

Review Article

Foot-and-Mouth Disease, an Economically Important Disease of Animals

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ABSTRACT

Foot-and-mouth disease virus (FMDV) was the first animal virus discovered by Friedrich Loeffler long back in 1898 and has been studied extensively. Despite this, it still remains mysterious due to its diverse nature and antigenic variability. Availability of the quick and reliable diagnostic tests and vaccines as well as logistical support required to eliminate this virus is still a matter of concern. In absence of quick and adequate control measures, it rapidly spreads across the continents. At present, Foot-and-mouth disease (FMD) is considered as one of the highly infectious, transboundary viral disease of cloven-hoofed animals which has a significant economic impact worldwide. Besides direct losses in terms of livestock producibility and productivity, it severely affects the trade of animal and animal products, the indirect losses of which may be higher than the direct losses. A significant success has been achieved in controlling the disease in several countries by means of effective and systematic vaccination programs, thorough sero-surveillance and vigorous stamping out policy (wherever possible). Countries like America, New Zealand, Australia and most of the Europe are free from FMD while it is still endemic in the Africa, most of the South America and several parts of the Asia including India. In India, the disease has emerged as one of the biggest hindrance for the growth of the livestock by adversely affecting productivity and international trade of animal and animal products. Prolonged convalescence, high contagiousness, wide geographical distribution, broader host spectrum, short duration of the immunity without inter-serotype cross protection, multiple modes of transmission and persistent infection (carrier state) all makes very difficult to control and eradicate this devastating disease. The FMDV also exists as a threat to developed nations due possible to trade and bio-terrorism attacks. The present review discusses FMD virus and the disease it causes, epidemiology, trends and advances in diagnosis, and appropriate prevention and control strategies to be adapted for combating this economical important disease of animals.

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INTRODUCTION

Foot-and-mouth disease (FMD) is a highly devastating and debilitating viral disease of the cloven-hoofed animals and considered as a serious threat to the livestock industry worldwide. (Rodriguez and Gay, 2011; Verma et al., 2012a; Ding et al., 2013; Xu et al., 2013). Affected species include domesticated ruminants (cattle, buffalo, camels, sheep, goats) and pigs along with more than 70 wildlife species (Verma et al., 2008; 2012a; Biswal et al., 2012; Teifke et al., 2012). The FMD is characterized by high rise of temperature, appearance of vesicles (blisters) on the mouth, muzzle, tongue, snout, nose, teats, inter digital space of feet and other hairless parts of skin (Teifke et al., 2012) which results into off-feeding and lameness.. It is difficult to milk

those animals which are having teat lesions; moreover they become prone to mastitis (Sharma, 2008). Morbidity can reach upto 100% in a susceptible population. However, with the exception in young animals where mortality can reach up to 50% due to myocarditis, the fatality due to this disease is rare (Verma, 2008; Verma et al., 2008, 2012a; Verma and Sahzad, 2011). The FMD is considered as a notifiable disease (previously List A disease) of animals as per World Organization for Animal Health (*Office International des Epizooties* (OIE) because of its high rate of transmissibility and imposition of international trade restrictions (Kumar et al., 2011). Therefore, FMD is considered as a threat for the developed countries due to trade embargo. Direct economic losses due to FMD are attributed to losses in the meat and



milk production (Ferrari et al., 2013), mortality in the young animals and reduced wool production in sheep (Howlader et al., 2004). Indirect losses occur in the form of decreased draught ability, reproductive disorders including abortions in pregnant animals and infertility in the recovered animals. In young calves, lambs, kids, and piglets FMDV-induced myocardial damage may lead to death before development of any vesicle (Singh et al., 1992). In a report published in The Financial Express newspaper (24 April 2008), a staggering revenue loss of about 4.45 billion US dollars i.e. about Rs 20,000 crores occurs in India annually due to FMD that affects the bovine population (Verma, 2008; Verma et al., 2012a,b). The outbreaks of FMD in certain nations particularly Taiwan (in 1997); United Kingdom (in 2001 and 2007); China in 2005; Japan and Korea in 2010-11; Bulgaria in 2011 led to significant increase in public awareness (Verma et al., 2012a,b,c; Park et al., 2012). Furthermore, livestock industry can be targeted as a feasible terrorist attack by employing the FMD virus (Dhama et al., 2013a).

ETIOLOGY

Loeffler and Frosch in 1897 first time established the FMDV as a filterable causative causative agent of an animal disease, a beginning of the science of virology. The causative agent of the FMD (FMDV) belongs to the genus *Aphthovirus* of the family *Picornaviridae* (Bachrach, 1968; Newman et al., 1973; King et al., 2000; Recaniello, 2001; Verma et al., 2012a). The size of the FMDV is about 30 nm characterized by the presence of single-stranded positive-sense RNA which is non-enveloped and has an icosahedral symmetry. Viral genome is of -8.5 Kb, encoding VP1, VP2, VP3 and VP4, the structural proteins and at least 10 non-structural proteins (NSPs) (Grubman et al., 1984; Robertson et al., 1985). The virion has sixty copies of each VP1-4, of which VP1, VP2 encapsidate the genome and VP3 are exposed outside (Jackson et al., 2002) while VP4 is completely lies underneath (Belsham et al., 1991). The three surface exposed capsid proteins carry the antigenic sites. The NSPs consist of L, 2A, 2B, 2C, 3A; 3B1, 3B2, 3B3; 3C and 3D along with some intermediate precursors (Ryan et al., 1989). Production of antibodies in infected animals is induced by both structural and non-structural proteins. The VP1-4 forms the virion. Most immunogenic protein VP1 has got maximum exposure on the capsid surface (Xu et al., 2013) whilst VP3 contributes mostly towards the capsid stability (Jackson et al., 2003). Polyprotein 3ABC and 3D are NSPs that play a significant role in virus replication. The 3D protein is the RNA-dependent RNA polymerase. The virus is considered as one of the fastest multiplying viruses.

Lipid solvents like ether and chloroform are ineffective whereas sodium hydroxide and sodium carbonate are effective disinfectants against FMDV. The FMDV is resistant to common chemical disinfectants especially when it is mixed with other organic materials. Phenolic-type disinfectants, alcohol, acetone, and other organic solvents and detergents have little effect on the virus. Formalin, KMnO_4 , sublimate of mercury, lactic acid and ethylene oxide are effective sterilizers. The virus can also be inactivated by 0.4% β -propiolactone and 1-2% NaOH, which destroys the virus in 2 minutes. A solution containing 4% sodium carbonate soap is effective under field conditions. The virus is also sensitive to drying. The sustainability of the virus in

the environment depends upon the environmental conditions; low temperature and high humidity rate always support the survival and propagation whereas hot and dry conditions as well as direct sunlight inactivate the virus (Verma et al., 2008).

ANTIGENIC AND GENETIC DIVERSITY

Antigenic variability and genetic diversity make FMDV difficult to eradicate through vaccination. Presence of variable antigenic type in different geographical area and even the concurrence of different antigenic type in same geographical area always put a need to acquire the knowledge of existing antigenic type prior to start a control and eradication program or for the selection of a vaccine (Rudreshappa et al., 2012). Antigenicity is mainly decided by the capsid coating proteins. Seven immunologically distinct serological types of FMDV have been classified namely serotypes O, A, C, Asia 1 and SAT (Southern African Territories) 1-3 based on the antigenicity of the capsid coating proteins (Pereira, 1977; Rodriguez and Gay, 2011; Ding et al., 2013). Within each serotype, there are a considerable number of strains with antigenic diversity and hence enforce to incorporate more than one FMDV strain to attain a significant protection. All the FMDV serotypes are clustered into genetic lineages distinctly with about 30-50% differences in the VP1 coding gene (capsid region genes) (Knowles and Samuel, 2003; Xu et al., 2013). New subtypes occasionally arise spontaneously. There is no cross protection between serotypes. Infection with one serotype type is fully susceptible with another six. Antigenic diversity led to variation in cross-protectivity particularly evident within the serotype A. Vaccines prepared from a single strain of serotype A virus may not provide immunity against other strains (Kitching, 1998; Jangra et al., 2005). Further, variant forms (quasispecies) having versatility in antigenicity evolves in the field at different times due to high error rate during genome replication (Domingo and Holland, 1997; Raies et al., 2009; Verma et al., 2010c). Like other RNA viruses, the FMDV has a high mutation rate as the RNA polymerase lacks the proof reading activity. The population size of FMDVs is large which is responsible for high antigenic variability together with continuous circulation of the field virus and plasticity of the major neutralizing sites on surface of the virion. They give rise to serious problems inspite of availability of good inactivated vaccine (Verma et al., 2010b).

There is increase in emergence of field variant due to antigenic variation over the time. Either the infected or vaccinated species of host may undergo immunologic pressure (Rudreshappa et al., 2012; Verma et al., 2010c) to generate antigenic variants. Polymorphism study indicated that the complexity in viral population is also affected during transmission between host to host; multiplication and evolution of virus within different tissues of host (Morelli et al., 2013). Variation in antigenicity in tissue culture forms the basis of production of vaccines worldwide. Required antigenic coverage may not be provided due to multiple passage steps for vaccine production (Food and Agricultural Organization, 2013).



RECEPTORS SPECIFICITY

Initiation of any infection requires the attachment and entry of potent infectious agent and these are governed by certain factors present at the site of predilection in target organ and most important among them are the cell surface receptors which specifically bind to antigen or pathogen (Rieder et al., 1996; Jackson et al., 2003; Tang, et al., 2012a). Integrins and heparan sulphate proteoglycan are two classes of receptors known to which FMDV binds (Jackson et al., 2003). By attaching VP1 RGD loop (on the viral capsid) to host integrins, FMDV initiates infection. Six types of integrins viz., $\alpha v\beta 1$, $\alpha v\beta 2$, $\alpha v\beta 3$, $\alpha v\beta 4$, $\alpha v\beta 5$, and $\alpha v\beta 6$ are found on the VP1 capsid protein of FMDV due to their ability of binding to the RGD amino acid found on the VP1 capsid protein which is highly conserved in nature. However, integrin $\alpha v\beta 6$ is expected to be the principal receptor binding molecule for FMDV (Rieder et al., 1996). Receptor(s) are considered as important host range determinants though with little evidence in support of it (Belsham et al., 1991; Jackson et al., 2002). The sequence of the capsid protein is also responsible for determination of infectivity of the virus in cells that are cultured. Works have been carried out from time to time for examining the influence of the substitution of single amino acid in the genome of the FMD virus. It has been found by such study that the quasispecies of the virus that evolves in separate biological environment attains the ability of several receptor recognition site selection (Zheng et al., 2010; Li et al., 2011; Xu et al., 2011). It has also been found that when a single amino acid in the FMD virus capsid gets substituted it can increase acid lability (similar to Herpes Simplex virus) thereby conferring resistance to uncoating inhibition that is dependent on acid (Gianni et al., 2010a, b; Martin-Acebes et al., 2010; Lawrence et al., 2013).

EPIDEMIOLOGY

Host Range/Species Affected

Host range always governs the existence of pathogen in environment. Larger host range always supports fast spread of disease with more chance of the antigenic diversity and hence makes the control programme a tedious task (Verma et al., 2010b; Teifke et al., 2012). FMDV infects mostly cloven-hoofed mammals (order- Artiodactyla) and many other species of different orders (Thomson et al., 1984). Susceptible livestock include a variety of domesticated animals viz. cattle, water buffalo, small ruminants like sheep, goats along with pigs and reindeer. Deer, antelope, elephant, and giraffe are also susceptible (Teifke et al., 2012). Camels have low susceptibility. The FMDV do not affect horses, pet animals and birds. Experimental infection can be reproduced in llamas as well as alpacas and camels. At least 70 wild animals species (including African buffalo, bison, elk, moose, chamois, giraffes, wildebeest, members related to deer as blackbuck, impala, and several species of deer along with the animals like warthogs, kudu, antelopes and gazelles) can also get infection (Michel and Bengis, 2012).

Susceptible species (apart from cloven-hoofed) include hedgehogs as well as armadillos and capybaras and many species of laboratory animals as guinea pigs, rats and mice. The FMD is still a disease of concern in African and Asian elephants in zoos. Usually the cattle are the most important maintenance hosts on most continents, while some strains

of virus has been reported to settle down permanently in pigs, sheep or goats. Pig is considered as an amplifier host for the virus as their exhaled breath contain virus in large quantity.

Human health is not affected by FMDV. Human infections with FMDV have been reported rarely without causing serious disease (Verma et al., 2012a). Up to one day, the virus can be carried in human nose and can be a source of infection for animals. The FMD is also not transmitted to humans in meat.

Morbidity and Mortality

Variation in the morbidity rate occurs and may depend on species, age, sex as well as the status of the immunity. Self recovery in the animals is the result of immunity against the infecting serotype of the virus. Mostly the disease occurs due to one type of virus and development of immunity also remains confined against specific serotype, thus no immunity develops to other serotypes, a reason behind occurrence of the disease in the endemic areas. The presence of a single serotype in an area or population lead to clinical disease that may be in mild form and mainly infects young animals because of loss of protection from antibodies from the dam. Presence of carriers are common in endemic areas (Chang et al., 2013) and the best example of the same is the presence of 50-70% and 15% to 50% of carrier animals in wild African buffalo/cattle and sheep respectively. Morbidity and mortality rate may go up to 100% in such areas. There is also a report on the involvement of a single host i.e. pig involvement during one Asian epidemic. A mortality rate of <1% in adult animals has been observed in non-endemic areas with morbidity a rate of 100%. However, young animals may suffer severe losses as 40-94% mortality rates in lambs have been observed (OIE, 2009).

Impalas are particularly susceptible among wild life in southern Africa where it becomes the common carrier for the spread of the disease. Depending upon the severity of the infection and environmental and physiological conditions, higher mortality rates may be observed. At least 50% case fatality rate was reported in mountain gazelles with few deaths in cattle in Israel with a recovery period of 8-15 days. Complications include various clinical conditions like erosions of tongue epithelium followed by bacterial super infection of the lesions. In advanced cases, hoof deformation, mastitis and ability to gain body weight along with abortion and loss of heat control ('panthers') are the common sequel. In young animals severity of disease depends upon the level of maternal antibodies and may lead to myocarditis and death (Sobrino and Domingo, 2001; Nishiura and Omori, 2010).

Geographic Distribution

The FMD was once prevalent all over the world but strict control and eradication measures adopted by developing countries have resulted in its lower prevalence. Worldwide 70 countries are officially recognized by the OIE as FMD free irrespective of vaccination, while India along with around 100 other countries are still considered as endemic or sporadic zones (OIE, 2009). Except New Zealand, outbreaks have occurred wherever livestock are present. However, the disease is present in enzootic form in all continents (except Australia and North America). In Africa all the different serotypes of the virus are present with the exception of Asia 1 (Rweyemamu et al., 2008). In the eastern

parts of Africa however serotypes: O and A; along with South African Territory (SAT-1 and 2) are still circulating (Ayelet et al., 2009; Ayebazibwe et al., 2010; Balinda et al., 2010; Habiela et al., 2010).

With advent of rapid transport system and global trade, even the strict quarantine measures sometimes fails to prevent entry of the virus into the FMD susceptible population; The FMD outbreak in 2010 in Republic of Korea and Japan are the current examples (Park et al., 2012).

Endemicity of FMD is observed in large areas of Asia (including Middle East), Africa, and South America (Astudillo et al., 1997). Occasional outbreaks of FMD have been reported from Europe, while Canada and United States are FMD free. Eradication is unfeasible due to persistence of the virus in wild African buffalo. Among the seven Serotypes of FMDV, the most common serotype that is prevalent all over world is type "O". It was also reported from pan-Asian epidemic that (1990) that resulted in severe economic losses in many countries throughout the world. There is also a few report of seasonal occurrence of FMD at low level sporadically in certain parts of Pakistan and northern states of India (OIE, 2007 and 2009).

Many countries have eradicated the FMD and are supposed to be free from this disease e. g. South Africa, Botswana, Namibia, Zimbabwe, Tunisia and Morocco in Africa and Chile, southern Argentina; Uruguay and Guyana; Surinam and French Guiana in South America. Countries like Iran, the southern countries of the former Soviet Union and South-East Asia including India and Pakistan, Philippines, Malaysia, Sub-Saharan Africa, Tanzania, Egypt, Ethiopia, and Eritrea (Jamal et al., 2010; Abbas et al., 2012; Abubakar et al., 2012; Verma et al., 2012a, (Kasanga et al., 2012a and 2012b; Tekleghiorgis et al., 2013). Many European countries claim to be free from FMD but sporadic outbreaks as in Greece in year 2000 and from UK, Republic of Ireland, Netherlands, and France in the year 2001 have been reported. The same strain caused outbreak throughout Asia. Eventually this outbreak was controlled in UK after slaughter of more than 4 million animals and no vaccination policy was adopted.

Serotype prevalent	Continent
O, A, C	South America,Europe
O, A, C, SAT 1, SAT 2, SAT 3	Africa
O, A, C, Asia 1	Asia
Virus free	North and Central America, New Zealand, Australia

Status of FMD in India

Since decades, FMD is endemic in India. Almost all parts of the country use to show its presence round the year. It is a major threat to the Indian livestock sector due to severe adverse impact on the economy (Verma et al., 2010b). The country has world's largest susceptible animal population; more than 500 million comprising of 199 million cattle, 105 million buffaloes, 71 million sheep, 140 million goats, and 11 million pigs (DAHD, 2007). Endemic nature of disease adversely affects India's livestock trade in the international market. Direct losses due to FMD are estimated to the tune from Rs 15,000-20,000 crores per annum (Venkataraman et al., 2006; Pattnaik et al., 2012; Verma et al., 2012a). Four different FMDV serotypes viz. O, A, C and Asia-1 are

prevalent in the country and the outbreaks of the disease are being reported round the year (Bhattacharya et al., 2005; Anon, 2007; Singh et al., 2007b; Verma, 2008; Verma et al., 2008). Type C is the least prevalent and the disease due to this serotype has not been recorded in the country since 1995 (Singh et al., 2007b; Verma, 2008; Verma et al., 2008; Verma et al., 2012a; b).

Realizing the importance of this disease, national FMD Control Programme (FMD-CP) has been initiated in 2003-04 in 54 districts of India, covering 30 million cattle and buffalo population for forming a FMD free zone (Pattnaik et al., 2012). With the success of this programme, another 167 districts have been added in 2010-11 and at present FMD control programme (FMD-CP) is operational in 221 districts where all the cattle and buffaloes totaling about 110 million are regularly vaccinated twice a year with trivalent (O, A and Asia1) vaccine. The Northern states, Himachal Pradesh, Punjab, Haryana and Delhi hold promise to become "Disease free zone" in the coming years due to intensive vaccination and monitoring (Pattnaik et al., 2012). Due to constant efforts in areas where Government of India has implemented FMD-CP, the disease has been controlled and the idea of development of herd immunity to prevent outbreak of FMD is very effective in controlling the disease (Singh et al., 2007b; Pattnaik et al., 2012; Verma et al., 2012a,b).

It has been reported that FMD outbreaks were more during 2007-2008 in comparison to 2010-2011 (on the basis of status of the disease during five fiscal years). Out of the three major serotypes (O and A; Asia 1), serotype O was responsible for causing 80 per cent of the disease outbreaks which had been subsequently confirmed. In comparison Asia 1 and A were responsible for causing 12 and 88 per cent of the outbreaks respectively. Assessment based on geographical region gave indication of variable rate of prevalence of the disease in several parts of India. The prevalence in various regions are: Eastern region (43 per cent); Southern region (31.5 per cent); North-eastern region (11.6 per cent); Central region (5 per cent); Western region (4.4. per cent); and Northern region (4 per cent). In the month of June the outbreaks are highest. When investigations were carried out in real time emergence as well as re-emergence of various genotypes (or lineages) became evident within the serotypes. The vaccine strain had undergone change due to antigenic divergence continuously during the year 2009. Within the serotypes the vaccine strain can tolerate well all kind of genetic diversity. It has also been speculated now that movement of animals in an unrestricted fashion plays a significant role in the disease spread (Biswal et al., 2012; Subramaniam et al., 2013).

TRANSMISSION

Following an acute disease, affected animals shed the virus in all the body secretions and excretions (including exhaled air) like saliva, nasal and lachrymal fluid, milk, urine, feces and semen (Woodbury, 1995). Mucosa of the pharynx is the primary predilection as well as replication site inspite of the viral entry via skin wounds or the gastrointestinal tract. Large quantities of viruses in aerosolized form are shed by pigs in particular. Four days prior to onset of symptoms, the infected animals usually start shedding the virus. Some animals can continue to excrete the virus for long periods (up to years) after recovery. The vesicles in buccal mucosa



(especially tongue and dental pad), bulbs of heels and in the inter-digital space, normally rupture within 24 hrs, releasing vesicular fluid containing up to 10^8 infectious virus units per ml. Contact with infected animals and contaminated fomites and fodder directly or indirectly can transmit the disease but majority of the transmission events occur by the movement of the infected animals. Many other sources of infections viz., wool as well as hair of infected animals, contaminated grass or straw, footwear and clothing of animal handlers stuck with mud or manure, livestock equipment or vehicle tyres or wind can play important role for spread of the disease (OIE, 2009).

Infected milk may be the source of infection to young calves and between the farms. Milk tankers have also been found to spread the virus (Metcalf and McElvaine, 1995; Donaldson 1997; Tomasula and Konstance, 2004). Inhaled aerosolized virus may also serve as cause infection (Alexandersen et al., 2003), ingestion of contaminated feed, fodder and the exposure of contaminated utensils which can lead to virus entry through skin wounds and mucosal barrier and hence spread the disease. However, the role of sources and chances of exposure through different routes show species variation as aerosolized virus more severely affect cattle or sheep in comparison to pigs (Alexandersen et al., 2003). Less obvious symptoms are seen in sheep compared to other species and in certain outbreaks they are important in disseminating the virus. The SAT type viruses in African buffalo populations may spread significantly through sexual contact. Infection in cattle can occur by breathing in the virus in small quantity.

Although horses, dogs and cats are resistant to FMD but similar to human beings these can act as mechanical vectors. Similarly, avian species do not get infected but the virus may spread along with their feet and feathers after contact with the infected material. Imported food derived from an infected animal when fed to pigs (as meat, offal, or milk) can spread the virus.

Cool and damp climate always supports the spread of the FMD virus when animals are penned or housed especially in cold weather (Bhattacharya et al., 2005; Verma, 2008; Verma et al., 2008). The virus survives well below 4°C temperature, but it can be easily inactivated with the rise of temperature and reduction in relative humidity less than 60%. Under favorable climatic conditions (high humidity), aerosol transmission of virus up to 250 km has been reported (Donaldson et al., 2001). The virus may survive at 4°C for up to a year. The virus loses its infectivity by rapidly heating at 56°C . A proportion of FMDV in infected milk will survive pasteurization as they are associated with animal proteins. The virus may survive for 14 days in dry faeces, more than 6 months in slurry and for 39 days in winter. Drying-off of the virus is prevented by organic material which also enhances virus survival. At 4°C , the viability persists for two months on wool. There is enhancement in survivability of FMDV provided there is protection from sunlight. Alteration in pH as below 6.5 or above 11 can easily inactivate the FMDV. Virus survivability in animal products including meat depend upon the pH; the virus survive best at pH 6.0 but is inactivated when there is rigor mortis that resulting in acidification of muscles. Frozen or chilled lymph nodes or bone marrow can also maintain the virus for long periods. Carriers (especially cattle and water buffalo)

convalescent animals and exposed vaccines can also transmit the disease (Klein et al., 2008). Pacheco et al. (2012) reported that different serotypes or strains of FMDV have different transmission characteristics and emphasized the need of research in this area, which may be helpful in understanding the pathogenesis and epidemiology of FMD.

FMDV PERSISTENCE

After recovery from the acute disease, a proportion of the animals may become carrier that shed the virus for long period (Perry and Rich 2007; Huang et al., 2011). Both the naïve animals and the vaccinated animals may become carrier on exposure to the FMDV. Persistence of virus varies from species to species; up to 12 months in cattle, 6-9 months in sheep and upto 4 months in goats. Virus does not persist in the swine and llamas after the recovery from the acute disease. Carrier state in the African buffalo has been observed up to 24 years. During carrier state, in the cattle, the virus persists in the epithelium of the dorsum of soft palate (pharynx) and secreted in the oropharyngeal fluid (Zhang and Kitching, 2001; Stenfeldt and Belsham, 2012) whereas in sheep it persist in the tonsils. The mechanisms of FMDV persistence in the ruminants is not known, but *in vitro* studies on BHK-21 cell lines revealed that the host cells interfere in the lysis of FMDV (Zhang et al., 2013). The FMDV transmit from carriers to other animals in close proximity; however, there is debate regarding route of transmission. In Africa, carriers can transmit the virus unequivocally, where African Cape buffalo (*Syncerus caffer*), commonly gets infected with two or more SAT serotypes in areas having no disease in cattle, and thus could spread the disease to cattle (Thomson et al., 1984; Condy et al., 1985). Domesticated animals can spread the disease in wild life. Persistence exists in some wild animals for example experimentally infected fallow (*Dama dama*); sika deer (*Cervus nippon*); kudu (*Tragelaphus strepsiceros*) and occasionally red (*Cervus elaphus*) and white tailed deer (Moniwa et al., 2012).

THE DISEASE (FMD)

Incubation Period

Incubation period depends on the dose of the virus, portal of entry, animal husbandry practices and animal species involved (Alexandersen and Mowat, 2005); 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.

Pathogenesis

In the cattle infected via the respiratory tract, the virus initially replicates in the pharynx (Alexandersen et al., 2003) from where it proceeds towards the epithelium of the mucosa associated lymphoid tissue of the nasopharynx (Pacheco et al., 2010; Arzt et al., 2010; 2011a), mucous membrane of oral cavity and invades the basal layer of the stratified epithelium of the tongue and produce primary lesions. FMD- vesicles are formed due to virus multiplication in the stratum spinosum layer where cytolysis takes place and hence giving rise to small cavities in the epithelial layer. The process continues for 24 h and huge quantity of the virus is produced in the vesicles of the tongue from primary lesions. Virus also invades the lymphatics (Henderson, 1948) and enter into the blood stream (Burrows et al., 1981) resulting in spread of virus to



other organs and tissues such as epithelium of mouth, dental pad, coronary band, interdigital space of hoof, mammary gland, teats (cattle) and snout (pigs) where the secondary lesions develop (Seibold, 1963; Alexandersen and Mowat, 2005; Arzt et al., 2009). One-two days after infection, fever and viraemia may be observed. In advanced and unaddressed cases, secondary bacterial infection may set up extensive damage of the tissue. Damage of feet may lead to loss of the horny covering and sloughing of the hoofs. Udder lesions may lead to mastitis due to secondary infections. Heart muscles of young animals may show acute degeneration of the myocardial fibers (tiger heart). Distribution of the virus via the lymphatics to replication sites in epithelium of different organs as mouth and muzzle, inter digital spaces of feet, and teats. Sometime involvement of damaged skin in pigs may be observed that are kept on concrete. Generally, the vesicular lesions appear at these sites (parts of knees and hocks) and within 48h it ruptures. The viremia persists for about 3 days (Burrows et al., 1981; Racaniello et al., 2001).

Clinical Signs

The disease is more severe in cattle and pigs but the sheep and the goats may even some time undergo undiagnosed. Anorexia and fever (up to 41°C) may develop in the cattle as well as in pigs. The clinical signs appear within 2 to 3 days after FMDV exposure and may last for 7-10 days. Fever and vesicles on the feet, between the toes as well as on heels, around the mouth, particularly in lips as well as tongue and palate, and on the mammary glands are noteworthy but characteristic lesions are observed in interdigital space and coronary bands of hooves (Alexandersen et al., 2003; Teifke et al., 2012; Verma et al., 2012a; Yoon et al., 2012). In rare cases, the external genitalia may also develop the lesions. Depending upon the severity, these vesicles may enlarge and swell. Blisters that rapidly rupture/erupt can leave painful and raw erosions and ulcers that may take up to 10 days to heal. Various clinical signs such as depression and anorexia; salivation in excess; lameness and reluctant movement and rising are observed due to pain and discomfort from the lesions (Yoon et al., 2012). Abortions in FMD may not be directly due to virus replication but rather due to high rise of temperature. Most adults recover within 2-3 weeks though it may prolong due to secondary bacterial infections. Depression and lethargy, rapid loss of condition, gradual or sudden drop in milk production either temporarily or permanently may be observed. Lameness or mastitis in chronic form, reduced growth rate, loss of weight, infertility and poor body condition are the common sequel of the disease. Although mortality rate in adult animals is very low but the young animals may die due to multifocal myocarditis. Severity in symptoms of FMD may vary according to host species, and the serotype and strain of the virus involved. In pigs, the mouth lesions are comparatively less severe but the hocks and elbows may progress to severe foot lesions. The temperature in pigs may be normal during the disease. The morbidity rate is 100% but a mortality of up to 5% in adults and up to 75% in piglets less than 8 weeks of age has been observed.

In sheep and goats, lesions are less pronounced with variable clinical signs (Callens et al., 1998; Barnett and Cox, 1999; Viuff et al., 2002; Yoon et al., 2012). Foot lesions may not be recognizable. Dental pad lesions in sheep can be seen.

In milking sheep and goats agalactia is characteristic. Mouth lesions are often remains unnoticed in the form of shallow erosions. Healing of the severe vesicles in the mouth occur within 7 days. Presence of vesicles on teats, vulva or prepuce is rare. There may be frequent development of feet and mammary gland lesions whereas in advance cases secondary infections lead to severe mastitis. The underrunning of the sole and painful blisters may lead to chronic lameness. There may be drop in milk production and reluctance of the rams for matting may persist. Abortions are rare but ewes may abort. Sheep may remain asymptomatic (25%) or lesion at one site (20%). The mortality in immature lambs as well as in the kids is mainly because of the heart failure without showing any obvious vesicular lesions.

Wild animals show symptoms similar to that in domesticated livestock with the formation of vesicle especially on the feet and in the mouth. Both the acute disease and subclinical infection or mild disease may be seen; SAT-type virus infection in African buffalo mostly remains subclinical. However, many wild species as gazelles, impala, blackbuck, white tailed-deer and warthogs show acute lesion with high mortality. Sometime FMDV may leads to swollen tongue similar to the allergic diseases (Longjam et al., 2011a; Deb et al., 2012). Myocarditis, losses in reproductive ability, and chronic heat intolerance are some of the common sequel of FMD that have also received little attention (Arzt et al., 2011b)

Post Mortem Lesions

The FMD is characterized by the formation of fluid-filled vesicles or bullae either in single or multiple varying in size from 2-10 mm in diameter. The initial lesions include the formation of tiny pale areas leading to vesicle and subsequently bullae formation. These vesicles lost in few hours leaving behind red, eroded areas or ulcers. Sometimes vesicles having fibrinous coat, gray in colour and surrounded by a distinct demarcating line of newly developing epithelium may form. "Dry" lesions, mainly in pigs, are formed due to the loss of vesicular fluid and many time lead to necrosis. In rare cases, lesions may extend to skin and further secondary infections may aggravate the condition. Presence of coronitis and vesicle formation in multiple organs viz., teats or udder; pressure points in legs, pillars of rumen and external genitalia are common in cattle. Involvement of heart in the form of cardiac degeneration and necrosis which mostly appear as gray or yellow streaks in the myocardium ("tiger heart" lesions) are observed in young calves (Deb et al., 2012).

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. To avoid any confusion particularly with vesicular diseases like Vesicular Stomatitis (VS) and Swine vesicular disease (SVD), differential diagnosis is necessary due to similarity in clinical signs (Teifke et al., 2012). Apart from these vesicular diseases, other infectious diseases viz., bovine mucosal disease, rinderpest (RP), peste des petits ruminants (PPR), malignant catarrhal fever (MCF), blue tongue (BT) and epizootic haemorrhagic disease (EHD);



physical injury; chemicals and thermal burns may also lead to stomatitis and foot lesions (Teifke et al., 2012). Lesions in sheep are often confused with those of bluetongue or contagious ecthyma and lip or leg ulceration. In pigs differentiation should be made from those of swine vesicular disease and vesicular exanthema. Other conditions which should be differentially diagnosed include border disease, bovine mamillitis and bovine papular stomatitis.

Identification and isolation of live FMDV facilitate definitive diagnosis. This is usually required at the phase of outbreak in a nation or region that has previously achieved disease-free status. Isolation and identification to detect antigen and genome of the virus or serological evidence in support of the presence of the virus are recommended for diagnosis on clinical ground and to trace the disease spread. Examination of serum samples by RT-PCR or virus isolation help in detection of viraemia. Apart from these tests, infrared thermography (IRT) can also be used for quick diagnosis of disease in outbreak conditions (Rainwater-Lovett et al., 2009). Recently, gold nanoparticle improved immuno-PCR based diagnostic has been developed to detect FMDV.

Sample collection

Epitheliums from vesicles that are either ruptured or unruptured or vesicular fluid are preferred for virus detection in acute cases (Verma et al., 2012a). The FMDV shows sensitivity to low pH. Good buffering ensures virus isolation; shipping in a transport medium (equal amounts of glycerol and phosphate buffer (0.04M) with pH 7.2–7.6 with addition of penicillin, neomycin sulphate, polymyxin B sulphate and mycostatin) (Kitching and Donaldson, 1987) either on ice or under refrigerated conditions (frozen) are recommended. In case of unavailability of vesicles, blood (serum) and esophageal or oropharyngeal fluid samples may be collected for virus isolation or RT-PCR detection. Probang method of esophageal-pharyngeal fluid collection from ruminants or swabs from throat of pigs is preferable. Myocardium and blood are preferred in absence of vesicles from the animals died due to heart failure. Milk, other secretions and excretions along with other organs may contain the virus. Serum may be collected for detection of FMDV specific antibodies. In suspected carrier animals probang cup must be used to collect esophageal or pharyngeal fluids (Stenfeldt et al., 2013). One gram of epithelial tissue (minimum requirement) must be collected from an unruptured or recently ruptured tongue vesicle or that from buccal mucosa or feet. Samples (vesicular epithelium or vesicular fluid) have to be sent to the national laboratory in phosphate-buffered saline (pH 7.4) for the diagnosis of FMD. Otherwise they may be sent to OIE/FAO World Reference Laboratory for FMD (Pirbright in United Kingdom). Samples should be securely packed in double leak-proof containers following guidelines for shipping of hazardous samples (FAO / OIE Reference Laboratory Report, 2006; Tufan, 2006).

LABORATORY TESTS

Virus isolation

Isolation of FMDV can be carried out in primary bovine thyroid cells (Snowdon 1966; Ferris and Dawson, 1988) or primary pig, calf or lamb kidney cells (House and House, 1989, Ahl et al., 1996); BHK-21 or IB-RS-2 cells (Whiteside

et al., 1983; Saha and Sen, 1987; Singh et al., 1987; Sakamoto et al., 2002) though the cell lines show less sensitivity than the primary cells. The virus if required may be passaged in unweaned mice. FMDV may be suspected in clinical material by appearance of the cytopathic effects (CPE) within 24–48 h following infection to BHK-21 cell. The results may be confirmed by virus neutralization (VNT) assay and typing of the virus by ELISA (OIE, 2009).

Detection of viral antigens

Before 1997, FMDV was identified by complement fixation test (CFT) (Ferris et al., 1984). After that various serological tests like enzyme linked immunosorbant assays were developed.

Serological tests

Use of serological tests is essential for supplementary diagnosis of the cases suspected for FMD, for certification of animals for import/export, in determining the freedom from infection and for demonstrating vaccine efficacy. Serological diagnosis of FMDV is done by enzyme linked immunosorbant assay (ELISA), agar gel immunodiffusion test (AGID) and virus neutralization test (VNT). The FMD vaccination or recovery from infection can be shown by performing ELISA that becomes serologically evident (competitive or blocking). Previous or current infections can be diagnosed by using antibodies to FMDV structural proteins and include: ELISAs [Solid-phase competition ELISA, Liquid-phase blocking ELISA (LPBE)] and virus neutralization tests (VNT) (Gold standard test) which are serotype specific. The LPBE has been widely utilized for analysis of post vaccination immune response in the herd (Singh et al., 2007a, 2008; Verma et al., 2009; Deb et al., 2013).

Differentiation of infected and vaccinated animals (DIVA)

There is opposition to the use of FMD vaccine in developing countries even though they have many advantages because of the heavy penalty put on by international trade regulation. These trade regulations are based on the fact that there may be perpetuation of infection in FMD free countries due to vaccination. In addition, in the vaccinated population, carriers can not be detected accurately. Emergency vaccination is however recommended in certain EU countries recently because of which DIVA strategy has got preference both in endemic and FMD free countries (Raaf et al., 2011).

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 (Clavijo et al., 2004; Hassanein et al., 2011). 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. NSPs generated in vaccinated stock can also be detected by DIVA.

Virus infection-associated antigen (VIAA) is the viral RNA polymerase (3D poly) that can be detected by agar-gel immuno-diffusion (AGID) (Cowan and Graves, 1966; Polatnick and Arlinghaus, 1967; McVicar and Sutmoller, 1970; Newman et al., 1979). However, later it was found that the sera from multiple vaccinated animals (Rowlands et al.,



1974; Pinto and Garland, 1979; MacKay et al., 1998) and from some animals which have even received a single dose of vaccine (Lubroth and Brown, 1995; MacKay et al., 1998), also developed antibodies to VIAA. The immune response elicited by vaccination against VIAA usually disappears within 60-90 days (O'Donnell et al., 1997). Impure vaccine contaminated with NSPs is the sole reason for generation of non-specific antibodies interfering with test result (Lubroth et al., 1996).

Alonso et al. (1990) developed liquid phase ELISA based on detection of VIAA showing better sensitivity than AGID. Berger et al. (1990) suggested that simultaneous detection of at least two NSPs antibodies (excluding 3D) should be sufficient to demonstrate viral replication.

Later on more sensitive assays viz., enzyme-linked immuno-electrotransfer blot (EITB) (based on the use of a set of purified recombinant DNA derived NSP antigens not VIAA) and EITB assays were compared along with virus isolation and EITB was found most sensitive (Bermann et al., 1993; Bernmann et al., 1996; Dekker et al., 2008).

The magnitude of the antibody response against NSPs is variable; 3A, 3B, 3D and 3 ABC could be detected in cattle as early as 7-10 days post infection (Bergmann et al., 1993; Sorensen et al., 1998) and up to 560-742 days post infection (Silberstein et al., 1997; Malirat et al., 1998). However, in sheep, these develop later; against 3ABC at 14 days and against 3D after 22 days post infection. Although 3D protein is not the best choice for DIVA, its antigenicity is highest among all the NSPs (Mavkay et al., 1998) and therefore the 3D NSP-ELISA is highest but less specific. Mackay et al. (1998) found that the 3ABC is the most reliable single indicator of the infection (examining with bovine and ovine sera) eliciting early immune response after infection. Antibodies to 3ABC could be detected for longer than antibodies to any other NSP. NSP-3A generally induces a similar response; some animals fail to react against 3B, whilst 3C alone is very weak immunogenic. Detection of antibodies to one or more of the NSPs: 2C, 3A and 3 AB in addition to those against 3ABC provides further confirmation to infection. The sera from multiple vaccinated animals are considered to be free from antibodies against 2C which is explained by the association of this viral protein with cellular debris that can be separated from the virus harvest prior to inactivation of the supernatant for vaccine production (Lubroth et al., 1996). Antibodies to 2C could be detected in cattle up to 365 days after infection (Lubroth and Brown, 1995).

The adjuvant in the FMD vaccine enhances immune response against NSPs but detectable antibodies are generated for short duration in vaccinated animals than in infected animals. The OIE guidelines 'Standards for diagnostics for pathogen and their products and for the production of vaccine' recommend the manufacturers to exclude the NSPs from their product. However it is not possible to prepare a FMD vaccine absolutely free from NSPs. Because of the high cost involved that may be unaffordable for the farmers of developing nations (Dhama et al., 2010; Kumar et al., 2011).

Later on, ELISA based assays with various NSPs produced by recombinant baculovirus (Sorensen et al., 1998; Kweon et al., 2003; Kumar et al., 2007), in *E. coli* (Rodriguez et al., 1994; Silberstein et al., 1997; De Diego et al., 1997;

Mackay et al., 1998; Bergmann et al., 2000), insect larva (Lopez et al., 2004) or synthetically produced peptides to NSPs (Shen et al., 1999; Hohlich et al., 2003; Oem et al., 2005) were developed. Baculovirus expression system has several advantages over *E. coli* expression system due to higher expression level, more native conformation of expressed product (eukaryotic expression system), ability to express multiple and large fragments of foreign DNA and the less stringent biosafety requirement as it is not a human pathogen (Meyer et al., 1997).

Three commercial tests (kits) are available to detect antibodies against NSP (based on NSP-3ABC) viz., United Biomedical, Inc., New York, Cedi-Diagnostics B.V., The Netherlands and SYANOVA Biotech AB, Sweden. These tests vary with each other for their sensitivity and specificity (Lee et al., 2004; Moonen et al., 2004; Bruderer et al., 2004). Furthermore, all these tests are very expensive to be afforded by developing countries. OIE index system recently has combined 3ABC ELISA supported by immunoblot test confirming antibodies against NSPs- 3A, 3B, 2C, 3D and 3ABC NSPs (Uttenthal et al., 2010). Anti-NSP tests are not serotype specific thus reactive across all the seven serotypes. (Bronsvort et al., 2006; Inoue et al., 2006; Kumar et al., 2007; Verma et al., 2010d and 2010e; Sangula et al., 2010; Ma et al., 2011; Mohapatra et al., 2011a; Lather et al., 2012). However, no NSP-ELISA can differentiate infected and vaccinated animal with 100% accuracy (Ma et al., 2011).

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 (Parida et al., 2006; Biswas et al., 2008). 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 (Parida, 2009).

Molecular tools

Diagnosis of FMD should not only be rapid but also be capable of handling large number of sample simultaneously. Also test should not miss carrier animals which are equally important in spreading the disease. The technique of reverse transcription - polymerase chain reaction (RT-PCR) and long distance polymerase chain reaction (LD-PCR) (Shawky and Daoud, 2005) has been employed for the rapid detection of viral nucleic acids from different kinds of biological specimens such as nasal swabs (Marquardt et al., 1995), vesicular epithelium (Knowles and Samuel 1995; Callens and De Clercq 1997; Reid et al., 1998, 1999, 2001; Tosh et al., 2003; Verma, 2008; Raies et al., 2009; Reid et al., 2009; Verma et al., 2010a, 2011), milk, serum and probang samples (Amarel-Doel et al., 1993; Donn et al., 1996; Bastos, 1998; Reid et al., 2002; Van-Rijn et al., 2004; Bao et al., 2011). The virus serotype can be also be determined by RT-PCR ELISA (Callens et al., 1998), nested RT-PCR (Moss and Haas, 1999), real-time RT-PCR (Reid et al., 2002; Moonen et al., 2003), portable real time RT-PCR (Donaldson et al., 2001; Hearps et al., 2002) and automated RT-PCR (Reid et al., 2002), nucleic acid sequence based amplification (NASBA) test (Collins et al., 2002; Lau et al., 2008), RT loop mediated amplification (LAMP) test (Dukes et al., 2006; Chen et al., 2011a and 2011b), real-time reverse



transcription-loop-mediated isothermal amplification assay (RT-LAMP) (Ding et al., 2013; Madhan Mohan et al., 2013), universal RT-PCR (Xu et al., 2013), gold nano-particle immuno-PCR (GNP-IPCR) (Ding et al., 2013). By isolation of FMDV from the esophageal-pharyngeal fluids identification of carrier animals can be done but there may be presence of that are intermittently shed the virus, and thus requires repeated serial sampling. These asymptomatic animals can be identified by RT-PCR. These assays are highly specific and sensitive and viral RNA can be detected in clinical samples well in advance (Bergmann et al., 1996). Newer methods of typing have been developed and widely utilized now a days based on genotype specific multiplex polymerase chain reaction (PCR) (Mohapatra et al., 2011b), lineage differentiating RT-PCR for serotype A (Mohapatra et al., 2007) and Asia-1 (Mohapatra et al., 2006) for simultaneously test and gives serotype identification also (Giridharan et al., 2005). The PCR is multiplexed with all serotype primers which gives on amplification of different product size specific to serotypes. Research is going on mobile portable nucleic acid extraction (in field) and real-time PCR amplification platform that can produce same results as that of test conducted in established diagnostic laboratory (Madi et al., 2012).

Reference antisera (with existing FMD vaccine strains) can be used for characterization of the isolated virus. For comparing with the other strains of the same serotype and in order to provide useful information on the origin of the outbreak, the RT-PCR amplified FMDV RNA must be compared with the other strains of the same serotype (Mohapatra et al., 2006). On-farm diagnosis is possible due to rapid diagnostic kits but stringent validation is required. Confirmatory diagnosis and virus matching is now relative easy to perform with full automation of nucleotide sequencer. The DIVA diagnostics include virus isolation, RT-PCR, VNT, IgA ELISA and NSP ELISA. NSP based ELISA is most promising test for large scale sero-surveillance especially endemic country like India (Giridharan et al., 2005; Longjam et al., 2011b, 2012).

Lateral flow devices (LFD) (Ferris et al., 2009, 2010), latex beads agglutination test, enzyme-linked immune electrotransfer blot assay, monoclonal antibody based ELISA, and multiplexed Luminex assay have been developed for FMDV (Ding et al., 2013). A chromatographic strip assay (Pen-side test) has been developed to rapidly detect serum antibodies to FMDV-NSP (Chen et al., 2009; Sammin et al., 2010). One-step, reverse transcription loop-mediated isothermal amplification (RT-LAMP) assay (Dukes et al., 2006; Ding et al., 2013) enables FMDV detection without thermal cycling under an hour in a single tube (Anonymous, 2010; Dhama et al., 2014). Recently, based on principles of bio-barcode amplification (BCA) assays, gold nanoparticle (GNP) improved immuno-PCR (GNP-IPCR) assay were developed for ultrasensitive detection of FMDV antigen (Ding et al., 2011, 2013).

Mutational analysis under immunological pressure must be undertaken because of high antigenic variation. Phage display technology was used to undertake molecular study of the antibody response in bovines. Isolation of CH1-VH chain binding Fabs has been performed after selecting from a library constructed from those cattle that are vaccinated. Recently, random 12-peptide library has been

displayed by a phage on screening. The ETTXLE consensus motif [X is any amino acid (aa)] is displayed by positive phages and shows high homology to 6ETTLLEII at the N-terminus end of VP2 protein (structural protein). Moreover a monoclonal antibody to serotype independent FMDV must bind to a minimal epitopic region (MAb 4B2) in order to use it as a universal diagnostic candidate (Kim et al., 2004; Longjam et al., 2011a).

TREATMENT

Instead of specific treatment, depending on the clinical manifestations symptomatic treatment may be rendered. Potassium permanganate mixed antiseptic mouth wash, sodium carbonate, boric acid and glycerin may be applied over the lesion. Feet of the affected animals may be washed with 2% copper sulphate solution. Washing of the wounds with soda ash solution and topical application of honey and finger millet is found suitable in foot lesions (Gakuya et al., 2011). Antiviral approaches including 2'-C-Methylcytidine (Meyer et al., 1997; Lefebvre et al., 2013), ribavirin (Kim et al., 2012); cytokine therapy inclusive of IFN- α/β as an anti-FMD agent is useful for the purpose of prophylaxis in susceptible animals. Development of antiviral drug therapy targeting specific viral protein is limited.

PREVENTION AND CONTROL

To control FMD effectively, there is 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 (Corrales Irrazabal, 2012; Ding et al., 2013; Namatovu et al., 2013). Timely determination of exact status of disease in ruminants, particularly in small ruminants, is considered as gauze to monitor the virus activity in an area (Rashtibaf et al., 2012). In order to protect FMD free countries stringent import and cross-border animal movement, controls and surveillance are required in specific areas or zones. If FMD is suspected, notification of regulatory veterinary authorities immediately to obtain a rapid diagnosis is essential. For containment of an FMD outbreak a quick response is vital. If there is any suspicion regarding vesicular disease, immediate information must be provided to the state and central veterinary authorities.

Due to the detrimental economic consequences resulting from the presence of FMD, there have been introduction of certain measures to retain a country's disease free status. There is requirement of initial implementation of test and slaughter policy of all infected as well as susceptible animals (at close proximity) for controlling FMD in a disease free country with movement restriction of susceptible animals, disinfecting infective premises and intensified surveillance to prevent further spread. Restriction over the import of suspected livestock or animal products including fresh meat from countries where FMD prevails is essential. FMD endemic countries like India are facing problems such as economic barriers and social or religious taboos in implementing test and slaughter policy. Vaccination followed by sero-monitoring is best alternative for effective control in endemic countries. In fact, in past many European countries like France have adopted



vaccination and after control seized the vaccination (Dhama et al., 2010).

For the development of an efficacious strategy of vaccination it is important to understand the disease dynamics. It indicates the suitable time points to administer vaccine. It is thereby easy to perform individual vaccination in population of large ruminants. It must be kept in mind that majority of the infections due to this virus is sub clinical in nature and thereby becomes unrecognizable for which vaccines having varying quality as well as efficiency must be used with caution (Klein et al., 2008).

Some developed countries do not allow emergency vaccination as the vaccine interferes in effective diagnosis. There has been assumption regarding carrier animals and their role in the epidemiology of FMD; any animal with FMD virus antibody is considered a potential carrier thereby must not be considered for international trade. If there is recurrence of any epidemic similar to the one in UK (in 2001), safe and effective vaccination is mandatory (Mukhopadhyay, 1992; Mishra et al., 1998; Sobrino and Domingo, 2001).

Implementation of a programme (location specific) called 'Foot and Mouth Disease Control Programme' (FMD-CP) in India in more than 200 specified districts has been undertaken. This has prevented significant economic losses and facilitated the development of herd immunity in cloven-footed animals. For this purpose funds are being provided by the central authority to purchase vaccine and to maintain cold chain and other logistic support along with support from the state authorities to provide manpower (DADH, 2011).

RECOMMENDATIONS FOR CONTROLLING FMD OUTBREAKS AT THE FARM LEVEL INCLUDE:

Restrictions over the movements of livestock, workers, equipment and vehicles along with strict quarantine practices are of utmost importance for controlling FMD outbreaks. Introduction of new animals to existing stock should be avoided. Affected animals in contact must be euthanized. Cleaning, sanitization and disinfection of the affected premises/pens, should be followed. All the infected material (equipments, clothes, vehicles etc.) should be disinfected with effective disinfectants like sodium hydroxide (2%) and sodium carbonate (4%) (Krug et al., 2011), citric acid (2.0%) (Krug et al., 2012) and Virkon-S®. Hypochlorite and phenols are less effective especially in presence of organic matter (iodophores and quaternary ammonium compounds). All the infected animal products, manure and carcasses must be appropriately disposed off with safety by incinerating or rendering; burial or by other methods and burning or burial must be done close to the premises. Heating at 100°C for >20 minutes is required to inactivate the virus in the milk from the infected animals. Slurry requires heating upto 67°C for 3 minutes. Killing of vectors including rodents will prevent them from disseminating the virus mechanically. Livestock owners and producers on uninfected farms must practice sound biosecurity measures to prevent the introduction or spread of the virus. There is also need to immediately monitor disease status, regular surveillance and tracing of livestock having potential exposure or infection along with reporting of illness. Vaccination around (and possibly within) the

affected premises are followed in several countries. In endemic areas, culling and vaccination for susceptible livestock are complementary to each other (EUFMD - The European Commission for the Control of Foot-and-Mouth Disease, 2007). Protection of high yielders by combining vaccination and prevention of FMDV entering the dairy premises is useful in endemic zones. Due to prevalence of FMD in non-vaccinated animals and climatic conditions favouring air-borne transmission is sometimes difficult to control the disease (Huber et al., 1999; Kesy, 2002).

Introduction of the FMDV in a country usually occurs via feed and animals infected with the virus. Feeding of waste food (swill) to swine is particularly of concern. Import of animals and animal products from endemic to free zones must be restricted. The risk of an outbreak can be reduced by heating swill. The FMDV does not get inactivated by low-temperature long time (LTLT) pasteurization (72°C for 15 seconds). There is great reduction of the viable virus concentration in milk due to high temperature short time (HTST) pasteurization but residual virus may sometimes persist (according to some studies). In view of the above facts, the veterinarian with their knowledge related to science and the disease have to come forward to face the challenges of the future (Dhama et al., 2010). We should be aware of the demand of food supply from animal origin, thus try to reduce the health risk to animals as well as human (Mahima et al., 2012a).

VACCINATION

The most effective strategy of the prevention of the viral diseases is through vaccination including FMD (Pastoret, 2012; Pattnaik et al., 2012). The veterinary vaccines account for 26% of global vaccine market (Pastoret, 2012). However there is lack of vaccines which can prevent infection and its transmission. The currently available vaccine provides protection from the disease but not from infection/virus replication. Moreover the vaccinated animals may become asymptomatic carrier that shed the virus for months or even up to years (Rodriguez and Gay, 2011; Parida, 2009). In a recent FMD outbreak in the Netherlands, the vaccines were slaughtered which subsequently enabled rapid re-establishment of the nation's status of freedom from FMD but vaccination by conventional vaccines has certainly reduced spread of the disease. 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. Sheep and goats play an important role in the epidemiology and transmission of the FMDV, though the FMD vaccine policies are mainly targeted towards the cattle and buffalo. In order to reduce the mortality in kids/lambs and to reduce the likelihood of transmission of the FMDV, vaccination of sheep and goats is equally important (Singh et al., 1994; Shankar et al., 1998; Dhama et al., 2010).

Inactivated FMD vaccines

The FMD vaccine is a suspension of whole FMDV particles produced in cell cultures, inactivated by aziridine (binary ethylenimine) and mixed with adjuvants like mineral oil, aluminum hydroxide and saponin. Mineral oil emulsions are employed particularly for vaccination of the pigs (Nandi et al., 2008). Vaccination with one serotype does not provide



cross protection against other six, even vaccination with one strain may not provide protection against the strain within the same serotype. Therefore the choice of incorporation of FMDV serotype/strain into the vaccine should be decided by through investigation of the circulating FMDV strain prevalent in that particular geographical area. The inactivated FMD vaccines 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, limited shelf life and repeated booster requirement have forced the researchers to think over development of alternative vaccines for FMD (Rodriguez and Gay, 2011). Monovalent FMD vaccine is formulated with strain of virus closely related to the field virus. However, these vaccines are frequently multivalent containing different serotypes. Currently, there is no universally accepted vaccine for FMD. Vaccines are recommended particularly against those having highest threat of introduction to check outbreak depending upon the endemicity and serotype of strain.

Bank of FMD virus antigen helps to provide rapid formulation into FMD vaccine. Individual vaccine banks are maintained by some nations. Three international vaccine banks are:

- a) The North American FMD Vaccine Bank (In United States as well as Canada and Mexico).
- b) The E.U. Vaccine Bank (In every country of European Union).
- c) The International Vaccine Bank (In several nations including Australia, New Zealand and some European nations).

Presently, the traditional FMD inactivated vaccine is widely used worldwide, particularly in the developing countries for preventing and controlling this disease (Uddowla et al., 2012). Now a days, scientists have realized many disadvantages of this vaccine and it is very difficult to maintain consistent potency of vaccine and much research continues for developing alternative vaccine strategies that do not require infectious virus viz. proteins/peptides and various recombinant DNA-based strategies, including vectored, virus-like particle (Mohana et al., 2012; Scotti and Rybicki, 2013), gene replacement (Zhang et al., 2012), empty viral capsids having desired immunogens but lacking infectious nucleic acid and DNA vaccines, synthetic peptide vaccine, epitope based vaccines, chimeric virus vaccines using reverse genetics technology and so on (Seago et al., 2012; Tang et al., 2012b; Zheng et al., 2013). Live attenuated vaccines have also been attempted by serial passaging in non-permissive cell culture or animals (classically), but with limited success. Recently, with the advancement in technology like genomic sequencing and protein peptide chemical synthesis technology, the studies on FMDV epitopes become possible and researchers are now trying to develop the poly-vaccine containing highly conserved epitopes of different serotypes that can be a key guarantee of cross immune response of vaccine (King et al., 2012; Tang et al., 2012a; Ayelet et al., 2013). Differentiation of infected and vaccinated animals (DIVA) vaccines along with companion diagnostic tests approaches are being explored for FMD

(Uddowla et al., 2012; Verma et al., 2012d). Besides providing cross protection among different strains (within serotype), high potency emergency FMD vaccines (vaccines with high antigen pay load) have been shown to reduce the development of the carrier state in cattle (Brehm et al., 2008).

There is induction of quick humoral response in either infected animals or vaccinated ones and high levels of neutralizing antibodies provide protection. After either infection or vaccination a protective immunity develops apparently between 7 and 14 days.

Commercial vaccines available in India

Most of the FMD vaccines available in India are BHK-21 cell culture based, inactivated trivalent vaccines containing serotype A-22, O and Asia 1. Primary vaccination is done at the age of 4 months, followed by booster after 6 month of primary vaccination. Routine vaccination is practiced twice a year each after a period of 6 months. Some of commercial vaccines are Raksha-FMD vaccine, Raksha-Ovac (Indian Immunological), Bovilis FMDV- Gel, Bovilis Clovax (Intervet), Bio-vet FMD vaccine etc.

New generation vaccine trials against FMD

Various DNA vaccine against FMD were studied viz. VP1 and IL-2 based chimeric DNA vaccine were developed which showed a better protection in swine (Wong et al., 2002). Recently, Gülcé et al. (2013) reported that Co-expression of the Bcl-x Lanti apoptotic protein enhances the induction of Th1-like immune responses (in mice) immunized with DNA vaccines encoding FMDV B and T cell epitopes. VP1 and 3D genes based rDNA and protein based cocktail vaccine were developed and shown to induce better immunity in murine model (Bae et al., 2009). Wu et al. (2003) developed recombinant adenovirus based vaccine co-expressing protein (capsid) of different serotypes of FMDV. Again, Chan et al. (2000) developed a chimeric protein based vaccine joining FMDV VP1 to a swine immunoglobulin G single heavy chain constant region (scIgG). This creates a novel chimeric vaccine: Fl-scIgG. Recently, it was reported that combination of poly (I: C) with multi-epitope protein vaccine provides complete protection against challenge with virulent virus in swine (Cao et al., 2013). Replicase-based DNA vaccine with prime-boosting strategy may efficiently provide strategy of vaccination against FMDV (Dar et al., 2012a). Dar et al. (2012b) also have shown that a replicase-based DNA vaccine (using Sindbis virus) construct that encodes multivalent epitope gene of FMDV may protect guinea pigs in a better way. Li et al. (2012a) has developed a reverse genetic based modified foot-and-mouth disease virus vaccine candidate. A cDNA clone (full length and infectious) of inter-genotypic chimeric FMDV was developed for a novel candidate vaccine (Li et al., 2012 b). Now-a-days plant based edible vaccine are in trial for FMD control viz. multiepitope based (Dhama et al., 2008, 2010) and fusion vaccine (Huang et al., 2005).

Advanced diagnostic tools supported with modern disease monitoring systems need to be exploited fully for detecting FMD virus (Knowles and Samuel, 2003; Clavijo et al., 2004; Schmitt and Henderson, 2005; Lau et al., 2008; Anonymous, 2010; Chen et al., 2011a,b; Ding et al., 2011; Longjam et al., 2011a,b; Mohapatra et al., 2006, 2007, 2011a,b; Deb and Chakraborty, 2012; Verma et al., 2012a; Dhama et al., 2012,



2013a,b, 2014; Deb et al., 2012, 2013; Madi et al., 2012; Teifke et al., 2012; Madhan Mohan et al., 2013; Xu et al., 2013). Recent developments in prophylaxis/vaccines and therapeutics also need to be utilized to their best potentials along with designing appropriate prevention and control measures for combating FMD and lessening economic losses being caused by this economically important disease of animals (Meeusen et al., 2007; Dhama et al., 2008, 2013c, 2013d, 2013e; Bae et al., 2009; Parida, 2009; Gakuya et al., 2011; Rodriguez and Gay, 2011; Deb et al., 2012; Dar et al., 2012a; Kim et al., 2012; Li et al., 2012a; Mahima et al., 2012b; Mohana et al., 2012; Pattnaik et al., 2012; Uddowla et al., 2012; Ayelet et al., 2013; Ding et al., 2013; Zheng et al., 2013; Tiwari et al., 2014).

CONCLUSION AND FUTURE PERSPECTIVES

Foot and Mouth Disease is an acute highly contagious devastating vesicular disease that has significant economic impact on the global livestock industry. It spread quickly affecting both domesticated as well as wild ruminants along with pigs. Mild symptoms are seen in sheep and goat; but in pigs severe lameness and in cattle obvious mouth lesions are characteristic. Carrier state may be observed both in ruminants recovered from the acute infection and in vaccinated ruminants provided there is subsequent exposure to infectious virus. The disease has emerged as one of the greatest obstacles for the livestock sector and the economic growth of the country. Diagnosis and control of the disease has become difficult due to presence of seven serotypes and multiple subtypes and strains. Further, the endemic presence of the FMD adversely affects livestock trade in the international market. Efforts are being made to control the disease globally by means of effective and systematic vaccination programs, sero-surveillance and vigorous stamping out policy wherever possible. With the potential of devastation of animal industry, both FMD free and endemic countries are now vigorously monitoring the disease by sero-surveillance and genetic analysis. Detection of FMD requires a simple, rapid, non-invasive and sensitive test which is capable of testing large number of samples. In addition to clinically infected, carrier animals should not be missed. Phenotypic and genotypic characterization of FMDVs is required for formulation of appropriate vaccine for effective control and eradication of the disease. Countries adopting vaccination as control policy or undertaking vaccination as emergency measure should have reliable test for proper differentiation of infected from vaccinated animals. Molecular cloning has given a way for production of recombinant antigen and antibody for use in diagnostic test. In endemic countries like India where control is mainly sought by vaccination, constant monitoring by antigenic and phylogenetic studies is required for effective protection induced by vaccine. Vaccination against FMD should be strengthened in all susceptible population for generating "herd immunity". A mass vaccination programme is recommended twice in a year for all the cattle and buffalo as well in sheep and goats. Apart from diagnostics and vaccines, there is a strong need of efficient veterinary disease prevention system, good governance and intensive extension work as well as need to initiate disease resistant breeding policy. Farmers and animal keepers should be educated to adopt control

measures against FMD and losses due the disease. Freedom from FMD is essential for healthier economy and greater food security. In summary, continuous sero-monitoring, biannual vaccination with existing serotype and culling of seropositive animals is the key to success against FMD.

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