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Review Article

Review on Foot and Mouth Disease and Its Status in Ethiopia

Yalew ST*

Animal Biotechnology Research Program, National Agricultural Biotechnology Research Centre, Ethiopian Institute of Agricultural Research, Holetta, Ethiopia

***Corresponding author:** Yalew ST, Animal Biotechnology Research Program, National Agricultural Biotechnology Research Centre, Ethiopian Institute of Agricultural Research, P. O. Box: 249, Holetta, Ethiopia

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Abstract

Foot and Mouth Disease (FMD) is among the highly contagious diseases of domestic animals. It is caused by genus *Aphthous* virus known as foot and mouth disease virus, which is an RNA virus, a positive sense, single stranded, a small non-enveloped belongs to family *Picornaviridae*. The virus exists in seven immunologically distinct serotypes O, A, C, Southern African Territories (SAT) 1, SAT2, SAT3 and Asia1. The disease is characterized by fever, loss of appetite, salivation, vesicular eruptions in the mouth, on the feet and teats and sudden death of young stock. The disease hinders to global trade in live animals and animal products. In Ethiopia endemic distributions of five of seven serotypes of FMDV are maintained and FMD is posing a major threat thereby causing substantial economic losses through morbidity and mortality.

Keywords: Ethiopia; Foot and Mouth Disease; Serotypes

Abbreviations

%: Percent; ˚C: Degree Celsius; AA: Addis Ababa; BHK-21: Baby Hamster Kidney 21 day; CFT: Complement Fixation Tests; CPE: Cytopathic Effect; Cre: Cis-acting Replication Element; DNA: Deoxyribose Nucleic Acid; ELISA: Enzyme-Linked Immunosorbent Aassays; ETB: Ethiopian Birr; FAO: Food and Agriculture Organization; FMD: Foot and Mouth Disease; FMDV: Foot and Mouth Disease Virus; IRES: Internal Ribosome Entry Site; Kb: Kilo Base Pair; MAbs: Monoclonal Antibodies; NSP: Non Structural Protein; OIE: World Animal Health Organization; ORF: Open Reading Frame; PCR: Polymerase Chain Reaction; RdRp: RNA Dependent RNA Polymerase; RNA: Ribonucleic Acid; rRT-PCR: Real Time Reverse Transcriptase Polymerase Chain Reaction; RT-PCR: Reverse Transcriptase Polymerase Chain Reaction; SAT: South Africa Territories; SNNPs: Southern Nations, Nationalists and peoples; SP: Structural Protein; UK: United Kingdom; US$: United States Dollar; UTR: Untranslated Region; VNT: Virus Neutralization Test; VP: Virus Protein

Introduction

Foot-and-Mouth Disease (FMD) is a highly contagious trans boundary animal disease affecting *artiodactylae*, mostly cattle, swine, sheep, goats, and many species of wild ungulates [1]. It is caused by genus *Aphthous* virus known as foot and mouth disease virus, which is an RNA virus, a positive sense, single stranded, a small non-enveloped belongs to family *Picornaviridae* [2]. The viral genome has about 8.3 kb long and enclosed in a protein capsid. It contains a single Open Reading Frame (ORF) encodes the four structural proteins which form the capsid (VP1, VP2, VP3, VP4); the VP1-3 proteins are located on the surface, while VP4 is internal [3] and ten non-structural proteins (L, 2A, 2B, 2C, 3A, 3B1-3, 3C and 3D) [4]. FMDV has a high mutation rate because the viral RNA dependent RNA polymerase lacks proofreading ability and have seven antigenically different serotypes such as A, O, C, Southern African Territeries (SAT) 1, SAT2, SAT3 and Asia1 as well as over 60 subtypes. It is distributed in Africa, Asia, South America and parts of Europe. The disease can occur in any country, but Japan, New Zealand, Australia and some other countries are FMD free [5].

The virus enters a new susceptible animal either orally (especially swine) or via the respiratory tract (especially cattle). Aerosol transmission is the major means of animal-to-animal spread within premises. The disease is characterized by vesicular lesions and erosions of the epithelium of the mouth, nose, muzzle, feet, teats and udder. FMD-infected animals usually develop blister-like lesions in the mouth, tongue and lips, teats, or between the hooves, which causes them to salivate profusely or become lame. Though FMD virus (FMDV) is not typically considered a zoonotic disease, and is not a threat to public health [6].

FMDV is endemic in Ethiopia causing several outbreaks every year [7]. Previous studies have provided evidence for the presence of five FMDV serotypes from the seven serotypes (O, A, C, SAT1, SAT2) were reported in Ethiopia samples collected from different outbreaks. Currently the occurrence of FMD outbreaks in Ethiopia is increasing from time to time and cattle were under risk of infection, however, there is no government strategy in FMD control. Lack of vaccination strategies, presence of free animal movement, high rate of contact among animals at commercial markets, in communal grazing areas and watering points, poor surveillance and diagnostic facilities were among the reasons forwarded for increasing incidence of the disease.

Therefore, the main objective of the study is to review foot and mouth disease virus, disease, serotypes and its status in Ethiopia.

Definition

Foot and Mouth Disease (FMD) is a highly contagious viral disease of cloven-hooved animals with significant economic impact, in cattle and swine as well as sheep and goats [8-11]. The disease is characterized by fever, loss of appetite, salivation, vesicular eruptions in the mouth, on the feet and teats and sudden death of young stock [12-14].

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Etiology

Foot and mouth disease is associated with foot and mouth disease virus (FMDV), is classified within the *Aphthovirus* genus as a member of the *Picornaviridae* family, being small, a non-enveloped, single stranded RNA virus, icosahedral and is 26nm in diameter [12,15], which occurs as seven major serotypes, over 60 subtypes have been described.

Genomic Structure of FMDV

The FMDV genome is an 8.3kb single stranded positive sense RNA. It is divided into three sections; 5'Untranslated Region (UTR), a single Open Reading Frame (ORF) and 3'UTR [3,16,17]. The organization of the FMDV genome is shown in Figure 1. Following this protein is the 5'UTR which consists of an S fragment, poly C tract, pseudoknot structures, a cis-acting replication element (cre) and the internal ribosome entry site (IRES) [18].

The viral genome is enclosed in a protein capsid [3,17,19]. The viral genome encodes the four structural proteins which form the capsid (VP1-VP4); the VP1-3 proteins are located on the surface, while VP4 is internal [3,4,17,20] and ten non-structural proteins (L, 2A, 2B, 2C, 3A, 3B1-3, 3C and 3D) [4,21]. These four proteins form the capsid of the virus and are coded for by 1D, 1B, 1C and 1A coding sequences respectively. The genome is subject to a high rate of mutation because the FMDV RNA-dependent RNA polymerase lacks proof reading ability [22].

Lastly, the 3'UTR follows the ORF termination codon. It is involved in the replication of the RNA and consists of a stem-loop structure and a poly A tract which plays a role in the translation process (Figure 1) [21,23].

Error-Prone Replication of FMDV

FMDV RNA replicates within the cytoplasm of infected cells and requires the virus encoded RNA-dependent RNA polymerase. This enzyme catalysis the synthesis of a negative strand copy of the positive strand viral genome and then the nascent negative strand is used as the template for the production of new positive strand RNA molecules. The positive strand RNAs can be packaged by the virus capsid proteins to make new virus particles. The VPg acts as a protein primer for the synthesis of the viral RNA [24]. The replication process is error prone, i.e. incorrect nucleotides are incorporated into the RNA copies. On average the error rate suggest that about 1 error is made for every 10,000 nucleotide that are synthesized [25]. There is no known mechanism of proof reading activity in picornaviruses and thus the viral RNA represents a pool of closely related sequences; this pool is known as a quasi-species [26]. Modifications to the fidelity either to increase or decrease the error rate the 3Dpol from picornaviruses reduce the "fitness" of the virus [27]. Because of this continuous generation of errors, the virus population is always evolving. During the process of RNA replication, it is possible for the RNA polymerase (3Dpol) to switch from copying one positive strand template to another [28,29].

Serotypes of Foot and Mouth Disease Virus (FMDV)

There are seven immunologically distinct serotypes of FMDV namely O, A, C, SAT (Southern African Territories) 1, 2 and 3, and Asia 1, which infect cloven hoofed Animals [21,30-32]. In 1922 Vallée and Carré demonstrated that the existence of serotype O, they named these Vallée O after the regions they originated from department of Oise in France but latter shortened to O [33]. Serotype O is the pandemic and the most prevalent serotype worldwide, although there is no precise genetically explanation for this higher prevalence [34].

In 1922 Vallée and Carré demonstrated that the existence of serotype A, they named these Vallée A (Allemagne in French) but latter shortened to A [33]. FMDV serotype A is the most genetically and antigenically diverse among the seven FMDV serotypes and more than thirty subtypes have been identified [35,36]. The serotype C was identified by Waldmann & Trautwein in 1926, they named these Waldmann C but latter shortened to C [37]. Serotype C has a very limited distribution compared with most of the other FMDV serotypes [35].

The serotype Asia 1 was identified in the early 1950s in viruses isolated from India and Pakistan [38,39]. The members of this serotype seem to be the less virulent and are usually restricted to Asia [40-42]. Southern African Territories 1 and 2 serotypes were identified in 1948 in samples from Bechuanaland (Botswana) and Northern Rhodesia (Zambia) [43]. Retrospective testing of samples from Southern Rhodesia (Zimbabwe) from the 1930s found Southern African Territories 1 to 3 (SAT 1, SAT 2 and SAT 3). The natural host for the SAT viruses is the African buffalo which is persistently infected with multiple serotypes.

Genotypes of FMDV

The seven serotypes of FMDV cluster into distinct genetic lineages with approximately 30%-50% differences in the VP1 gene [44]. FMD viruses are classified into geographically restricted clusters also known as topotypes [44,45]. Topotypes generally refers to isolates that has <15% genetic variations for serotypes O, A and C and <20% for SAT serotypes [31,44]. Distinct genetic variants exist within these serotypes, with the serotypes being divided into topotypes based on genetic differences [44]. Serotype SAT1 can be grouped into eight topotypes I to VIII. This is based on nucleotide differences [46]. SAT2 viruses appear to be particularly diverse, with the largest number of topotypes, whilst serotype C, probably as a result of being the rarest serotype in the continent, has the fewest [47-49].

Mode of transmission

Susceptible animals are infected through direct or indirect contact with infected animals or other objects exposed to live virus. The most common route of infection of susceptible animals is by direct contact, either by mechanical transfer or by aerosol infection. Oral transmission is also possible especially when the animal has damaged skin in and around the mouth as well as on pre-existing abrasions on animals [50]. Some cases of airborne transmission as far as 300km from source of infection have been described [51,52].

Inhalation of aerosolized virus is also common mode of transmission for cattle [50]. Pigs are more likely to get infected by eating contaminated food [53]. Pigs can be infected by FMDV if placed in premises previously housing infected animals and like cattle; they are at risk of infection due to direct contact with infected animals [23].

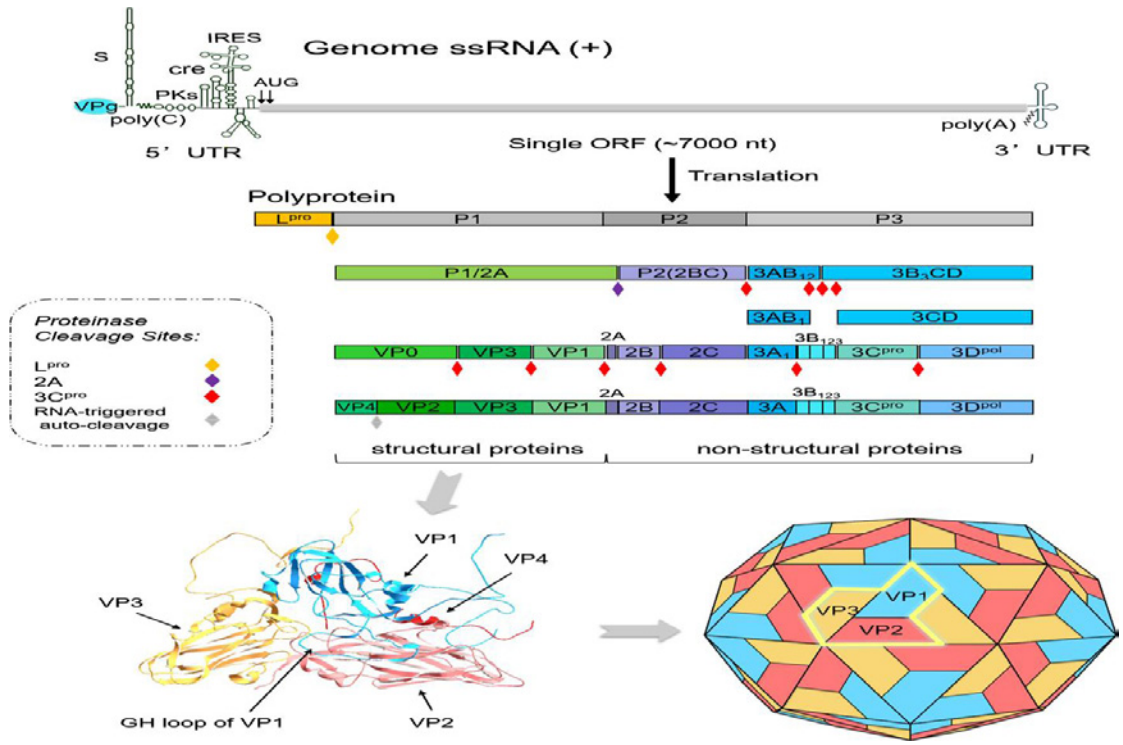

Figure 1: Schematic diagram of FMDV genome, processing of viral polypeptide and conformations of the structural proteins.
Source: [4]

Incubation period

Incubation period, depends on the dose of the virus, portal of entry, animal husbandry practices and animal species involved [23,54,55] in cattle it varies from 2-14 days in pigs it is usually 2 days (or more) but can be even short (18-24 hours) and in sheep normally it is 3-8 days [56]. The incubation period is most likely to be 2-6 days [54].

Clinical signs and lesions

The severity of clinical signs of the disease varies with the strain of the virus, the exposure dose, the age and breed of the animal, the host species, and its degree of immunity. The signs can range from a mild or in apparent in sheep and goats to a severe disease occurring in cattle and pigs [57].

FMD in Bovine is systemic vesicular disease characterized by fever (above 40°C), excessive salivation, lameness, depression and decreased milk production, which requires a differential diagnosis from other vesicular diseases [58]. The mucosa of the lips, dorsum of the tongue and the dental plate are most severely involved. Lesions are often observed initially as blanched areas, which subsequently develop into vesicles (Figure 2). The vesicles rupture and then heal whilst coronary band lesions may give rise to growth arrest lines that grow down the side of the hoof [59].

FMD in pigs primarily affects the feet. It is dominated by rather painful formation of vesicles in the epidermis of the feet (coronary band, interdigital clefts and bulbs) associated with severe lameness [60]. Clinical signs of FMD in sheep and goats are less severe; often only lameness through aphthae and inflammation at the cloves [55]. Lameness is usually the first indication of FMD in sheep and goats. An affected animal develops fever, is reluctant to walk and may separate itself from the rest of the flock. Vesicles may develop in the interdigital cleft, on the heal bulbs and on the coronary band but they usually rupture rapidly [60].

Pathogenesis

The predominant entrance of virus is most commonly through the upper respiratory tract by inspiration of infected aerosols, but infection may also occur through a skin injury [61]. After inhalation, the virus can affect the pharynx and primary multiplication of the virus in the mucous membrane is transported by lymphatic and blood circulation to the sites of secondary multiplication in the lymphatic glands, epithelial tissues in and around the mouth, feet and in the mammary glands. Secondary replication in other glandular tissues, the virus appears in different body fluids such as milk, urine, respiratory secretions and semen before the appearance of clinical signs of FMD. The virus can also persist in oral cavity of infected animals for long periods after the acute infection [50].

Morbidity and mortality rate

Variation in the morbidity rate occurs and may depend on species, age, sex as well as the status of the immunity. The morbidity rate in cattle is 100% but mortality rate is very low (2%) [62]. However, fatality in calves may reach up to 20% [62,63]. The death in young animals may be due to myocarditis [64].

Molecular Epidemiology of FMDV

The molecular epidemiology of FMDV is based on the comparison of genetic differences between viruses [44]. The molecular

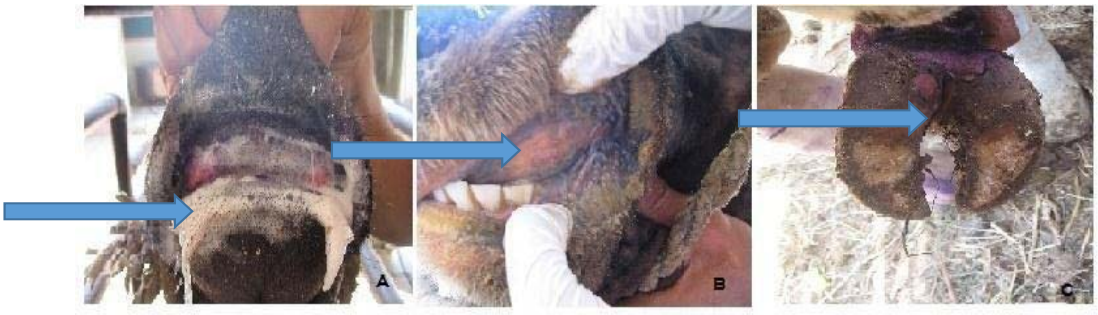

Figure 2: Clinical signs of FMD. (A) Salivation; (B) Erosion of oral mucosa and (C) erosion in interdigital space.
Source: [120]

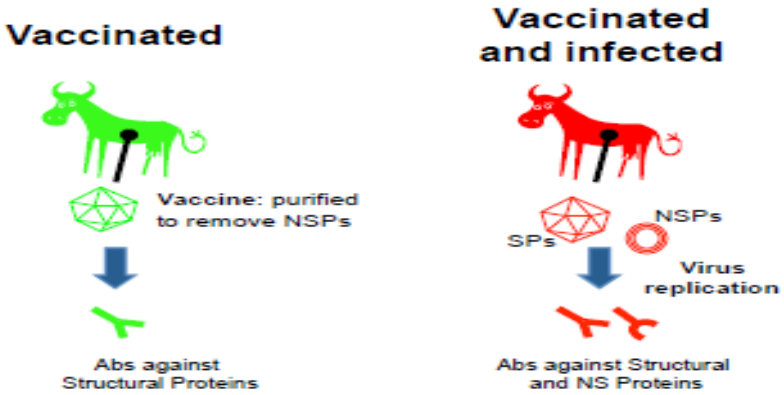

Figure 3: The principle of using NSPs tests to differentiate between vaccinated and infected animals.
Source: [19]

epidemiology of FMDV has been extensively studied using the VP1 coding region of the virus genome. Phylogenetic analysis of VP1 can be applied to categorize field strains into discrete topotypes and lineages which, despite the tendency for the virus to spread, frequently show geographical clustering based on the historical distribution of the virus [31]. VP1 is the most variable capsid protein includes a major immunogenic site of the virus has been used to genotype the seven serotypes of FMDV into geographically distinct groups called topotypes. In VP1 protein only 26% of its amino acids are universally conserved between serotypes [65]. Furthermore, comparison of VP1 coding sequences from isolates obtained during outbreaks provides evidence of relatedness between individual FMDV strains and hence the tracing of the spread and transmission of the virus from one region to another or across national borders [44]. The evolutionary changes of virus are determined by comparing genomic material from more than one virus with each other. At present, sequencing and phylogenetic trees are widely used to illustrate the genetic relationship between viruses [66].

Diagnosis Techniques of FMD

The disease is diagnosed based on clinical signs, including high temperature, excessive salivation, and formation of vesicles on the oral mucosa, on the nose plus the inter-digital spaces and coronary bands on the feet. However, the clinical signs can be confused with other diseases and thus laboratory based diagnosis is necessary [21].

For laboratory diagnosis, the sample of choice is tissue epithelium or vesicular fluid. In advanced or convalescent cases, or where infection is suspected in the absence of clinical signs, samples of oropharyngeal fluid is collected by means of a probang cup (or in pigs by swabbing the throat) for diagnosis. Serum samples are used for FMD diagnosis based on spiking of antibody against a particular serotype [67].

Diagnosis of FMD in the laboratory is conducted by virus isolation, demonstration of the FMD viral antigens or nucleic acid in a sample tissue or fluid. Detection of virus specific antibodies can also be used. Additionally, antibodies to viral nonstructural protein can be used as indicators of infection irrespective of vaccination status [23].

Virus isolation

The isolation and characterization of the virus is the "golden standard" for the diagnosis of viral diseases [14]. Virus Isolation (VI) remains the definitive proof of the presence of live FMDV. Virus isolation requires the presence of infectious virus, which depends on sample quality. Up to 4 days may be required to demonstrate the presence of virus, especially when the levels of virus are low [21].

Serological approaches

The virus infection can be diagnosed by the detection of specific antibody response [14]. Serological tests are widely used to monitor the immune status of animals exposed to FMDV or FMDV vaccines. Approaches used include Enzyme Linked Immunosorbent Assays (ELISAs) and Virus Neutralization Tests (VNTs), although Complement Fixation Tests (CFT) are still used in a limited number

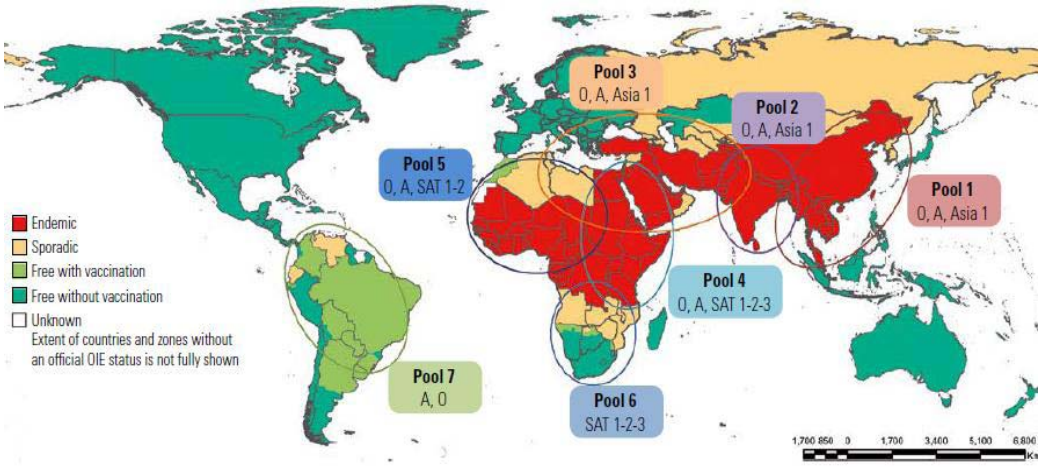

Figure 4: Global circulation of foot and mouth disease virus.
Source: [121]

Figure 5: Occurrence of FMD serotypes in Africa from 1990 to 2013. Countries colored with light grey: North Africa, white: West, Central and East Africa, dark grey: Southern Africa.
Source: [84]

of laboratories.

DIVA (differentiating infected from vaccinated animals) principle exploits differences in the antibody (humoral) responses generated in vaccinated animals compared to those animals naturally infected with FMDV (whether or not they have been vaccinated). During natural infection with FMDV, viral NSP are expressed that elicit a corresponding immune response that can be detected using diagnostic approaches (Figure 3) [19].

Nucleic acid recognition method

The Polymerase Chain Reaction (PCR) can be used to amplify the genome fragments of FMDV in diagnostic material [68]. The PCR techniques are the most widely used nucleic acid based diagnostic technique for rapid identification of FMD virus [69]. A specific reverse transcriptase polymerase chain reaction was developed and validated for the detection of the polymerase gene (3D) of FMD with an sensitivity equal to 1000 times higher than that of a single passage virus isolation [58]. RT-PCR is used as diagnostic tool for FMD virus where specific primers are designed to distinguish seven serotypes.

Real time PCR assays recommended by the World Organization for animal health (OIE) for detection of FMDV incorporate universal primers and fluorescent labeled probes that recognized conserved

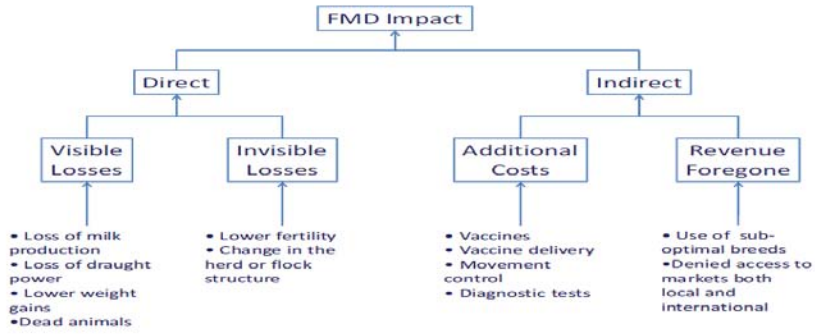

Figure 6: The impacts of foot and mouth disease.
Source: [122]

Table 1: Serotypes of foot and mouth disease virus isolated in Ethiopia from 1981 to 2018.

Year	Serotypes	Sample origin	References
1988-1991	O and SAT 2	Addis Ababa, Eritrea, Wellega, Hararge, Dire Dawa, Borena	[105]
1981-2007	O, A, C, SAT 1 and SAT 2	Addis Ababa, Ahmara and Tigray, Dire Dawa, Beneshangul-Gumuz, and Southern Nations Nationalities and Peoples Region	[107]
2007/08	O and SAT 1	Girar Jarso, Yabello, Surma, Maji, Ankesha Guagusa,	[106]
2007-2012	O, A, SAT 1 and SAT 2	Koka, Surma, Sheka, Yeki, Benshangul Gumuz, Debre Zeit, Addis Ababa, Bahir Dar	[101]
		Harar, Debre Birhan Sululta	
		East Shoa, Arbaminch	
		Abaya, Borena, Dama, Guji, Adama, Mekelle, Jille Timuga, Kombolcha, Wollayta Sodo, Sidama, Mekele	
2008/09	O and A	Bahirdar Zuria, South Achefer,	[108]
		Yilmana Densa, and Dangela, East	
		Harereghe (Haremaya University dairy farm), Borena	
		(Yabello District), and Bale (Sinana District)	
2009/10	O and SAT 2	AA, Debre-Birhan, Debre-Zeit, Sululta	[109]
2010/2011	O and SAT 2	Debrezeit (Ada clinic)	[110]
2011/12	O	Mekelle University Farm, Aynalem, Shibta, Cholekot, Debri	[111]
2011/2012	O	Alage Dairy Farm, Alaba, Adamitulu Jido kombolcha, Debre Zeit, Malga, Adama, Akaki-Kality, Mekele Universty Farm, Enderta, Debre Berehan	[112]
2015/16	A, O and SAT2	Guna, Ludehitosa, Adama, Boset, Kolfe	[113]
2016/17	O, A, SAT 1 and SAT 2	Wolmera, Adea Berga Kolfe keranyo, Mulo, Kimbit	[114]
2016/17	O and A	Mulo woreda, Aleltu, Kimbibit and Wochale woredas, Adea woreda and Kolfe Koraneyo subcity	[115]
2016/17	O	Addis Ababa, Bishoftu, Adama	[116]
2016/17	O and SAT 2	Akaki, Bole, Yeka sub city, Mojo, Koka, Alemtena, Angolela, Birbersa and Godoberet	[117]
2016/17	O and A	Mulo, Aleltu, Kimbibit, Wochale, Adea woredas and Kolfe Koraneyo sub city	[118]
2017/18	O and A	Meki, Bishoftu, Shewarobit, Bole sub city	[119]

region within the 5' UTR or conserved gene regions within the RNA-dependent RNA polymerase gene ($3D^{pol}$) [70]. This is most sensitive and rapid method to detect the nucleic acid [71].

Differential diagnosis

Clinical signs of FMD have got species variation but feet vesicles and erosions or those in the oral cavity or teats suggest the presence of disease. Clinical signs of excessive salivation (except in pigs and sheep) and laminitis with the history of high rise of temperature are always suggestive of FMD [56]. Clinically, it is impossible to distinguish foot and mouth disease from the other vesicular diseases of the viral origin. Vesicular stomatitis, Vesicular exanthema and Swine vesicular disease required laboratory studies to differentiate them from foot and mouth disease [72,73].

Geographical distribution

More than 100 countries are still affected by FMD worldwide and distribution of the disease roughly reflects economic development [21]. Globally and across multiple serotypes, there are distinct genetic and antigenic strains of FMDV circulating and evolving in defined geographical regions that are hence grouped into seven regional pools. Pools 1 and 2 occur in Asia, while pool 3 occurs in Asia, Middle East and North Africa. Virus pool 7 is found in South America while Africa contains 3 different pools roughly spread across East, West and

South Africa respectively (Figure 4) [74,75]. FMDV has an essentially global distribution, with the exception of North America and Central America, New Zealand, Australia, Greenland, Iceland and Western Europe.

The seven serotypes display different geographical distributions and epidemiology [44,76,77]. The cumulative incidence of FMD serotypes showed that six of the seven serotypes of FMD (O, A, C, SAT1, SAT2, SAT3) have occurred in Africa [30,47,78].

Distribution of FMDV Serotypes and Topotypes in Africa

Foot and mouth disease was first described in Africa in 1780 but the disease may have been present in the continent for centuries. Foot and mouth disease is endemic in Africa and the epidemiology of the disease is more complicated than in other parts of the world [79]. In Africa, the FMDV serotypes are not uniformly distributed and each serotype results in different epidemiological patterns. The cumulative incidence of FMDV serotypes show that six of the seven serotypes of FMD (O, A, C, SAT1, SAT2 and SAT3) have occurred in Africa with the exception of Asia-1 (Figure 5) [30,80].

Based on the antigenic relationship of the virus and genetic characterization of FMDV in Africa, the virus distribution has been divided into three virus pools: namely, pool 4 covering East and North Africa, with predominance of serotypes A, O, SAT1, and SAT2; pool 5 restricted to West and northern Africa, with serotypes O, A, SAT1, and SAT2; and pool 6 restricted mainly to South Africa, with SAT1, SAT2, and SAT3 serotypes (Figure 4) [80-83].

The term topotype is used to reflect the presence of genetically and geographically distinct evolutionary lineages [46]. In Africa, six topotypes have been identified for serotype O, two for serotype A, three for serotype C, nine for serotype SAT1, fourteen for serotype SAT2 and five topotypes for serotype SAT3 [31,84].

Table 2: Summary of topotype distribution of FMDV serotypes in Ethiopia from 1979 to 2018.

Serotype	Topotype	Genotype/strain	Country/year	References
O	EA-1		Ethiopia (1979–2001)	[66]
	EA-3		Ethiopia (1981–2007)	[107]
	EA-4		Ethiopia (1981–2007)	[107]
	EA-4		Ethiopia (2016-2017)	[114]
	EA-3		Ethiopia (2017-2018)	[119]
	EA-3		Ethiopia (2009/2010)	[109]
	EA-3		Ethiopia (2011/2012)	[112]
	EA-3		Ethiopia (2008/09)	[108]
	EA-3		Ethiopia (2011/2012)	[111]
	EA-4		Ethiopia (2016/17)	[116]
	EA-4		Ethiopia (2016/17)	[117]
A	Africa		Ethiopia (1981–2007)	[107]
	African	IV	Ethiopia (2015/2016)	[113]
	Africa	G-VII	Ethiopia (2008/09)	[108]
	African	G-I	Ethiopia (2017/2018)	[119]
C	Africa		Ethiopia (1981–2007)	[107]
SAT 1	IX		Ethiopia (2007)	[107]
	IX		Ethiopia (1981–2007)	
SAT 2	XIV		Ethiopia (1991)	[107]
	IV		Ethiopia (1989)	
	XIV		Ethiopia (1991)	
	XIII		Ethiopia (2007)	
	XIII		Ethiopia (2009/10)	[109]
	VII	Alx-12	Ethiopia (2015/2016)	[113]

Treatment

Currently, there is no specific drug, which can be recommended to treat foot and mouth disease [23]. Instead of specific treatment, symptomatic treatments may be applied depending on the clinical manifestations. Sodium carbonate, boric acid and glycerin may be applied over the lesion. Feet of the affected animals may be also washed with 2% copper sulphate solution. Washing of the wounds with soda ash solution and topical application of honey is found suitable in foot lesions [85]. Antiviral approaches including 2'-C-Methylcytidine and ribavirin are useful for the purpose of prophylaxis in susceptible animals [86,87].

However, proper animal husbandry practices and treatment of secondary bacterial infection of lesions and dressing to inflamed areas to prevent secondary infection is recommended in endemic countries where slaughter policy is not enforced. Sick animals may be treated by applying broad-spectrum antibiotics parentally, tetracycline in particular, in order to control the consequences of secondary bacterial infections [63]. Affected animals will recover however with loss of production based on the infection state of the disease. The recovery in animals may take around 15 days [23].

Prevention and control measures

Foot and mouth disease is subject to national and international control and the measures taken depend on whether the country is free from the disease, is subject to sporadic outbreaks or has endemic infection [30]. In countries free of FMD that have naive livestock populations, great attention is paid to reducing the possibility of incursions of the virus [88]. In disease free counties, strict movement controls and slaughter of infected and contact animals when outbreaks occur is applied. In endemic areas, the disease is generally controlled by vaccination and movement restriction of animals [89].

Preventive measures in the absence of disease should be implemented as follows: Control of national borders to prevent significant movement of animals and livestock products from non-free neighbors or trade partners. For officially free countries, prohibition of imports of animals and livestock products from endemic countries in accordance with the OIE standards. Emergency measures in the event of outbreaks through: Rapid slaughter of infected animals, in contact animals and herds considered to have received infection by contact, to reduce the quantity of virus released policy of "stamping-out", followed by cleaning and disinfection to reduce the risk of re-infection, strict movement controls, extending to movement on and off farms of livestock products. And also possible emergency vaccination is important [10,63].

In Ethiopia context the control of FMD is practiced by involvement

of quarantine, isolation of infected animals, restriction of animal movement, vaccination programs, proper disposal of infected carcass and other methods which are feasible to Ethiopian economy [14]. Currently there is no country-wide vaccination program aimed to control FMD and ring vaccination is carried out around an infected area. Considering the wide prevalence of serotypes the National Veterinary Institute (NVI) is producing an inactivated trivalent vaccine which contains O, A and SAT 2 serotypes [90].

Economic Impacts of FMD

Foot and mouth disease is one of the most important livestock diseases in the world in terms of economic impact [91,92]. FMD hinders the trading of milk, meat, animals and other agricultural products. The global impact of the disease can be separated in to direct and indirect loses (Figure 6) [13]. The direct and indirect losses associated with FMD are in terms of mortality, morbidity and milk production, import-export losses, growth rate and abortion [56]. The disease also interferes with agriculture [58,93,94]. Additional costs include application of control measures such as quarantines, slaughter, compensation, vaccination as well as conducting scientific surveillance after an outbreak in order to prove that the disease and the virus have been eliminated [95]. It has been estimated that the costs associated with FMD in endemic areas ranges between 6.5 to 21 billion USD annually [13,96]. Outbreaks in previously FMD-free countries are estimated to cost more than 1.5 billion USD per year [96]. Estimates of indirect costs due to lost exports for the US. have been estimated at $6.3 billion in beef exports and about $5.6 billion in pork exports each year [97].

In Ethiopia FMD is posing a major threat thereby causing substantial economic losses through morbidity and mortality [98]. The country lost more than 14 million USD in consequence of the Egyptian trade ban in 2005/2006 [72]. In 2011 the total annual economic loss due to bulls rejection from international market was estimated to be 3,322,269 USD [99]. According to [100] about 71,026.8 USD losses was recorded in terms of economic impact on export earnings. [101] reported that the estimated economic losses of FMD outbreak in cattle, arising from milk loss, mortality and draft power loss, average 76 USD per affected herd, 9.8 USD per head in crop-livestock mixed system, and 174 USD per affected herd and 5.3 USD per head in the pastoral system. In another study, the overall short-term farm level direct loss due to FMD outbreak in an urban dairy farm was estimated to €1962 [102].

FMD in Ethiopia

Disease status

FMD is endemic to Ethiopia as it is in all the bordering countries like Eritrea, Sudan, Kenya and Somalia and restriction of animal movement is limited. The disease is widely prevalent and previously used to occur frequently in the pastoral herds of the marginal lowland areas of the country. However, this trend has been changed and currently the disease is frequently noted in the highlands of the country [98].

FMD virus serotypes identified

In Ethiopia foot and mouth disease was first recorded in 1957 when serotypes O and C were found while serotype A was identified in 1969 [103,104]. The first isolation of SAT2 in Ethiopia was in 1989 in a sample collected from Awassa, Sidamo and Negelli Borena [105]. The presence of FMDV serotype SAT1 in Ethiopia was isolated and reported for the first time in 2008 from three species of animals; cattle, sheep and goats [106]. Currently FMD is endemic and widely prevalent and distributed in all areas of the country [98].

Endemic distributions of five of seven serotypes of FMDV are maintained in the country and serotypes O, A, C, SAT1 and SAT2 were responsible for FMD outbreaks during 1981-2018 as shown in Table 1. From the report, serotype O was the most predominant serotype circulating in the country [101]. The serotype C has not been reported in the country since 1983 [98,107].

Topotype is used to describe the presence of genetically and geographically distinct evolutionary lineages [46]. Previous studies have provided evidence for the presence of different topotypes of FMDV serotypes from the five serotypes (O, A, C, SAT1, SAT2) reported in Ethiopia samples collected from different outbreaks occurred from 1979-2018 as shown in Table 2.

Vaccine type

In Ethiopia trivalent inactivated vaccine manufactured from locally isolated FMDV serotypes O, A and SAT2 is produced by the National Veterinary Institute (NVI) [90]. The virus is propagated from cell culture and absorbed into aluminum hydroxide gel and inactivated with 0.3% formaldehyde and adjuvinated with saponin.

Conclusion

Foot and Mouth Disease (FMD) is a highly contagious viral disease of cloven-hooved animals with significant economic impact. The presence of foot and mouth disease in the country is a major obstacle to the development of livestock resource because of its adverse effects on production, live cattle exporting and their product exports. Therefore regular FMD outbreak investigation should be conducted to have more detailed information about the serotypes and topotypes circulating in the country and regular vaccination program should be started to control the outbreak of the disease.

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