

REVIEW PAPER

The Danger of Foot and Mouth Disease in Livestock – A Review

ASWIN RAFIF KHAIRULLAH¹, SHENDY CANADYA KURNIAWAN², MUSTOFA HELMI EFFENDI^{3*}, OTTO SAHAT MARTUA SILAEN⁴, IKECHUKWU BENJAMIN MOSES⁵, ABDULLAH HASIB⁶, SANCAKA CHASYER RAMANDINIANTO⁷, DANIAH ASHRI AFNANI⁸, AGUS WIDODO⁹, KATTY HENDRIANA PRISCILIA RIWU¹⁰, REICHAN LISA AZ ZAHRA¹¹ & SHEILA MARTY YANESTRIA¹²

¹Research Center for Veterinary Science, National Research and Innovation Agency (BRIN). Jl. Raya Bogor Km. 46 Cibinong, Bogor 16911, West Java, Indonesia; ²Master Program of Animal Sciences, Department of Animal Sciences, Specialisation in Molecule, Cell and Organ Functioning, Wageningen University and Research. Wageningen 6708 PB, Netherlands; ³Division of Veterinary Public Health, Faculty of Veterinary Medicine, Universitas Airlangga. Jl. Dr. Ir. H. Soekarno, Kampus C Mulyorejo, Surabaya 60115, East Java, Indonesia; ⁴Doctoral Program in Biomedical Science, Faculty of Medicine, Universitas Indonesia. Jl. Salemba Raya No. 6 Senen, Jakarta 10430, Indonesia; ⁵Department of Applied Microbiology, Faculty of Science, Ebonyi State University. Abakaliki 480211, Nigeria; ⁶School of Agriculture and Food Sustainability, The University of Queensland. Gatton, QLD, 4343, Queensland; ⁷Lingkar Satwa Animal Care Clinic. Jl. Sumatera No. 31L, Gubeng, Surabaya 60281, East Java, Indonesia; ⁸Department of Microbiology and Parasitology, Faculty of Veterinary Medicine, Universitas Pendidikan Mandalika. Jl. Pemuda No. 59A, Dasan Agung Baru, Mataram 83125, West Nusa Tenggara, Indonesia; ⁹Department of Health, Faculty of Vocational Studies, Universitas Airlangga. Jl. Dharmawangsa Dalam Selatan No. 28-30, Kampus B Airlangga, Surabaya 60115, East Java, Indonesia; ¹⁰Department of Veterinary Public Health, Faculty of Veterinary Medicine, Universitas Pendidikan Mandalika. Jl. Pemuda No. 59A, Dasan Agung Baru, Mataram 83125, Nusa Tenggara Barat, Indonesia; ¹¹Profession Program in Veterinary Medicine, Faculty of Veterinary Medicine, Universitas Airlangga. Jl. Dr. Ir. H. Soekarno, Kampus C Mulyorejo, Surabaya 60115, East Java, Indonesia; ¹²Faculty of Veterinary Medicine, Universitas Wijaya Kusuma Surabaya. Jl. Dukuh Kupang XXV No.54, Dukuh Kupang, Dukuh Pakis, Surabaya 60225, East Java, Indonesia

*Corresponding authors: mhelmiEFFENDI@gmail.com

Received: 15 August 2023

Accepted: 11 June 2024

Published: 31 December 2024

ABSTRACT

The FMD virus, also known as FMDV, is a member of the Picornaviridae family of the genus Aphthovirus. There are seven immunologically distinct FMD virus serotypes, known as Asia-1, A, C, O, South-African Territories (SAT) -1, -2, and -3. The disease's clinical symptoms include the development of vesicles on the lips, tongue, palate, tooth pads, nose, coronary band, gums, and interdigital spaces. There are many viral, host, and environmental factors that affect the epidemiology of FMD, including variations in viral virulence, particle stability in diverse microenvironments, and possible long-term survival. FMD can spread in a variety of ways, including through human contact with contaminated milk tankers or animal transport vehicles, the use of contaminated animal goods, equipment, or vehicles, or by the transmission of windborne viruses. Foot and mouth illness is not considered to be a serious public health hazard because the infection seems to be rare and the effects are self-limiting. Since the cost of disease control is added to the direct economic losses brought on by animal deaths, decreased milk production, and slowed animal growth rates, FMD epidemics indirectly harm the economy. Some of the techniques used to control FMD epidemics include mobility restrictions, quarantines, the death of infected and exposed animals, and cleaning and disinfecting impacted buildings, equipment, and vehicles.

Keywords: Foot and mouth disease, infectious disease, livestock, virus

Copyright: This is an open access article distributed under the terms of the CC-BY-NC-SA (Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License) which permits unrestricted use, distribution, and reproduction in any medium, for non-commercial purposes, provided the original work of the author(s) is properly cited.

INTRODUCTION

A highly contagious viral illness that affects animals with cloven hooves, foot and mouth disease (FMD) epidemics have a significant negative financial impact on the global livestock business (Chanchaidechachai *et al.*, 2022). This disease can attack livestock and wild animals such as cattle, sheep, buffalo, goats, pigs, deer, elephants, and camels (Rodríguez-Habibe *et al.*, 2020). The illness sometimes produces epidemics in once free nations and is endemic in portions of South America, Africa, the Middle East, and Asia (Jamal & Belsham, 2013). About 77% of the world's total livestock population is estimated to be affected by FMD; thus, making it one of the important illnesses that need to be reported to the World Organization for Animal Health (Knight-Jones *et al.*, 2017). The livestock sector has been seriously threatened by this since the sixteenth century (Longjam *et al.*, 2011).

An Italian monk named Hieronymus Fracastorius gave the earliest account of foot and mouth disease (FMD) in cattle in Venice in 1514 (Jamal & Belsham, 2013). Affected animals refuse to eat, display reddened oral mucosa, and have vesicles on their paws and in their mouths. Morbidity due to FMD can reach 90-100% among susceptible animal populations; however, most infected animals recover as mortality is generally low, especially in adult animals (1 – 5%) (Teifke *et al.*, 2012). This description, made 500 years ago, bears a strong resemblance to FMD when viewed today. An estimated 77 – 80% of the global livestock-keeping regions, especially in Asia, Africa, the Middle East, and some regions in South America have been affected by this disease.

Globally, FMD continues to afflict more than 100 nations, and its distribution largely corresponds to economic progress (Pattnaik *et al.*, 2012). The FMD virus (FMDV), which is a member of the Picornaviridae family of the genus Aphthovirus, is known for causing FMD (Malik *et al.*, 2017). There are seven different FMDV serotypes known: Asia 1, O, A, C, SAT1, SAT2, and SAT3 (Ranaweera *et al.*, 2019; Paton *et al.*, 2021). FMDV samples from the South African FMD outbreak were found to include the SAT1, SAT2, and SAT3 FMDV serotypes (Fana *et al.*, 2021). Asian serotype 1 was discovered in Pakistan. Meanwhile, the last serotype C was detected in Kenya and Brazil (Wekesa *et al.*,

2015). Cloven hooves play a critical epidemiological function in keeping the virus in the environment, even though FMD can inadvertently infect a wide range of host species (Grubman & Baxt, 2004).

Clinically, the disease manifests as the development of vesicles on the lips, tongue, palate, tooth pads, snout, coronary band, gums, and interdigital spaces (Arzt *et al.*, 2011). Additionally prevalent are drooling, depression, lameness, and anorexia, which have a negative impact on livestock systems productivity and efficiency (Jori *et al.*, 2021). Significant economic effects from these epidemics may include decreased milk and meat output, maintenance expenses, power outages, limitations on the trade in animals and animal products, and high implementation costs for control efforts (Espinosa *et al.*, 2020). The current requirement for mass slaughter of diseased animals and possible contacts when an outbreak arises in an FMD-free area also makes FMD a problem for animal welfare (Bradhurst *et al.*, 2019).

Even though FMD rarely results in the death of older animals, the virus can induce major cardiac lesions in young animals with a significant mortality rate of 20% or higher. FMD typically has a fatality rate below 5% (Mahmoud & Galbat, 2017). The main obstacles to containing this condition and the reasons it is regarded as the most feared viral disease are its high prevalence of transmission, wide geographic distribution, broad host range, ability to identify carrier status, antigenic diversity that results in poor cross-immunity, and relatively short duration of immunity (Shurbe *et al.*, 2022). The main issues with controlling this disease include a lack of surveillance, inadequate diagnostic tools, and ineffective control strategies (Maree *et al.*, 2014). Throughout the year, there are still periodic reports of these breakouts.

This disease has been wiped out in more affluent nations, but the disease's spread to underdeveloped nations that are often free of it can result in significant economic losses (Limon *et al.*, 2020). FMD outbreaks frequently recur in these nations despite the implementation of prevention and control strategies like a combination of stamp policies, increased biosecurity, preventative or emergency

vaccinations, movement restrictions, strengthened surveillance, education programs, and community outreach (Blacksell *et al.*, 2019). Due to disparities in animal health priorities, varied resources, and varying logistical capabilities, these techniques are adopted and enforced inconsistently among nations, which leads to partial or no results (Gordon *et al.*, 2022).

The FMD virus is regarded as a serious global health issue. The goal of this review is to provide a comprehensive explanation of the etiology, pathophysiology, epidemiology, diagnosis, clinical symptoms, transmission, impact on public health, economic impact, and control measures against the development of FMD in livestock. This review's information was compiled to present recent scientific research, identify knowledge gaps and study restrictions surrounding FMD disease, and provide current scientific literature.

Etiology

The Foot and Mouth Disease Virus (FMDV) is the sole genus-level representative of the Aphthovirus genus that belongs to the Picornaviridae family and the first viral pathogen to be recognized (Malik *et al.*, 2017). There are seven immunologically distinct FMDV virus serotypes, identified as A, O, C, Asia-1, South-African Territories (SAT) -1, -2, and -3, which include more than 65 subtypes (Ranaweera *et al.*, 2019). Type O stood for the Oise in France, while Type A stood for Allemagne (Germany). The type C is then referred to as the supplementary type in Germany (Jamal & Belsham, 2013). About 30 years later, researchers at The Pirbright Institute, United Kingdom in England identified 3 novel FMDV serotypes called SAT1, SAT2, and SAT3 in samples taken from an FMD outbreak in South Africa (Banda *et al.*, 2022). First identified in a sample from Pakistan was a seventh serotype called Asia 1 (Longjam *et al.*, 2011).

A single-stranded RNA with a positive charge and a length of roughly 8500 nucleotides is found inside the viral particle, or virion (Gao *et al.*, 2016). These are icosahedral particles with a smooth surface that have a diameter of about 30 nm. The structural proteins VP1, VP2, VP3, and VP4 are each present in 60 copies (Dong *et*

al., 2021). The fourth structural protein (MW8.5 kDa) is internal, whereas the first three (MW24 kDa) include a surface component. Additionally, virions typically contain one or two VP0 units, which are the forerunners of VP2 and VP4 (Park *et al.*, 2022). The structural protein VP1-3 folds into eight strands that join to create the majority of the capsid structure, forming a 13-barrel wedge shape (Longjam *et al.*, 2011). The FMDV's three-dimensional structure has shown notable surface features made of loops between the G and H strands of VP1 (Burman *et al.*, 2006).

Located inside the capsid is the VP4 protein. Loops connecting the 13-barrel VP1-3 strands make up the virion's outer surface (Yuan *et al.*, 2017). FMDV lacks surface gorges or pits, which are receptor binding sites for enteroviruses and cardioviruses. This makes it different from other picornaviruses (Wang *et al.*, 2015). The channel on the fivefold axis of this virion, which facilitates the entry of tiny molecules like Cscl into the capsid and gives FMDV the highest buoyant density among the picornaviruses, is another characteristic of this organism (Yuan *et al.*, 2017). The trypsin-sensitive region of VP1 contains the FMDV's primary cell attachment site and immunodominant region, which are both situated in solvent-exposed regions of the virion surface (Lawrence *et al.*, 2013). Previous serological research showed that one of the main antigenic regions of the virus, the highly variable VP1 region, which is comprised of residues 135 to 155, is shared by various FMDV serotypes (Ludi *et al.*, 2014).

Pathogenesis

After the virus enters the animal's body through the digestive and respiratory tracts, it replicates in the lymphoid tissue, particularly in the upper respiratory tract, before entering the bloodstream and circulating for three to five days (Rodríguez-Habibe *et al.*, 2020). Prior to the virus entering the bloodstream and the onset of clinical symptoms, the virus can be found in the oropharynx one to three days earlier. The virus then travels and replicates through the circulation in its predilected epithelial tissues, including the heart muscle in young animals, between the nails, female animal nipples, and the tongue (Dash *et al.*, 2010). The virus was ejected from infected animals two days before clinical

signs manifested (the virus in milk was discovered four days prior to the onset of clinical signs), and considerable amounts of the virus were no longer expelled 4 – 5 days after vesicles developed (Stenfeldt *et al.*, 2016a). Skin wounds typically recover in 10 days, but animals with secondary infections need longer time of about 2 weeks to recover (Dillon, 2011).

The epithelium turns pale and gradually fills with fluid on the first day that clinical indications in the form of skin lesions occur. On the second day, the vesicles burst, and a layer of epithelium with distinct borders could be seen at the lesion's edges and at its red base. On the third day, the lesion's edges are hazy and the ground turns a faint crimson tint; fibrin deposition starts. On the fourth day, fibrin deposition increased in size and epithelial tissue started to regrow around the lesion's margins (Mohebbi *et al.*, 2017). The scars are still visible as pale areas even though the lesions are typically healed by day 10 and scar tissue has formed by day 7. Although the age of lesions can be determined, the accuracy will decrease since the rate of lesions healing varies between animals (Gornik *et al.*, 2019). Due to their smaller size compared to cattle, lesions in goats and sheep are typically more challenging to observe. Additionally, these small ruminants frequently have leg lesions in the coronary band of the leg, which are typically milder lesions (Muthukrishnan *et al.*, 2020). In pigs, foot lesions are more frequently observed to identify the age of the lesions (Stenfeldt *et al.*, 2016a).

Even though ruminants have immunity to the FMD virus, virus particles can still be discovered in their oropharynx up to 28 days after infection, and 50% of ruminants may develop persistent infection (Stenfeldt *et al.*, 2016b). Animals whose oropharynx is still found to have the virus after 28 days post-infection are referred to as disease-carrying animals (Jamal & Belsham, 2013). Cattle, small ruminants, African buffalo, and Asian water buffalo have all been observed to be chronic carriers of the virus for up to five years, three years, and nine months, respectively, although pigs are not thought to be such persistent carriers (Bertram *et al.*, 2018). The amount of viral excretion in carriers is variable (not constant), and it gets smaller over time. With the exception of the African buffalo, which is considered to have contributed to the FMD outbreak in Zimbabwe in 1989 and 1991, the

epidemiological significance of these carriers (especially cattle and small ruminant animals such as pigs) in disease transmission is unknown (Guerrini *et al.*, 2019).

Epidemiology

The epidemiology of FMD is complicated and is influenced by a variety of viral, host, and environmental factors, including variations in viral virulence (lesional severity, number, and duration of viral shedding), stability of the particles in different microenvironments, and potential long-term persistence (Paton *et al.*, 2018). The host species (cattle, sheep, water buffalo, goats, pigs, deer, antelope, and bison), nutritional and immunological state, population densities, animal migration, and contact between various domestic and wild host species and animals that might mechanically transport the virus are other factors that affect FMDV replication and transmission (Ranjan *et al.*, 2016). The environment can act as a geographical barrier to the spread of a virus or, on the other hand, it can promote transmission of a virus when the correct climatic circumstances are present (Bessell *et al.*, 2008). The tremendous potential for FMDV variation and adaptation in this multifactorial scenario has mimicked complicated evolutionary patterns discovered by molecular epidemiological investigations, which are mostly based on nucleotide sequencing of capsid protein genes (Caridi *et al.*, 2021).

Various regions of Asia, Africa, the Middle East, and South America are plagued with foot and mouth disease (Maree *et al.*, 2014). While serotypes O and A are common, SAT virus is primarily found in Africa (with sporadic incursions into the Middle East), and Asia 1 is now solely found in Asia (Bachanek-Bankowska *et al.*, 2018). FMDV is not present in Western Europe, New Zealand, Australia, Greenland, Iceland, North and Central America (Brown *et al.*, 2021). However, FMD has not been detected in North America for more than 60 years despite recent outbreaks in Western Europe (where eradication efforts have been successful) (Valarcher *et al.*, 2008). The last FMD outbreak occurred in the US in 1929, whereas it has not occurred in Canada or Mexico since the 1950s (Jamal & Belsham, 2013). After being proclaimed cured of the disease in 1986, an FMD

outbreak returned to Indonesia recently in 2022 (Sutawi *et al.*, 2023).

FMDV serotypes are not evenly distributed around the world. The virus strains O, A, and C have persistent and aggressive distribution patterns throughout Europe, America, Asia, and Africa (Woldemariyam *et al.*, 2023). However, FMDV serotype C may no longer exist outside of laboratories because the last FMDV serotype C infection was documented in Ethiopia in 2005 (Ayelet *et al.*, 2009). Sub-Saharan Africa is typically the only place where the SAT1-3 virus is found (Wubshet *et al.*, 2019). The three continental reservoirs in Asia, Africa, and South America, which can be further divided into seven primary infectious viral pools, are currently maintaining the worldwide burden of FMDV infection (Woldemariyam *et al.*, 2023). Each of these seven primary infectious viral pools has at least three different serotypes of the virus, and because circulating viruses are mostly found in these local reservoirs, local strains have developed that are sometimes (as with type A and SAT viruses) difficult to control without specialized testing and vaccinations (Ludi *et al.*, 2014).

Diagnosis

The control and eradication of disease in endemic areas depend on an accurate diagnosis of FMDV infection. Clinical indicators are typically utilized to make the initial diagnosis of FMD, but these can be easily mistaken for those of other vesicular illnesses. Therefore, breeders must identify illness symptoms quickly and report them to the appropriate veterinary authorities to confirm. Samples of suspected disease should also be sent to a reference laboratory for confirmation (Ding *et al.*, 2013). Important support for FMD control and vaccination campaigns is provided by quick and accurate laboratory data generation (Capozzo *et al.*, 2023). However, because of inefficient cold chains and prolonged transport times, samples that laboratories acquire from many impoverished nations may be of low quality (Blacksell *et al.*, 2019). These circumstances render laboratory diagnosis unreliable, necessitating the use of a diagnostic instrument that is suited for the situation to enable quick diagnosis and the implementation of the necessary controls (van Vuren *et al.*, 2022).

The following ideas form the foundation of the majority of current diagnostic methods for FMD detection: Viral isolation involving proliferation in susceptible cell cultures is used to identify the infectious agent, use of an FMDV-specific antibody or capture reagent in an Enzyme-linked Immunosorbent Assay (ELISA) technique for viral antigen detection, genetic analysis of nucleotide sequences and reverse transcription polymerase chain reaction (RT-PCR)-based viral nucleic acid detection, detection of FMDV-specific antibodies in animals that have already been exposed to the virus (Rémond *et al.*, 2002). Typically, sera determined to be positive by ELISA are confirmed by Virus Neutralization Test (VNT) (Ma *et al.*, 2011). These methods are especially appropriate for well-equipped labs, which are typically national or regional reference labs.

For instance, the use of viral cell culture systems necessitates educated people, a biosafety level 3 (BSL-3) laboratory, and cautious handling of samples to prevent cross-contamination and environmental contamination (Artika & Ma'roef, 2017). A high-quality sample is necessary for successful viral isolation, which also calls for transportation conditions from the sampling location to the lab (Burrell *et al.*, 2017). In diagnostic labs in endemic areas, it is simple to deploy both solid-phase competition ELISA and liquid-phase inhibitory ELISA for the serological detection of FMDV-specific antibodies to structural proteins (Cao *et al.*, 2022).

Clinical Symptoms

The intensity of clinical indications can range from moderate or subclinical to severe, depending on the virus type, exposure dose, age and species of the infected animal, and degree of host immunity. Death is uncommon, with the exception of young animals, who can pass away through malnutrition or multifocal myocarditis (Hammond *et al.*, 2021). Most adult animals recover in two to three weeks, however subsequent infections can prolong recovery (Park *et al.*, 2022). Morbidity can be close to 100%. The mortality rate is typically 1% to 5% for adults, but 20% or more for young lambs, piglets, and calves (Mahmoud *et al.*, 2017). Recovery typically takes two weeks in simple cases.

Cattle

The most severe FMD symptoms are found in highly productive dairy cows found in developed nations (Lyons *et al.*, 2015). The following signs and symptoms appear after 24 hours: pyrexia, anorexia, chills, decreased milk production for a couple of days, smacking of the lips, drooling, grinding of teeth, limping, kicking, or stamping of the feet. These symptoms are caused by vesicles (aphthae) between the coronary bands and claws, and in the mucous membranes of the buccal and nasal cavities. Vesicles can burst in the mammary glands and leave behind erosions (Shmeiger *et al.*, 2021). Recovery typically takes 8 to 15 days. There are several complications, including tongue erosion, superinfection of lesions, nail distortion, mastitis and a persistent disruption of milk production, myocarditis, infertility, abortion, a persistent loss of weight, and loss of heat regulation. Myocarditis causes the death of young animals (Tufani, 2013).

Sheep and Goat

Many diseased sheep or goats could not show any symptoms or may only have one lesion. Typical symptoms include fever and mild to severe lameness in one or more legs. Vesicles develop on the feet, in the coronary bands, and in the interdigital gaps, but they may burst or become concealed by foot lesions from other causes (Muthukrishnan *et al.*, 2020). Mouth lesions typically present as shallow erosions and are frequently undetectable or severe. It is typical for sheep and goats to be milked to exhibit pyrexia and agalactia. Several epidemics resulted in the death of numerous ewes. Young animals can die without showing any clinical symptoms (Kitching & Hughes, 2002).

Pigs

Pigs exposed to concrete in particular can experience pyrexia, develop severe leg lesions, and become lame with detached claws (Perez & Willeberg, 2017). Vesicles frequently develop at pressure sites on the legs, particularly along the knuckles. There may be dry lesions on the tongue and vesicular lesions on the muzzle (Stenfeldt *et al.*, 2016a). Piglets younger than 8 weeks of age are especially susceptible to sudden death from heart failure in young pigs up to 14 weeks of age (Moreno-Torres *et al.*, 2022).

Transmission

There are numerous ways that FMD can spread, including human contact with contaminated equipment, animal transport vehicles, milk tankers, animal products, vehicles, and windborne virus transmission (Auty *et al.*, 2019). One of the main ways that FMD spreads is by the aerosol route, which involves passing the disease from one animal to another (Brown *et al.*, 2022). Virus concentrations in downstream air are primarily determined by meteorological factors. The quantity and species of afflicted animals, the type of virus, the environment, and the species and number of animals under the wind are all factors that determine how quickly an infection spreads through the air (Subramaniam *et al.*, 2022). Inhibiting the spread of disease-causing aerosols during the rainy season are persistent downpours, high relative humidity, and humid winds. Additionally, during this season, strong rains or flooding in some locations hinder the movement and transportation of animals from one place to another (Rahman *et al.*, 2020).

The number of FMD outbreaks rises in the winter because of environmental factors that favor dry weather, dry winds, and low to moderate temperatures (Hegde *et al.*, 2014). Viral infections may spread more quickly among susceptible animal populations as a result of these favorable environmental conditions (Mielke & Garabed, 2020). Due to the summer's oppressive heat, there are fewer FMD outbreaks (Hagerman *et al.*, 2018). Additionally, migration to new pastures, large-scale movements and animal groupings, as well as cow and buffalo exhibits, are all associated with seasonal peaks in FMD prevalence (Wubshet *et al.*, 2019). Cattle are regarded as an indication of this illness because they are typically the first species to exhibit FMD symptoms (Mohebbi *et al.*, 2017). Because the minimum 20TCID₅₀ (tissue culture infective dose) of virus is needed to initiate infection in these animals (cattle and buffalo), they are extremely sensitive to infection (Walz *et al.*, 2020).

Pigs are regarded as a reinforcing host for the illness due to their high airborne virus transmission rates and relative resistance to airborne infection (Valarcher *et al.*, 2008). Sheep and cattle both excrete airborne viruses at a

similar rate, but due to sheep's smaller respiratory volume than cattle, it is believed that they are less susceptible to airborne infections (Marcos *et al.*, 2019). Sheep are thought of as maintenance hosts since they do not often exhibit conventional clinical symptoms or cardinal indicators that are similar to those of other airborne diseases (Stenfeldt *et al.*, 2019). Conditions that are conducive to the spread of this disease include low relative humidity (>60%), dim sunlight, a lack of heavy rain, and slow and consistent wind speed and direction (Brown *et al.*, 2022).

FMD virus can be shed into blood, milk, pharynx, rectum, and vagina before the appearance of clinical manifestations of disease in infected cows (Suchowski *et al.*, 2021). The possibility exists for raw milk to spread the virus both inside the farm and from farm to farm because the virus is shed into the milk before the dairy cows exhibit clinical signs of sickness (Shaban *et al.*, 2022). Further study is required in areas including virus emission, particle size and virus content, virus challenge times, and meteorological consequences to better understand airborne FMD transmission and its significance in upcoming outbreaks. The genetic and antigenic diversity of FMDV is one of its most crucial characteristics.

Public Health Impact

Humans can also contract FMDV, which has moderate flu-like symptoms as well as conjunctivitis symptoms, small vesicular eruptions on the skin, and tissue erosion (Dillon, 2011). Most of the symptoms are extremely mild, self-limiting, and unnoticeable. When handling infected or suspect animals and conducting laboratory sample processing, precautions should be used (Longjam *et al.*, 2011). Since the infection seems to be uncommon and the consequences are moderate, foot and mouth disease is not seen as a severe public health issue (Knight-Jones *et al.*, 2017). There have only been a relatively small number of clinical cases, even though many persons who previously worked with FMDV in vaccine labs or other settings generated antibodies to this virus (Di Giacomo *et al.*, 2022). One lab reported only 2 occurrences in more than 50 years, and a significant FMD vaccine manufacturer found 3 cases among its employees (Chanchaidechachai *et al.*, 2022). Perhaps exposure to extremely high

levels of virus or predisposing circumstances is required for infection.

Between 1921 and 1969, there were reports of more than 40 human instances of FMD that were confirmed in labs (Bauer, 1997). Vesicular lesions and influenza-like symptoms are among the signs and symptoms of this illness, which is often mild, transient, and self-limiting (Wong *et al.*, 2020). Some human cases are known to enter via wound infection, with the initial lesion forming at the site of inoculation (Prempeh *et al.*, 2001). There are also claims that three veterinarians purposefully exposed themselves to the FMD virus by consuming tainted unpasteurized milk for three days (Shaban *et al.*, 2022). Another study claimed that youngsters may be more likely than adults to contract the virus (Dubie & Negash, 2021). The FMD virus is present in the vesicles from an infected individual, despite their being no reports of person-to-person transmission (Li *et al.*, 2021).

Economic Impact

The genetic makeup of the animals (usually their expressed genotype which were inherited from their parents) in a country, common livestock management techniques, costs for inputs and products used in livestock production, and the country's ability to produce livestock for export markets are all factors that affect the prevalence and danger of disease attack (Adamchick *et al.*, 2021). Disease impact is not the same in all countries and livestock populations as a result of these differences. Live animal commerce between FMD-affected and FMD-free nations is prohibited (Knight-Jones *et al.*, 2017). The EU, US, and Japan often have the highest pricing for FMD-free meat, with prices being 50% higher on average (Dinku & Matsuda, 2018). Additionally, trade in cattle products is prohibited. Only processed, canned goods may be shipped in the event of the usual outbreak; however, boneless meat may be exported if FMD is effectively controlled by vaccination administered by an experienced veterinary service capable of identifying an outbreak (Paton *et al.*, 2009).

FMD outbreaks damage the economy indirectly since the cost of disease control adds to the direct economic losses brought on by animal fatalities, decreased milk output, and slowed animal growth rates (de Menezes *et al.*,

2023). A nation that has been identified as having FMD will face barriers in international trade due to the disease's ease of spread, particularly when dealing with products derived from animals that may carry the FMD virus (Auty *et al.*, 2019). The socioeconomic circumstances of those impacted by limitations on the movement of animals and animal products are likewise impacted by FMD epidemics (Naranjo & Cosivi, 2013). To stop the spread of the virus when FMD first appeared in the UK in 2001, around 6.2 million animals were euthanised (Davies, 2002). The outbreak in Japan in 2010 resulted in 290 thousand animals having to be slaughtered (Muroga *et al.*, 2012), while in South Korea as many as 3.47 million animals were slaughtered in 2010 to 2011 (Park *et al.*, 2013). According to a 2013 study, the annual economic losses caused by lower productivity and the cost of FMD vaccine range from 6.5 to 21 billion US dollars worldwide (Alhaji *et al.*, 2020).

Control And Preventive Measures

In a region endemic with FMD, quick action is crucial for controlling an outbreak. Veterinarians should adhere to their local and national illness reporting procedures when they uncover or suspect this disease (Eschbaumer *et al.*, 2020). Import restrictions aid in preventing the spread of FMDV from endemic regions to diseased animals or tainted food fed to animals (Woldemariyam *et al.*, 2023). Particularly concerning is food waste provided to pigs. FMDV can be killed by heat treatment, which also lowers the danger of outbreaks; nevertheless, several nations have outright banned feeding because it is impossible to ensure that proper heat treatment techniques are followed (Kristensen *et al.*, 2021). The WOAHA has published guidelines for eradicating FMDV from animal products such as dairy, meat, leather, and wool (Marcos & Perez, 2019). Recently, a global FMD control campaign was launched to lower the spread of the virus and the incidence of this disease (Naranjo & Cosivi, 2013).

Among the steps employed to contain FMD epidemics include quarantine and mobility restrictions, the killing of afflicted and exposed animals, and the cleaning and disinfection of impacted buildings, machinery, and vehicles (Clemmons *et al.*, 2021). Euthanasia of animals at risk of infection and immunization are

possible further interventions (Costa & Akdeniz, 2019). Infected carcasses must be safely disposed of using methods such as rendering, burying, or burning (Guan *et al.*, 2010). The carcass should not be fed to carnivores, including dogs and cats, which may become infected with the virus in raw tissue (Waters *et al.*, 2021). To stop the virus from spreading mechanically, rats and other vectors can be eliminated (Auty *et al.*, 2019). People who have been exposed to FMDV may be advised to refrain from contact with vulnerable animals for a while, as well as decontaminating clothing and other personal items (Orsel & Bouma, 2009). To avoid virus entry, farms that are not infected should implement good biosecurity practices (Fountain *et al.*, 2018).

During some outbreaks, vaccination can be used to prevent the spread of FMDV or to save some animals (such as zoo animals) (Muleme *et al.*, 2013). The choice to utilize vaccination is complicated and depends on the outbreak's scientific, economic, political, and social considerations (Rawdon *et al.*, 2018). Additionally, vaccines are utilized in endemic regions to safeguard animals from sickness (Railey & Marsh, 2019). The FMDV vaccination (such as the use of live-attenuated vaccines, DNA vaccines, peptide vaccines, and live viral vector vaccines) only offers protection against the serotype it contains; to provide appropriate protection, the vaccine strain must also be modified to account for field strains (Singh *et al.*, 2019).

CONCLUSION

FMD is considered to be a significant global veterinary concern especially as the FMD virus sub-lineages have been recognized to evolve into novel strains with the capacity to escape vaccination and result into major livestock epidemics. Limitations on the transportation of animals and animal products have an influence on people whose socioeconomic conditions are affected by FMD epidemics. Farms that are not afflicted should employ appropriate biosecurity procedures to prevent virus entry. Finally, it is imperative to continue implementing measures and research studies directed at vaccine matching, vaccine design improvement, vaccine quality control, and continued surveillance in order to control and to keep track of FMD virus epidemiology and transmission.

ACKNOWLEDGEMENTS

The authors would like to thank the Faculty of Veterinary Medicine, Universitas Airlangga, Indonesia and National Research and Innovation Agency (BRIN), Indonesia.

REFERENCES

- Adamchick, J., Rich, K.M. & Perez, A.M. (2021). Assessment of the risk of foot and mouth disease among beef cattle at slaughter from east african production systems. *Viruses*, 13(12): 2407. DOI: 10.3390%2Fv13122407
- Alhaji, N.B., Amin, J., Aliyu, M.B., Mohammad, B., Babalobi, O.O., Wungak, Y. & Odetokun, I.A. (2020). Economic impact assessment of foot-and-mouth disease burden and control in pastoral local dairy cattle production systems in Northern Nigeria: A cross-sectional survey. *Preventive Veterinary Medicine*, 177(1): 104974. DOI: 10.1016/j.prevetmed.2020.104974
- Artika, I.M. & Ma'roef, C.N. (2017). Laboratory biosafety for handling emerging viruses. *Asian Pacific Journal of Tropical Biomedicine*, 7(5): 483-491. DOI: 10.1016/j.apjtb.2017.01.020
- Arzt, J., Baxt, B., Grubman, M.J., Jackson, T., Juleff, N., Rhyan, J., Rieder, E., Waters, R. & Rodriguez, L.L. (2011). The pathogenesis of foot-and-mouth disease II: viral pathways in swine, small ruminants, and wildlife; myotropism, chronic syndromes, and molecular virus-host interactions. *Transboundary and Emerging Diseases*, 58(4): 305-326. DOI: 10.1111/j.1865-1682.2011.01236.x
- Auty, H., Mellor, D., Gunn, G. & Boden, L.A. (2019). The risk of foot and mouth disease transmission posed by public access to the countryside during an outbreak. *Frontiers in Veterinary Science*, 6(1): 381. DOI: 10.3389/fvets.2019.00381
- Ayelet, G., Mahapatra, M., Gelaye, E., Egziabher, B.G., Rufeal, T., Sahle, M., Ferris, N.P., Wadsworth, J., Hutchings, G.H. & Knowles, N.J. (2009). Genetic characterization of foot-and-mouth disease viruses, Ethiopia, 1981-2007. *Emerging Infectious Diseases*, 15(9): 1409-1417. DOI: 10.3201%2F1509.090091
- Bachanek-Bankowska, K., Di Nardo, A., Wadsworth, J., Henry, E.K.M., Parlak, Ü., Timina, A., Mischenko, A., Qasim, I.A., Abdollahi, D., Sultana, M., Hossain, M.A., King, D.P. & Knowles, N.J. (2018). Foot-and-Mouth disease in the middle east caused by an a/asia/g-vii virus lineage, 2015-2016. *Emerging Infectious Diseases*, 24(6): 1073-1078. DOI: 10.3201%2F2406.170715
- Banda, F., Shilongo, A., Hikufe, E.H., Khaiseb, S., Kabajani, J., Shikongo, B., Set, P., Kapapero, J.K., Shoombe, K.K., Zaire, G., Kabilika, S., Quan, M., Fana, E.M., Mokopasetso, M., Hyera, J.M.K., Wadsworth, J., Knowles, N.J., Nardo, A.D. & King, D.P. (2022). The first detection of a serotype O foot-and-mouth disease virus in Namibia. *Transboundary and Emerging Diseases*, 69: e3261-e3267. DOI: 10.1111/tbed.14561
- Bauer, K. (1997). Foot- and-mouth disease as zoonosis. *Archives of Virology Supplementum*, 13(1): 95-97. DOI: 10.1007/978-3-7091-6534-8_9
- Bertram, M.R., Vu, L.T., Pauszek, S.J., Brito, B.P., Hartwig, E.J., Smoliga, G.R., Hoang, B.H., Phuong, N.T., Stenfeldt, C., Fish, I.H., Hung, V.V., Delgado, A., VanderWaal, K., Rodriguez, L.L., Long, N.T., Dung, D.H. & Arzt, J. (2018). Lack of transmission of foot-and-mouth disease virus from persistently infected cattle to naïve cattle under field conditions in Vietnam. *Frontiers in Veterinary Science*, 5(1): 174. DOI: 10.3389/fvets.2018.00174
- Bessell, P.R., Shaw, D.J., Savill, N.J. & Woolhouse, M.E. (2008). Geographic and topographic determinants of local FMD transmission applied to the 2001 UK FMD epidemic. *BMC Veterinary Research*, 4(1): 40. DOI: 10.1186/1746-6148-4-40
- Blacksell, S.D., Siengsan-Lamont, J., Kamolsiripichaiorn, S., Gleeson, L.J. & Windsor, P.A. (2019). A history of FMD research and control programmes in Southeast Asia: lessons from the past informing the future. *Epidemiology and Infection*, 147: e171. DOI: 10.1186/1746-6148-4-40
- Bradhurst, R., Garner, G., East, I., Death, C., Dodd, A. & Kompas, T. (2019). Management strategies for vaccinated animals after an outbreak of foot-and-mouth disease and the impact on return to trade. *PLoS ONE*, 14(10): e0223518. DOI: 10.1371%2Fjournal.pone.0223518
- Brown, E., Nelson, N., Gubbins, S. & Colenutt, C. (2022). Airborne transmission of foot-and-mouth disease virus: A review of past and present perspectives. *Viruses*, 14(5): 1009. DOI: 10.3390/v14051009

- Brown, V.R., Miller, R.S., McKee, S.C., Ernst, K.H., Didero, N.M., Maison, R.M., Grady, M.J. & Shwiff, S.A. (2021). Risks of introduction and economic consequences associated with African swine fever, classical swine fever and foot-and-mouth disease: A review of the literature. *Transboundary and Emerging Diseases*, 68(4): 1910-1965. DOI: 10.1111/tbed.13919
- Burrell, C.J., Howard, C.R. & Murphy, F.A. (2017). Laboratory diagnosis of virus diseases. *Fenner and White's Medical Virology*, 135-154. DOI: 10.1016%2FB978-0-12-375156-0.00010-2
- Burman, A., Clark, S., Abrescia, N.G., Fry, E.E., Stuart, D.I. & Jackson, T. (2006). Specificity of the VP1 GH loop of foot-and-mouth disease virus for alphavirus integrins. *Journal of Virology*, 80(19): 9798-9810. DOI: 10.1128%2FJVI.00577-06
- Cao, Y., Li, K., Xing, X., Zhu, G., Fu, Y., Bao, H., Bai, X., Sun, P., Li, P., Zhang, J., Ma, X., Wang, J., Zhao, Z., Li, D., Liu, Z. & Lu, Z. (2022). Development and validation of a competitive elisa based on bovine monoclonal antibodies for the detection of neutralizing antibodies against foot-and-mouth disease virus serotype A. *Journal of Clinical Microbiology*, 60(4): e0214221. DOI: 10.1128/jcm.02142-21
- Capozzo, A.V., Vosloo, W., de Los Santos, T., Pérez, A.M. & Pérez-Filgueira, M. (2023). Editorial: Foot-and-mouth disease epidemiology, vaccines and vaccination: moving forward. *Frontiers in Veterinary Science*, 10(1): 1231005. DOI: 10.3389/fvets.2023.1231005
- Caridi, F., Cañas-Arranz, R., Vázquez-Calvo, Á., de León, P., Calderón, K.I., Domingo, E., Sobrino, F. & Martín-Acebes, M.A. (2021). Adaptive value of foot-and-mouth disease virus capsid substitutions with opposite effects on particle acid stability. *Scientific Reports*, 11(1): 23494. DOI: 10.1038/s41598-021-02757-3
- Chanchaidechachai, T., Saatkamp, H., Inchaisri, C. & Hogeveen, H. (2022). Analysis of epidemiological and economic impact of foot-and-mouth disease outbreaks in four district areas in thailand. *Frontiers in Veterinary Science*, 9(1): 904630. DOI: 10.3389/fvets.2022.904630
- Clemmons, E.A., Alfson, K.J. & Dutton, J.W. (2021). Transboundary animal diseases, an overview of 17 diseases with potential for global spread and serious consequences. *Animals*, 11(7): 2039. DOI: 10.3390%2Fani11072039
- Costa, T. & Akdeniz, N. (2019). A review of the animal disease outbreaks and biosecure animal mortality composting systems. *Waste Management*, 90(1): 121-131. DOI: 10.1016/j.wasman.2019.04.047
- Dash, P., Barnett, P.V., Denyer, M.S., Jackson, T., Stirling, C.M., Hawes, P.C., Simpson, J.L., Monaghan, P. & Takamatsu, H.H. (2010). Foot-and-mouth disease virus replicates only transiently in well-differentiated porcine nasal epithelial cells. *Journal of Virology*, 84(18): 9149-9160. DOI: 10.1128%2FJVI.00642-10
- Davies, G. (2002). The foot and mouth disease (FMD) epidemic in the United Kingdom 2001. *Comparative Immunology, Microbiology and Infectious Diseases*, 25(5-6): 331-343. DOI: 10.1016/s0147-9571(02)00030-9
- de Menezes, T.C., Filho, J.B.S.F. & Countryman, A.M. (2023). Potential economic impacts of foot-and-mouth disease in Brazil: A case study for Mato Grosso and Paraná. *Journal of the Agricultural and Applied Economics Association*, 1-16. DOI: 10.1002/jaa2.73
- Di Giacomo, S., Bucafusco, D., Schammas, J.M., Pega, J., Miraglia, M.C., Barrionuevo, F., Capozzo, A.V. & Perez-Filgueira, D.M. (2022). Assessment on different vaccine formulation parameters in the protection against heterologous challenge with FMDV in Cattle. *Viruses*, 14(8): 1781. DOI: 10.3390%2Fv14081781
- Dillon, M.B. (2011). Skin as a potential source of infectious foot and mouth disease aerosols. *Proceedings: Biological Sciences*, 278(1713): 1761-1769. DOI: 10.1098%2Frspsb.2010.2430
- Ding, Y.Z., Chen, H.T., Zhang, J., Zhou, J.H., Ma, L.N., Zhang, L., Gu, Y. & Liu, Y.S. (2013). An overview of control strategy and diagnostic technology for foot-and-mouth disease in China. *Virology Journal*, 10(1): 78. DOI: 10.1186%2F1743-422X-10-78
- Dinku, S.Y. & Matsuda, T. (2018). Evaluating the impact of the bse and fmd outbreaks on meat demand: An engel curve analysis of japanese daily data. *Japanese Society of Agricultural Technology Management*, 25(1): 1-12. DOI: 10.20809/seisan.25.1_1
- Dong, H., Lu, Y., Zhang, Y., Mu, S., Wang, N., Du, P., Zhi, X., Wen, X., Wang, X., Sun, S., Zhang, Y. & Guo, H. (2021). A heat-induced mutation on VP1 of foot-and-mouth disease virus serotype o enhanced capsid stability and immunogenicity.

- Journal of Virology*, 95(16): e0017721. DOI: 10.1128/jvi.00177-21
- Dubie, T. & Negash, W. (2021). Seroprevalence of bovine foot and mouth disease (FMD) and its associated risk factors in selected districts of Afar region, Ethiopia. *Veterinary Medicine and Science*, 7(5): 1678-1687. DOI: 10.1002/vms3.574
- Eschbaumer, M., Vögtlin, A., Paton, D.J., Barnabei, J.L., Sanchez-Vazquez, M.J., Pituco, E.M., Rivera, A.M., O'Brien, D., Nfon, C., Brocchi, E., Kassimi, L.B., Lefebvre, D.J., López, R.N., Maradei, E., Duffy, S.J., Loitsch, A., De Clercq, K., King, D.P., Zientara, S., Griot, C. & Beer, M. (2020). Non-discriminatory exclusion testing as a tool for the early detection of foot-and-mouth disease incursions. *Frontiers in Veterinary Science*, 7(1): 552670. DOI: 10.3389/fvets.2020.552670
- Espinosa, R., Tago, D. & Treich, N. (2020). Infectious diseases and meat production. *Environmental and Resource Economics*, 76: 1019-1044. DOI: 10.1007/s10640-020-00484-3
- Fana, E.M., Mpoloka, S.W., Leteane, M., Seoke, L., Masoba, K., Mokopasetso, M., Rapharing, A., Kabelo, T., Made, P. & Hyera, J. (2021). A five-year retrospective study of foot-and-mouth disease outbreaks in Southern Africa, 2014 to 2018. *Veterinary Medicine International*, 2021(1): 7438809. DOI: 10.1155/2021/7438809
- Fountain, J., Woodgate, R., Rast, L. & Hernández-Jover, M. (2018). Assessing biosecurity risks for the introduction and spread of diseases among commercial sheep properties in New South Wales, Australia, using foot-and-mouth disease as a case study. *Frontiers in Veterinary Science*, 5(1): 80. DOI: 10.3389/fvets.2018.00080
- Gao, Y., Sun, S.Q. & Guo, H.C. (2016). Biological function of Foot-and-mouth disease virus non-structural proteins and non-coding elements. *Virology Journal*, 13(1): 107. DOI: 10.1186/s12985-016-0561-z
- Gordon, L.G., Porphyre, T., Muhanguzi, D., Muwonge, A., Boden, L. & Bronsvort, B.M.C. (2022). A scoping review of foot-and-mouth disease risk, based on spatial and spatio-temporal analysis of outbreaks in endemic settings. *Transboundary and Emerging Diseases*, 69(6): 3198-3215. DOI: 10.1111/tbed.14769
- Gornik, H.L., Persu, A., Adlam, D., Aparicio, L.S., Azizi, M., Boulanger, M., Bruno, R.M., de Leeuw, P., Fendrikova-Mahlay, N., Froehlich, J., Ganesh, S.K., Gray, B.H., Jamison, C., Januszewicz, A., Jeunemaitre, X., Kadian-Dodov, D., Kim, E.S., Kovacic, J.C., Mace, P., Morganti, A., Sharma, A., Southerland, A.M., Touzé, E., van der Niepen, P., Wang, J., Weinberg, I., Wilson, S., Olin, J.W. & Plouin, P.F. (2019). First international consensus on the diagnosis and management of fibromuscular dysplasia. *Vascular Medicine*, 24(2): 164-189. DOI: 10.1177/1358863x18821816
- Grubman, M.J. & Baxt, B. (2004). Foot-and-mouth disease. *Clinical Microbiology Reviews*, 17(2): 465-493. DOI: 10.1128/cmr.17.2.465-493.2004
- Guan, J., Chan, M., Grenier, C., Brooks, B.W., Spencer, J.L., Kranendonk, C., Coppes, J. & Clavijo, A. (2010). Degradation of foot-and-mouth disease virus during composting of infected pig carcasses. *Canadian Journal of Veterinary Research*, 74(1): 40-44.
- Guerrini, L., Pfukenyi, D.M., Etter, E., Bouyer, J., Njagu, C., Ndhlovu, F., Bourgarel, M., de Garine-Wichatitsky, M., Foggin, C., Grosbois, V. & Caron, A. (2019). Spatial and seasonal patterns of FMD primary outbreaks in cattle in Zimbabwe between 1931 and 2016. *Veterinary Research*, 50(1): 73. DOI: 10.1186/s13567-019-0690-7
- Hagerman, A.D., South, D.D., Sondgerath, T.C., Patyk, K.A., Sanson, R.L., Schumacher, R.S., Delgado, A.H. & Magzamen, S. (2018). Temporal and geographic distribution of weather conditions favorable to airborne spread of foot-and-mouth disease in the coterminous United States. *Preventive Veterinary Medicine*, 161(1): 41-49. DOI: 10.1016/j.prevetmed.2018.10.016
- Hammond, J.M., Maulidi, B. & Henning, N. (2021). Targeted FMD Vaccines for Eastern Africa: The AgResults foot and mouth disease vaccine challenge project. *Viruses*, 13(9): 1830. DOI: 10.3390/v13091830
- Hegde, R., Gomes, A.R., Giridhar, P., Kowalli, S., Shivashankar, B.P., Sudharshana, K.J., Nagaraj, K., Sesharao, R., Mallinath, K.C., Shankar, B.P., Nagaraj, D., Seema, C.M., Khan, T.A., Nagaraj, G.V., Srikala, K., Dharanesh, N.K., Venkatesha, M.D. & Renukaprasad, C. (2014). Epidemiology of foot and mouth disease in Karnataka state, India: a retrospective study. *Virusdisease*, 25(4): 504-509. DOI: 10.1007%2Fs13337-014-0239-3
- Jamal, S.M. & Belsham, G.J. (2013). Foot-and-mouth disease: past, present and future. *Veterinary Research*, 44(1): 116. DOI: 10.1186/1297-9716-44-116

- Jori, F., Hernandez-Jover, M., Magouras, I., Dürr, S. & Brookes, V.J. (2021). Wildlife–livestock interactions in animal production systems: what are the biosecurity and health implications? *Animal Frontiers*, 11: 8-19. DOI: 10.1093/af/vfab045
- Kitching, R.P. & Hughes, G.J. (2002). Clinical variation in foot and mouth disease: sheep and goats. *Revue Scientifique et Technique de*, 21(3): 505-512. DOI: 10.20506/rst.21.3.1342
- Knight-Jones, T.J.D., McLaws, M. & Rushton, J. (2017). Foot-and-Mouth disease impact on smallholders - what do we know, what don't we know and how can we find out more? *Transboundary and Emerging Diseases*, 64(4): 1079-1094. DOI: 10.1111/tbed.12507
- Kristensen, T., Belsham, G.J. & Tjørnehøj, K. (2021). Heat inactivation of foot-and-mouth disease virus, swine vesicular disease virus and classical swine fever virus when air-dried on plastic and glass surfaces. *Biosafety and Health*, 3(4): 217-223. DOI: 10.1016/j.bsheal.2021.07.002
- Lawrence, P., Pacheco, J.M., Uddowla, S., Hollister, J., Kotecha, A., Fry, E. & Rieder, E. (2013). Foot-and-mouth disease virus (FMDV) with a stable FLAG epitope in the VP1 G-H loop as a new tool for studying FMDV pathogenesis. *Virology*, 436(1): 150-161. DOI: 10.1016/j.virol.2012.11.001
- Li, K., Wang, C., Yang, F., Cao, W., Zhu, Z. & Zheng, H. (2021). Virus-Host Interactions in Foot-and-Mouth Disease Virus Infection. *Frontiers in Immunology*, 12(1): 571509. DOI: 10.3389/fimmu.2021.571509
- Limon, G., Ulziibat, G., Sandag, B., Dorj, S., Purevtseren, D., Khishgee, B., Basan, G., Bandi, T., Ruuragch, S., Bruce, M., Rushton, J., Beard, P.M. & Lyons, N.A. (2020). Socio-economic impact of foot-and-mouth disease outbreaks and control measures: An analysis of Mongolian outbreaks in 2017. *Transboundary and Emerging Diseases*, 1(1): 1-16. DOI: 10.1111/tbed.13547
- Longjam, N., Deb, R., Sarmah, A.K., Tayo, T., Awachat, V.B. & Saxena, V.K. (2011). A brief review on diagnosis of foot-and-mouth disease of livestock: Conventional to molecular tools. *Veterinary Medicine International*, 2011(1): 905768. DOI: 10.4061/2F2011%2F905768
- Ludi, A.B., Horton, D.L., Li, Y., Mahapatra, M., King, D.P., Knowles, N.J., Russell, C.A., Paton, D.J., Wood, J.L.N., Smith, D.J. & Hammond, J.M. (2014). Antigenic variation of foot-and-mouth disease virus serotype A. *Journal of General Virology*, 95(2): 384-392. DOI: 10.1099/2Fvir.0.057521-0
- Lyons, N.A., Alexander, N., Stärk, K.D., Dulu, T.D., Rushton, J. & Fine, P.E.M. (2015). Impact of foot-and-mouth disease on mastitis and culling on a large-scale dairy farm in Kenya. *Veterinary Research*, 46(1): 41. DOI: 10.1186/s13567-015-0173-4
- Ma, L.N., Zhang, J., Chen, H.T., Zhou, J.H., Ding, Y.Z. & Liu, Y.S. (2011). An overview on ELISA techniques for FMD. *Virology Journal*, 8(1): 419. DOI: 10.1186/1743-422x-8-419
- Mahmoud, M.A. & Galbat, S.A. (2017). Outbreak of foot and mouth disease and peste des petits ruminants in sheep flock imported for immediate slaughter in Riyadh. *Veterinary World*, 10(2): 238-243. DOI: 10.14202/vetworld.2017.238-243
- Malik, N., Kotecha, A., Gold, S., Asfor, A., Ren, J., Huiskonen, J.T., Tuthill, T.J., Fry, E.E. & Stuart, D.I. (2017). Structures of foot and mouth disease virus pentamers: Insight into capsid dissociation and unexpected pentamer reassociation. *PLoS Pathogens*, 13: e1006607. DOI: 10.1371/journal.ppat.1006607
- Marcos, A. & Perez, A.M. (2019). Quantitative risk assessment of foot-and-mouth disease (FMD) virus introduction into the fmd-free zone without vaccination of argentina through legal and illegal trade of bone-in beef and unvaccinated susceptible species. *Frontiers in Veterinary Science*, 6(1): 78. DOI: 10.3389/fvets.2019.00078
- Maree, F.F., Kasanga, C.J., Scott, K.A., Opperman, P.A., Melanie, C., Sangula, A.K., Raphael, S., Yona, S., Wambura, P.N., King, D.P., Paton, D.J. & Rweyemamu, M.M. (2014). Challenges and prospects for the control of foot-and-mouth disease: an African perspective. *Veterinary medicine (Auckland, N.Z.)*, 5: 119-138. DOI: 10.2147/2FVMRR.S62607
- Mielke, S.R. & Garabed, R. (2020). Environmental persistence of foot-and-mouth disease virus applied to endemic regions. *Transboundary and Emerging Diseases*, 67(2): 543-554. DOI: 10.1111/tbed.13383
- Mohebbi, M.R., Barani, S.M. & Mahravani, H. (2017). An uncommon clinical form of foot-and-mouth disease in beef cattle presented with corneal skin lesions. *Iranian Journal of Veterinary Research*, 18(4): 291-293.

- Moreno-Torres, K.I., Delgado, A.H., Branan, M.A., Yadav, S., Stenfeldt, C. & Arzt, J. (2022). Parameterization of the durations of phases of foot-and-mouth disease in pigs. *Preventive Veterinary Medicine*, 202(1): 105615. DOI: 10.1016/j.prevetmed.2022.105615
- Muleme, M., Barigye, R., Khaitsa, M.L., Berry, E., Wamono, A.W. & Ayebazibwe, C. (2013). Effectiveness of vaccines and vaccination programs for the control of foot-and-mouth disease in Uganda, 2001-2010. *Tropical Animal Health and Production*, 45(1): 35-43. DOI: 10.1007/s11250-012-0254-6
- Muroga, N., Hayama, Y., Yamamoto, T., Kurogi, A., Tsuda, T. & Tsutsui, T. (2012). The 2010 foot-and-mouth disease epidemic in Japan. *The Journal of Veterinary Medical Science*, 74(4): 399-404. DOI: 10.1292/jvms.11-0271
- Muthukrishnan, M., Balasubramanian, N.S. & Alwar, S.V. (2020). Experimental Infection of Foot and Mouth Disease in Indian Sheep and Goats. *Frontiers in Veterinary Science*, 7(1): 356. DOI: 10.3389/fvets.2020.00356
- Naranjo, J. & Cosivi, O. (2013). Elimination of foot-and-mouth disease in South America: lessons and challenges. *Philosophical Transactions of the Royal Society B*, 368(1623): 20120381. DOI: 10.1098/rstb.2012.0381
- Orsel, K. & Bouma, A. (2009). The effect of foot-and-mouth disease (FMD) vaccination on virus transmission and the significance for the field. *Canadian Veterinary Journal*, 50: 1059-1063.
- Park, J.H., Lee, K.N., Ko, Y.J., Kim, S.M., Lee, H.S., Shin, Y.K., Sohn, H.J., Park, J.Y., Yeh, J.Y., Lee, Y.H., Kim, M.J., Joo, Y.S., Yoon, H., Yoon, S.S., Cho, I.S. & Kim, B. (2013). Control of foot-and-mouth disease during 2010-2011 epidemic, South Korea. *Emerging Infectious Diseases*, 19(4): 655-659. DOI: 10.3201/e1904.121320
- Park, S.Y., Jin, J.S., Kim, D., Kim, J.Y., Park, S.H., Park, J.H., Park, C.K. & Ko, Y.J. (2022). Development of Monoclonal Antibody to Specifically recognize VP0 but not VP4 and VP2 of foot-and-mouth disease virus. *Pathogens*, 11(12): 1493. DOI: 10.3390/pathogens11121493
- Paton, D.J., Gubbins, S. & King, D.P. (2018). Understanding the transmission of foot-and-mouth disease virus at different scales. *Current Opinion in Virology*, 28(1): 85-91. DOI: 10.1016/j.coviro.2017.11.013
- Paton, D.J., Di Nardo, A., Knowles, N.J., Wadsworth, J., Pituco, E.M., Cosivi, O., Rivera, A.M., Kassimi, L.B., Brocchi, E., de Clercq, K., Carrillo, C., Maree, F.F., Singh, R.K., Vosloo, W., Park, M.K., Sumption, K.J., Ludi, A.B. & King, D.P. (2021). The history of foot-and-mouth disease virus serotype C: the first known extinct serotype?, *Virus Evolution*, 7: veab009. DOI: 10.1093/ve/veab009
- Paton, D.J., Sumption, K.J. & Charleston, B. (2009). Options for control of foot-and-mouth disease: knowledge, capability and policy. *Philosophical Transactions of the Royal Society B*, 364(1530): 2657-2667. DOI: 10.1098/rstb.2009.0100
- Pattnaik, B., Subramaniam, S., Sanyal, A., Mohapatra, J.K., Dash, B.B., Ranjan, R. & Rout, M. (2012). Foot-and-mouth disease: Global status and future road map for control and prevention in India. *Agricultural Research*, 1: 132-147. DOI: 10.1007/978-11259-022-10010-z
- Perez, A.M. & Willeberg, P.W. (2017). Editorial: Foot-and-Mouth disease in Swine. *Frontiers in Veterinary Science*, 4: 133. DOI: 10.3389/fvets.2017.00133
- Prempeh, H., Smith, R. & Müller, B. (2001). Foot and mouth disease: the human consequences. The health consequences are slight, the economic ones huge. *BMJ*, 322(7286): 565-566. DOI: 10.1136/bmj.322.7286.565
- Rahman, A.K.M.A., Islam, S.K.S., Sufian, M.A., Talukder, M.H., Ward, M.P. & Martínez-López, B. (2020). Foot-and-Mouth disease space-time clusters and risk factors in Cattle and Buffalo in Bangladesh. *Pathogens*, 9(6): 423. DOI: 10.3390/pathogens9060423
- Railey, A.F. & Marsh, T.L. (2019). A Rational explanation of limited FMD vaccine uptake in endemic regions. *Pathogens*, 8(4): 181. DOI: 10.3390/pathogens8040181
- Ranaweera, L.T., Wijesundara, U.K., Jayarathne, H.S., Knowles, N., Wadsworth, J., Mioulet, V., Adikari, J., Weebadde, C. & Sooriyapathirana, S.S. (2019). Characterization of the FMDV-serotype-O isolates collected during 1962 and 1997 discloses new topotypes, CEY-1 and WCSA-1, and six new lineages. *Scientific Reports*, 9(1): 14526. DOI: 10.1038/s41598-019-51120-0
- Ranjan, R., Biswal, J.K., Subramaniam, S., Singh, K.P., Stenfeldt, C., Rodriguez, L.L., Pattnaik, B.

- & Arzt, J. (2016). Foot-and-Mouth disease virus-associated abortion and vertical transmission following acute infection in Cattle under natural conditions. *PLoS One*, 11(12): e0167163. DOI: 10.1371/journal.pone.0167163
- Rawdon, T.G., Garner, M.G., Sanson, R.L., Stevenson, M.A., Cook, C., Birch, C., Roche, S.E., Patyk, K.A., Forde-Folle, K.N., Dubé, C., Smylie, T. & Yu, Z.D. (2018). Evaluating vaccination strategies to control foot-and-mouth disease: a country comparison study. *Epidemiology and Infection*, 146(9): 1138-1150. DOI: 10.1017/S0950268818001243
- Rémond, M., Kaiser, C. & Lebreton, F. (2002). Diagnosis and screening of foot-and-mouth disease. *Comparative Immunology, Microbiology & Infectious Diseases*, 25(5-6): 309-320. DOI: 10.1016/S0147-9571(02)00028-0
- Rodríguez-Habibe, I., Celis-Giraldo, C., Patarroyo, M.E., Avendaño, C. & Patarroyo, M.A. (2020). A Comprehensive Review of the Immunological Response against Foot-and-Mouth Disease Virus Infection and Its Evasion Mechanisms. *Vaccines (Basel)*, 8(4): 764. DOI: 10.3390/Vvaccines8040764
- Shaban, A.K., Mohamed, R.H., Zakaria, A.M. & Baheeg, E.M. (2022). Detection of foot-and-mouth disease virus in raw milk in Menofia Governorate and its effect on reproductive hormones and physiochemical properties of milk. *Veterinary World*, 15(9): 2202-2209. DOI: 10.14202/Vvvetworld.2022.2202-2209
- Shmeiger, Z., Miculitzki, M., Gelman, B., Vaxman, I. & Goshen, T. (2021). The Effect of Foot and Mouth Disease Morbidity Influencing Periparturient Diseases and Culling on Nir Yitzhak Dairy Cattle Farm. *Israel Journal of Veterinary Medicine*, 76(1): 27-34.
- Shurbe, M., Simeon, B., Seyoum, W., Muluneh, A., Tora, E. & Abayneh, E. (2022). Seroprevalence and associated risk factors for foot and mouth disease virus seropositivity in cattle in selected districts of Gamo zone, Southern Ethiopia. *Frontiers in Veterinary Science*, 9: 931643. DOI: 10.3389/Vvfvets.2022.931643
- Singh, R.K., Sharma, G.K., Mahajan, S., Dhama, K., Basagoudanavar, S.H., Hosamani, M., Sreenivasa, B.P., Chaicumpa, W., Gupta, V.K. & Sanyal, A. (2019). Foot-and-Mouth disease virus: Immunobiology, advances in vaccines and vaccination strategies addressing vaccine failures-An Indian perspective. *Vaccines (Basel)*, 7(3): 90. DOI: 10.3390/Vvaccines7030090
- Stenfeldt, C., Eschbaumer, M., Rekant, S.I., Pacheco, J.M., Smoliga, G.R., Hartwig, E.J., Rodriguez, L.L. & Arzt, J. (2016a). The foot-and-mouth disease carrier state divergence in Cattle. *Journal of Virology*, 90(14): 6344-6364. DOI: 10.1128/jvi.00388-16
- Stenfeldt, C., Pacheco, J.M., Brito, B.P., Moreno-Torres, K.I., Branán, M.A., Delgado, A.H., Rodriguez, L.L. & Arzt, J. (2016b). Transmission of Foot-and-Mouth Disease Virus during the Incubation Period in Pigs. *Frontiers in Veterinary Science*, 3(1): 105. DOI: 10.3389/Vvfvets.2016.00105
- Stenfeldt, C., Pacheco, J.M., Singanallur, N.B., Vosloo, W., Rodriguez, L.L. & Arzt, J. (2019). Virulence beneath the fleece; a tale of foot-and-mouth disease virus pathogenesis in sheep. *PLoS One*, 14(1): e0227061. DOI: 10.1371/journal.pone.0227061
- Subramaniam, S., Mohapatra, J.K., Sahoo, N.R., Sahoo, A.P., Dahiya, S.S., Rout, M., Biswal, J.K., Ashok, K.S., Mallick, S., Ranjan, R., Jana, C. & Singh, R.P. (2022). Foot-and-mouth disease status in India during the second decade of the twenty-first century (2011-2020). *Veterinary Research Communications*, 46(4): 1011-1022. DOI: 10.1007/s11259-022-10010-z
- Suchowski, M., Eschbaumer, M., Teifke, J.P. & Ulrich, R. (2021). After nasopharyngeal infection, foot-and-mouth disease virus serotype A RNA is shed in bovine milk without associated mastitis. *Journal of Veterinary Diagnostic Investigation*, 33: 997-1001. DOI: 10.1177/10406387211022467
- Sutawi, Wahyudi, A., Malik, A., Suyatno, Hidayati, A., Rahayu, I.D. & Hartatie, E.S. (2023). Re-emergence of foot and mouth disease outbreak in Indonesia: A review. *Advances in Animal and Veterinary Sciences*, 11(2): 263-270. DOI: 10.17582/journal.aavs/2023/11.2.264.271
- Teifke, J.P., Breithaupt, A. & Haas, B. (2012). Foot-and-mouth disease and its differential diagnoses. *Tierärztliche Praxis Ausgabe G: Grosstiere – Nutztiere*, 40(4): 225-237.
- Tufani, N.A. (2013). Complications of foot and mouth disease in cattle and their clinical management. *Progress Research*, 8(1): 127-129.
- Valarcher, J.F., Leforban, Y., Rweyemamu, M., Roeder, P.L., Gerbier, G., Mackay, D.K., Sumption, K.J., Paton, D.J. & Knowles, N.J. (2008). Incursions of foot-and-mouth disease virus into Europe between 1985 and 2006.

- Transboundary and Emerging Diseases*, 55(1): 14-34. DOI: 10.1111/j.1865-1682.2007.01010.x
- van Vuren, P.J., Singanallur, N.B., Keck, H., Eschbaumer, M. & Vosloo, W. (2022). Chemical inactivation of foot-and-mouth disease virus in bovine tongue epithelium for safe transport and downstream processing. *Journal of Virological Methods*, 305(1): 114539. DOI: 10.1016/j.jviromet.2022.114539
- Walz, E., Evanson, J., Sampedro, F., VanderWaal, K. & Goldsmith, T. (2020). Planning "Plan B": the case of moving cattle from an infected feedlot premises during a hypothetical widespread fmd outbreak in the United States. *Frontiers in Veterinary Science*, 6(1): 484. DOI: 10.3389/fvets.2019.00484
- Wang, G., Wang, Y., Shang, Y., Zhang, Z. & Liu, X. (2015). How foot-and-mouth disease virus receptor mediates foot-and-mouth disease virus infection. *Virology Journal*, 12(1): 9. DOI: 10.1186/12985-015-0246-z
- Waters, R.A., Wadsworth, J., Mioulet, V., Shaw, A.E., Knowles, N.J., Abdollahi, D., Hassanzadeh, R., Sumption, K. & King, D.P. (2021). Foot-and-mouth disease virus infection in the domestic dog (*Canis lupus familiaris*), Iran. *BMC Veterinary Research*, 17(1): 63. DOI: 10.1186/s12917-021-02769-1
- Wekesa, S.N., Sangula, A.K., Belsham, G.J., Tjornehoj, K., Muwanika, V.B., Gakuya, F., Mijele, D. & Siegismund, H.R. (2015). Characterisation of recent foot-and-mouth disease viruses from African buffalo (*Syncerus caffer*) and cattle in Kenya is consistent with independent virus populations. *BMC Veterinary Research*, 11(1): 17. DOI: 10.1186/s12917-015-0333-9
- Woldemariyam, F.T., Kariuki, C.K., Kamau, J., De Vleeschauwer, A., De Clercq, K., Lefebvre, D.J. & Paeshuyse, J. (2023). Epidemiological dynamics of foot-and-mouth disease in the horn of Africa: The role of virus diversity and animal movement. *Viruses*, 15(4): 969. DOI: 10.3390/v15040969
- Wong, C.L., Yong, C.Y., Ong, H.K., Ho, K.L. & Tan, W.S. (2020). Advances in the diagnosis of foot-and-mouth disease. *Frontiers in Veterinary Science*, 7(1): 477. DOI: 10.3389/fvets.2020.00477
- Wubshet, A.K., Dai, J., Li, Q., & Zhang, J. (2019). Review on outbreak dynamics, the endemic serotypes, and diversified topotypic profiles of foot and mouth disease virus isolates in Ethiopia from 2008 to 2018. *Viruses*, 11(11): 1076. DOI: 10.3390/v11111076
- Yuan, H., Li, P., Ma, X., Lu, Z., Sun, P., Bai, X., Zhang, J., Bao, H., Cao, Y., Li, D., Fu, Y., Chen, Y., Bai, Q., Zhang, J. & Liu, Z. (2017). The pH stability of foot-and-mouth disease virus. *Virology Journal*, 14(1): 233. DOI: 10.1186/s12985-017-0897-z