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Review on the Control of Foot and Mouth Disease by Vaccination

[1,2]Belege Tadesse, [3]Kefale Alamir and [4]Eyasu Demssie

[1]University of Gondar, College of Veterinary Medicine and Animal Sciences,
Department of Epidemiology and Public Health, Gondar, Ethiopia
[2]Amedguya Sheep Breed Improvement and Multiplication Center, North Shoa, Ethiopia
[3]Veterinary Drug and Animal feed Administration and
Control Authority of Ethiopia, Addis Ababa, Ethiopia
[4]Gondar Zuria woreda Livestock and Fishery Resource Office, Gondar Ethiopia

Abstract: Foot and mouth disease (FMD) is one of the most economically devastating diseases affecting cloven-hoofed livestock worldwide. It is among the widespread endemic diseases in Ethiopia. The control strategies for FMD vary between countries based on status of the disease in the country, the financial and technical ability of the country. Vaccination is an effective method of control of FMD especially in FMD endemic countries but its effectiveness is not evaluated routinely. This seminar is done with the objective of reviewing strategies for the control of FMD. Although present conventional foot-and-mouth disease (FMD) vaccines can prevent clinical disease, protection is short lived (~6 months), often requiring frequent revaccination for prophylactic control. Under this review method for the differentiation of vaccinated and infected animals and checking matching of vaccine strain and the strain circulating in the region were discussed. Recommendations are made for the development of effective FMD control program and maintaining the efficacy of a FMD vaccine and effectiveness of a vaccination program.

Key words: Efficacy · FMD · FMDV · Vaccine

INTRODUCTION

Foot and mouth disease (FMD) is one of the most economically devastating diseases affecting cloven-hoofed livestock worldwide [1]. FMD is caused by a highly variable RNA virus of the genus Aphthovirus and family Picornaviridae [2]. Seven serotypes (A, O, C, Asia 1, SAT 1, SAT 2and SAT 3) and a large number of topotypes were identified [3]. Further, new subtypes of FMDV are continuously evolving due to an infinite mutation rate in the RNA genome of the virus [4]. FMD is widely distributed with high prevalence in developing countries. In Ethiopia it is endemic and distributed in most part of the country [5]

The control strategy of FMD varies based on the status of the country and its neighbor country to this disease. Generally, it can be controlled by movement control/quarantine (Animals, animal products and infected materials), diagnostics and surveillance, vaccination, slaughtering of infected and in-contact animals, bio-security measures etc. [6].

Vaccination has proven to be a very effective way of controlling and eliminating FMD from certain regions of the world, such as Western Europe and parts of South America [7]. If used strategically, vaccination can create a barrier between infected and disease-free areas, provided that FMDV vaccine serotypes and subtypes match with those causing outbreaks in a given area. Vaccination against one FMDV serotype does not usually protect animals against other serotypes of the virus or other strains of the same serotype [8].

Different types of vaccination programs are implemented in different regions of the world, with varying challenges to their success. One key challenge is the limited availability and high cost of the vaccine. Furthermore, the duration of immunity induced is short

Corresponding Author: Belege Tadesse, University of Gondar, College of Veterinary medicine and animal sciences, Department of Epidemiology and Public health, Gondar, Ethiopia or Amedguya Sheep Breed Improvement and Multiplication Center, North Shoa, Ethiopia. Tel: +251931201843.

and booster inoculations need to be administered at 4 to 6 monthly intervals in most animals, including young cattle. The vaccine also needs to contain a large quantity of specific antigen (1 µg per dose or perhaps closer to 5 µg per dose) and the production of large volumes of FMD virus needs to be conducted in a bio-secure facility that will prevent virus escape into the environment, this makes it expensive to produce [9].

Despite the advantages the vaccination may provide by reducing the number of animals culled/lost due to the disease; there are inherent factors which may offset the likely effectiveness of a vaccination strategy. For example, the vaccine requires 4-5 days for immunity to develop and the vaccine efficacy is related to the antigenic match between the vaccine strain and the circulating strain and the effectiveness of vaccination program [10]. These limitations render the effectiveness of vaccination policies [11]. Complementing the required control measures with vaccination-to-live has the potential to reduce disease spread by protecting the susceptible population, leading to shorter epidemics and fewer animals culled. Given the enormous scale and implications of vaccine use in terms of both health and economics, it is clearly important that their effectiveness should be thoroughly evaluated. FMD can be controlled using various strategies and veterinary vaccines are evaluated in very different ways. Therefore, this review was done with the objective of:

- Reviewing the control strategies of FMD

General Overview of FMD

Epidemiology, Clinical Sign and Diagnosis: FMD is the most contagious trans-boundary animal disease affecting cloven hoofed animals of domesticated and wildlife species [12].It is still wide spread throughout the world, particularly in Asia, Africa, Middle East and parts of the South America [13].Clinical effects of the disease vary with the species and breed of animal, the viral strain concerned and epidemiological circumstance. FMD is transmitted by a variety of methods (Via aerosol, contaminated fomites and personnel, infected animal products, direct contact with infected animal) between herds, countries and continent, but spread from one animal to another animal is inhalation, ingestion and contact with animals and fomites [14].

Symptomatically, the disease is characterized by fever, loss of appetite and weight, vesicles/blisters on the mucus membranes, especially those of mouth, feet (Interdigial space and coronary band) and udder [1]. The incubation period of FMD virus infection is 2 to 14 days [15].

In cattle, FMD should be considered whenever salivation and lameness occur simultaneously and when a vesicular lesion is seen or suspected. FMDV can be isolated by inoculating suspected specimens in to cell culture. The serological tests, Virus Neutralization test (VNT) and liquid phase blocking ELISA are used to detect antibody against FMD. The antibody detection by 3 ABC ELISA can be used on a herd basis to detect FMDV infection in vaccinated and unvaccinated population [16]. The polymerase chain reaction (PCR) can be used to amplify the genome fragments of FMDV in diagnostic material [1].

Economic Impact of FMD: FMD causes huge economic loss either directly or indirectly. The direct effects of the disease are loss of milk production, loss of draught power, retardation of growth, abortion in pregnant animals, death in calves and lambs [17] while indirect losses can be attributed to the disruption in trade of animals and derivative products [18].For example the Egyptian ban of 2003 on Ethiopia livestock alone cause market loss of 14.36 million USD [19]. It reduces milk yields by 80% [20] and also leads a cost of $0.4–3 or occasionally $9 per dose including delivery and application [21].

Status of FMD in Ethiopia: FMD is endemic in Ethiopia in all production systems since its first recorded in 1957 [22] and a large number of outbreaks are reported every year [5]. Based on data over the years 2007-2012, annual district level incidence of FMD out-break was estimated at 0.24, 0.39 and 0.85 per district year in the crop livestock mixed, pastoral and market oriented districts, that are caused by serotypes O, A, SAT 2 and SAT 1 [23]. The most dominant serotype is O (70%) of the investigated outbreaks occurring in the country, followed by SAT2 (20%). The remaining are A and SAT1. Serotype C has not been reported in Ethiopia since 1983 [5].

Different Studies undertaken on FMD so far revealed the existence of the disease in different parts of the country, with different sero-prevalence; 5.6% in Afar [24]; 24.6% in Borana plateau and Guji highlands of southern Ethiopia [25]; 24.2% in Adama and Assela (i.e. central Ethiopia) [26]; 21.4% in Kellem Wolega Zone, West Ethiopia [27]; 14.05% in Awbere and Babille districts of Jijiga zone, Somalia Regional State [28] and 15.4% in Tigray region [29]. Extensive movement of livestock and the high rate of contact among animals at commercial markets, in communal grazing areas and watering points, have been forwarded as the main risk factors of FMD spread in Ethiopia [30, 31].

Prevention and Control of FMD

Global FMD Control Strategies: Depending on the status of the country or zone, an FMD control program should be designed and implemented with a clear purpose at the outset [32]. Therefore, FMD 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. The official attitude of a country regarding control of a disease depends on how seriously the disease affects the country, the financial and technical ability of the country and what its neighbors are doing [6].

To control FMD effectively, there is a need of good infrastructure, trained veterinary staff, well equipped laboratories, good governance, rapid and accurate diagnostics, rapid response measures, continuous monitoring and surveillance and compulsory vaccination [33]. Timely determination of exact status of the disease in ruminants is considered as measure to monitor the virus activity in an area [34].

In addition to the serological evidence of immunity, it is important also to monitor the occurrence of FMD outbreaks and/or infection. In most circumstances, it is likely that the vaccination program is one, among other control elements. Movement controls (Animal, animal products and fomites), other bio-security measures and stamping out are typically part of the response mechanism to prevent incursions of the virus and occurrence of secondary outbreaks, while vaccination can be used either as a response mechanism (Emergency vaccination) or as a preventive tool to mitigate the impact of FMDV incursions in the area or farming system targeted for vaccination. Therefore, the evaluation of the effectiveness of a control program will be the result of a combined effect of vaccination (If used) and additional measures [32].

Control in FMD Endemic Countries: In countries where the disease is endemic, efforts are generally directed at protecting susceptible animals by a combination of routine mass vaccination, diagnostic, surveillance and control of animal movement (Quarantine) [35, 36].

Vaccination: Routine vaccination with a vaccine containing the virus strain circulating in the region is mandatory. The extent of vaccination coverage is of considerable importance to the protection of livestock populations, a concept called "herd immunity". When protective levels of immunity are achieved in the majority of individuals, the establishment or maintenance of the disease within the population is unlikely to occur. For FMD, it is estimated that 80 to 85% of individuals must have protective levels of virus-neutralizing antibody to achieve herd immunity [37].

In Infected countries or zones the proposed food and agriculture organization of the United States (FAO) FMD control strategy is based on a progressive control pathway (PCP) and regional roadmaps for infected countries/zones to initiate FMD control. The PCP includes six different stages ranging from level 0 when there is continuous FMDV circulation with no reporting or control actions, to level 5 when a country is officially recognized by the OIE as free without vaccination (Figure 1). Currently, the OIE recognizes only three different statuses for countries with regard to FMD: countries not free from FMD (PCP stages 0-3), FMD-free countries or zones applying vaccination (PCP stage 4) and FMD-free countries or zones without vaccination (PCP stage 5) [38]. In 2001, FMD spread throughout the UK, the Netherlands, France and Ireland were controlled by depopulation of infected and neighboring herds was used to control the epidemic in the UK, while vaccination of neighboring herds was the control strategy adopted in the Netherlands [39].

Diagnostics: Due to the fast spread of FMD and the serious economic consequences that can arise from an outbreak, prompt, sensitive and specific diagnosis and identification of the virus serotype is essential. Initially, presumptive diagnosis is based upon clinical signs. However, confirmed laboratory diagnosis of any suspected FMD case is a matter of urgency. Furthermore, determination of the serotype involved in field outbreaks has to be established within laboratories to enable proper control of the disease. Various techniques have been developed and are used to diagnose FMD and to ascertain the serotype/subtype of the virus [35].

Surveillance: As part of FMD control, surveillance represents a very important fraction directly linked to diagnostics. It requires a concerted effort by the individual livestock owner, private veterinarians and the government's veterinary services. Unfortunately, FMD outbreaks may still go undetected until the disease has spread beyond the initial site of infection. This can partially be due to subtle or unidentifiable FMD clinical signs of disease, to a delay in reporting the index case, or to a lack of reporting because of illegal movement of animals or contaminated animal products [40, 41].

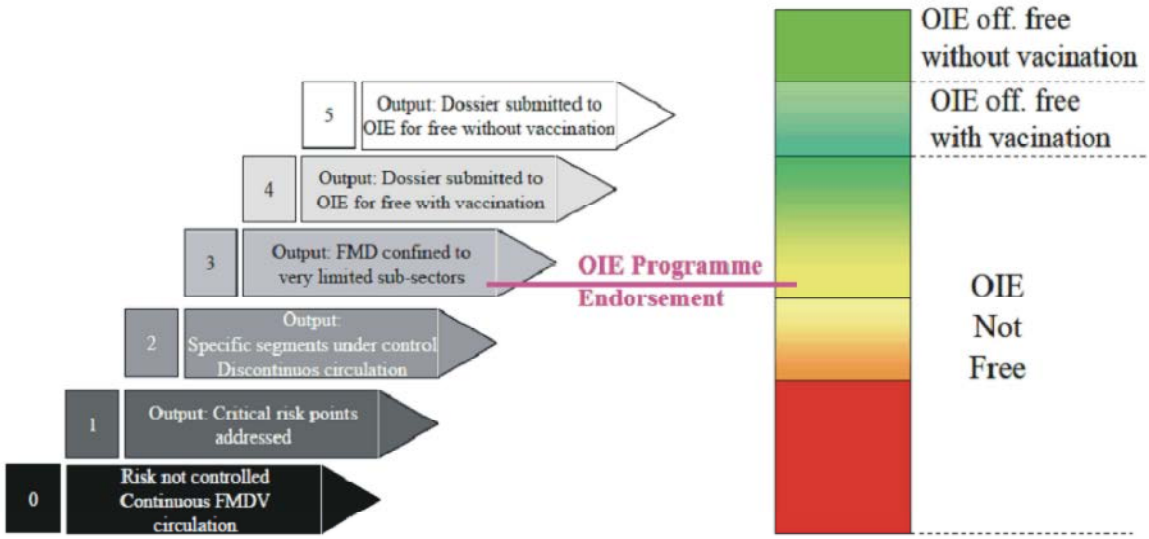

Fig. 1: Relationship between FAO's Progressive Control Pathway and OIE's official FMD Statuses. Source: Gideonand Victor Emmanoel [38]

Control in FMD Free Countries: The objective of a strategy in FMD-free countries or zones 'without vaccination' is based on three essential risk mitigation principles, namely: application of measures to avoid the introduction of the infection; implementation of surveillance to ensure the detection of the infection; development of contingency plans in case of an emergency [16]In FMD-free countries and zones 'With vaccination' in addition to the above requirements, countries or zones applying vaccination should ensure that vaccination coverage is sufficient to stop virus circulation [38].

In FMD-free countries (Like countries of the EU and North America), the control policy has been primarily based upon slaughtering of infected and in-contact animals (Stamping out), together with restrictions on movement of animals and animal products and impose strict import regulation on animals, animal products and potentially contaminated materials from FMD endemic countries [16]. There has been provision to resort to vaccination under emergency circumstances where the outbreak is extensive and the slaughtering of large numbers of animals becomes unmanageable [42].

FMD Control Strategy in Ethiopia: Although there have been several attempts to lay out a national level FMD Control Strategy in Ethiopia an officially authorized control plan for FMD has not been established, except for government coordinated vaccination activities in some market oriented dairy farms and feedlots in urban and peri-urban areas [31]. These vaccination efforts have either been reactive vaccinations in response to outbreaks or regular preventive vaccinations. FMD infected cattle are also commonly treated with palliative antibiotics or traditional treatments in all types of production systems [43]. Lack of sufficient vaccine, poor surveillance and unregulated animal movement and animal marketing are the major challenges for the control of FMD in Ethiopia. Considering the wide prevalence of serotypes O and A Ethiopia was used serotype O281 and A110 locally to produce bivalent vaccine since 2009/2010 [44]. Later many outbreaks were reported due to serotype SAT2 and the National Veterinary Institute (NVI) is producing an inactivated trivalent vaccine containing serotype O-ETH/38/2005, A-ETH/7/2008 and SAT2-ETH/76/2009 [45].

Control of FMD by Vaccination: There are seven antigenically distinct serotypes of FMDV and each serotype has many intratypic variants. This antigenic variation creates a major problem for the control of FMD, as infection or vaccination with one serotype of FMDV does not protect against other serotypes and may fail to protect fully against other subtypes within the same serotype [18, 46]. In some cases, inactivated bi-, tri-, or polyvalent vaccine, which contains the representative strains of the serotypes that are in circulation in the region, must be used; therefore, active disease

surveillance and diagnosis must be effective which needs a strong field service as well as proper laboratory facilities with efficient methods of detection and characterization of the virus [16].

The most effective strategy of the control of the viral diseases is through vaccination including FMD [8]. The veterinary vaccines account for 26% of global vaccine market. However, the currently available inactivated vaccine provides protection from the disease/ clinical FMD but not from primary infection of the nasopharyngeal mucosa [47]. Moreover the vaccinated animals may become asymptomatic carrier that shed the virus for months or even up to years [48]. During outbreaks, besides providing protection, the vaccination decreases FMDV spread to the adjoining areas. Decision to vaccinate varies with the specific scientific and economic as well as political and social factors and is complex. Understanding the disease dynamics is important for the implementation of effective vaccination program [15].

Current Major Vaccines: There are different types of FMD vaccine such as: Conventional/inactivated vaccine, Protein vaccine, protein fragments and viral subunits vaccine, peptide vaccine, Genetically-engineered attenuated strain vaccine and DNA vaccine [49].

Most currently used FMD vaccines consist of whole virus made in cell suspension, inactivated with binary Ethylenimine, mixed with an oil based adjuvant (Like mineral oil, aluminum hydroxide and saponin) [48]. As immunity is serotype/strain specific, the choice of incorporation of FMDV serotype/strain into the vaccine should be decided by thorough investigation of the circulating FMDV strain prevalent in that particular geographical area. Often, many serotypes are included in the same polyvalent vaccine [50]. Protection from a primary course of vaccination typically lasts for up to six months, depending on the potency [15, 50]. The global usage of FMD vaccines is vast, with over two billion doses used a year [51] mostly as part of national or regional mass vaccination programs, revaccinating cattle once, twice or three or more times a year.

The inactivated FMD vaccines are the mostly used vaccines that are available since long time but provide immunity only for 4-6 months and require boosters biannually. Lack of cross protection from field serotypes, requirement of live virus growth and possibilities of escape of virus from laboratories or manufacturing areas, inadequate disease protection, limited shelf life and repeated booster requirement, need for adequate cold chain of formulated vaccines, difficulties of certain serotypes and subtypes to grow well in cell culture which is required for vaccine production have forced the researchers to think over development of alternative effective and safe vaccines for FMD [48].

Determination of VP1 as the most antigenic region of the viral genome, led to the development of protein/peptide vaccines as alternatives to the inactivated vaccine. These vaccines do not involve infectious virus, can easily be stored and can reach 95% purity [52]. DNA vaccines also represent another promising alternative for inactivated vaccines since they do not require high containment facilities for production, have a relatively stable shelf-life, allow for rapid incorporation of emerging field strain sequences, can incorporate marker genes and can co-express multiple antigenic sites from different serotypes [53]. Recombinant proteins of FMDV are also an alternative immunization method and are based on a set of effective epitopes within a single polypeptide chain [54] but, still it is not used popularly.

Adequate epidemiological data and revaccination times for different circulating serotypes are important for control of FMD in endemic regions [55]. Production of FMD vaccine requires large-scale antigen propagation, viral treatment for loss of pathogenicity and adjuvant addition to enhance the immunogenicity. Good quality vaccines will allow avoidance of production loss and incidence of FMD [56].

Type of Vaccine Strain Available in East Africa: Inactivated FMD vaccines having different serotypes were used in East Africa (Table 1) and specifically in Ethiopia (Table 2). In Ethiopia conventional type of bivalent (Serotype O and A) vaccine is produced at National Veterinary Institute (NVI) since 2009/10 [44].

FMD Vaccine Selection and Matching: Efficacy of vaccination is affected by the lack of cross-protection between serotypes, as well as incomplete protection between some subtypes [46]. In addition, new variant viruses are emerging periodically. Consequently, vaccine strain requirements differ according to the types and subtypes of virus prevailing globally and vaccines have to be selected with care, whether it is for prophylactic use in FMD endemic countries or for incorporation into the antigenic reserves for emergency use in FMD free countries. In the case of FMD outbreaks, the immediate requirement is to detect the serotype of the circulating

Table 1: Vaccine strains those are suitable for use in East Africa

Serotype	Internationally available	Locally produced in 2009/2010
O	O1 Manisa	Kenya 77/78, Egypt 2/72, Ethiopia O281
A	Eritrea 98	Kenya 5/80, Egypt 06, Ethiopia A110
SAT 1	(Rhodesia 12/78, Botswana 1/68)	Kenya T155/71
SAT 2	Saudi 2000, Eritrea 98, (Zimbabwe 7/830).	Kenya 52/84

Source: adapted from OIE/FAO [44].

Table 2: FMDV Candidate Vaccine Strain Selected for vaccine in Ethiopia

Name of candidate vaccine strains	Site of isolation	Year of isolation	Serotype	Topotype
O-ETH/38/2005	Addis Ababa	2005	O	EA-3
O-ETH/58/2008	Benchimaji	2005	O	EA-4
A-ETH/7/2008	Sinana	2008	A	A Africa
A-ETH/6/2000	Konso	2000	A	A Africa
SAT2-ETH/76/2009	Sululta	2009	SAT2	XIII
SAT2-ETH/64/2009	Debre Berhan	2009	SAT2	XIII

Source: adapted from Ayelet *et al*. [45]

virus, which is generally achieved by antigen-typing ELISA or by genetic typing (sequencing of the *VP1* gene). Once the serotype of the virus is established, *invitro* vaccine-matching assays are carried out to select a suitable vaccine strain [18].

Currently, methods of vaccine strain selection mainly rely on serological [18]. A commonly used method is to derive relationship values ('r' values) between FMDVs using pools of antisera prepared against each vaccine strain to be matched. The antigenic similarities between vaccine strains and field isolates are estimated from their comparative reactivity with the appropriate serum pool using a virus neutralization test (VNT) or an ELISA-based method Kitching *et al.* [57]. The advantages of ELISA over VNT are that the test is rapid and requires inactivated antigen. If VNT is used to determine the antigenic similarity an r1 value of 0.3 or greater indicates a close antigenic match between the vaccine strain and the field isolate[58]. In the case of the two-step ELISA [57] an r1 value of 0.4-1.0 indicates a close match between the vaccine strain and the field isolates; otherwise there is a need to include another vaccine strain.

FMD Vaccine Application and Effectiveness: The antigenic variation of FMDV creates a major problem for the control of FMD [18]. The closeness of match between the outbreak strain and the vaccine applied will affect vaccine performance in an emergency situation and more recent experimental work has attempted to also address the issue that outbreaks will involve isolates not homologous to the vaccine strain by using heterogonous challenges [59].

Previous studies at International Animal Health Institute, Pirbright (UK) in cattle, to assess the efficacy of a high potency O1 Manisa oil formulated vaccine applied 21 days prior to a direct contact challenge from infected cattle against both clinical disease and sub-clinical infection using larger group size, have shown more conclusively that vaccination greatly reduces the amount of virus recovered from vaccinated cattle as compared to unvaccinated cattle [47].

Control of FMD is mainly carried out by controlling its spread from infected to susceptible animals, either by preventing the movement of the virus from the infected animals, animal products, fomites and aerosol, or by reducing the number of susceptible animals by vaccination [60]. It has been observed from previous outbreaks that both a restriction of the movement of the virus and a reduction of susceptible animals by vaccination synergistically helps to control FMD [21].

Immunity Induced by FMD Virus and FMD Vaccine: Immune response against FMDV has been related to circulating humoral antibody titer, which is considered to be the most important factor in conferring protection against FMD. IgM is the first serum-neutralizing antibody that appears at 3-4 days following infection or vaccination and peaks in concentration approximately 10-14 days after infection and then declines [61]. IgG is detected at 4-7 days post infection or post vaccination and becomes the major neutralizing antibody by 2 weeks following immunization. It is well known that parenterally administered inactivated FMD vaccine in cattle elicit very little or no IgA in mucosal secretions, but if the vaccinated or naturally infected animal becomes a carrier of FMDV, oropharyngeal replication of virus acts as a constant stimulus to produce a higher amount of IgA in saliva, nasal and oropharyngeal secretions [62].

Although FMDV elicits a rapid humoral response in both naturally infected and vaccinated animals, it is slightly faster in natural infection. Protection has been correlated with high level of neutralizing antibody. Vaccination against FMD gives short-term serotype-specific protection in comparison with naturally infected animals [63].There is a suggestion that long-term antibody response detectable after FMDV infection is maintained due to the persistence of non-replicating FMDV antigen (Structural proteins) in the follicular dendritic cells in the light zone of the germinal center of the mandibular lymph node and also due to the presence of NSPs [64]. The shorter duration of immunity in the case of vaccinated animals in comparison with naturally infected animals may be due to vaccination with unstable, inactivated and non-replicative virus particles that might not induce much cell-mediated immunity. Elimination of NSPs during the antigen purification process of high-potency emergency vaccine may be another cause of lesser induction of cell-mediated immunity in vaccinated animals [65].

Differentiating Infected and Vaccinated Animals: Inactivated and adjuvanted whole FMDV vaccine is currently used worldwide generating antibody response only against viral structural proteins. In infected animals however active virus replication generated antibodies against NSPs [66]. Only structural proteins are detected by conventional liquid phase blocking (LPB)-ELISA allowing detection of antibodies against structural proteins only and thus is unsuitable for DIVA. This makes non-structural proteins important target for DIVA [67].

Viral non-structural proteins are required by the virus for replication within the host cell. The OIE guidelines 'Standards for diagnostics for pathogen and their products and for the production of vaccine like FMD vaccine' recommend the manufacturers to exclude the NSPs from their product through additional purification steps [35]. This allows previously infected animals to be distinguished from those with no history of infection regardless of vaccination status, as only infection will lead to the production of antibodies against NSPs. However, sometimes purification may not be perfect and NSP antibodies may be generated in some animals after vaccination, particularly after repeated doses [68]. OIE index system recently has assigned 3ABC ELISA to confirm antibodies against 3ABC NSPs [69].

Salivary IgA test has been proved as an effective alternative DIVA test for the detection of FMDV carrier animals taking advantage of the fact that high level of mucosal antibodies are generated in cattle with persistent oropharyngeal infection [70]. Little contamination with NSPs can be ruled out by the use of this mucosal test especially in developing nations wherein partially purified FMD vaccine is used resulting in repeated vaccination [15].

CONCLUSION AND RECOMMENDATIONS

Currently FMD is endemic in many countries including Ethiopia. FMD can be controlled by different strategies based on the status of the disease in the country and the neighboring countries. FMD free countries maintain their free status by preventing the introduction of the virus into their country. Vaccination is one of the best options for the control of disease in veterinary medicine including FMD. Immunity induced by the current inactivated FMD vaccine is short lived and needs regular revaccination in endemic countries. Checking the matching of vaccine strain and the strain circulating in the region to be vaccinated is mandatory for effective control of FMD using vaccination. Based on the above conclusive ideas the following points are forwarded:

- In FMD endemic situations, for the efficient control of the disease, a country must apply routine mass vaccination together with the control of animal movement and other effective biosecurity measures.
- In FMD free situations, countries must apply strategies to prevent introduction of the virus.
- Before a vaccination program is conducted the matching of the vaccine strain and the strain of the virus circulating in the region to be vaccinated must be checked.
- Regular surveillance and monitoring of the status of FMD in the country must be applied.

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