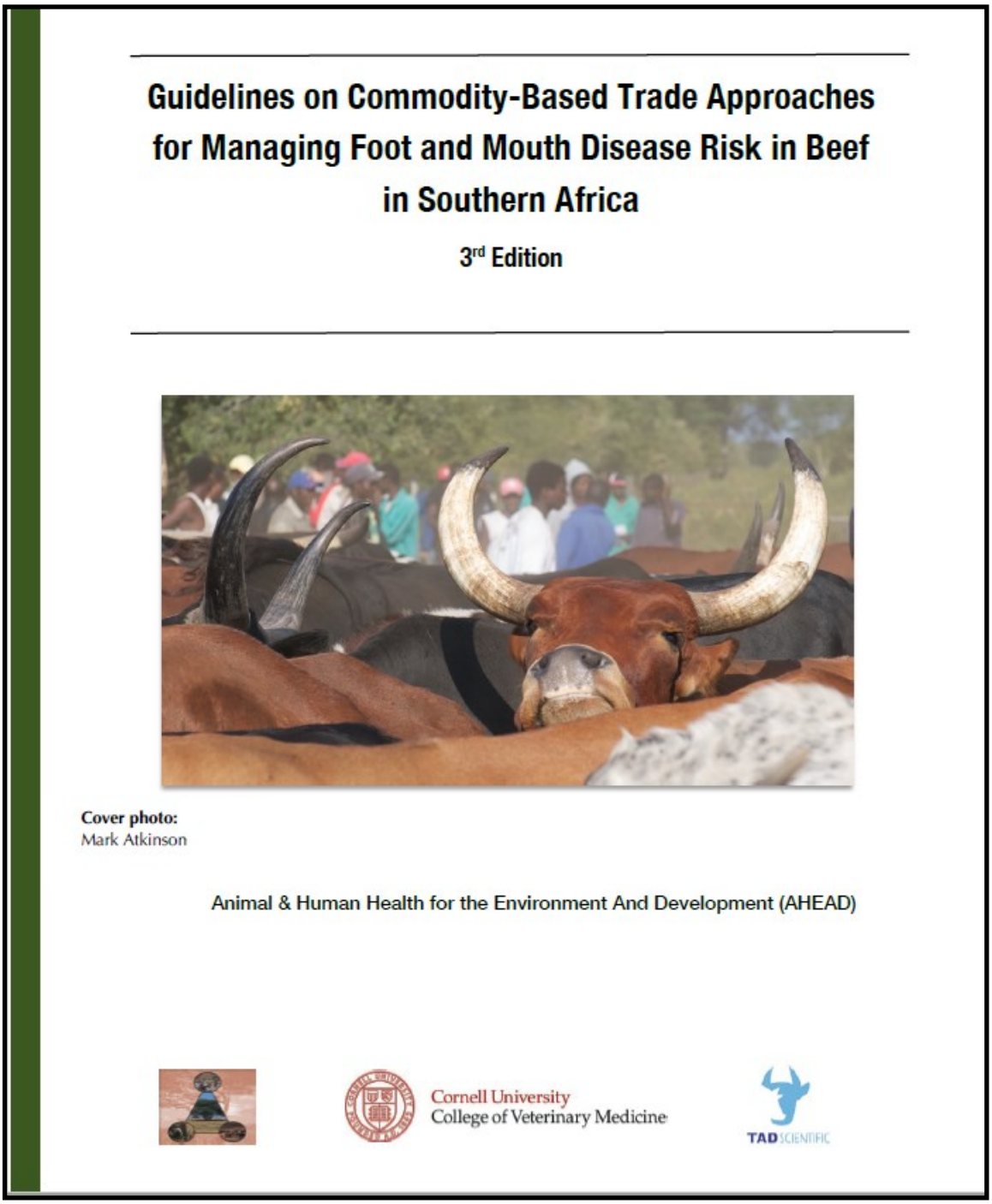
www.pirbright.ac.uk
THE Pirbright INSTITUTE



***Guidelines on Commodity-Based Trade Approaches for Managing Foot and Mouth Disease Risk in Beef in Southern Africa, 3rd edition (2018) Thomson G, Penrith M-L, Atkinson SJ, and Osofsky SA, Cornell University's AHEAD Program (**cornell-ahead.org**) –** Updated after very helpful discussions with the SADC Livestock Technical Committee, this 3rd edition includes additional materials on risk mitigation measures, scenarios related to the transit of beef, and animal identification and traceability, among other topics. This document, like its previous editions, demonstrates that export of beef from SADC countries or zones not recognised as free from FMD is possible, especially to regional markets (because the sanitary circumstances that prevail in the southern Africa region are common to many countries). Furthermore, several alternative approaches, under the umbrella term commodity-based trade, are potentially possible, and this guide outlines those that comply with international trade standards as well as their respective advantages, disadvantages and requirements. Integration of sanitary risk management (i.e. for both food safety and animal disease) together with measures that improve the quality and quantity of the end-product along value chains offers an approach that, until recently, has been largely unrecognised, despite providing clear advantages for southern Africa specifically. We hope and believe this is the most helpful version of the *Guidelines* yet!

http://wcs-ahead.org/kaza/181114-guidelines-for-implementing-cbt-final.pdf

SUMMARY

In most of southern Africa the vast majority of cattle are located in areas not free of foot and mouth disease (FMD), leaving owners of these cattle with limited access to regional and international beef markets. This situation constrains investment in cattle production, thereby limiting rural development and helping to entrench rural poverty.

For decades, this situation has simply been accepted because the types of FMD viruses prevalent in the region are maintained by wildlife and are therefore essentially impossible to eliminate. Moreover, until recently, international trade rules and conventions were founded on the need for the locality of beef production to be free of FMD. Fortunately, this situation is changing and options include, among others, management of risk of FMD along individual value chains to enable assurance that the final products are free of FMD virus and therefore can be traded with negligible risk of transmission of infection, irrespective of the FMD status of the locality of production (i.e. commodity-based trade [CBT]).

The first edition of these Guidelines was published early in 2015 to inform beef producing enterprises of the nature of developments at that time and specifically how, step by step, a value chain approach could be exploited to broaden market access. Since May 2015, further changes in international animal health standards for trade in beef produced in FMD-endemic areas have been adopted by the OIE (World Organisation for Animal Health). These changes necessitated an updated edition because they expand options for enabling market access for beef producers in southern Africa not located in areas free from FMD. In this new (2018) document, further changes have been made to incorporate topics identified during consultation at a meeting of the Southern African Development Community (SADC) Livestock Technical Committee in July 2018.

This document, like its previous editions, demonstrates that export of beef from SADC countries or zones not recognised as free from FMD is possible, especially to regional markets (because the sanitary circumstances that prevail in the southern Africa region are common to many countries). Furthermore, several alternative approaches, under the umbrella term commodity-based trade, are potentially possible, and this guide outlines those that comply with international trade standards as well as their respective advantages, disadvantages and requirements. Integration of sanitary risk management (i.e. for both food safety and animal disease) together with measures that improve the quality and quantity of the end-product along value chains offers an approach that, until recently, has been largely unrecognised, despite providing clear advantages for southern Africa specifically.

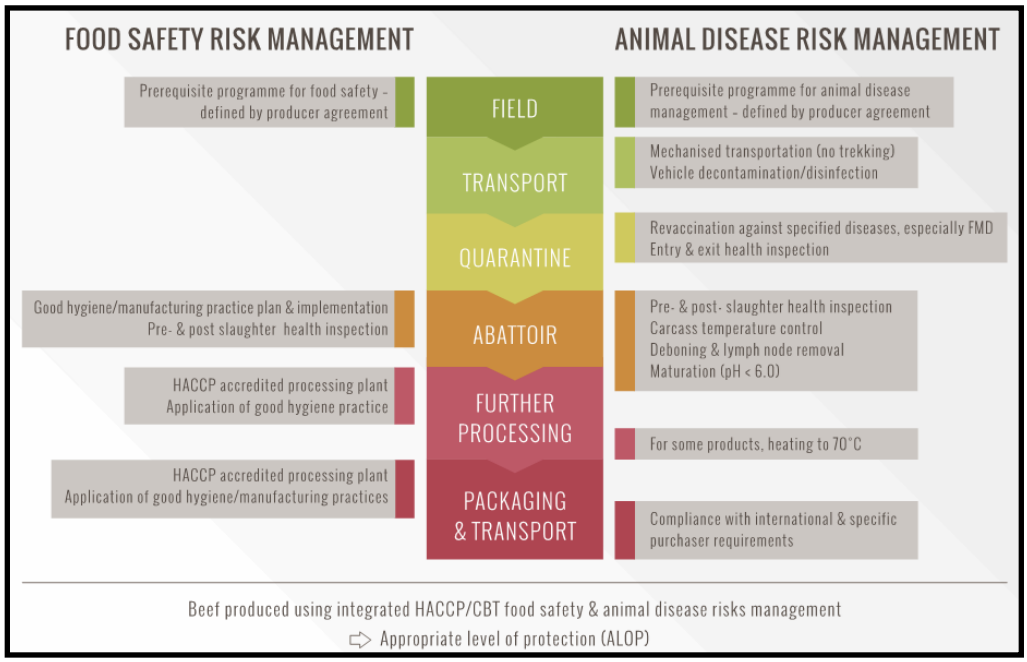


Figure 1: Parallel application of food safety and animal disease risk management measures along a value chain for beef production in a location that is not recognised as free from FMD.

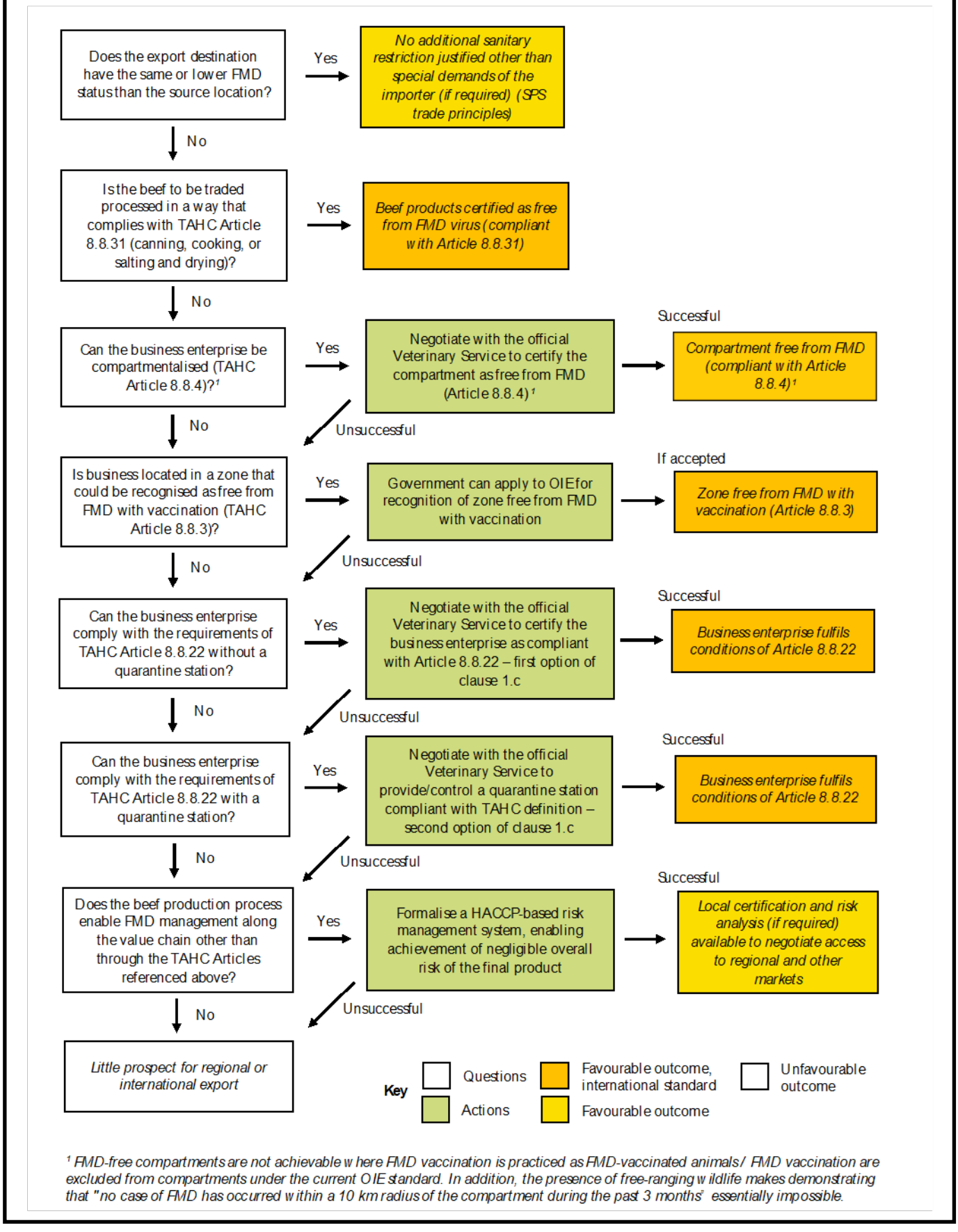


Figure 2: Decision tree for beef business enterprises located in areas not recognized internationally as free from FMD without vaccination.

UPCOMING EVENTS

GFRA Scientific Meeting 2019
Bangkok, Thailand
29-31st October 2019

Why?

Foot-and-mouth disease (FMD) is highly infectious and remains a threat to livestock economies worldwide. Through the efforts of research centers we've learnt a lot about this complex disease - now is the time to accelerate progress by working more closely together.

Who?

Launched in 2003, GFRA is a worldwide association of animal research organizations that are involved in combating FMD. Its aim is to build a global alliance of partners to generate and share knowledge - in a virtual FMD laboratory - to develop tools that can better combat the threat of the disease.

How?

GFRA will facilitate the mission of the alliance by supporting strategic objectives that will advance the progressive control and eradication of FMD.

Find out by joining us at the GFRA Scientific meeting!
29-31st October 2019 in beautiful Bangkok, Thailand.

Want to know more?

The Global Foot-and-Mouth Disease Research Alliance (GFRA)

A worldwide association of animal health research organisations to assist the global control and eventual eradication of foot-and-mouth disease.

www.ars.usda.gov/gfra

The GFRA Executive Committee

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*Please note the contents of this newsletter are not peer reviewed.