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Vaccines & Vaccination Open Access
ISSN: 2578-5044

Foot-and-Mouth Disease: A Strategic Analysis for the Control of Disease

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Mini Review

Volume 3 Issue 2

Received Date: September 07, 2018

Published Date: September 14, 2018

DOI: 10.23880/vvoa-16000125

Abstract

Foot-and-mouth disease virus is highly contagious and endemic disease of cloven-hooved animals. The broad host range and direct as well as indirect settings are key concerns in the virus spread. The antigenic variations in the viral genome lead to vaccine failure in the animals. For an effective control of the disease, new vaccine techniques must be adopted. The present review is to highlight the global distribution of the disease and its effective control strategies. Pakistan is an agricultural country which basically relies on the production of livestock and related products. Due to the high prevalence of the FMDV, the economy of the country has been disturbed. The seven serotypes of FMDV are antigenically different from each other and high sequence variability is associated with a VP1 region of the viral genome. In Pakistan, the serotypes A, O and Asia 1 are more prevalent, but recent outbreaks in Pakistan were found to be associated mostly with serotype O and Asia I in 2017. In 2018 again the trend has been changed and most of the outbreaks reported are due to serotype A and O. Various control strategies have been adopted to eradicate the virus through vaccination, although there is no cross-protection among the different serotypes of FMDV. New trends should be adopted in the development of the safe vaccine with long-lasting immunity for immunization of animals. More economical and improved ways to immunize the animals are need of the hour. Recently, the concept of plant-based edible vaccines, DNA vaccines, and anti-idiotype based vaccines are under research to control the disease.

Keywords: FMDV; Serotypes; Immunization; Vaccine; Genome

Abbreviations: FMD: Foot-and-Mouth Disease; VP: Viral Protein; BEI: Binary Ethylenimine; mAB: Monoclonal Antibodies.

Background

Foot-and-mouth Disease (FMD) is considered as an endemic in cattle and buffalo and its outbreaks are

reported every year across the country. This disease is also known as major killing disease of economy and responsible for maximum production losses in animals throughout the country. Outbreaks may occur even after using multivalent vaccines (using inactivated gel based). At present, vaccines used for FMD prophylactic are short-term, expensive and have narrow spectrum. Regardless of the fact that this disease is of prime economic importance, there is unavailability of proper investigated study/data at filed level regarding the outbreaks and disease occurrence and different risk factors causing the disease. The present review is to highlight the importance of the disease in terms of genetic variations and vaccine trends. It is need of the hour to thoroughly understand the virus structure and genomic variations associated with the virus. The recent concepts of vaccine are based on the antigenic structure of the virus.

Overview of FMD Virus

FMDV is positive-sense; single-stranded RNA viruses belong to genus Aphthovirus, family Picornaviridae. This viral genome is 8.3Kb, packed in a protein capsid. The capsid basically poised by 60 copies of four different structural proteins from (VP1-VP2-VP3-VP4) that have exposed surface. In some cases, VP4 is completely internal [1].

Within the past few decades, several outbreaks have been reported in Pakistan. Quite a lot of global animal health issues are related to serotypes A, O, C, SAT1, SAT2, SAT3, and Asia1. Different outbreaks in developed countries are reported due to the Virion structure of serotype O1BFS. VP4 is the major cause of antigenic variation. This site comprises of Myristyl group attached covalently to N-terminal. The viral antigenicity is related to the binding of the Arg-Gly-Asp motif with recogVP1, VP2, and VP3 that have structural and sequence similarity. The stretch terminal of the VP1 that have an extension of loops on both strands provides an antigenic site in serotype O. Their carboxyl and amino terminal are located on 5" of icosahedral viral protein. VP2 and VP3 have the same structure and alternate around two axes [2]. These three proteins (VP1, VP3, and VP4) make a complex network on the B-C loop of VP2 and provide several antigenic sites. The non-structural proteins of FMDV evade the host immune response. Different antigenic variations increased with the secondary structures that encode non-structural and structural proteins [3]. There are several serotypes of FMDV which share high variable sites of VP1 containing 135-155 amino acid residue and prove to be major antigenic sites of FMDV. Different coverings of Beta-cell epitopes (located in the non-structural proteins) induce both non-neutralizing and neutralizing antibody response. There is high sequence variability in Beta-cell epitopes leading to low cross-reactivity. The Beta-sheet of H and G in VP1 Beta-barrel connects these coverings, named as GH loop. These regions also contain antigenic site A that faces the substitution due to the high mutation in RNA replication [4].

Quasi-species (those species which show the same mutation) are also involved in antigenic variation that is more immunogenic than structural and non-structural proteins. The neutralization reaction is in-vitro reference test to accesses the antigenic variation of FMDV. Neutralization test involves different antigenic determinants which are responsible for virion strain specificity and protective antibody response. The virus variation can affect the vaccine manufacturing, variation may occur during strain adaptation to cell culture, the difference in the field and vaccinating strain or there may be variation in vaccine and challenge virus strain [5]. The two-dimensional micro-neutralization test was found more suitable for FMDV strain differentiation that indicates the dose-response relationships in quantal micro neutralizations [6].

Crystallographic Studies

Many crystallographic studies identify the basic structure of FMDV capsid. According to crystallographic studies, immunological epitopes found in interconnecting loops oriented on a surface containing different structural elements. Some monoclonal antibodies (mAB) also provide antigenic sites that cause antigenic variation. The antigenic sites are sequenced by mAB neutralization resistant mutants [7]. Among all antigenic sites which are VP1 140-142, VP2 67-79, VP3 58-59 and VP3 218, five antigenic sites of serotype O most extensively cause antigenic variation. Site 1 in the G-H loop is trypsin sensitive and have a linear structure, whereas, the others serotypes are trypsin resistant. Some antigenic sites are also identified for serotype A but have critical deposits present at equal positions [8].

The Genome of FMD Virus

FMDV is a single standard positive sense RNA virus the genomic size of virus varies according to the serotype, but it is estimated at about 8.5Kb. The genome has a single open reading frame, where, untranslated 5' and 3' regions of the viral genome are highly structured. The 5' UTR is about 1300 nucleotides while 3' UTR is 100

nucleotides. The viral genome replication is mainly under 5' UTR, it also initiates the viral polyprotein through cap-independent translation. The 5' UTR mainly consists of a short fragment of 350-380 nucleotides. The Poly-C tract is 100-420 nucleotides and a long fragment at the terminus is 700 nucleotides. The long fragment of 5' UTR has 3 pseudoknots, a cis-acting replicating element and type II internal entry site for ribosomes. The 3' UTR is also considered to be involved in genome replication through its cis-acting elements, but it is only 90 nucleotides in length [9]. Several antigenic sites on the FMD Virion adapted to the new environment. About 5-7 serotypes are identified which are responsible for the mutation and antigenic diversity. Results from negative selection (natural selection) also showed varying results of mutation due to several serotypes.

Antigenic Variation in FMD Virus

The microorganism changes its surface proteins to provoke the host immune response. The immune response is associated with the mutation rate that causes amino acid replacement. Mostly, it occurs at hyper variable sites of the G-H loops in the variable protein 1 (VP1). The main factor of antigenic variation is an abrupt antigenic change which also causes mutation in B-cell epitope. The basic alteration in the antigenic profile follows the antigenic diversity in which the virus or bacteria pass through the host population and hold the system of the original infected host cell. The antigenic diversity of an organism is important because of its easy transmission or repeated infection to target host [10]. All the microorganisms that exhibit these features and undergo such types of variation have some advantage over the genetically stable counterparts. Genetic variation also produced by those RNA viruses that exhibit an error-prone RNA replication process. FMDV continue to adapt and evolve new environments during RNA replication process to gives high mutation rates. However, these mutations will be eliminated by negative selection also called natural selection in which all deleterious alleles are deleted. Other viruses undergo a specific condition (immune evasion or other environmental factors) for antigenic variation during replication [11].

Antigenic variation is the most remarkable character of the FMD virus. The infectious virus alters its surface proteins by a special process to dodge a host immune response that is specifically related to replacement of amino acid causing mutation [12]. These mutations either result in the laboratory or in the field, developing pandemic strains like serotype O of virus FMD. The new serotype might be totally different from the field strain, perplexing new vaccine strains used to control the diseases. Mostly, the affected animals are recovered but the disease signs remain in the body of animals for a long period of time. It spreads quickly and broadly because it causes severe clinical loses as well as financial losses. Disease signs appear 1-8 days' post incubation. The virus lives in lymph nodes and bone marrow at neutral pH, but it causes the problem in the muscles when pH is less than 6. The virus survives in contaminated food, based on pH and temperature [13]. The genetic recombination, the rate of mutation, quasi-species nature and continuous circulation of strains in the field, cause economic loss in the livestock production due to the high degree of antigenic variation.

Economic Impact and Global Distribution of FMD

The national and international trading of a country strengthens its backbone. FMD hinders the trading of milk, meat, animals and other agricultural products. The losses of FMD in terms of production, mortality, and import-export are too much to economically weaken any country [14]. The direct and indirect losses associated with FMD are in terms of mortality, morbidity and milk production, growth rate and abortion.

The movement of affected animals from one to another area is the main source of virus distribution. The review of FMD serotypes on the global scale showed serotype A, O, and Asia1 are distributed in Asia and Indo-Pak region while A, O, and C are distributed in European countries. Serotype SAT1, SAT2, and SAT3 are rusticated to South Saharan Africa, other serotypes as A, O, and C are also present in Africa. FMD is endemic in Pakistan, the country has a more complex epidemiology [15,16]. North and Central America, New Zealand, Australia, Greenland, Iceland and Western Europe are free of FMDV. Western Europe was affected by some recent outbreaks (eradication was successful), but FMD has not been reported in North America for more than 60 years.

Recently in 2015 in Tanzania, the social and economic impact of FMD was studied using a standard questionnaire from forty households keeping livestock in different districts. The cross-sectional study indicated the social impact of the disease in terms of food security, educational expenditures the medical expenditures to an extent of 85 %, 90 %, and 75.5 %, respectively. The other losses associated with FMD were production and treatment costs. The fertility, abortion and other livestock

market losses made the farmers socially and economically weak. The studies showed, there was no FMD control through vaccination programs [17].

FMD remained endemic in Pakistan during the last few years. Serotype O and A were most common serotypes circling in Pakistan among the seven serotypes. The current strains of FMD have sequence homology with previous strains of Pakistan, India, Afghanistan and other neighboring countries. The O serotype is clustered with Pan-Asia II and other previously identified strains of FMD [18]. During the year 2011 to 2012, FMD was more prevalent in cattle population as compared to the buffaloes in Pakistan. Different parameters as, species, age, sex, and lactation states indicated the variable prevalence of the disease in different locations. The control of FMD via vaccination and other control strategies was devised in Pakistan to flourish in the sector of livestock [19]. A survey of the data from recent outbreaks during the past few years (Table1) shows the prevalence of FMD in different regions of Pakistan.

S. No	Year of outbreak	Total no/ % age of reported outbreaks	Serotype identified/ reported	References
1	2001-2002	52.13%	A, O, Asia-1	[20]
2	2002-2007	62 %, 153	O, A, Asia-1	[21]
3	2012	1088	O, A, Asia-1	[22]
4	2012-2013	51.2%	O, A, Asia-1	[23]
5	During 2013	78.1%	A, O, Asia-1	[24]
6	2013-2014	9.83%	O, A	[25]
7	2014	205	A, O, Asia-1	[26]
8	2015	152	A, O, Asia-1	[27]
9	Feb, 2018	66	A, O, Asia-1	[28]

Table 1: A detailed review of FMD outbreaks reported in different years in Pakistan.

FMD Virus to the Susceptible Host

The entry of virus in cattle is mainly through inhalation of virus particles, but the skin and alimentary tract may also be the route of viral entry. The virus mostly attacks the thick populated and humid areas where the virus can be transmitted through direct or indirect contact and cause severe clinical symptoms. The immunized animals either through vaccination or infection can be the carrier of virus for several months [29]. There is some variability in the clinical signs among species. Foot-and-mouth disease is typically an acute febrile illness with vesicles on the feet in and around the mouth and the mammary gland. Vesicles occur occasionally at other locations, including the vulva, prepuce, or pressure points on the legs and other sites. The vesicles usually rupture rapidly, becoming erosions. Pain and discomfort from the lesions lead to clinical signs such as depression, anorexia, excessive salivation, lameness and reluctance to move or rise. In serious cases, the hooves or footpads may be sloughed. Reproductive losses are possible, particularly in sheep and goats. Deaths are uncommon except in young animals. The pathogenesis of FMD can be studied by replacing the protein tag of FLAG epitopes (polypeptide) with Arg-Gly-Asp (RGD) tripeptide sequence motifs of FMDV. On viral recombination, the animal gives the same phenotype and growth characteristics as the parent viral particle. The animal did not produce antibodies against FLAG as it remained cryptic site and not detected by the immune system. The recombination can be a tool for studying antigenicity and pathogenicity of the virus [30]. FMDV antigenic variants can be isolated in different conditions as, in partially immune animals or persistently infected cattle. In case, absence or presence of an immune response and antigenic variations are remarkably diverse [31].

FMD Control Strategy

The past era of conventional vaccine and the new era of advanced vaccine may be envisioned in terms of FMD control and eradication program worldwide. Vaccination and control of animal movement were different control strategies that had been used in FMD free countries. In some countries as European Union, vaccination has been ceased and control of animal movement has been adopted since 1991. In some circumstances, ring vaccination and ring culling were allowed for the eradication of FMD. Vaccines were used to prepare or maintain the immunity for a specific disease. Foot-and-mouth disease is accessible to the United States Department of agriculture through the North American Foot and Mouth Vaccine Bank. Mexico and Canada were also the partners of the vaccine bank. There is no general suitable vaccine for the disease, however, the vaccines for the foot-and-mouth disease are according to the type and subtype in the affected area. When comparing the type and subtype, the vaccine has generally been defending animals from mounting clinical indications of disease. It was not necessarily defending the animals for foot-and-mouth disease infectivity [32]. The North American foot and mouth vaccine banks preserve different types of strong, inactivated foot and mouth virus antigens (Ag) at

extremely low temperatures per liquid nitrogen. In this region, various types of Ag are reserved for an indefinite period and formulated into vaccine quickly. Foot-and-mouth disease Ag was prepared by 1st growing the virus in cell culture, then filter the virus to remove the extra material, and inactivating it using a chemical like Binary ethylenimine (BEI). The Ag obtained was concentrated, pure and kept in cold conditions which protect the binding ability. The vaccine bank keeps various foot - and - mouth diseases, Ag. The Ag are sent by different countries and formulated when the vaccine for a specific serotype is required in that country. Animals that take the vaccine generally increase some degree of security besides clinical indications of foot-and-mouth disease in seven to eight days [33].

In Netherland, the cleaning, disinfection, and ring vaccination were recommended as an effective control measure [34]. In a study performed in California, it was recommended that vaccination remained a cost-effective strategy for FMD control if the animals were vaccinated but not slaughtered. The cost of different control strategies was higher as compared to effective vaccination. If the trade and other restrictions on animals vaccinated for FMD were displaced the vaccination was considered as the best control measure [35].

The antigenic variation has serious consequences in vaccine design because synthetic vaccines include multiple sovereign epitopes that decrease the chances of selection of FMDV which may be resistant to immune responses [36]. Inactivated FMD vaccines are used worldwide and in Pakistan. The importance to select a proper vaccine strain for the elimination and inhibition of FMDV remained intact. The quality of the vaccine was improved to control FMD outbreaks and also the control of risk factors that may create problems in livestock vaccination. Vaccines always remained the basic tool for the eradication and control of viral diseases that create a serious threat to humans and animals, distorted the trade in products and animals, reduced food security and undermined the agricultural development. Climate change and globalization increase the new patterns of spreading livestock viruses. Inactivated, livestock viral vaccines and adjuvants have spectacular success in global eradication of FMDV. However, live viral vaccine proves to be more efficient in the eradication due to having improved properties such speed of onset, stability, cross-protection to different serotypes and the duration of the immunity [37]. Still, there is a need to develop the safe vaccine. Table 2 is showing different vaccines which are developed against FMDV.

Vaccine type	Nature	Serotype
Bivalent vaccines	Killed	A22, O1
Trivalent vaccines	Killed	O, A, C
Adjuvants Oil-based	Killed	Type A, O, Asia-1, C
Adjuvant ISA 70VG	Killed	O, A, C, Asia I, SAT123
Adjuvant double oil emulsion	Killed	O, SAT
Adjuvant Aqueous	Killed	O, A, Asia I
Adjuvant Montanide ISA 50	Killed	A Pan Asia, SAT2
Aluminum Hydroxide saponin	Killed	O, A, SAT1, SAT2, SAT3
Subunit Vaccine	Attenuated	A
Virus-Like Particles (VLP) Vaccine	Killed	Asia I
Sabin Vaccine killed polio	Live Attenuated	
Synthetic Peptide Vaccine	Killed	A,O
DNA Vaccine	Recombinant	O, A
Chitosan Mediated Nano particle	Killed	O

Table 2: A detailed review of vaccines developed against foot-and-mouth disease virus.

Improvements in vaccine production should be based on the use of attenuated virus strain that has a high level of immunity. Improvements in the vaccine production should have superior immunization of all infected animals like swine and cattle. Moreover, these vaccines should have protective advantages without causing any persistent infection. The new method of vaccine design is developed as vector vaccine technology and reverse genetics. These technologies have been replaced by the capability of specific antigens, even only a single vaccine generates protective effects with a long period of immunity. Therefore, a review of all current FMD adjuvants and vaccines evaluated that these vaccines provide high immunization of all infected animals including swine and cattle. Cell-mediated immunity is an important task for the protection and security against foot-and-mouth disease virus. In spite of major advancement in present vaccinology, inactivated total virus vaccines for the foot-and-mouth disease is continued to be the base for prophylaxis and used in accidental conditions. Accidental vaccination as a component of protection strategies for foot-and-mouth disease virus would be the cause of spreading the virus. Many strategies were recently committed to developing

the immune response. Adjuvants used to potentiate the immune response, give outstanding suggestions for the efficiency of foot-and-mouth disease vaccines. The three oil adjuvant Montanide ISA-61, ISA-206, and ISA 201 are used extensively in the inactivated foot-and-mouth disease vaccine. The combination of Montanide adjuvanted vaccine and interferon-gamma produce cell-mediated immunity in the vaccinated animals.

New trends in the development of FMD vaccines: New methods and alternative approaches have been developed for the direct use of the FMDV genome. Moreover, proteins antigens and virus-like particles also express through the influence of FMDV protective genes (neutralizing epitopes and P1, VP1 sequences). The epitopes of VP1 and VP2 are protective genes and expressed in E. coli or other mammalian cells that enhance the cell-mediated immunity. Besides all these facts, the use of human Adenoviruses, insect viruses, bacilli, mammal cells and herpes viruses recently introduced in this field. These methods show successful results, including replication-defective system yet the protective immunity, is durable for at least 7 months in human [38]. The conventional inactivated foot-and-mouth disease virus vaccines were expensive to use. Being sensitive to heat and pH the inactivation of virus makes it less immunogenic. The frequent vaccination is another drawback associated with conventional inactivated vaccines. The concept of idiotype based protein vaccines is more recently used as virus surrogate. The vaccines may be more immunogenically active and provide consistent immunity [39].

Conclusions

FMD is the most devastating disease of animals. The current understandings revealed high antigenic variation in the genome of the virus. The limitation in conventional disease control strategies has been associated with genomic variation. Vaccine failure may be associated with poorly inactivated virus/ virus escape during vaccine development. There is a dire need to adopt modern vaccine development practices to ensure safe vaccination. Protein in nature, anti-idiotype based vaccine can be an alternative approach for the persistent immunization status of the animals.

Declaration

Ethics Approval and Consent to Participate

Not required

Consent for Publication

Not required

Availability of Data and Material

Not required

Competing Interests

None of the authors have any competing interest

Funding

Not available

Authors' Contributions

Ahsan Naveed was the main author of the article
The idea was generated by Professor Sajjad Ur Rahman, technical supporter.
Dr. M Imran Arshad helped in data collection and review
Dr. Bilal Aslam supported critically and helped in paper write up

Acknowledgment

We would like to acknowledge US-PAK Center for the advanced studies for their support.

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