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Foot-And-Mouth Disease: History, Present Scenario and Future Aspects

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A B S T R A C T

Foot-and-mouth disease in short (FMD) is a highly contagious viral disease that affects up to 70 species of cloven-footed mammals including cattle, pigs, sheep and many wildlife species posing the greatest economic threat to agriculture. FMDV is characterized by rapid transmission, high morbidity, and low mortality and can cause serious economic losses and social impacts. Outbreaks of FMD cause severe financial losses and often lead to quarantining and export limitations in affected countries, as well as culling of herds. The disease is characterized by the formation of painful, serous vesicles on the tongue, lips and other tissues of the mouth, and on less stratified integumentary parts of the body such as the udder and teats, the interdigital space and the coronary band above the hooves. The basic control of Foot and Mouth disease is dependent on preventive policies and extensive vaccination of all susceptible individuals. Conventional FMDV vaccines are formulated with inactivated virus. But for the production of such vaccines enormous amounts of the infectious agent are needed and therefore represent a serious risk of viral dispersion.

Introduction

Foot-and-mouth disease in short (FMD) is a highly contagious viral disease that affects up to 70 species of cloven-footed mammals including cattle, pigs, sheep and many wildlife species posing the greatest economic threat to agriculture. Among the different species of animals affected by FMD virus, domestic cattle and buffalo are most susceptible one. Cattle are the indicator host of the disease. In cattle the disease is characterized by high fever and vesicular lesion followed by blisters on the mouth, tongue, muzzle, hooves and udder which ultimately leads to profuse salivation and lameness. Secondary bacterial infections and maggoted wound frequently occur, especially on the feet. Myocarditis may occur in animals of young age sometimes resulting in death. Role of Domestic pigs is also important; they act as amplifiers of the disease by secreting large amounts of virus particle in the form of aerosols. Most of the

time in sheep and goats, the infection can be almost in apparent and clinical manifestations are less severe or subclinical and they are considered to be the maintenance hosts. Natural infection of Indian elephants, gaur, bison and camels has also been reported so far. The horses are refractory to the infection with this virus. Among various wild animals, deer, antelope and probably other ruminants are highly susceptible. Under laboratory conditions, infection in wide range of animals including Australian marsupials and birds has been reported. The infection in man has also been reported in some articles but there are limited reports. Guinea pigs and suckling mice are the laboratory animals used for laboratory detection of the virus. The lesions in guinea pigs are quite similar with those of naturally infected susceptible species. Intraperitoneal infection of suckling mice results in rapid death and is useful for the titration and quantification of the virus. The virus can be propagated in primary cell cultures of bovine and porcine origin cells. The virus can be titrated effectively by plaque assay. Among the different cell lines, Vero and BHK-21 are used for cultivation and the latter is widely used for production of vaccine. The FMD virus spreads by inhalation of virus particle or ingestion of contaminated feed, through semen, clothing, contaminated bedding, veterinary instruments, contaminated vaccines etc. The aerosols can be transmitted over considerable distances (upto 250 km) under appropriate meteorological conditions. In addition to mucosal secretions, the virus is also secreted in the milk, urine and faeces of infected animals. The virus can persist in the pharynx and respiratory tract for very long period of time.

The causative agent of FMD belongs to the family *Picornaviridae and genus Apthovirus* which is very small, non-enveloped, positive-sense, single-stranded RNA virus. The virus particle is roughly spherical in shape, about 25–30 nm in diameter. There are seven recognised serotypes of FMD (O, A, C, Asia 1, SAT 1, SAT 2 and SAT 3), which differ in distribution across the world. The serotypes SAT-1, SAT-2 and SAT-3 are restricted to the African continent. There is no evidence of cross-protection between different serotypes and sometimes protection conferred by vaccines even of the same serotype can be limited. Thus characterization of the viruses is very important that viruses that are circulating if vaccination is being used for disease control. Molecular Sequence information is increasingly being used for identifying the source of outbreaks. The situation of FMD in affected areas indicates that FMD types continually spread within the endemic regions, and periodically and unpredictably give rise to virus types that "break immunity" and cause regional epidemics. Prevention of FMD epidemics requires a good understanding of the virus types within a country or region and sufficient surveillance to identify emergent infections before regional spread occurs within that area.

History

The first and foremost description of probable foot-and-mouth disease (FMD) in cattle was made by an Italian monk, Hieronymus Fracastorius, in Venice in 1514. He demonstrated the disease, which occurred in Northern Italy in 1514, as being unusual and affecting only bovines. The infected animals refused their feed, the oral mucosa showed red discolouration and the animals had vesicles in the oral cavity and on their feet. Most of the affected animals eventually recovered with time. This description, made 500 years ago, shows strong similarities to that of FMD when seen currently. It was the first animal disease where Loeffler and Frosch demonstrated virus etiology in 1897. It was also the first virus for which serotype differences and full three-dimensional atomic structure of the virion was demonstrated. The developments related to the production of synthetic and genetically engineered vaccines in 1980s closely linked to the study of picornaviruses. In 1922, Vallée and Carré first showed the presence of two immunological types of FMDV by cross-immunity tests in cattle. They were named by their areas of origin, O (Oise, a department in northern France) and A (Allemagne - Germany). Comparison of these virus types revealed

that Waldmann and Trautwein's types A and B were the same as Vallée and Carré's types O and A, respectively; type C was distinct. Thus the three types became known, by international agreement, as Vallée O, Vallée A and Waldmann C and later simply as O, A and C. Many atypical virus strains were later described, mainly from Africa, until in 1948 a sample submitted to the WRL from Bechuanaland yielded a virus (BEC/1/48) which in cross-protection tests in cattle and guinea pigs was found to be distinct from O, A and C. Subsequently a virus isolate from Northern Rhodesia (RHO/1/48) was identified as yet another distinct type. Retrospective testing of viruses isolated between 1931 and 1937 revealed isolates from Southern Rhodesia in 1937 (RV/11/37) and 1931 (RV/1/31) which were similar to the 1948 isolates from Bechuanaland and Northern Rhodesia, respectively (Brooksby, 1958). A further virus isolate from Southern Rhodesia in 1934 (RV/7/34) was found to be a third new type. These new types were designated SAT (Southern African Territories) types 1, 2 and 3. The seventh serotype, designated Asia 1, was first recognised in the early 1950's as viruses isolated from India in 1951 and 1952 and Pakistan in 1954 (Brooksby, 1958).

Present Scenario

Many farmers in India depend on animal husbandry for their livelihood. In addition to supplying milk, meat, eggs, wool, their castings (dung) and hides, animals, mainly bullocks, are the major source of power for both farmers and drayers. Thus, animal husbandry plays an important role in the rural economy. FMD can cause tremendous economic losses to the farmers on accounts of its long-term effects by reduced animal productivity and the limitations on international trade in animal products.

The economic losses caused by the disease are mainly due to decrease in milk production of milking hard and reduction in the working ability of drought animals. As per some report direct losses due to FMD in India are estimated to be more than Rs. 1200-1500 crores per year. Moreover, the countries free from the disease deny accepting milk and milk products, and meat and hide. Which may causes reduction in the export potential of livestock industry in our country. The various factors like antigenic variation within virus, wide host range, highly contagious nature, carrier status in convalescent animals and loss of productivity due to reduction in meat and milk yields and mortality of young animals make it a disease of major concern. Moreover, an unusually high rate of replication, extreme transmissibility, very wide species tropism and high antigenic diversity have made its etiologic agent, Apthovirus, a difficult pathogen to defeat.

The first vaccines against FMD were produced from lymph drawn from lesions on the tongue of infected cattle by inactivating them with formalin. Later Frenkel method of culture in fragments of epithelium stripped from the tongues of slaughtered cattle was practiced. Present day vaccines are prepared by growing the virus in suspensions of BHK-21 cells and then inactivated and adjuvanted by adsorption on to aluminum hydroxide gel and saponin to enhance the potency of the vaccine. Although considerable information is available about the virus, the disease and vaccines, FMD is still endemic in different areas of the world.

Current scenerio of FMD vaccines

The currently used FMD vaccine is an inactivated virus formulation prepared in suspension-growing BHK-21 cells.

Chemically inactivated FMDV is used as a commercial vaccine. In the early time, formalin and aziridine compounds were used widely for inactivation; however, they had a safety problem.

The inactivation of the virus is achieved with binary ethylenimine and viral particles are purified by various procedures such as precipitation with polyethylene glycol, ultrafiltration and chromatography. Finally, the vaccine is generally formulated in an oil-based adjuvant.

Table.1 A summary of the properties of current vaccine and the 'ideal FMD vaccine profile' is shown in table below

Ideal FMD vaccine profile	Characteristics	Commercially available current inactivated antigen vaccine.	Ideal vaccine
Efficacy	Protective immunity after one dose	No	Yes
	Onset of protection (days post vaccination)	7–21	1
	Long-lasting immunity (>1 year)	No	Yes
	Cross-protection within serotype	No	Yes
	Cross protection across serotypes	No	Yes
	Prevents primary infection	No	Yes
	Prevents carrier state in ruminants	No	Yes
	Efficacious by multiple routes of inoculation	No	Yes
Safety	Does not require high containment for manufacturing	No	Yes
	Safe in all target species	Yes	Yes
	Withdrawal for food consumption (days post vaccination)	60	<30
	Genetically stable (unable to revert-to-virulence)	Yes	Yes
Other	Development of relevant antigens against emerging viral strains	Months	Days/weeks
	Featured long shelf life (>2 years)	No	Yes
	Intrinsic negative DIVA markers	No	Yes
	Cost	Moderate	Low
	Thermal stability	No	Yes

Table.2 List of FMD vaccines are shown in table below

FMD vaccines	Type	Description	Reference
Inactivated vaccines	Current inactivated vaccines	Currently used FMD vaccines consist of BEI inactivated purified antigen in formulation with various adjuvants. Protect cattle against FMDV challenge.	Doel *et al.*, 2003; Paton, *et al.*, 2009
	New marked inactivated vaccines	BEI inactivated vaccines manufactured using avirulent FMDV with intrinsic DIVA markers in different NS proteins (Lpro, 3AB) formulated with various adjuvants are safer for production and protect cattle.	Uddowla *et al.*, 2012
Viral vector vaccines	Vaccinia	Vaccinia virus used as a vector to deliver FMDV empty capsids. Not tested in a natural host.	Sanz-Parra *et al.*, 1999

	Avian poxvirus	Fowlpox virus expressing VLPs, partially protect swine against FMDV challenge.	Ma *et al.*, 2008
	Pseudo rabies	Attenuated PRV vector expressing VLPs; partially protect swine against FMDV challenge.	Zhang *et al.*, 2011
	Alphavirus	"Single cycle" packaged alphavirus self-replicating RNA vector [Semliki Forest virus (SFV)] expressing VLPs, protect cattle against FMDV challenge if animals receive booster inoculations.	Gullberg *et al.*, 2016
	Adenovirus	Recombinant-replication- defective human adenovirus type 5 (Ad5) expressing FMDV P1 and NS 3Cpro coding regions expressing VLPs, protects cattle and swine against FMDV challenge.	Mayr et a., 1999; Moraes *et al.*, 2002; Grubman *et al.*, 2012; Schutta *et al.*, 2016
VLPs	Baculovirus/empty capsid	Purified VLPs expressed from recombinant baculovirus, confers partial protection of cattle against FMDV challenge	. Belsham *et al.*, 1991; Grubman *et al.*, 1993; Li *et al.*, 2012; Porta *et al.*, 2013
	Bacterial produced empty capsid	Purified VLPs expressed in *E. coli*, confers full protection of cattle against FMDV challenge2016. Sumoylation of three capsid proteins simultaneously expressed in E. coli, protects swine and cattle.	Xiao *et al.*,2016 Guo *et al.*, 2013
	Plant produced empty capsid	Purified VLPs expressed in transgenic alfalfa plants, tomato fruits or tobacco, successfully immunizes mice. Not tested with or without FMDV challenge in a natural host	Dus Santos and Wigdorovitz, 2005; Veerapen *et al.*, 2017
Peptide vaccines	VP1 peptide epitopes	Purified VP1 produced in E. coli, protects swine and cattle against FMDV challenge.	Bachrach *et al.*, 1975
	T and B cell peptide epitopes	G-H loop synthetic peptides with B cell epitopes protects cattle and swineRetro-inverso peptidomimetics enhances immunogenicity and antibody cross reactivity Multiepitope peptide in combination with poly (IC) protects swine against multiple topotypes of FMDV O A dendrimeric peptide containing one T-cell epitope and four B-cell epitopes protects swine and cattle.	DiMarchi et al. 1986 Wang *et al.*, 2002 Briand *et al.*, 1997 Cao *et al.*, 2014 Cubillos *et al.*, 2008; Blanco *et al.*, 2016; Soria *et al.*, 2017
DNA vaccines	cDNA	cDNA encoding partial or modified viral genome protects swine against homologous FMDV challenge if large amounts of DNA and several	Beard *et al.*, 1999; Cedillo-Barron *et al.*, 2001; Wong *et*

		immunizations are used.	*al.,* 2000
	Electroporation	DNA vaccine containing P1 and NS 2A, 3C and 3D administered by electroporation, induces partial protection of cattle against FMDV challenge only after multiple boosts.	Fowler at el., 2012
	APC targeting	B and T cell FMDV epitopes fused to a single chain antibody that recognizes the SLAII or combined with Bcl-xL anti-apopototic signal improve vaccine efficacy, but only induce partial protection in swine.	Borrego *et al.,* 2011; Gu¨ lc¸ e _Iz *et al.,* 2013
Modified liveattenuated vaccines	Leaderless virus	Virus with a deletion of entire Lpro coding sequence renders an attenuated virus in cattle and swine but is not able of inducing a neutralizing antibody response sufficient to protect against FMDV challenge	. Chinsangaram *et al.,* 1998
	SAP mutant virus	Mutations in Lpro SAP (for SAF-A/B, Acinus, and PIAS) domain generates a virus with impaired Lpro nuclear retention that is attenuated in swine and induces complete protection of swine against FMDV challenge at 2 dpv.	Diaz-San Segundo *et al.,* 2012
	Chimeric virus	A chimeric FMDV A24 constructed with Lpro region of bovine rhinitis B virus is attenuated and induces protection against homologous FMDV challenge in cattle and exhibits low virulence in pigs	Uddowla *et al.,* 2013
	Deoptimized virus	Deoptimization of P1 coding region in FMDV A12 results in an attenuated virus in swine, inducing high levels of neutralizing antibodies.	Diaz-San Segundo *et al.,* 2015

Other commercially available FMD vaccine, consist of binary ethyleneimine (BEI) inactivated purified antigen (killed virus) depleted from viral NS proteins and manufactured with adjuvants as monovalent or multivalent vaccine. After formulating, antigen concentrates can be kept frozen under liquid nitrogen for long-term preservation.

Some high potency vaccines have been shown to provide protection from challenge within seven to ten days post-vaccination in cattle, swine and sheep. However, manufacturer companies recommend a booster 30 days post vaccination for the first two years of animal age with subsequent annual revaccination. Inclusion of adjuvants in inactivated FMD antigen preparations is essential for protection.

Vaccine production requires cell-culture adapted wild-type FMDV strains, hence high containment facilities for biological safety are required to minimize the risk of virus escape during manufacturing. Manufactured vaccine is heat sensitive, therefore demanding cold chain from storage to point of use.

However, due to complex epidemiological dynamics

affecting wildlife and livestock maintenance, added to the emergence of viral strains poorly covered by current vaccines, and lack of resources to support sustained vaccination programs in field conditions, result in continuous virus circulation in endemic area.

These vaccines confer protection against clinical FMD, but do not always prevent primary infection resulting in about 50% of vaccinated animals becoming carriers, with similar prevalence in newly affected animals. Additionally, DIVA (differentiation between infected and vaccinated animals) characteristics of current vaccines are dependent on the antigen purification strategy used to reduce or remove non-structural viral proteins.

FMD vaccines consist of chemically inactivated purified whole virus preparations. The high level of antigenic variation in FMDV means that currently there is no universal vaccine that can afford protection against all serotypes of the virus. Indeed current vaccines can fail to cross protect some strains of the same serotype

Future Aspects

Despite considerable information being available about the virus, the disease and vaccines, FMD remains a major threat to the livestock industry world-wide. As the antigenic diversity of FMDV is a major concern for FMD control, regular vaccine matching and strain selection studies appropriate for each region is essential for disease control. Moreover new sub lineages of FMDV continue to evolve to produce novel strains which sometimes break through vaccine induced immunity and can result in major epidemics. This warrants the need for continued surveillance, vaccine matching and vaccine quality control. Vaccination alone is unlikely to control the disease unless it is coupled with animal movement control. Animal identification systems and animal movement controls are therefore also needed to be in place for effective control of the disease. In regions free of FMD, natural protection afforded by geographical barriers is rigorously reinforced by strict control measures particularly on the import of animals and potentially contaminated materials. In areas where outbreaks occur sporadically, imposition of restriction on animal movement and slaughter of infected animals have been successful in maintaining a disease free national herd. In endemic areas like India, control is by mass vaccination. Ring or barrier vaccination is also used to limit the spread of infection. At present many researchers are trying to use alternative vaccines which are more safe and effective to prevent and eradicate this viral disease. For the successful control and eradication of FMD, detailed characterization of virus isolates including antigenic analysis and molecular epidemiology is essential to ensure the virus strains to be incorporated in the vaccines. Vaccination strategies should include creation of zones based on the prevalence and distribution of disease. Monovalent vaccines have to be employed to control the most prevalent type so as to reduce the incidence of disease and also to remove the foci of infection. In addition control of animal movement, creation of disease free zones and building up buffer zones helps in successful control and eradication of foot and mouth disease. Nowadays, many researchers have tried to use alternative vaccines which are more safe and effective but much research as well as different protocols to be done for complete eradication of the virus from the world.

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