Indian Journal of Animal Sciences **82** (6): 543–551, June 2012

Epidemiology and diagnosis of foot-and-mouth disease: A review

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Received: 29 August 2011; Accepted: 23 September 2011

ABSTRACT

Foot-and-mouth disease, the most devastating and highly contagious viral disease of cloven-footed animals, causes significant financial losses either due to deaths of young animals, loss of milk, meat and drastic fall in productive performances or serious limitations on development of livestock industry due to restrictions on international trade. In spite of the considerable information accumulated in the last years on the disease, it still affects extensive areas of the world and ranks as first in the list 'A' of infectious diseases of animals according to the Office International des Epizooties, Perris, France. In this review, we have to summarize the state of knowledge in basic and applied areas of FMD research with emphasis on epidemiology and diagnosis to make progress in controlling the disease from the livestock.

Key words: Animal, Diagnosis, Epidemiology, Foot-and-mouth disease

The recent outbreaks of foot-and-mouth disease (FMD) in a number of FMD free countries particularly, the United Kingdom in 2007, Japan and Korea in 2010 have significantly increased public awareness of this highly contagious disease of cloven-hoofed livestock. Furthermore, the endemicity of this disease in several parts of South American countries (Astudillo *et al.* 1997), Africa and the Middle East, Central and South-East Asia, the Indian subcontinent (Ahuja *et al.* 1996, Verma 2008) have directed the efforts of the scientific community to re-examine their knowledge about FMD, the virus that causes the disease, its diagnosis and methods of disease control. FMD is a highly contagious and one of the most devastating diseases of cloven-hoofed animals, including domestic animals such as cattle, water buffalo, sheep, goats and pigs, as well as antelope, bison and other wild bovids (OIE 2007) and deer. This disease has a significant economic impact on livestock industry worldwide. The majority of economic losses results either from mortality of young animals, loss of milk and meat and drastic fall in productive performances or indirect losses due to the imposition of trade restrictions (Anonymous 2001, Rweyemamu and Leforban 1999). As per the *The Financial Express* (24 April 2008) India annually suffers a staggering revenue loss of about ₹ 20 000 crores due to FMD that affects the bovine population.

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Epidemiology

The earliest written description of FMD probably occurred in Northern Italy in 1514 and in Southern Africa in 1780 by Fracastorius (1546) and Le Vailant (1785), respectively. Almost 400 years later, in 1897, Loeffler and Frosch (1897) demonstrated that a filterable agent caused FMD. This was the first demonstration that a disease of animals was caused by a filterable agent and ushered in the era of virology. The etiological agent of FMD is apthovirus of family Picornaviridae. The virus particle or virion also referred to as 146S particle, contains a single stranded and positive sense RNA genome of 8500 nucleotides in length (Domingo *et al.* 1990, Racaniello 2001). The disease has high morbidity up to 100% and low mortality (Woodbury 1995, Salt *et al.* 1996, OIE 2007, Verma 2008, Verma *et al.* 2008), although mortality rate may be as high as 50% (Woodbury 1995), when the virus replicates in the heart muscles of younger animals (Gulbahar *et al.* 2007). The virus affects some vital hormone glands such as pituitary, which control the metabolic functions in the body. The resulting malfunction of these glands may cause panting, restlessness and reduced breeding capacity, and in draught animals loss of strength. In cows,

infection of udders and teats may progress to mastitis that causes permanent loss of teats thus milk loss. The infected animals remain severely debilitated for a considerable period of time, and the disease is accompanied by permanent loss (~25%) of productivity (Brooksby 1982). There are seven recognized serotypes of FMD (O, A, C, Asia, SAT-1, SAT-2 and SAT-3), which differ in distribution across the world (Pereira 1977) and comprise more than 65 subtypes. Serotypes 'O' and 'A' have the widest distribution, occurring in Africa, Asia and South America. Types SAT-1, 2 and 3 are currently restricted to Africa only and Asia-1 to Asia; the capacity to invade free areas is common to all types and periodically SATs are introduced into the Near East, and Asia-1 into western and eastern parts of Eurasia. In India most of the outbreaks of FMD is due to serotype 'O' followed by serotype 'A' and serotype Asia-1 (Mann *et al.* 1998, Sharma and Kakkar 2005, Bhattacharya *et al.* 2005, Verma 2008, Verma *et al.* 2008).

Transmission: Various modes of transmission, including the movement of infected animals, contaminated animal products, equipment and vehicles (Metcalf and McElvaine 1995, Donaldson 1997), in particular by milk tankers or animal transport vehicles, by people and transmission of virus by the wind (Woodbury 1995) have been described. Transmission of the FMDV from one animal to another through an aerosol pathway is one of the major routes for spread of the disease (Alexandersen *et al*. 2003). Meteorological conditions are the major determinant of the downwind concentrations of airborne virus. Amongst the determinants of air-borne spread are the number and species of animals affected, the virus strain, the environmental conditions, and the species and number of animals located downwind (Gloster 2004). During the rainy season, heavy rain, high relative humidity (RH) and moist winds may inhibit aerosol transmission of the disease. During this season also, the movement and transport of animals from one place to another is hindered in some areas by heavy rains or floods. The number of FMD outbreaks increase in winter due to favourable climatic conditions of dry weather and dry winds with low temperatures and moderate RH. Such favourable climatic factors might cause more rapid propagation of the viral disease among the susceptible animal population (Bhattacharya *et al.* 2005, Verma 2008, Verma *et al.* 2008). The number of FMD outbreaks is low due to extremely hot weather in summer. Seasonal peaks in FMD frequency was also related to mass movement and congregation of animals caused by migration to new pastures, and cattle and buffalo fairs (Verma 2008, Verma *et al.* 2008). Cattle are generally the first species to manifest signs of FMD, so are considered 'indicators' of this disease. They are very sensitive to infection because the infective dose is very low requiring as little as $20TCID_{50}$ (tissue culture infective dose) of virus to establish infection (Kitching 2002). Pigs are regarded as amplifier hosts for the disease because it emit high levels of air-borne virus (Alexandersen and Donaldson 2001), but are relatively resistant to infection by the air-borne route. Sheep excrete air-borne virus at levels similar to cattle but are thought to be less susceptible to air-borne infection than cattle due to their smaller respiration volume. Sheep are considered as maintenance hosts because they do not always show typical clinical symptoms or as the cardinal signs mimicked other diseases (Callens *et al.* 1998, Barnett and Cox 1999, Ganter *et al.* 2001). Slow and steady wind speed and direction, high relative humidity (>60%), weak sunlight and absence of heavy rain are the suitable conditions for the spread of the disease (Bhattacharya *et al.* 2005, Verma 2008, Verma *et al.* 2008). FMD virus can shed into the milk, blood, pharynx, vagina, and rectum before onset of clinical manifestations of the disease in infected cows. Because the virus is shed into milk before dairy cattle show clinical signs of the disease, there is opportunity for raw milk to spread the virus within the farm and from farm to farm (Tomasula and Konstance 2004). In order to improve the understanding of airborne transmission of FMD and its importance in future outbreaks further research is required in the areas like virus emission, particle size and virus content, virus challenge period and meteorological implications. One of the most important features of FMDV is its genetic and antigenic diversity (Tosh *et al.* 2003, Mohapatra *et al.* 2007, Verma *et al.* 2008).

Antigenic diversity: Antigenic variation in FMDV leading to emergence of variants is of great importance from epidemiological point of view and for formulating suitable control strategy. Rowlands *et al.* (1971) found that the antigenic variation even within a serotype can be so great that immunity against the homologous strain need not necessarily ensure protection against the infection by other strains of same serotype. The virus capsid is non-enveloped and has icosahedral symmetry with a diameter of approximately 300 Å, consisting of 60 copies of each of the structural proteins VP1, VP2, VP3 and VP4, while the first 3 structural proteins have surface components, the fourth is internal. The antigenic diversity of FMD viruses has made the diagnosis and control of these viruses very difficult in countries where the disease is endemic. Selection of antigenic variants from such a hetrogenous population occurs either in the presence (Borrego *et al.* 1993) or absence of immune pressures (Domingo *et al.* 1993).

Genetic diversity: VP1 (encoded by 1D gene) is the most important protein in FMD virus both for its antigenic properties and as the virus-cell attachment site. The first report of mutation through recombination in picornavirus was given by Hirst (1962). Perira (1977) identified more than 65 subtypes. RNA viruses in general and FMDV in particular, are very prone to error in replication, which gives them greater chance for variation (Domingo *et al*. 1990, 1992). Natural populations of FMDV from a single disease outbreak have been shown to be highly heterogeneous and moreover, "individual" isolates were reported to include 2 different

nucleotide sequences. The high variability of FMDV led to the proposal that FMDV natural populations are quasispecies, i.e. pools of variant genomes statistically defined but individually indeterminate (Domingo *et al.* 1990 and 1992, Novella *et al.* 1996, Sobrino *et al*. 2001). The genetic heterogenecity is due to high mutation rate, lack of proof reading activity during viral genome replication and other selective pressures in the environment (Martinez *et al.* 1997, Carrillo *et al.* 1998, Baranowski *et al.* 1998). Haydon *et al.* (2001) estimated an average of about one base mis-incorporation to occur each time a single FMDV genome replicates. Genetic variation in foot-and-mouth disease virus (FMDV) is of interest for 2 reasons. First, changes to the genes encoding capsid proteins results in antigenic variation, and affects vaccine efficiency and effectiveness of vaccination programs; second, genetic changes can lead to important insights into the transport of virus between countries, regions, herds, and individuals.

Diagnosis

An essential component of any disease control strategy includes diagnostic assays to rapidly confirm the initial clinical determination of infection. For FMD this is of particular importance, since swine vesicular disease (SVD), vesicular stomatitis, and vesicular exanthema of swine cause vesicular lesions in swine and cattle that cannot be distinguished from those caused by FMD (Bachrach 1968). In addition, FMDV infection of sheep and goats can be difficult to detect clinically (Donaldson and Sellers 2000). FMD is suspected on the basis of clinical signs and macroscopic lesions on tongue and feet, with or without a history of contact between the herd and the infected animal, or report of FMD outbreak in the surrounding area. In a highly susceptible animal the clinical signs are pathognomic however in the endemic region, due to partial natural immunity or vaccinal immunity, clinical signs may be mild or confusing.

Clinical signs: The incubation period in cattle is between 2–14 days, depending on the infecting dose, the strain of the virus and the susceptibility of individual host (Kitching 2002). Animals suffering with high fever can be examined cautiously for lesions on tongue (Fig. 1), feet (Fig. 2) or teat, concurrent drooling of saliva and lameness with vesicles and/or erosions. Acutely infected animal salivate profusely and develop a nasal discharge, first mucoid and subsequently change to mucopurulent, which covers the muzzle. Abortion may occur in pregnant animals due to high fever (FMDV does not cross the placenta). Death in young animals is due to severe myocardial necrosis. Suspected cases can be confirmed by using laboratory tests to differentiate FMD from other diseases such as swine vesicular disease, vesicular stomatitis, vesicular exanthema of swine, foot rot, traumatic stomatitis which have almost identical clinical signs.

Beside clinical diagnosis based on lesion identification, in the early stage of infection, FMD virus or viral antigen can be detected using several diagnostic techniques. Originally the typing of FMD virus was performed by cross

Figs 1–2. **1.** Cattle with ruptured tongue vesicle **2.** Ruptured vesicle on foot.

challenge experiments in cattle and it was later replaced by serological techniques. The laboratory diagnosis is obtained by detection of antigen or isolation of FMD virus from clinical samples like vesicular epithelium of tongue and feet.

Sampling: The success of the laboratory diagnosis test depends on the submission of the adequate material, sent under suitable condition. A minimum of 2 cm^2 of epithelium from a ruptured vesicle in equal amounts of glycerol and phosphate buffer saline (50% PBS-glycerol), pH 7.2–7.6 should be sent to laboratory (Verma 2008). Whole and clotted blood sample and probang sample (esopharyngeal fluid) may also be sent (Yadav 2009). Contamination from the environment is not a big problem, if fresh material is used and standard virological procedures are applied. Many researchers (Bhattacharya *et al*. 2005, Verma 2008, Verma *et al.* 2008) observed that FMDV could not be identified in few clinical samples, probably due to either late reporting or the very poor quality of samples. The possibility that cases could have been misdiagnosed on purely clinical grounds should not be ignored. Most of the times the symptoms were not obvious and were very mild, and these may remain undiagnosed. In addition, in developing countries like India many of the outbreaks are occurring in villages in the interior, where poor transport facilities mean that samples can not be dispatched with sufficient speed to the diagnostic laboratory. Bhattacharya *et al.* (2005) from West Bengal state, India revealed that at least 80% of the cases in the less accessible areas of the state had gone unreported. It may be estimated that only 10% to 20% of the cases of FMD were reported, due to an inadequate reporting system and lack of awareness among farmers.

Detection of virus: Prior to 1997, confirmation of the disease was performed by a complement fixation test, following the protocol laid down by Ferris *et al.* (1984). Since 1997/1998, an indirect sandwich enzyme-linked immunosorbent assay (ELISA) and isolation of virus were the gold standard test for the detection of FMDV. Various protocols were given time to time with slight modification viz., Roeder and Smith (1987), Alonso *et al.* (1993), Bhattacharya *et al.* (1996). The result of ELISA can be

obtained in 3–4 h after the sample is received by the laboratory, a negative result must be confirmed by inoculation of the sample into sensitive cell cultures followed by confirmation of the virus serotype by ELISA. Various cell lines were found to be sensitive for detecting field strains of FMDV, viz. primary Bovine thyroid cells (BTY cells) (Snowdon 1966, Ferris and Dawson 1988), primary foetal lamb kidney cells (House and House 1989, Ahl *et al.* 1996) and baby hamster kidney (BHK) cells (Whiteside *et al.* 1983, Saha and Sen 1987, Singh *et al.* 1987, Sakamato *et al.* 2002). In the absence of CPE after 3 blind passages, the sample can be declared negative for the presence of live virus. Virus isolation is the most reliable diagnostic method, but it is labor-intensive, time-consuming, and requires properly equipped facilities. Sandwich ELISA is a much faster approach to detect viral antigens, but it has low sensitivity, so its primary indication is to confirm and type the FMDV after isolation in cell culture. As a consequence, several researchers have been developing alternative assay systems that allow more rapid confirmation of clinical diagnosis, which do not require a laboratory setting and may be performed 'pen side.'

Molecular diagnosis: Ever since the demonstration of plurality of FMDV, attempts have been made to differentiate the virus, it was realized that the studies based on antigenic characterization alone would not be able to provide complete information on an epizootiological tracing of an outbreak. To overcome this inadequacy, help of other methods were sought to compliment the antigenic studies. The polymerase chain reaction (PCR) is a technique which amplifies a specific genome segment of virus in a diagnostic sample. It relies on prior knowledge of the nucleotide sequences flanking the region to be amplified. Due to the rapid spread of FMD virus and the devastating economic consequences of the disease, it is essential to have a diagnostic test that is sensitive, accurate, rapid and easy to use.

Several groups have been developing quick diagnostic methods based on amplification of specific sequences of viral genome by reverse transcription polymerase chain reaction (RT-PCR), which can be applied to 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 and 1999, Suryanarayana *et al*. 1999; Reid *et al*. 2001, Tosh *et al*. 2003, Mittal *et al*. 2005, Jangra *et al.* 2005, Verma 2008), milk, serum and probang samples (Amarel-Doel *et al.* 1993, Donn *et al.* 1996, Bastos 1998, Reid *et al.* 2002, Yadav 2009). This approach was used to rapidly detect and type FMDV (Amarel-Doel *et al.* 1993, Knowles and Samuel 1995, Bastos 1998), to differentiate with other vesicular diseases such as SVD or BVD (Callens and De Clercq 1997) and to detect virus infection in animals even before the development of clinical signs (Marquardt *et al*. 1995) as well as for identification of positive cattle at the end of the course of infection when virus isolation may be negative. This assay is superior in sensitivity and time saving to ELISA and virus isolation (Paprocka *et al*. 2002, Clavijo *et al.* 2003). Because of the presence of inhibitory substances not all samples that contain virus or viral genome gives a positive result by PCR. However, conventional RT-PCR does not have optimal results in terms of specificity and sensitivity. Recently, real-time (RT-PCR) methods have been examined by a number of groups with the aim to improve sensitivity and develop portable on-site diagnosis (Hearps *et al.* 2002, Reid *et al.* 2003). However, these tests are labor-intensive and very sophisticated. So, there is need to assess and validate these tests for other possible field samples, viz. blood, milk, tissue, etc. and under field conditions.

Unlike many living organisms where the hereditary information is encoded within a DNA genome, FMD virus has a RNA genome that can be sequenced directly, but RNA is unstable and it usually first transcribed into cDNA prior of performing the nucleotide sequence. Reverse transcription (RT) when combined with PCR provides a rapid and powerful technique for studying diverse RNA genomes. In epidemiological studies of FMD virus, nucleotide sequencing of the VP 1 (1D gene), has been used extensively to determine the relationships between the field isolates. The technique is also routinely used to investigate genetic variation, molecular evolution in carrier animals, and to identify the source of an infection in outbreak conditions. Beck and Strohmaier (1987) constructed genetic relationship of FMDV A, O and C serotypes nucleotide sequencing for the study of the FMD outbreaks in Europe over a 20-year period. Since then a number of similar studies have been published; serotype O (Marquardt and Adam 1990, Samuel *et al*. 1990, 1993, 1997, 1999, Armstrong *et al.* 1992, Saiz *et al.* 1993, Singh *et al.* 1996, Pattnaik *et al.* 1998, Huang *et al.* 2001, Sangare *et al.* 2001), serotype A (Carrillo *et al.* 1990, Konig *et al.* 2001, Arujo *et al.* 2002, Tosh *et al.* 2002a and 2002b, Mohapatra *et al.* 2007, Verma 2008, Verma *et al*. 2010a), serotype C (Hemadri *et al.* 2003, Nagendrakumar *et al.* 2005), serotype Asia 1 (Ansell *et al*. 1994, Woodbury *et al.* 1994, Gurumurthy *et al.* 2002, Ul Islam *et al.* 2009), SAT-1 (Carrillo *et al.* 2005), SAT-2 (Vosloo *et al.* 1992) and SAT-3 (Carrillo *et al.* 2005). The accurate prediction of the virus origin is often dependent on having the large database of sequences for a geographical region as well as for other more distant geographical region. Many laboratories such as WRL, Pilbright, Project Directorate on Foot-and-Mouth Disease (PDFMD), Mukteshwar, India, have developed techniques for performing these studies, and reference laboratories hold databases containing over 3000 partial sequences of this virus. Reverse-transcription PCR (RT-PCR) amplification of FMD virus RNA, followed by nucleotide sequencing, is the current preferred option for generating the sequence data to perform these comparisons.

Differentiation of infected and vaccinated animals (DIVA)

There is considerable interest in techniques capable of differentiating vaccinated or non-vaccinated animals that have had contact with live FMD virus from those animals that have been vaccinated against FMD virus. Using conventional diagnostic techniques, up to now it was not possible to differentiate between these two groups because both groups have neutralizing antibodies circulating in their serum. The term DIVA strategy is applied to those tests that function to differentiate infected from vaccinated animals. Several diagnostic tests were developed to distinguish infected from vaccinated animals, all based on detection of antibodies to the non-structural proteins (NSPs) of FMD virus. The use of NSP tests is based on the fact that viral replication results in the production of NSPs in the host and will therefore induce the production of anti-NSP antibodies. Purification of viral antigen in vaccine production should remove all NSPs from the antigen mixture. In addition administration of inactivated vaccine is not followed by viral replications, so no NSPs are produced in the host. Vaccinated animals, therefore, will have circulating antibody against structural proteins, but not against NSPs.

Sensitive diagnostic assays are also necessary to distinguish vaccinated from infected or convalescent animals, so that trade markets could reopen to countries that may have used vaccination as part of their disease control program and to identify carrier animals. In addition, these assays can be used for epidemiological surveillance to confirm the naive status of animals in field situations. Cowan and Graves (1966) identified a highly immunogenic FMDV NS antigen, called the virus infection-associated antigen (VIAA), which reacted with sera from convalescent animals but not with sera from vaccinated animals (Cowan and Graves 1966). Later on, researchers found that sera from vaccinated animals (Mackay *et al.* 1998), and even from some animals which had received a single vaccination, had antibodies to VIAA (Lubroth and Brown 1995, Mackay *et al.* 1998, Moraes *et al.* 2002). The reason behind this is that FMD vaccines are not purified and, contain various amounts of contaminating NS proteins (Lubroth *et al.* 1996). To improve the sensitivity, specificity and reliability of this test, researchers found other non-structural proteins as potential reagents. The FMDV RNA genome encodes 12 viral proteins, L, 1A, 1B, 1C, 1D, 2A, 2B, 2C, 3A, 3B, 3C, and 3D; some of these (e.g., 3ABC) exist as uncleaved precursors. Four viral structural proteins 1A, 1B, 1C, and 1D make up the protein shell of the virion, which also contains traces of 3D. The other eight viral proteins (L, 2A, 2B, 2C, 3A, 3B, 3C, and 3D) play a role in replication and other functions within the host cell are not part of the virion structure; hence collectively named, nonstructural proteins, or NSPs. Berger *et al.* 1990 used radio immunoprecipitation to identify a number of non-structural proteins that reacted with sera from infected animals and not with sera from vaccinated animals. Various researchers suggested the use of non-structural proteins such as 2B (Inoue *et al.* 2006), 2C (Lubroth and Brown 1995, Oem *et al*. 2005), 3A (Bergmann *et al.* 2000, Kumar *et al.* 2007), 3B (Bergmann *et al.* 2000, Chung *et al.* 2002), 3C (Bergmann *et al*. 2000) and 3ABC (DeDiego *et al.* 1997, Lubroth and Brown 1995, Sorensen *et al.* 1998, Bergamann *et al.* 2000, Georgieve *et al.* 2003, Lee *et al.* 2003) as antigens in an ELISA-based test. ELISA-based assays with various non-structural proteins produced by recombinant baculovirus (Meyer *et al.* 1997, Sorensen *et al.* 1998, Chung *et al.* 2002, Kumar *et al.* 2007), in *E. coli* (De Diego *et al.* 1997, Mackay *et al.* 1998), or with synthetically produced peptides to non structural proteins (Shen *et al.* 1999, Oem *et al.* 2005, Inoue *et al.* 2006) were developed. These tests are being compared and evaluated by various scientists (Chung *et al*. 2002, Georgiev *et al.* 2003, Lee *et al.* 2003, Niedbalski 2004, Bronsvoort *et al.* 2006, Inoue *et al.* 2006, Kumar *et al*. 2007, Verma 2008, Verma *et al.* 2010b) to differentiate infected animals from vaccinated ones. It was concluded that the current NSP-ELISA can be successfully used to monitor the FMDV circulation in endemic areas. The test is easy to perform, quicker with reproducible results and with high specificity (De Diego *et al.* 1997, Georgiev *et al.* 2003, Verma 2008, Verma *et al.* 2010b).

Public health: FMDV is transmissible to humans and may produce conjunctivitis, small vesicular eruption on skin with erosion of tissue and symptoms like mild influenza. Mostly the symptoms are so mild and self limiting and remain unnoticed. Precaution should be taken while handling the infected or suspected animals and processing the samples in laboratory.

Foot-and-mouth disease is considered to be the major viral disease problems in the livestock industry world-wide and this disease constitute significant economic losses in many countries. The economic burden of this disease has made this topic time demanding. This article offers valuable insights for better understanding the various aspects of epidemiology and diagnosis as a whole. At the same time, this article also underlines the need to give more attention to key areas that in turn will provide insight information to help in timely diagnosis of infected animals and formulating a more effective control strategy to prevent the spread of the disease,

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