Review On Foot And Mouth Disease

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Abstract: Foot and mouth disease (FMD) is one of the most contagious diseases of mammals and has a great potential for causing severe economic loss in susceptible cloven hoofed animals. It causes production losses, high mortality in young animals, and is a major constraint to international trade in live animals and their products. There are seven serotypes of FMD virus (FMDV), namely, O, A, C, SAT 1, SAT 2, SAT 3 and Asia 1. Within this serotypes there are also a number of subtypes of the virus. Infection with one serotype does not confer immunity against another. Even if the frequency of outbreaks and the distribution of serotypes are not uniform, the disease has a global distribution. Serotype O, A and C viruses have had the widest distribution and have been responsible for many outbreaks in Europe, America, Asia and Africa. FMDV can be spread either by direct or indirect contact. Further spread between cattle is more likely to be by airborne means. Clinical signs can vary from mild to severe, and fatalities may occur, especially in young animals. Typical cases of FMD are characterized by a vesicular condition of the feet, buccal mucosa and, in females, the mammary glands. FMD cannot be differentiated clinically from other vesicular diseases, such as swine vesicular disease, vesicular stomatitis and vesicular exanthema. Laboratory diagnosis of any suspected FMD case is therefore important. The control of FMD depends on prevention of the introduction of virus, prevention of infection of stock and the prevention of spread of the virus from infected animals. Although inactivated FMD vaccines have been available for decades, there is little or no cross-protection across serotypes and subtypes, requiring vaccines that are matched to circulating field strains. Therefore there should be production of safe and inexpensive vaccine that is easy to deliver and also capable of inducing lifelong immunity against multiple serotypes and subtypes.

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1. Introduction

Foot and mouth disease (FMD) is an economically important contagious disease of domestic (cattle, pigs, sheep and goats) and wild cloven hoofed animals (Alexandersen and Mowat, 2005). It causes loss of production and with high mortalities in the young animals (Rushton *et al.,* 2012). Although not usually fatal, FMD, as a renewed public and political high profile disease, has aroused the global concerns (Sumption *et al*., 2008**).** It does not only reduces animals' commercial value by decreasing animals' weight and milk output, but is also the most important animal disease limiting commerce of animals and animal products (Mort *et al*., 2005).

The causative agent of FMD is a small positive sense single stranded RNA virus which belongs to the *Aphthovirus* genus of the family *Picornaviridae* (Belsham, 2005). FMD virus (FMDV) is an antigenically variable virus, reflected in seven serotypes (A, O, C, Asia 1, Southern African Territories (SAT)-1, SAT-2 and SAT-3), that do not confer cross immunity to each other in addition to having many subtypes and variants within each serotype (Pariente *et al.,*2005).

Globally, there is great disparity in progress towards FMD control and eradication. While some countries are either FMD free or well on the road to achieving freedom, others are at an early stage of FMD control. Recently, there has been international endorsement of a progressive control pathway for FMD and this has stimulated new national and regional efforts to control the disease (OIE, 2012).

Nowadays, FMD vaccine is produced by growing live velogenic FMDV in Baby hamster kidney-21 cell cultures and inactivating it by using a chemical such as binary ethylene mine. However, the mode of production exist a risk to reveal live FMDV to environment. The risk should be considered by government when FMD has been effectively controlled. Moreover, at the beginning of the 21st century, the protocol for production of inactivated FMD vaccines allows the use of serological tests that can differentiate infected from vaccinated animals, formulation of vaccines that include multiple

serotypes and subtypes and a number of adjuvants (Doel, 2003). Besides, there are other important shortcomings of current inactivated vaccines, including short shelf life, the need for adequate cold chain of formulated vaccines and difficulties of certain serotypes and subtypes to grow well in cell culture for vaccine production (Rodriguez and Grub man, 2009). Therefore, the objectives of this seminar paper are:

- ❖ To give an over view of FMD mainly on epidemiology, diagnosis, vaccination and economic importance of the disease.
- ❖ To indicate the situation of the disease in Ethiopia and to suggest possible prevention and control strategies.
- ❖

2. Foot And Mouth Disease

2.1. Etiology

FMD virus is a single-stranded, non-segmented, positive sense RNA virus of approximately 8.2 kb that belongs to the genus *Aphthovirus* of the family *Picornaviridae*. There are seven FMDV serotypes (types A, O, C, Asia 1, and South African Territories (SAT) types 1–3) and many intratypic variants.). Within these serotypes, more than 60 strains have been identified (Knowles *et al.,* 2005). Serotypes O, A, C are widely distributed, whereas serotypes SAT-1, SAT-2, and SAT-3 are normally restricted to Africa and serotype Asia-1 to Asia (Domingo *et al*., 2003).

2.2. Epidemiology

2.2.1. Geographical distribution

The serotypes of FMDV are not distributed uniformly around the world. The serotype O, A and C viruses have had the widest distribution and have been responsible for outbreaks in Europe, America, Asia and Africa. However, the last reported outbreak due to serotype C FMDV was in Ethiopia during 2005 (Roeder *et al.,* 2008) and so serotype C viruses may no longer exist outside of laboratories. The SAT1-3 viruses are normally restricted to sub-Saharan Africa. However, there have been some limited outbreaks due to SAT1 viruses in the Middle East between 1962–1965 and 1969–1970 and then in Greece in 1962 (Knowles and Samuel, 2003). Similarly, there have been reports of minor incursions of the serotype SAT2 in Yemen in 1990 and in Kuwait and Saudi Arabia in 2000. More recently, FMD outbreaks due to serotype SAT2 spread from sub-Saharan Africa through northern African countries (Egypt and Libya) and into Palestine (Grubman and Baxt, 2004).

Table 1: Geographical distribution of foot and mouth disease serotypes

Region	Virus
South America	O,A,C
Europe	O,A,C
Africa	O,A,C,SAT1,SAT2,SAT3
Asia	O,A,Asia1
North and Central America	Virus free
Caribbean	Virus free
Oceania	Virus free

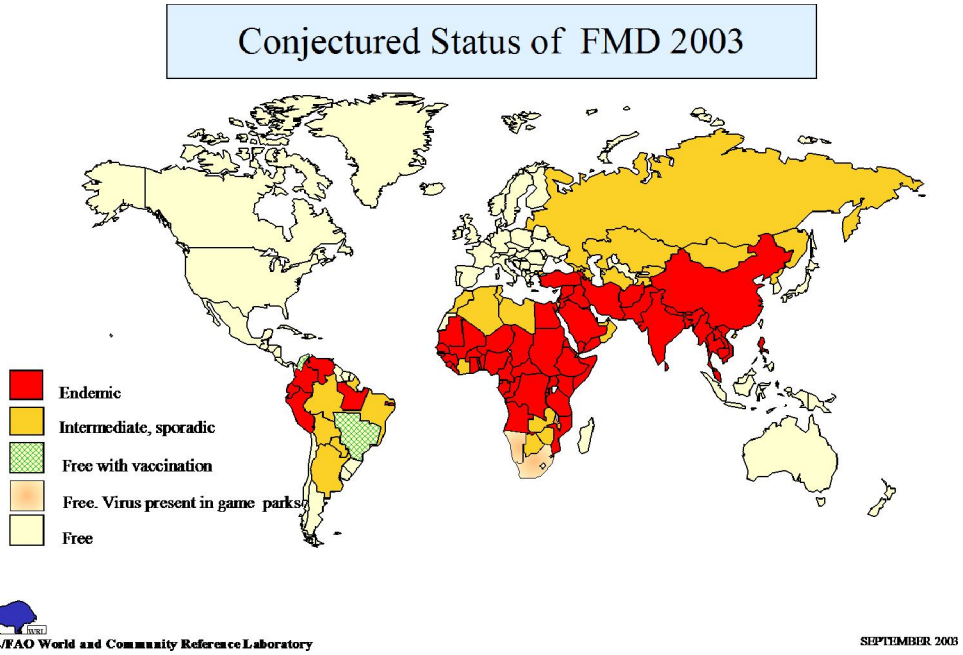

Figure 1: The geographical distribution of FMD virus serotype
Source: (Knipe *et al.*, 2001)

2.2.1. Mode of transmission

FMD is probably transmitted in one of two ways: contact transmission between acutely infected and susceptible individuals, which is likely to account for the majority of infections, and occasional transmission between carrier buffalo and susceptible individuals. It is widely accepted that the most mechanism of FMD transmission is through physical contact between infected and susceptible animals, often as a result of movement of infected animals (Pharo, 2002).

For SAT-serotype infections in southern Africa the usual start of FMD outbreaks in livestock results from close contact between infected buffalo and susceptible cattle (Thomson and Bastos, 2004a). However, because buffalo rarely show evidence of disease the mechanism whereby this occurs is open to conjecture. Recently, it was shown in a series of experiments in cattle that the amounts of virus excreted before the development of clinical signs were insufficient to result in transmission; only about half a day after clinical signs developed did transmission occur (Charleston *et al.,* 2011).

Airborne FMDV can result from a large number of infected pigs, resulting in plumes of aerosolized virus in the atmosphere (Morris *et al.,* 2002). Cattle, because they inhale more air and are easily infected through respiration, are the species frequently infected when FMDV is airborne (Alexandersen *et al.,* 2003). Under specific climate conditions (particularly downwind), aerosolized FMDV produced by infected pigs can travel a significant distance infecting cattle from 20 kilometers (km) up to 300 km and infecting sheep from 10–100 km away. Transmission of FMD has never been convincingly demonstrated under controlled conditions (Bartering *et al.,* 2003).

2.3. Pathogenesis

In cattle the tissues most consistently infected during the pre-viraemic phase of the disease are the epithelia of the naso-pharynx and larynx (Arzt *et al*., 2011a). It is therefore likely this is the primary replication site in ruminants. The tissues of the naso-pharynx and FMD viruses have a complex relationship because not only does initial infection of ruminants take place there but the naso-pharynx is also the site of viral persistence in chronically infected animals (so-called carriers). Vesicle formation, cell lysis and significant inflammation occur at secondary replication sites (oral mucosa, skin of the horn-hoof junction and skin of the teats) but not in the epithelium of the primary replication site. The cells which support viral replication are located in the basal layer of naso-pharyngeal epithelium. However, the mechanism by which viral replication occurs in the naso-pharyngeal epithelium without causing cell lysis is unknown; nor is there an explanation as to why virus can be readily cultured from pharyngeal scrapings (obtained using probing cups) that, in recently infected animals, may contain high levels of antibody (mainly IgA) directed against the infecting virus. In pigs, delayed clearance of viral RNA from pharyngeal and lymphoid tissues has been observed but that has not been shown for infectious virus (Arzt *et al*., 2011b).

2.4. Clinical Signs

3. FMD is characterized by development of vesicles, which soon rupture leaving erosions, in the mouth, including the tongue (but not the ventral surface of the tongue), and at the skin-hoof junction of the feet. However, before that occurs, affected animals develop fever, lose their appetite and the milk production of dairy cows declines sharply. In sheep and goats, lesions may be small and unnoticeable making these species dangerous source of infection (Donaldson and Sellers, 2000). Affected animals may lie down continuously, evidence pain when walking or show lameness in one or more legs. The lesions in the mouth frequently result in salivation, and grinding of the teeth or ‘lip smacking’. Abortion may result from infection with FMD viruses and is thought to occur more frequently in sheep than other species (Arzt *et al*., 2011b).

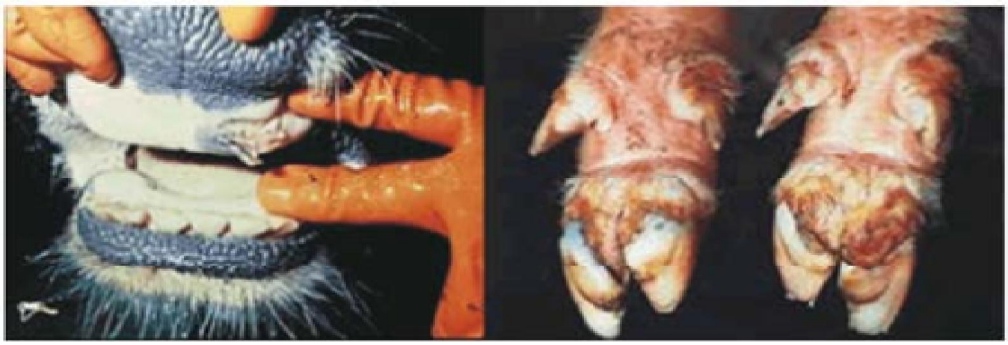

Figure 2: Ruptured oral and feet blister in diseased cow and pig
Source: Hughes *et al.,* 2002

3.1. Diagnosis

3.1.1. Clinical diagnosis

In cattle and pigs the clinical diagnosis of FMD is usually not difficult because the signs and lesions are characteristic and consistent. However, in other species such as sheep and goats, clinical diagnosis may be difficult because the signs are often less pronounced or even unapparent (Arzt *et al.*, 2011b).

3.1.2. Serological tests

Serological tests for FMD are of two types; those that detect antibodies to viral structural proteins (SP) and those that detect antibodies to viral nonstructural proteins (NSPs). The SP tests are **serotype specific** and detect and quantify antibodies elicited by vaccination and infection examples, the solid-phase competition ELISA (SPCE). These tests are serotype-specific and are highly sensitive, providing that the virus or antigen used in the test is closely matched to the strain circulating in the field. They are the prescribed tests for trade and are appropriate for confirming previous or ongoing infection in non-vaccinated animals as well as for monitoring the immunity conferred by vaccination in the field (Mackay *et al.,* 2001).

Antibody to expressed recombinant FMD virus non-structural proteins (NSPs) can be measured by different ELISA formats or immunoblotting. These assays are used as screening tests and need a confirmatory system, consisting of either a confirmatory assay, or a follow-up of epidemiological units showing results positive at the screening test, or a testing system with known performance (Brocchi *et al.,* 2006).

Enzyme-linked immunosorbent assay (ELISA): Dilution of samples to be tested and controls are incubated in the wells of antigen coated plate. Any antibody specific for 3 ABC antigen binds to the wells and form antigen-antibody complex on the plate well surface. Unbound material is removed from the wells by washing. A peroxidase labeled anti-Ig-G Conjugate is added which binds to the antibodies of the sample which formed complement with 3ABC antigen. Unbound conjugate is removed by washing and the TMB- containing substrate is added to the wells. The degree of color, which develops, is directly proportional to the amount of antibody specific present in the sample for the 3ABC (Skinner, 1990).

Complement fixation test (CFT): is used to indicate the presence of antibodies to FMD virus. Complement will combine (be fixed) with an antigen. If all the complements are fixed in the complement fixation stage, then none remain to cause hemolysis of the red blood cells in the indicator stage. Results: Positive test: All available complement is fixed by the antigen-antibody reaction; no hemolysis occurs, so the test is positive for the presences of antibodies. Negative Test, No antigen –antibody reaction occurs. The complement remains and the red blood cells are lysed in the indicator stage, so the test is negative (Gerald, 2007).

3.1.3. Identification of the agent

Virus isolation: The best source of material for diagnosis of FMD and characterization of the virus involved is fragments of epithelium from freshly ruptured vesicles in the mouths or on the feet of affected animals. These are only available for a day or two days following rupture of the vesicle and for that reason acute cases are the best source of diagnostic material. Such fragments usually contain high levels of infectivity and for that reason the outer surfaces of containers and packaging need to be properly decontaminated prior to dispatch (Thomson and Bastos, 2004a).

A suspension should be prepared by grinding the sample in sterile pestle and mortar with a small volume of tissue of tissue culture medium and antibiotics. Samples suspected to contain FMD virus are inoculated into cell culture or unweaned mice. Sensitive cell culture system includes bovine thyroid cells and primary pig, calf, or lamb kidney cell. Established cell line, like BHK-21(baby hamster kidney) may be used but are less sensitive than primary cells for detecting low amounts of infectivity (Clarker and Spier, 1990).

The polymerase chain reaction (PCR) techniques are increasingly used for rapid identification of FMD virus and sequence analysis of any PCR positive. The reverse-transcription PCR (RT-PCR) can be used to amplify the genome fragment of FMD virus in diagnostic material. Specific primers have been designed between each of the seven serotypes (OIE, 2004).

3.2. Differential diagnosis

Table 2: Differentiation of vesicular diseases

Animal species	FMD	Vesicular stomatitis	Vesicular exanthema	Swine vesicular disease
Cattle	+	+	-	-
Pig	+	+	+	+
Sheep and goat	+	+ or -	-	-
Horse	-	+	-	-

Source: Sharma and Adlakha, 2003.

Due to economic and political significance of FMD and its similarity to other vesicular disease, vesicular stomatitis, swine vesicular disease, vesicular exanthema, a rapid definitive diagnosis is essential.

3.3. Treatment

No treatment exists for foot and mouth disease (Quinn and Markey, 2003). However, proper animal

husbandry practices and treatment of secondary bacterial infection 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 topically with mild disinfectants but also by applying broad-spectrum antibiotics parentally, tetracycline in particular, in order to control the consequences of secondary bacterial infections (Radostits *et al.,* 2007).

3.4. Prevention and control

The control of FMD depends on prevention of the introduction of virus, prevention of infection of stock and the prevention of spread of the virus from infected animals. This is achieved by individual countries depending on a variety of economic and practical considerations (Kitching *et al.,* 1998). In order to prevent introduction of FMD, FMD free countries may refuse entry of any animals from FMD endemic areas or may insist that any animal entering the country has no serum antibody to FMD virus and that esophageal-pharyngeal scrapings taken by probing are negative for the presence of FMD virus (Alexanderson *et al.*, 2003).

FMD virus could enter in the case of product of animal infected before slaughter. In skeletal muscle the virus is inactivated as the PH of the meat falls but virus in bone and lymph glands is not subject to this increased acidity and will escape inactivation so that regulations in FMD free countries requires that meat imported from endemic areas has had the bones and lymph nodes removed and may also impose additional requirements such as vaccination and certification of the absence of FMD from the farm of origin of the meat, the slaughter house and the surrounding areas (OIE.2001).

Because pigs excrete large quantities of FMD virus, especially in the case in large piggeries which may contain many thousands of pigs, prevention of pigs becoming infected is vital in the control of FMD. For that reason the feeding of swill or at least untreated swill is illegal in most countries. However airborne spread of the virus cannot be controlled by these means (Kao, 2001).

3.4.1. Vaccination

Vaccination prevents clinical disease but not viral infection, nor the eventual viral persistence (carrier state). As previously stated, although the carrier state has been documented and studied in naïve and vaccinated cattle (Zhang *et al.,* 2002). Effective and efficient tests for “vaccine matching” are critical to determine and predict the expected efficacy of available FMD vaccines. Appropriate vaccine strain selection is a critical element in the control of FMD and is necessary for the application of vaccination programs in FMD affected regions as well as for the establishment and maintenance of vaccine antigen concentrates to be used in the event of new FMD incursions (OIE, 2004).

All currently available FMD vaccines are based on cell culture derived preparations of whole virus, chemically inactivated and blended with suitable adjuvant (s), to potentiate the immune response to vaccination. Typically, FMD vaccines formulated with the adjuvants aluminium hydroxide and/or saponin provide protective immunity in cattle, sheep and goats, but are poor at conferring a similar response in pigs. However, mineral oil adjuvanted vaccines, developed for use in pigs, afford protection in all target species. The introduction of the killed FMD vaccine has been extremely successful in reducing the number of disease outbreak in many parts of the world where the disease is enzootic (Doel, 2003).

Killed trivalent (containing O, A and C strains) vaccines are in general use, but because of the increasing occurrence of antigenically dissimilar substrains the production of vaccines from locally isolated virus is becoming a more common practice (Radostits *et al.,* 2007).

4. Conomic Importance Of Fmd

FMD causes production losses, particularly to the dairy and pig industries and high mortality in young animals, and is a major constraint to international trade in live animals and their products. The impact of disease is not equal across all countries and livestock populations due to differences in the genetics of the livestock, the management of the livestock and the prevailing prices for the livestock systems inputs and outputs (Rushton *et al.,* 2009).

The presence of FMD provides reason to restrict trade in animal products from affected countries to those without FMD, and thereby denies access by developing economies to the rich markets of the developed world, reducing incentives to improve productivity and efficiency. Thus loss in animal production and international trade restrictions imposed following an outbreak make FMD a major concern (Perry, 2003).

The losses are more pronounced in cattle and pig production systems; the impact in goat and sheep production systems is generally low. The effects are also much more dramatic in intensive systems of cattle and pigs; in particular FMD can cause devastating losses in dairy and in intensive pig production systems. However, the impact of the disease in extensive cattle systems is small and the incentives to control the disease are also small (Rushton, 2009).

FMD out breaks incur significant social and economic costs and affected countries are limited in their ability to trade with subsequent reduction in the value of their meat commodities (Sileshi *et al.*, 2006).

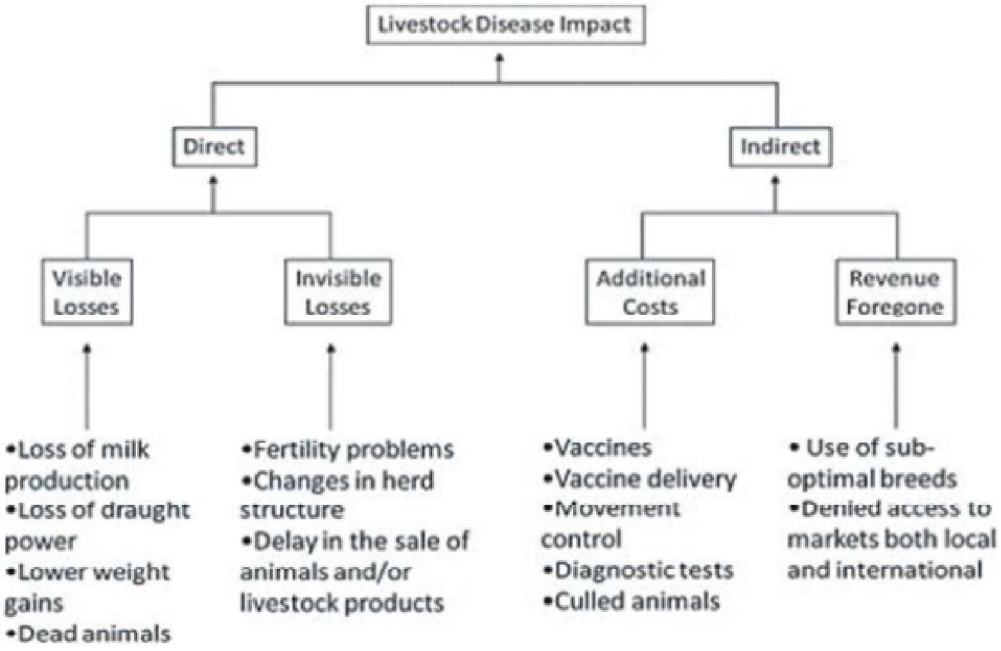

Figure 3: The impacts of foot-mouth-disease
Source: James and Rushton, 2003

4. Status Of Fmd In Ethiopia

According to the animal health division report of the Ministry of Agriculture and Rural Development of Ethiopia (2007), the incidence of FMD has increased between 1.3 to 1.5 times since 1990. In the time period between1990 to 1999, the World reference laboratory at Pirbright typed FMD outbreaks as detected serotype O, A, and SAT-2. It is clear that serotype O remains dominant in FMD outbreaks and has led to a considerable economic loss of the rural communities. However, it is important to note that only a small percentage of FMD outbreaks is reported and typed, therefore the above mentioned is an underestimation of the actual problem caused by FMD (Sahle *et al*., 2004). In time period from 2000 to 2006, there were 215 FMD outbreaks in the country and outbreaks occurred every year and the highest being in 2001 with 88 outbreaks (MoARD, 2007). Of the total samples examined from the outbreak, by National veterinary institute, the serotypes identified were O, A, C and SAT 2 in addition, SAT1 was also reported. Type O was the dominant serotypes identified with 73.93% rate, while type A (19.68%), C (1.59%) and SAT 2 (4.79%) rate were detected (Ayelet *et al*., 2007).

Despite the wide distribution and economic impact of FMD in Ethiopia, few clinical and serological studies have been reported. The only attempt to date by the government to control the disease is by limited vaccination campaigns in dairy herds. The serotype of the circulating viruses and their relation compared to the vaccine strain currently in use in Ethiopia is not clearly known (Leforban, 2005). In recent finding in the other corner of the country, in pastoral livestock herds of Maji and Surma areas of SNNP national state, there has been new record of SAT 1 strain of FMDV (Legesse *et al.,* 2008).

FMD is endemic and known for its wider distribution in Ethiopia, although its level of prevalence may have significant variations across the different farming system and agro- ecological zones of the country and frequently occur in the pastoral herds of the country (Sileshi *et al.,* 2006).

According to ministry of Ethiopia (2000) the incidence of FMD has increased between 1.3-1.5 times since 1990. Small-scale vaccination practice against FMD is released in commercial dairy farms around big towns.

However, FMD control by vaccination does not seem to be successful as vaccination coverage itself is limited and some cases farms that made use of bivalent A and C vaccine were found affected by sever outbreak by virtue of these facts and given the mode of livestock farming (no restriction of movement of animals) the FMD virus contamination is maintained in the population making the disease endemic in nature. Recent finding (Mesfin, 2004) during 2001 FMD out breaks have also shown the wide spread existence of serotype O, A, SAT1 and SAT2 in the wild and domestic hosts of the virus Ethiopia.

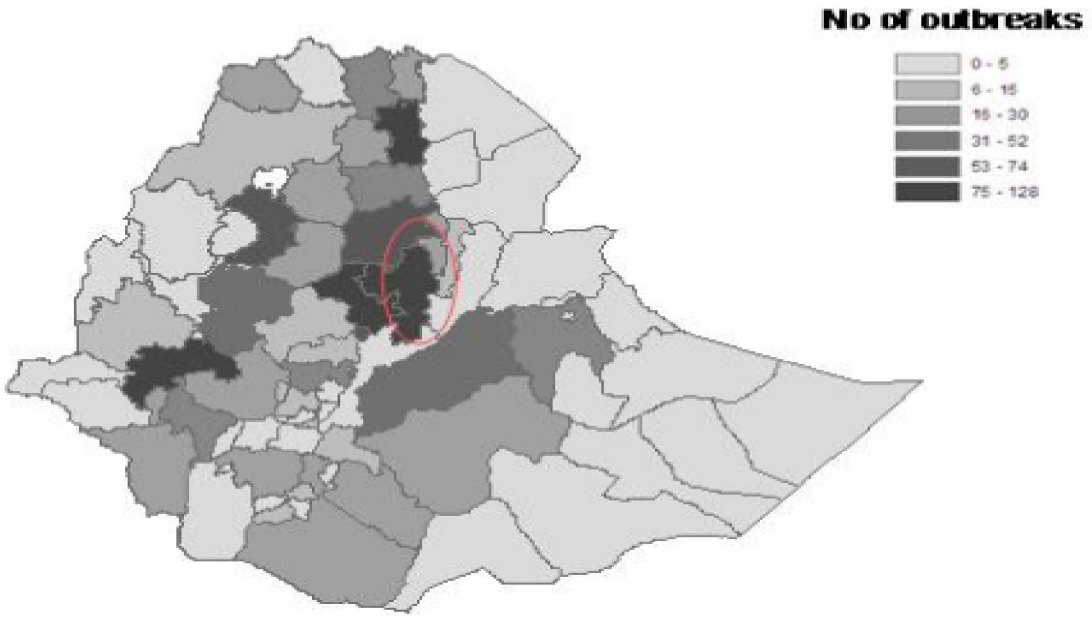

Figure 4: Map showing no FMD outbreaks recorded in different part of Ethiopia (1999-06)
Source: Ayelet *et al*., 2009

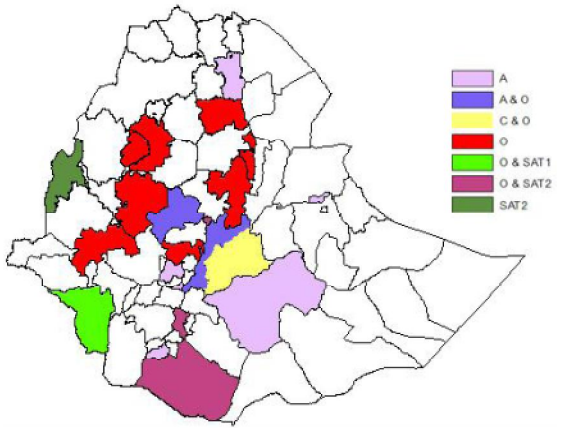

Figure 5: Map showing distribution of FMD virus serotypes in different part of Ethiopia
Source: (Ayelet *et al*., 2009)

SAT2 was identified for the first time in 1989 from a bovine sample collected from Borona area, southern Ethiopia however SAT3 has never been reported in Ethiopia (Gelagay, 2009). Moreover SAT1 and SAT2 were isolated recently from Mezan Teferi and Benishangul- Gumuz areas bordering Kenya and Sudan respectively from 2007 collected samples (Gelagay, 2009).

Conclusions And Recommendations

FMD is one of the most economically and socially devastating diseases affecting animal production throughout the world. The FMDV is a highly variable RNA virus occurring in seven serotypes (A, O, C, and Asia 1, Sat 1, Sat 2 and Sat 3) and a large number of subtypes. FMDV persists in endemic regions impacting millions of people dependent on livestock for food and their livelihood; usually associated with developing countries due to lack the resources to control and eradicate it. Although inactivated FMD vaccines have been available for decades, there is little or no cross-protection across serotypes and subtypes, requiring vaccines that are matched to circulating field strains. Current inactivated vaccines require growth of virulent virus, posing a threat of escape from manufacturing sites, have limited shelf life and require re-vaccination every 4-12 months. The new vaccine will feature an antibody test that will enable veterinarians to tell the difference between field infection and vaccination. Based on the above conclusions the following points are recommended.

- There should be production of safe and inexpensive vaccine that is easy to deliver and also capable of inducing lifelong immunity against multiple serotypes and subtypes.
- A novel vaccine that will enable veterinarians to differentiate vaccinated animals from naturally infected animals should be produced.
- Role of wild life in the epidemiology of FMD should be studied.
- Quarantine of infected farms should be practiced through awareness creation among professionals, farmers and employees in the farms taking consideration the iatrogenic and nosocomial transmission of foot and mouth disease.

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