Review Article

Spatio-Temporal Dynamics of Foot and Mouth Disease in the Maghreb Countries

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Abstract | Foot-and-mouth disease (FMD) is a highly infectious and contagious transboundary animal disease and one of the most economically devastating diseases that affect cloven-hoofed livestock including cattle, goats, sheep, pigs and wild ungulates. Wide prevalence of the disease in Asia and Africa associated with huge economic losses to livestock farming and industry has increased global concern for the disease. Currently, 3 serotypes of FMD virus (O, A and SAT-2) and 06 lineage are circulating in the North Africa, of which serotype O is responsible for most of the outbreaks. However, the rapid spread of SAT2 and other exotic FMDV lineages in Libya and Egypt demonstrated the need for a robust surveillance system to detect and respond effectively to exotic infections. Emergence and re-emergence of FMD virus genotypes/lineages has been detected necessitating frequent replacement of the vaccine strains. The present review summarizes the knowledge generated in epidemiology, diagnosis and surveillance of the disease in the Maghreb countries.

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Introduction

Foot-and-mouth disease (FMD) is a highly infectious and contagious transboundary animal disease and one of the most economically devastating diseases that affect cloven-hoofed livestock including cattle, goats, sheep, pigs and wild ungulates (Alexandersen and Mowat, 2005). FMD is caused by Foot-and-mouth disease virus (FMDV) a highly variable RNA virus that belongs to the genus Aphthovirus and family *picornaviridae* with seven serotypes (A, O, C, Asia 1, SAT 1, SAT 2, and SAT 3), Within these serotypes, more than 65 subtypes have been recognized (Di Nardo et al., 2011). The high degree of antigenic variation may be attributed to the high rate of mutation, genetic recombination and the quasi species nature of the virus (Domingo et al., 2005). This antigenic variation is the basis for maintenance of FMDV circulation resulting in severe economic loss in livestock productions. FMDV serotypes show genetically and geographically distinct evolutionary lineages (topotypes) based on nucleotide differences of up to 15% for serotype O, A, C, and Asia 1. In the case of the SAT serotypes, the level for inclusion within a topotype was raised to 20% since the VP1 coding sequence of these viruses appears to be more inherently variable (Belsham, 2005).

FMD is endemic in much of Africa and Asia and occurs in defined areas of South America (Di Nardo et

al., 2011). Each serotype has a different geographical range with type O being the most widespread (Di Nardo et al., 2011; Sobrino et al., 2001). Vaccination or recovery from infection with one serotype will not protect against subsequent infection with another serotype. Even within a particular serotype emergence of antigenically variant topotypes/lineages/strains can evade homologous immunity (Belsham, 2004). Control of FMD is difficult due to variations in viral serotype and the emergence of new strains (Belsham, 2005; Domingo et al., 2005; Di Nardo et al., 2011). Outbreaks of FMD continuously threaten the livestock industries in countries that are free of FMDV (with or without vaccination). Millions of animals are sacrificed every year worldwide under FMDV eradication programs (Di Nardo et al., 2011). However, periodic surveillance and molecular epidemiological studies help us to detect the introduction of new variant and possible source of spread of the disease into a community or region. Within each FMDV serotype, genetic analysis can group viruses together into distinct topotypes, which often correspond to geographically defined regions and also reflect the presence of genetically and geographically distinct evolutionary genotypes (Rweyemamu et al., 2008; Knowles and Samuel, 2003).

The Maghreb region include Morocco, Algeria, Tunisia, and Libya however it was later superseded, following the 1989 formation of the Arab Maghreb union by the inclusion of Mauritania and the disputed territory of Western Sahara (mostly controlled by Morocco). By virtue of its geographical location and its borders with the Middle East and Sahel countries, Maghreb countries are vulnerable to several transboundary diseases, including FMD. Currently, the livestock population susceptible and at risk to FMD in the Maghreb countries is approximately 100 million heads (cattle, sheep and goats) and the epidemiological situation and control measures applied by member nations are not homogeneous (OIE, 2015).

To implement effective control program against FMD, it is essential to have information on the pattern of outbreaks, the circulating viruses involved and eventually through regular vaccine matching, determine the ability of the current vaccine candidates to confer immune-protection. Regular monitoring of the circulating FMDV strains for possible genetic and antigenic variations which is essential for understanding the dynamics of the virus and the use of appropriate vaccine at any given time becomes a relevant requirement for appropriate and adequate control strategy implementation (Paton et al., 2009; Volsoo et al., 2004).

This article describes the geography and time disposition of outbreaks, control strategies towards free status and re-introduction of the disease into Maghreb states until 2015. We also discussed the role of cross border movement in the incidence of the disease, the serotyped and genotyped isolates from the various countries to discuss the risk of FMDV introduction from the Maghreb countries into Europe. Data available in research papers and reports of international organisation and databases (the website of the World Reference Laboratory (WRL) for FMD in Pirbright, www.wrlfmd.org, OIE, http://www.oie.int/ and FAO http://www.fao.int/) were also utilized.

History of FMD Epidemics in Maghreb Countries before 1999

Situation report

Historically, 4 serotypes have circulated in the Maghreb region (O, A, SAT2 and C) with type O being the most prevalent serotype, followed by serotype A. The serotype C and SAT2 has been reported in Mauritania and Tunisia, respectively (Table 1).

Table 1: *History of FMD serotypes in Maghreb region before 1999 (WRLFMD, 2015)*

Country	Year	FMD serotype
Algeria	1966- 1990	O
	1977	A
Libya	1959, 1962, 1967-1968, 1972, 1981-1983, 1988-1989, 1994	O
	1979	A
Morocco	1991-1992	O
	1952, 1977, 1983	A
Mauritania	1975-1976	SAT2
	1997	A
Tunisia	1970, 1975, 1989-1990, 1994	O
	1979, 1982	A
	1965, 1967, 1969	C

Prior to 1999, the last reported outbreaks in Maghreb member countries were (WRLFMD, 2015): in Algeria, (December 1990, serotype O), in Morocco (September, 1992, serotype O), in Libya (January 1994,

serotype O), in Tunisia (August 1994, serotype O) and in Mauritania (1997 serotype A).

Control strategies

The Algerian government in 1993 and 1994 embarked on vaccination for the cattle herds using a monovalent type O vaccine; however the vaccination programme was discontinued due to the political situation at the time. The same strategy was adopted in Morocco, where annual vaccination of cattle was performed up to December 1997 with a monovalent type O vaccine. Additionally, Tunisia also vaccinated susceptible animal populations annually since 1989. The small ruminants populations were also vaccinated with a monovalent type O while cattle received a trivalent (O, A, C types) vaccine (FAO, 1999).

The story for Libya and Mauritania was different because of scanty information about animal heath situation and control programs made available. There was however, no information about the vaccination program(s) in these two countries (FAO, 1999).

The 1999 Epidemic

Situation report

At a time the livestock population at risk for FMD in the Maghreb countries was approximately 78 million heads because most of these livestock were not vaccinated against any of the FMD serotype. Subsequently, on the 20 and 21st February 1999, 2 cases of Foot-and-Mouth Disease (FMD) were suspected in cattle in Algiers district, Algeria. The vesicular material was collected aseptically and sent to the World Reference Laboratory (WRL), Pirbright and after been confirmed as type O, OIE and FAO were informed appropriately (FAO, 1999). Sequence analysis of the virus revealed a genetically different type O virus similar to previous ones isolated in the Maghreb between 1989 and 1994 but different from the strains that were currently circulating in the Middle East. The sequenced analysis also showed that the Algerian viruses (O/ALG/1/99), (O/ALG/2/99), (O/ALG/3/99) belong to the West-African topotype with 99% similarity to a strain isolated in the Côte d'Ivoire (O/CIV/8/99) and Guinea (O/GNA/6/99) in 1999 (Samuel and Knowles, 2001; Samuel et al., 1999).

However, this confirmed the suspicion about the origin of the disease. Indeed, zebu cattle introduced illegally across the Algeria southern frontiers during the month of February 1999, were intercepted within the southern borders of the country. At the time of capture, these zebu cattle did not present any clinical signs of FMD (Samuel and Knowles, 2001; Samuel et al., 1999). Still their presence demonstrated that transboundary animal movements took place on the southern frontier with Niger and Mali, which are endemic for FMD.

From the beginning of the epizootic up to the 22th June 1999; 179 outbreaks were recorded in 36 districts out of 48 to be infected by the disease (Table 2). On the 22nd February 1999 cases of FMD were declared in Souk-Ahras district 50 kilometers (km) from the Tunisian border and Tlemcen at the west border of the country with Morocco (FAO, 1999).

Table 2: *Chronology of spreading of FMD in the Maghreb in 1999 (FAO, 1999)*

	Algeria	Morocco	Tunisia
Date of first outbreak	20/02/1999	25/02/1999	01/03/1999
Date of last outbreak	22/06/1999	03/04/1999	05/04/1999
Number of outbreaks	179	11	2

In Morocco; the first case of foot-and-mouth disease was suspected on the 25th June 1999, in the district of Oujda, five days after its declaration in Algeria. Clinical signs and lesions typical of foot-and-mouth disease were observed (FAO, 1999). The WRL, Pirbright confirm the presence of the serotype O (O/MOR/1/99) and (O/MOR/2/99) very similar (99%) to the virus that had appeared in Algeria. Furthermore, approximately two weeks later the disease was detected in the Khouribga and Beni Mellal district (600 km from the Oujda outbreak), highlighting the contagious nature of the disease, covering wide geo-graphic areas and infecting susceptible animals in affected flocks (Samuel and Knowles, 2001; Samuel et al., 1999; WRLFMD, 2015).

In Tunisia, despite the launch of a booster vaccination campaign of cattle, sheep and goats in the border district to prevent the FMDV introduction from the Algerian border; on 1st March, 1999 an FMD outbreak was detected in Naboul district (FAO, 1999). The FMDV from all susceptible animals was confirmed by the WRL, Pirbright with the serotype O

(O/TUN/1/99) and (O/TUN/5/99) that was very similar (99%) to the virus that had appeared in Algeria and Morocco (Samuel and Knowles, 2001; Samuel et al., 1999; WRLFMD, 2015).

There was no outbreak recorded during this epidemic in Libya and Mauritania (OIE, 2015).

Control strategies

An appeal for vigilance was launched throughout the national territories in Algeria, Tunisia and Morocco with active surveillance in all farms and all veterinary professionals were mobilized and biosafety measures observed. The media was used to sensitize and disseminate information on the benefits of farmer's participation in disease prevention and control program to protect their livestock. In the affected farms, all cattle were destroyed and there owners compensated, along with intensification of surveillance on a 10 kilometer radius from the diseased area. The vaccine used for this campaign contains the O Manisa strain in accordance with the recommendations of the WRL, Pirbright (FAO, 1999; Thomson, 2002).

In the first week of the epizootic in Algeria, ring vaccination around the outbreak locations was carried out and subsequently generalized to the entire national herd, including small ruminants along the frontier on the east of the country following the appearance of cases of FMD in sheep in Tunisia. A total of 1.4 million cattle were vaccinated and 160,551 received a booster vaccination after one month. Furthermore, 600,000 sheep and 34,733 goats were also vaccinated around the outbreaks. However in Morocco, over 2, 500, 000 cattle were vaccinated against FMD since the beginning of the outbreaks while in Tunisia; a total of 193 686 cattle and 1 083 628 small ruminants were vaccinated out of 313 960 cattle and 2 102 000 small ruminants, respectively (FAO, 1999; Thomson, 2002).

FMD Epidemic from 2000 to 2013

Situation report

In late 2000, several African countries witness a severe outbreak of FMD with the serotype O, topotype West-Africa (Volsoo et al., 2002; Sangaré, 2002). However, the outbreak in Mauritania was probably the modest compared to other countries. Afterwards the serotypes O (topotype West-Africa) and A (topotype Africa, lineage; G IV) was consistently reported to be circulating since 2005 as a result, Mauritania was eventually considered endemic for FMD because there was no specific monitoring and/or control program (s) against FMD or vaccination campaigns put in place (Volsoo et al., 2002; Sangaré, 2002).

In Libya, several outbreaks of FMD were reported in 2000-2013; the first wave of the outbreak in 2003 was cause by SAT 2 strain of the virus which was eventually self-limiting and never spread across international borders. In 2009, a different serotype (A), topotype Asia lineage Iran-05 was revealed to be circulating. Other outbreaks were reported in 2011-2013 Subsequently (WRLFMD, 2015):

- In 2012, with the O serotype, topotype ME-SA, lineage PanAsia-2 and the topotype EA- 3;
- In 2012, with the SAT 2 serotype, topotype VII;
- In 2013, With the O serotype, topotype ME-SA, lineage India 2001d;

Due to the political instability in Libya, information about the incidence of the disease became scarce. Control measures (including vaccination) were implemented, particularly after the introduction of new strains of serotype SAT-2 in 2012. A sero-surveillance was implemented by the IZS Brescia, Italy (Hall et al., 2013).

During the period under review (2000-2013), Algeria, Morocco and Tunisia reported no cases of FMD since the 1999 major episodes (OIE, 2015; WRLFMD, 2015).

Control strategies

The disease is endemic in Libya and Mauritania therefore, the introduction and spread of FMDV to other Maghreb countries free or without cases is therefore an important risk that needs to be addressed (Knowles et al., 2007; OIE, 2015; WRLFMD, 2015).

After the 1999 epidemic, yearly FMD vaccination with the O Manisa strain was carried in Algeria (cattle only), Morocco (cattle only) and Tunisia (cattle, sheep and goats) (OIE, 2015). Tunisia added respectively SAT2 and the A22 strains to the FMD vaccine since the serotype SAT2 and A incursion from Libya in 2003 and in Egypt and in 2006. Algeria also added the A22 strains to the FMD vaccine (Ahmed el al., 2012). Since 2007, Morocco has stopped FMD vaccination following several sero-ep

Table 3: *Livestock populations in the Maghreb in 2014 and FMD vaccine serotype used (OIE, 2015)*

Species	Cattle	Sheep	Goats	FMD vaccine serotype used
Libya	150,000	5,100,000	1,200,000	O/A/SAT2 from 2013 (cattle)
Tunisia	600,000	6,600,000	1,500,000	O/A/SAT2 (cattle), O/SAT2 (small ruminants)
Algeria	2,008,000	26,000,000	5,000,000	O/A (cattle)
Morocco	2,800,000	20,000,000	5,000,000	O Stopped since 2007
Mauritania	1,700,000	10,000,000	3,000,000	Didn't vaccine
Total	**7,258,000**	**67,700,000**	**15,700,000**	

idemiological surveys conducted in cattle and small ruminants, which confirmed the absence of FMDV circulation. The country prepared an FMD contingency plan, relying on epidemio-surveillance and has constituted a vaccine antigen bank to be used in case of emergency.

In 2011, Algeria, Morocco and Tunisia commenced working together using a regional approach to controlling the disease and involved in a common process to be officially recognized free of FMD. In October 2011, these three countries submitted their dossiers to OIE. The dossiers were evaluated by the FMD *ad hoc* group and the Scientific Commission of the OIE before presentation to the General Assembly in May 2012. This work is fully consistent with the FAO/OIE FMD Progressive Control Pathway (PCP-FMD) and the final aim is to achieve OIE official status of countries free with vaccination (for Algeria and Tunisia) and without (for Morocco). In May 2012, Algeria, Morocco and Tunisia were recognised by the OIE as Member Countries with endorsed official control programme for FMD, in accordance with the Chapter 8.5 of the Terrestrial Animal Health Code (OIE, 2012; OIE, 2013).

Algeria and Tunisia carry out annual vaccination campaigns (Algeria; O Manisa + A22. Tunisia; O Manisa + A22+ SAT2 Eritrea) while Morocco stopped vaccination since 2007 (OIE, 2012; OIE, 2013). National laboratories in the Maghreb countries are fully associated and in partnership with the work of the European network of FMD reference laboratories. They participate in the annual ring trial and attend technical meetings for capacity building and cooperation (OIE, 2012; OIE, 2013).

The 2014-2015 Epidemics

The livestock population susceptible and at risk for FMD in the Maghreb countries put together was approximately 100 million heads. The epidemiological situation of FMD in the Maghreb countries and the control measures applied in the region are not uniform (Table 3) (OIE, 2015).

Situation report

On 24 April, 2014 two cows with clinical signs suggestive of FMD were reported in Nabeul district, Tunisia (OIE, 2015). The disease was confirmed by real-time RT-PCR and the phylogenetic analysis performed by Experimental Zooprophylactic Institute (IZSLER), Brescia (OIE's Reference Laboratory) identified topotype O/ME-SA/Ind 2001d which is closely related (99%) to recent viruses isolates from Libya (LIB/2/2013 and Saudi Arabia (SAU/3/2013) *(12)*. According to OIE report, the source of the outbreak was due to the illegal movement of animals from Libya (OIE, 2015).

During the first month (May 2014), 32 new outbreaks were reported in domestic sheep, goats and cattle, in 11 different districts. In June, new cases were subsequently declared in Jendouba districts 50 km to the west border of the country with Algeria (Table 4) (OIE, 2015).

Table 4: *Chronology of spreading of FMD in the Maghreb in 2014 (OIE, 2015)*

	Algeria	Tunisia
Date of first outbreak	25/07/2014	24/04/2014
Date of last outbreak	22/10/2014	13/10/2014
Number of outbreaks	420	140

On the 23rd of July, 2014, FMD outbreak was detected in Setif district at the East of the Algeria, 260 km from border with Tunisia. The first outbreak occurred on a fattening cattle farm, the source of the outbreak was due to the illegal introduction of animals from Tunisia. Clinical signs of the disease included fever, blisters, lameness and mammary lesions (OIE, 2015). Samples were forwarded to IZSLER, Brescia and

the virus isolated was identified as O/ME-SA/Ind-2001d lineage with identity of 99.69% and 99.37%, respectively to field strains O/TUN/1031/2014 and O/TUN/1054/2014, isolated during the current outbreaks in Tunisia (WRLFMD, 2015).

Outbreaks were reported in the first week in 6 different districts. Again the second week 35 also witness new outbreaks in 13 new districts, and by the end of August more than 350 outbreaks were recorded since the epidemic started in 33 different districts. Cases were subsequently declared in Oran districts 160 km to the west border of the country with Morocco. All the cases recorded were from cattle and there were no clinical, serological signs of FMD in small ruminants. However, in March 2015, twelve FMD outbreaks involving sheep re-emerged in El Bayadh and El Oued districts ending nearly five months of absence of the disease in the Algeria (OIE, 2015).

There was no outbreak recorded during this epidemic in Morocco. Due to the political situation in Libya, information about FMD was scarce. In Mauritania, the SAT2 serotype (topotype VII) was identified in 2014 (OIE, 2015; WRLFMD, 2015).

Control strategies

Following the FMD epidemic in Tunisia in April 2014, several measures were implemented in both Tunisia and Algeria (OIE, 2015): - Crisis cells centres at national and regional levels were instituted, - Disinfection of vehicles leaving affected or suspected district, - Vaccination points of susceptible species at the entrance of livestock markets, Peri-focal vaccination in 5 km radius, - Epidemiological investigation to determine the origin of the infection - closing of livestock markets, ban on movement of animals within the infected districts. Treatment of animals is not being carried out. In the affected farms, all cattle infected were destroyed and there owners were compensated. Further control measures are; stamping out, screening, vaccination in response to outbreaks, disinfection of infected premises/establishments.

Vaccination campaign throughout Algeria and Tunisia was performed. The vaccination was carried out with the same vaccine (O Manisa) used in Libya. In Algeria the vaccination campaign rate by June 2014 was 85% in cattle (O Manisa, A 22), however the small ruminants were completely naïve (OIE, 2015; WRLFMD, 2015).

A summary of vaccine matching data generated at the WRLFMD for representative member countries for the O/ME-SA/Ind2001d lineage that shows results for 22 field virus samples sent to WRLFMD contains data for viruses from Algeria and Tunisia. In general, three vaccine antigens (O/TUR/5/09, O-3039 and O/TAW/98) are matched against these viruses, while the in-vitro test indicates a poorer match for O-Manisa and O-BFS; the vaccine strains used in Algeria and Tunisia. Arguably, this is may be the reason why the FMD epidemic occurred in Tunisia and Algeria despite the vaccination efforts applied by the two countries, and until August 2014 where the vaccine strain O/TUR/5/09 was used that allowed the control and resolution of the episodes (WRLFMD, 2015).

In Morocco, following the FMD epidemic in Algeria in July 2014 several measures were applied such as activation of the vigilance committee - Strengthening surveillance mainly at the borders - High alert for any suspicious case - In August 2014, preventive vaccination campaign in cattle (strain O/TUR/5/09) was carried out in phases. First phase: regions at the border with Algeria (East of Morocco - about 1.000.000 heads); as of 7 September 2014 a total of 84% of the targeted population was vaccinated; Second phase: rest of the territory (about 1.700.000 heads); as a results no FMD case was declared in Morocco (OIE, 2015; WRLFMD, 2015).

Table 5: *FMD lineage in the North-African countries 2011-2015 (WRLFMD, 2015)*

FMD lineage	Year and countries occurrence
O/ME-SA/PanAsia-2	Egypt (2014), Libya (2011 and 2012)
A/ASIA/Iran-05	Libya (2009), Egypt (2012, 2013 and 2014)
O/ME-SA/Ind-2001	Libya (2013), Tunisia (2014), Algeria (2014)
SAT 2 topotype VII	Egypt (2012 and 2014), Libya (2012) and Mauritania (2015)
A/AFRICA/G-IV	Egypt (2014)
O/EA-3	Egypt (2013 and 2014)

Discussion

Three FMD serotypes (O, A and SAT2) and 06 lineage (Table 5) has been introduced North African countries from West Africa and Middle east and

consistently put the livestock industry at risk due to outbreaks and due to proximity putting Europe too at risk. However Algeria, Tunisia and Morocco have contingency plans and funding for immediate procurement of vaccines; although Libya and Mauritania do not which invariably put their neighbours at constant risk as result of free movement of animals across borders.

The livestock population in Algeria and Morocco is highly susceptible to SAT2, and effective vaccines are only used in Tunisia. In Libya, the routine implementation of vaccination program has been severely affected by civil unrest and changes in government leadership and policies. It is expected that serotype SAT2 will spread widely and may affect a high proportion of livestock until limited by natural immunity or imposition of effective biosecurity measures and vaccination programmes at a regional level (Ahmed et al., 2012; Hall et al., 2013; Ryan et al., 2015). The rapid spread of SAT2 and other exotic FMDV in Libya and Egypt demonstrates the need for a robust surveillance systems to detect and respond effectively to exotic infections in an endemic FMD country and region, and necessitates the importance of virological intelligence gathering to pick up related FMDV from epidemics in the Sahelian countries to the immediate south of the Sahara or in eastern regions.

The Mediterranean Sea could not represent a sufficient barrier to ensure that viral infections do not cross the Sea to Europe; due to the proximity of the Maghreb Region with the European continent: Morocco and Spain (≈ 14 Km), Tunisia and Italy (≈ 155 Km), Algeria and Spain (≈ 150 Km). The increased and intense volume of trade between both shores with amplified movements of people, commodities, vehicles and transports (both legal and illegal) poses a risk to FMD-free Europe. It is estimated that over 1 million people have already migrated into Europe in 2014-2015 ; these persons do not hesitate to bring with them agri-food products, in particular, lamb meat during their regular round-trip journey (as certified during the FMD outbreaks in the Maghreb in 1999).

In conclusion, Control and prevention measures for FMD like other transboundary animal diseases include surveillance, animal movement control, vaccination, quarantine, humane culling and just compensation. FMD endemic countries in the Maghreb and the Middle East need to intensively monitor the pattern of FMD and thoroughly investigate outbreaks to ensure that exotic serotypes are detected from among the endemic serotypes, through syndromic surveillance for patterns such as mortalities in young stock or among well vaccinated animals, and through adequate and rapid strain typing of FMD at OIE or FAO Reference Centres.

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