Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Infection, Genetics and Evolution 9 (2009) 153–161

Contents lists available at ScienceDirect

Infection, Genetics and Evolution

journal homepage: www.elsevier.com/locate/meegid

Review

Understanding the molecular epidemiology of foot-and-mouth-disease virus

Joern Klein *

Norwegian University of Science and Technology, Faculty of Medicine, Department of Cancer Research and Molecular Medicine, N-7489 Trondheim, Norway

ARTICLE INFO

Article history:
Received 4 July 2008
Received in revised form 20 November 2008
Accepted 20 November 2008
Available online 28 November 2008

Keywords:
Molecular epidemiology
Foot-and-mouth disease
FMDV
Epidemiology
Evolution

ABSTRACT

The use of molecular epidemiology is an important tool in understanding and consequently controlling FMDV. In this review I will present basic information about the disease, needed to perform molecular epidemiology.

I will give a short introduction to the history and impact of foot-and-mouth disease, clinical picture, infection route, subclinical and persistent infections, general aspects of the transmission of FMDV, serotype-specific epidemiological characteristics, field epidemiology of FMDV, evolution and molecular epidemiology of FMDV. This is followed by two chapters describing the molecular epidemiology of foot-and-mouth disease in global surveillance and molecular epidemiology of foot-and-mouth disease in outbreak investigation.

Contents

1. Introduction

The combination of molecular biology, epidemiology and population genetics in the science of molecular epidemiology is a powerful tool to develop control strategies for infectious disease.

* Tel.: +47 72573132; fax: +47 72576400.
E-mail address: jorn.klein@ntnu.no.

1567-1348/$ – see front matter © 2008 Elsevier B.V. All rights reserved.
doi:10.1016/j.meegid.2008.11.005

This is especially significant for viral diseases, due to the rapid changes in the viral genome, regardless of it consists of DNA or RNA, which allows the drawing of conclusions about the origin of the virus lineage and/or the influence of immunologic and environmental pressures, like the introduction of vaccination campaigns or climate changes. The latter implicate, in the authors opinion, that each researcher working with the molecular epidemiology of infectious disease should have knowledge about the actual situation in the field, which will certainly help to avoid the proposal of wrong hypotheses. It is equally important to be aware that most of the techniques used, e.g. phylogenetic analysis or selection pressure analysis, are by themselves based on hypotheses and models, with their intrinsic assumptions, biases and fuzziness. Furthermore, there should be a general awareness about the illusion that we, particularly with the derived nucleotide sequence information, have knowledge about the viral genetics. Beside the quasispecies structure of the RNA virus populations, there are manifold possibilities of virus–host interactions we still do not understand.

This review gives the minimum background information needed for the understanding of the molecular epidemiology of foot-and-mouth disease virus and presents the current developments within this field.

2. History and impact of foot-and-mouth disease

The first indication of foot-and-mouth disease (FMD) in the literature can be found in a book from the Italian physician Hieronymi Fracastorii (Wright, 1930), where he describes a cattle disease similar to the signs of FMD. Since then, several indications of FMD can be found in the literature (Thalmann and Nockler, 2001). From the second half of the 19th century, on the account of the increase of animal trade due to the development of new transport routes (O'Rourke and Williamson, 2002), the disease became more important and started to cause severe economic losses. In Germany, in 1897, a commission had been set up by the Prussian Ministry of Culture, following a request from the "Partei der Landwirte" of the Reichstag to set up measures of FMD control (Rott and Siddell, 1998). One year later, Friedrich Loeffler and Paul Frosch wrote in their report that the causative agent of FMD was neither a known bacterium nor a toxin but an "ultravisible, ultrafilterable substance" (Loeffler and Frosch, 1897), and described thereby the first animal virus, foot-and-mouth disease virus (FMDV). In 1910, the first FMD research institute was built on the island of Riems in Germany, followed by other research institutes in Europe, e.g. in Pirbright, United Kingdom in 1925 and on Lindholm island, Denmark in 1926. The major milestones in these early years of FMD research were the introduction of guinea pigs as research animals (Waldmann and Pape, 1920) and the first steps towards the development of an FMD vaccine in 1937 (Waldmann et al., 1937).

After the Second World War, FMD vaccines became available in all European countries and the disease was controlled by systematic vaccination until the end of 1991 when the European Union adopted a non-vaccination policy (Directive 85/511/CEE du conseil du 18 novembre 1985 établissant des mesures communautaires de lutte contre la fièvre aphteuse).

In 1967/1968 the United Kingdom experienced a large FMD outbreak in which more than 430,000 animals were slaughtered (Gloster et al., 2005). Since then FMD has occurred only sporadically and only a few minor outbreaks have been detected in Europe, e.g. in Denmark in 1982/1983 (Christensen et al., 2005) and in Italy in 1993 (Nunez et al., 2006). For the latter it has been shown that the causative virus was closely related to viruses that circulated previously in the Middle East (Nunez et al., 2006). In 2001 a large FMD outbreak started in the United Kingdom (Alexandersen et al., 2003a) and spread to France, Ireland and The Netherlands. The losses to agriculture in the United Kingdom alone were about £3.1 billion (Thompson et al., 2002). The causative FMDV here showed phylogenetic similarity to the virus from the outbreak in Italy in 1993 and was closely related to viruses that circulated previously in Asia and Middle East (Knowles et al., 2005).

3. The disease

3.1. The virus

Foot-and-mouth disease is an acute, highly contagious viral disease, which has a great potential for causing severe economic losses in susceptible cloven-hoofed animals (Alexandersen and Mowat, 2005).

The causative agent of FMD is the foot-and-mouth disease virus (FMDV), a small positive sense ssRNA virus (approx. 8.3 kb) which belongs to the *Aphthovirus* genus of the family *Picornaviridae* (Belsham, 1993). FMDV replicates through negative strand RNA which was recently used in quantitative strand specific real time RT-PCR as a tool to determine strain virulence and replication patterns (Horsington and Zhang, 2007). The high genetic and phenotypic variability of FMDV is reflected in the existence of seven serotypes: O, A, C, Asia 1, SAT 1, SAT 2 and SAT 3 and further numerous variants and lineages, described as topotypes (Knowles and Samuel, 2003). The antigenic diversity within the serotypes is crucial to consider when selecting vaccine strains, as cross-reactivity may be variable (Kitching, 2005). The virus capsid is composed of 60 copies of each of the four structural polypeptides designated VP1 to VP4. A region in the G-H loop (around residues 140-160) of the VP1 protein exposed on the surface of the viral capsid was determined to be the main antigenic site recognized by neutralizing antibodies (Bittle et al., 1982). The natural FMDV infection is initiated when the RGD motif within the G-H loop binds to certain cellular integrin receptors, which are expressed in the epithelial cells targeted during the acute phase of infection (Alexandersen et al., 2003b; Monaghan et al., 2005). In the process of cell culture adaptation, FMDV acquire the ability to use other receptors like glycosaminoglycans (GAGs), which do not require the RGD motif. The host specificity to natural FMDV infection is thought to depend on FMDV binding to specific integrins although there are some other, yet undiscovered, mechanisms which determine FMDV susceptibility.

3.2. Clinical picture

Animals that can be affected include cattle, swine, sheep, goats, buffaloes and wild ruminants (Alexandersen and Mowat, 2005).

FMD in *Bovinae* is characterized by fever (often above 40 °C), excessive salivation, lameness, depression and decreased milk production. The mucosa of the lips, dorsum of the tongue, and the dental plate are most severely involved. The mortality rate is low and mostly young animals are affected due to myocardial necrosis (Alexandersen et al., 2003b; Gulbahar et al., 2007; Kitching, 2002).

FMD in pigs primarily affects the feet. It is dominated by rather painful formation of vesicles in the epidermis of the feet (coronary band, interdigital clefts, bulbs), associated with severe lameness. Complications are seen, such as detachment of the hoof and secondary infection of disrupted aphthae (fluid-filled blisters), which may cause purulent arthritis of the pedal joint (Kitching and Alexandersen, 2002).

Clinical signs of FMD in sheep and goats are less severe; often only lameness through aphthae and inflammation at the cloves (Alexandersen and Mowat, 2005).

3.3. Infection route

The mechanism of spread of FMDV is primarily in the form of either aerosolized droplets, saliva, or through indirect contact by personnel or contaminated surfaces and then subsequently back to the respiratory tract (Alexandersen and Mowat, 2005). However, infection can also occur through lesion of the skin or mucous membranes, but this is a very inefficient entering route, unless abrasions or cuts are present (Alexandersen et al., 2003a; Donaldson et al., 1987). The site of penetration is influenced by droplet size, since only the smallest inhaled droplets reaching the alveoli of the lungs. Initial infection occurs predominantly at the epithelial surface of the soft palate and adjacent nasopharynx, with subsequent spread of virus through regional lymph nodes (Alexandersen et al., 2003a; Donaldson et al., 1987). The virus can be detected in the oral cavity by real time RT-PCR 1-3 days before the onset of the viraemia (Alexandersen et al., 2003b).

3.4. Subclinical and persistent infections

Inapparent infections of FMDV can be divided into two types. First, those animals that become infected and spread the virus without showing clinical signs and second, those animals in which the virus persists after recovering from FMD with clinical signs (Sutmoller and Casas, 2002).

FMDV persistently infected animals are defined as those being virus positive for a minimum of 28 days (Sutmoller et al., 1968) and usually are referred to as carriers. Persistently infected animals show only low-level excretion of FMDV from the pharynx of ruminants, for periods that are species and virus lineage associated (Salt, 1993). The maximum duration of the persistent infection ranges from 4 months in goats to 5 years in African Buffaloes (*Syncerus caffer*) (Alexandersen et al., 2002b). FMDV persistence in pigs could not be demonstrated and there is no information about persistence in Asian Buffaloes (*Bubalus bubalis*) (Alexandersen et al., 2002b).

Transmission of FMDV from carrier animals to susceptible hosts, under field conditions, has so far only been shown for African Buffaloes to cattle and impala (*Aepyceros melampus*) (Bastos et al., 2000; Dawe et al., 1994). However, under experimental conditions, saliva obtained from carrier animals injected into cattle and pigs has caused infection, although there is no information as to whether this also can happen under field conditions (Alexandersen et al., 2002b), or with closely related species as the Asian Buffaloes.

Unlike persistently infected animals, subclinically infected animals, i.e. those animals not developing obvious clinical signs, may be highly contagious (Gibbens et al., 2001; Holzhauer et al., 2001). Beside the immune status of the host, also the involved FMDV lineage plays a role in the subclinical course of the disease (Bouma and Dekker, 2002). If an outbreak is caused by vaccine strains, which shows reduced virulence (Sa-Carvalho et al., 1997), subclinical infections can also be found. For example, during the FMD outbreak in 2007 in the United Kingdom, which was caused by a vaccine strain (Enserink, 2007), only few of the FMDV infected animals showed clinical signs.

Subclinical infection can also be produced within vaccinated ruminant herds, with a high FMDV challenge in those animals with high immunity or a low challenge in animals with low vaccine titer (Hutber et al., 1999; Yadin et al., 2007). The possibility of those animals becoming carriers has, to the author's knowledge, not been examined. Nevertheless, it is likely that such animals may play an important role in the maintenance of FMD in endemic countries (Kitching, 2005).

4. Epidemiology of FMD

Even though there are some common features in the spread of FMD, each of the seven serotypes, or even their variations (topotypes), has a different way of transmission, clinical appearance and species tropism (Kitching, 2005).

4.1. General aspects of the transmission of FMDV

Large amounts of the virus are found in all body secretions and excretions over a relatively long time and can be carried in contaminated feed (Donaldson, 1997; Wijnker et al., 2007), on the tires of vehicles, and on the shoes and clothes of people (Alexandersen et al., 2003a; Grubman and Baxt, 2004).

The transmission via aerosols can also occur, depending on weather conditions and the characteristics of virus survival and dissemination (Alexandersen et al., 2002a; Alexandersen and Donaldson, 2002; Donaldson, 1972; Donaldson et al., 1987; Sellers and Gloster, 2008). The host plays a major role for this transmission route; cattle, sheep and goats may exhale up to 5.2 log10 $TCID_{50}$ of virus per day, but pigs which produce up to 8.6 log10 $TCID_{50}$ per day represent a significantly greater source of airborne FMDV infections than infected ruminants (Alexandersen et al., 2002a,c; Alexandersen and Donaldson, 2002).

However, the most common route of introduction of FMD into a country free of FMD has been the illegal use of contaminated swill feed (Hartnett et al., 2007). The reduction in pH of meat at post mortem due to accumulation of lactic acid is usually sufficient to kill FMDV, but there is no change of pH in the glands and bone marrow, and the virus will persist between −20 °C and 4 °C (Kitching, 2005).

4.2. Serotype-specific epidemiological characteristics

4.2.1. Serotype O

The pandemic strain of FMDV serotype O is a major threat to Europe. It is the most prevalent serotype worldwide, although there is no precise genetically explanation for this higher prevalence (Mason et al., 2003). Some lineages of the type O are restricted in their host range to *suidea* (Cheng et al., 2006), whereas others, like the Panasia strain, are not restricted to a specific host (Knowles et al., 2005).

4.2.2. Serotype A

There is a great antigenic diversity between the members of this serotype, and there is also often no cross-protection between them (Bronsvoort et al., 2004; Islam et al., 2001; Klein et al., 2006; Konig et al., 2007; Mattion et al., 2004; Muthuchelvan et al., 2001; Tosh et al., 2002a). There is also evidence that recombination in serotype A occurs much more than in the other serotypes (Carrillo et al., 2005; Jackson et al., 2007; Simmonds, 2006). However, it is still unclear why so many new lineages of serotype A regularly appear and disappear (Kitching, 2005).

4.2.3. Serotype Asia 1

The members of this serotype seem to be the less virulent and are usually restricted to Asia (Biswas et al., 2006; Chang et al., 2007; Mohapatra et al., 2002, 2004; Sanyal et al., 2003; Sanyal et al., 2004a,b). However, in recent years an increase of Asia 1 caused outbreaks in Asia has been reported, as well as further spread of viruses of this type to Turkey and Greece in 2000 (Valarcher et al., 2005).

4.2.4. Serotypes SAT 1,2,3

The SAT (Southern African Territories) serotypes are usually found in Africa, but there have also been sporadic outbreaks in Saudi Arabia and Kuwait in 2000 (Aidaros, 2002). There is a higher

sequence variation within each of the three SAT types than in serotype O (Bastos et al., 2001, 2003a).

4.2.5. Serotype C

During the last 20 years there have been no major outbreaks reported of this serotype (only sporadically in South America, East Africa and Pakistan between 2000 and 2006 (OIE, 2008)), and there is no explanation for the apparent disappearance. However, vaccines containing serotype C are still in use in some countries, comprising a risk of vaccine induced serotype C outbreaks (Kitching, 2005).

4.3. Field epidemiology of FMDV

Generally, field epidemiology is the practice of epidemiology in response to problems of a magnitude significant enough to require a rapid or immediate action (Goodman and Buehler, 2002), i.e. it is required to consider when the obtained data are sufficient to make practical recommendations, rather than to ask what additional, more academic, questions might be answered by the data.

Rapid field epidemiological action in case of FMD outbreaks is required to trace potential sources of infection to limit the spread of the disease. For example, during the 2001 outbreak of FMD in the United Kingdom (Gibbens et al., 2001; Gibbens and Wilesmith, 2002), all animal, vehicle and personnel movements through animal markets were traced and investigations of infected farms performed, in order to identify potential contact farms and to subsequently apply the appropriate control measures.

Disease surveillance, on the other hand, can be considered as immediate field epidemiological action. According to the Office International des Épizooties (OIÉ), surveillance means "*the investigation of a given population or subpopulation to detect the presence of a pathogenic agent or disease; the frequency and type of surveillance will be determined by the epidemiology of the pathogenic agent or disease, and the desired outputs*" (Thiermann, 2008).

FMD surveillance usually has the following objectives: (a) confirmation of absence of disease (DEFRA, 2008) (b) development and/or evaluation of FMD control programs in endemic countries (Chung et al., 2002) or (c) to detect the occurrence of new FMDV lineages (del Rio Vilas et al., 2006).

Sources of data for FMD surveillance can be either purely laboratory results of biological samples collected or participatory information obtained from the farmers or a combination of both. Key information, beside laboratory data like PCR results, sequence analysis and serology, are in the authors opinion:

1. clinical signs
2. vaccination status and date
3. vaccine used
4. species and age of the animal
5. beginning of outbreak (month/year)
6. sampling date and place
7. outbreak history
8. likely source of outbreak
9. morbidity rate
10. environmental information

Though it should be a strived aim to obtain all information, it has to be accepted that this is sometimes, due to various reasons, not possible. This is especially true for rural areas and less developed countries.

4.4. Evolution and molecular epidemiology of FMDV

FMDV shares its antigenic variability with many other picornaviruses. However, the extent of this variation is not equal in all picornaviruses, e.g. there are three polio serotypes and more than hundred rhinovirus serotypes (Domingo et al., 1996; Duarte et al., 1994).

There are three major forces driving the molecular evolution of all RNA viruses:

1. Spontaneous mutation: RNA virus encoded RNA-dependent-RNA-polymerase lacks the 3′→5′ exonuclease activity (proof-reading activity), leading to a very high mutation rate (approx. one mutation per genome per replication (Drake, 1993). These viruses have adapted their genome size to the so called error threshold (maximum mutation rate, tolerable for a genome size) to avoid fitness loss (Biebricher and Eigen, 2005, 2006; Bull et al., 2005; Escarmis et al., 2006; Gonzalez-Lopez et al., 2005; Sole et al., 2006).
2. The phenomenon of spontaneous mutation leads to a statistical effect called genetic drift. For an extremely large, highly diverse population, the ratio of highly fit to less fit genotypes may be very small. During a transmission event, only a few particles might be transmitted. Those genotypes do not represent the full genetic or fitness distribution of the original population and therefore often do not include the highly fit genotypes, because of their comparatively small numbers. The outcome is a new population established in a similar environment but with members of a small, less fit (on average) class of viruses (Knipe et al., 2006). FMDV is thought to evolve mainly through genetic drift, due to the high error-prone nature of its RNA polymerase (Domingo et al., 2005a,c). The FMDV RNA transcription error frequencies are estimated to vary between 10^{-3} and 10^{-5} nucleotide misincorporations per site per replication cycle (Haydon et al., 2004).
3. Recombination: Recombination describes a process in which the fragments of nucleic acid sequences from two genotypically different parental viruses are exchanged so that the progeny contain sequences derived from both parental viruses. Inter alia picornaviruses, coronaviruses and togaviruses display efficient recombination, which probably occurs during replication via "copy choice" (Enami et al., 1989; Jarvis and Kirkegaard, 1992; Kirkegaard and Baltimore, 1986; Kuge et al., 1989; Meier et al., 1984). Recombination seems to play an important role in FMDV evolution and occurs mainly in the gene regions coding for the non-structural proteins (Carrillo et al., 2005; Domingo et al., 2003; Jackson et al., 2007; Klein et al., 2007; Lee et al., 2009), but also sometimes in the gene regions coding for the structural proteins (Haydon et al., 2004; Haydon and Woolhouse, 1998; Tosh et al., 2002b). Changes in the non-structural proteins may potentially modify the virulence of the virus (Klein et al., 2007). The evolution of the structural proteins, especially VP1, which plays a major role in virus entry, seems to be mainly shaped by genetic drift (Domingo et al., 2005b,c; Domingo, 2006).
4. Migration: A population acquires new genetic information primarily through the immigration of individuals from surrounding populations (gene flow or genetically effective migration). This also applies within a single infected host, where different virus variants sometimes can be isolated from different tissues, reflecting the adaptation of quasispecies (Domingo et al., 2005a,b,c, 2003). This means that single host populations will compete with new, different virus genotypes for the limited number of susceptible host cells; which may lead to an increase in virulence. The virus strain with the higher basic reproductive rate will overtake the less-virulent, but finally end in a stage of equilibrium (Alexopoulou and Dourakis, 2005; Mao et al., 2001; Miralles et al., 1999; Sitia et al., 2001). Evolution experiments *in vitro* (Domingo et al., 2002; Domingo et al., 2005a,b,c; Martinez et al., 1992, 1991, 1997; Villaverde et al., 1991) demonstrate FMDV's capability of survival, despite

accumulation of mutations upon repeated bottleneck events (where population size is greatly reduced by a catastrophe). Therefore, a range of mutation rate must have evolved to ensure a continuous heterogeneity to find population subsets that can invade cells after bottleneck events and staying below the error-threshold. This can be exemplified by the RGDLXXL motif in the highly variable GH loop of VP1. This motif is responsible for receptor recognition ($\alpha v\beta 6$) and is invariant in most field isolates, even after bottleneck events like the introduction of vaccination (Monaghan et al., 2005).

A consequence of the high evolutionary rate of FMDV is that strains of virus with a common origin quickly diverge in sequence as they replicate and spread into new areas. Therefore, the greater the number of differences, the greater the distance between the strains in space and time. Conversely, strains with homologous sequences must have had a common, more recent, origin (Bastos et al., 2003b; Bronsvoort et al., 2004; Cottam et al., 2006; Klein et al., 2006; Knowles and Samuel, 2003; Konig et al., 2007; Malirat et al., 2007; Martin et al., 2006; Sahle et al., 2004; Sangare et al., 2004).

This usage of molecular biological methods for the study of the distribution and determinants of infectious disease is the subject of molecular epidemiology (Thompson, 2000).

It is however, important to recognize, that for the study of the molecular epidemiology of a certain virus, like FMDV, the knowledge of the molecular evolution is equally important, thus knowing the (genetic) factors which have shaped the evolution of the pathogens will improve the development of vaccines, as well as control strategies (Chareonsirisuthigul et al., 2007; de Freitas et al., 2007; Holmes, 2007; Holmes and Drummond, 2007).

Unlike taxonomy, which describes how closely related organisms are based on evolutionary grouping by ancestral traits, molecular epidemiology correlates phylogenetic information with biological variables and classical epidemiological information. Furthermore, it develops hypotheses about evolutionary changes considering different selection pressures, inter alia caused by the host's immune system and new environmental challenges.

Despite its potential, it is important to stress the limits of molecular epidemiology:

- Phylogenies are based on simplified models.
- The available sequences are most likely biased, and very often do not represent a complete spatial and temporal random sample.
- The majority of sequence analysis for RNA viruses is biased, because they are, despite the quasispecies structure of RNA viruses, based on a single consensus sequence, and thus not mirroring all intrahost viral populations.

In addition, two types of probability error must be considered in molecular epidemiology (Thompson, 2000):

- Type 1 probability error: a subtyping assignment claims epidemiologic relationship of strains when there is none,
- Type 2 probability error: a subtyping assignment concludes that there is no epidemiological relationship when in actuality there is.

Generally, phylogenetic analysis is a statistical inference of relationship, using a probability model of nucleotide and amino-acid substitution (evolutionary model). Assuming the wrong evolutionary model can affect the outcome of a phylogenetic analysis, e.g. by incorrectly estimating tree topology (Bruno and Halpern, 1999; Penny et al., 1994), influencing branch length estimation (Posada, 2001; Posada and Crandall, 2001), and biasing statistical support values (Buckley and Cunningham, 2002). The correct evolutionary model becomes a powerful tool when, despite its simplified assumptions, it can fit the data and make accurate predictions (minimizing probability error 1 and 2). The correct model can help to understand the linkage among the spatial, temporal, and genetic processes taking place during virus transmission in a changed environment, thus evolutionary events occur early during the initial expansion and advantageous changes become fixed in the genetic population structure.

By using hierarchical likelihood ratio tests (Goldman, 1993; Posada and Crandall, 2001; Rzhetsky and Nei, 1995) or Akaike information criterion (AIC) tests (Saffron et al., 2006; Seghouane and Amari, 2007), it is possible to identify the most appropriate model for the sequence analysis, through a hierarchical set of evolutionary models (Arndt, 2007; Buckley and Cunningham, 2002; Fan et al., 2007; Lemey et al., 2005a,b; Lemey and Vandamme, 2005; Lunter and Hein, 2004; Salemi et al., 1999; Van Brussel et al., 1999; Vandamme et al., 2000, 1998; Vercauteren and Vandamme, 2006; Yang, 2002).

4.5. Molecular epidemiology of foot-and-mouth disease in global surveillance

FMD endemic areas in the world are high-risk zones for introducing FMD to countries free of the disease and for the origin of new FMDV lineages. Therefore, a continuing surveillance of FMDV is needed for the early recognition and understanding of emerging risks or changes in the global FMD situation. The detection and characterization of new FMDV lineages and control of possible conformation changes of circulating immuno-relevant epitopes, is of special interest, as it may indicate that a change in the current used vaccine strains is needed.

One recent example of a newly occurred FMDV lineage is A/IRN/2005.

During 2005, a new FMDV A subtype, A/IRN/2005, spread throughout Iran and moved westwards into Saudi Arabia, Turkey and in 2007 reached Jordan (ProMED, 2007). In 2006 this subtype was also detected in Pakistan (Klein et al., 2007). This particular FMDV subtype has proven to be highly virulent and has caused severe disease in all ages of cattle (EUFMD, 2007).

Serum neutralization assays demonstrated a closer relationship to A22 than to other serotype A subtypes (Paton, 2006) and the World Reference Laboratory as well as the FAO European Commission for the control of FMD recommend, in the absence of an homologous vaccine strain, the use of the widely available A22 Iraq strain as vaccine (Paton et al., 2006). It has been hypothesized that the A/IRN/2005 sublineage has undergone two different paths of evolution for the structural and non-structural genome regions (Klein et al., 2007).

The structural genome regions may have had their evolutionary starting point in the A22 sublineage. It can be assumed that, due to the quasispecies structure of FMDV populations and the error-prone replication process, advantageous mutations in a changed environment have been fixed and have lead to the occurrence of the new A/IRN/2005 sublineage.

Together with this mechanism, recombination within the non-structural genome regions, potentially modifying the virulence of the virus, may be involved in the success of this new sublineage. The possible origin of this recombinant virus may be a co-infection with Asia1 and a serotype A precursor of the A/IRN/2005 sublineage within Asian Buffaloes.

Another example of a new FMDV lineage is the currently described PanAsia II lineage described so far in Bhutan, Nepal, Malaysia and Pakistan, which seems to evolve away from the "old"

PanAsia lineage (Klein et al., 2008), leading possible to a decrease in the used O1/Manisa vaccine efficiency.

A special situation is the Office International des Epizooties (OIE) status of "FMD-free countries where vaccination is practiced". In these countries FMDV is not eradicated and still circulates in the susceptible population. This leads to a permanent bottleneck situation for the virus, and the emergence of vaccine escape mutants is likely, as seen for the serotype A outbreaks in South America during the last years (Konig et al., 2007; Mattion et al., 2004; Perez et al., 2008). However, molecular epidemiology may also be helpful to detect low vaccine coverage (Klein et al., 2006; Malirat et al., 2007).

4.6. Molecular epidemiology of foot-and-mouth disease in outbreak investigation

In an ongoing outbreak situation molecular epidemiology is a useful tool to track virus and to consequently stop the transmission. But also the post-outbreak investigation is important with regard to the claim for damages.

The best examples for this particular field are given by work done on the United Kingdom outbreaks in 2001 and 2007.

In 2001, Great Britain experienced an epidemic of FMDV caused by the Pan Asia O strain of the virus (Alexandersen et al., 2003a; Cottam et al., 2006). The disease spread rapidly and widely throughout the country and further to the Republic of Ireland, France and the Netherlands. Due to the size of the outbreak it was not possible to track the transmission route and many cases were simply attributed to "local spread." However, many tissue samples have been collected during the seven-month lasting outbreak and it was possible to study the microevolution of the virus and thereby recover particular transmission pathways of the acting FMDV lineage (Cottam et al., 2006).

On August 3, 2007 a new outbreak of FMD was confirmed in Surrey, United Kingdom. The causing FMDV lineage was identified as OFS 1860/UK/67, a virus isolated not in circulation in animals since 1967. However, this lineage was used at the nearby Pirbright laboratory site, which houses separate units of the Institute for Animal Health and Merial Animal Health Ltd and it was soon clear that this was the origin of the virus. Thus, the question arose from which unit the virus escaped. Full length genome sequencing of the virus isolates obtained from infected animals have shown typical amino acid adaptations for FMDV propagated for several passages in cell culture systems, as used in vaccine production, and Merial Animal Health Ltd. was identified as the source of the outbreak (Cottam et al., 2008).

5. Conclusion

Molecular epidemiology of FMD is a powerful tool if applied correctly with regard to the statistical methods and when supplied with classical epidemiological information. It is important to stress, that taxonomical relationship deduction alone is not enough to understand the dynamics of FMDV. Furthermore, it should be a strived aim to develop bioinformatics tools, which are able to handle the complex virus–host interactions during infection, as for example seen in the action of microRNA's during viral infection.

Although active surveillance of FMD has decreased dramatically the incidence of the disease in Europe, the fear of new outbreaks still exists and, as the example of last outbreak in UK in 2007 demonstrates, it is not unreasonable (Cottam et al., 2008). Moreover, FMD remains endemic in developing countries of Asia, South America, and Africa, where new FMDV strains are most likely to evolve and where the only solution for the effective eradication/reduction is the application of measures based on the molecular and genetic characterization of the virus (Bronsvoort et al., 2004; Klein et al., 2007, 2006, 2008). Introduction of new fast methods such as real time RT-PCR into FMD diagnostics together with viral sequence analysis allows the study of viral biodiversity and evolution and thereby to track transmission events and sources, as well as to assure vaccine coverage of corresponding field FMDV lineages.

Acknowledgement

I would like to thank Dr. Magdalena Larska, Dr. Pål Sætrom and Ms. Lene C. Olsen for reviewing the manuscript and helpful suggestions.

References

Aidaros, H.A., 2002. Regional status and approaches to control and eradication of foot and mouth disease in the Middle East and North Africa. Rev Sci Tech 21, 451–458.
Alexandersen, S., Brotherhood, I., Donaldson, A.I., 2002a. Natural aerosol transmission of foot-and-mouth disease virus to pigs: minimal infectious dose for strain O1 Lausanne. Epidemiol Infect 128, 301–312.
Alexandersen, S., Donaldson, A.I., 2002. Further studies to quantify the dose of natural aerosols of foot-and-mouth disease virus for pigs. Epidemiol Infect 128, 313–323.
Alexandersen, S., Kitching, R.P., Mansley, L.M., Donaldson, A.I., 2003a. Clinical and laboratory investigations of five outbreaks of foot-and-mouth disease during the 2001 epidemic in the United Kingdom. Vet Rec 152, 489–496.
Alexandersen, S., Mowat, N., 2005. Foot-and-mouth disease: host range and pathogenesis. Curr Top Microbiol Immunol 288, 9–42.
Alexandersen, S., Quan, M., Murphy, C., Knight, J., Zhang, Z., 2003b. Studies of quantitative parameters of virus excretion and transmission in pigs and cattle experimentally infected with foot-and-mouth disease virus. J Comp Pathol 129, 268–282.
Alexandersen, S., Zhang, Z., Donaldson, A.I., 2002b. Aspects of the persistence of foot-and-mouth disease virus in animals—the carrier problem. Microbes Infect 4, 1099–1110.
Alexandersen, S., Zhang, Z., Reid, S.M., Hutchings, G.H., Donaldson, A.I., 2002c. Quantities of infectious virus and viral RNA recovered from sheep and cattle experimentally infected with foot-and-mouth disease virus O UK 2001. J Gen Virol 83, 1915–1923.
Alexopoulou, A., Dourakis, S.P., 2005. Genetic heterogeneity of hepatitis viruses and its clinical significance. Curr Drug Targets Inflamm Allergy 4, 47–55.
Arndt, P.F., 2007. Reconstruction of ancestral nucleotide sequences and estimation of substitution frequencies in a star phylogeny. Gene 390, 75–83.
Bastos, A.D., Anderson, E.C., Bengis, R.G., Keet, D.F., Winterbach, H.K., Thomson, G.R., 2003a. Molecular epidemiology of SAT3-type foot-and-mouth disease. Virus genes 27, 283–290.
Bastos, A.D., Boshoff, C.I., Keet, D.F., Bengis, R.G., Thomson, G.R., 2000. Natural transmission of foot-and-mouth disease virus between African buffalo (Syncerus caffer) and impala (Aepyceros melampus) in the Kruger National Park, South Africa. Epidemiol Infect 124, 591–598.
Bastos, A.D., Haydon, D.T., Forsberg, R., Knowles, N.J., Anderson, E.C., Bengis, R.G., Nel, L.H., Thomson, G.R., 2001. Genetic heterogeneity of SAT-1 type foot-and-mouth disease viruses in southern Africa. Arch Virol 146, 1537–1551.
Bastos, A.D., Haydon, D.T., Sangare, O., Boshoff, C.I., Edrich, J.L., Thomson, G.R., 2003b. The implications of virus diversity within the SAT 2 serotype for control of foot-and-mouth disease in sub-Saharan Africa. J Gen Virol 84, 1595–1606.
Belsham, G.J., 1993. Distinctive features of foot-and-mouth disease virus, a member of the picornavirus family; aspects of virus protein synthesis, protein processing and structure. Prog Biophys Mol Biol 60, 241–260.
Biebricher, C.K., Eigen, M., 2005. The error threshold. Virus Res 107, 117–127.
Biebricher, C.K., Eigen, M., 2006. What is a quasispecies? Curr Top Microbiol Immunol 299, 1–31.
Biswas, S., Sanyal, A., Hemadri, D., Tosh, C., Mohapatra, J.K., Manoj Kumar, R., Bandyopadhyay, S.K., 2006. Sequence analysis of the non-structural 3A and 3C protein-coding regions of foot-and-mouth disease virus serotype Asia1 field isolates from an endemic country. Vet Microbiol 116, 187–193.
Bittle, J.L., Houghten, R.A., Alexander, H., Shinnick, T.M., Sutcliffe, J.G., Lerner, R.A., Rowlands, D.J., Brown, F., 1982. Protection against foot-and-mouth disease by immunization with a chemically synthesized peptide predicted from the viral nucleotide sequence. Nature 298, 30–33.
Bouma, A., Dekker, A., 2002. Foot and mouth disease in (meat)calves: clinical signs and viral shedding. Tijdschr Diergeneeskd 127, 83–84.
Bronsvoort, B.M., Radford, A.D., Tanya, V.N., Nfon, C., Kitching, R.P., Morgan, K.L., 2004. Molecular epidemiology of foot-and-mouth disease viruses in the Adamawa province of Cameroon. J Clin Microbiol 42, 2186–2196.
Bruno, W.J., Halpern, A.L., 1999. Topological bias and inconsistency of maximum likelihood using wrong models. Mol Biol Evol 16, 564–566.

Buckley, T.R., Cunningham, C.W., 2002. The effects of nucleotide substitution model assumptions on estimates of nonparametric bootstrap support. Mol Biol Evol 19, 394–405.
Bull, J.J., Meyers, L.A., Lachmann, M., 2005. Quasispecies made simple. PLoS Comput Biol 1, e61.
Carrillo, C., Tulman, E.R., Delhon, G., Lu, Z., Carreno, A., Vagnozzi, A., Kutish, G.F., Rock, D.L., 2005. Comparative genomics of foot-and-mouth disease virus. J Virol 79, 6487–6504.
Chang, H.Y., Du, J.Z., Cong, G.Z., Shao, J.J., Lin, T., Xie, Q.G., 2007. Genome sequencing and analysis of foot-and-mouth disease virus Asia1/YNBS/58 strain. Bing Du Xue Bao 23, 407–411.
Chareonsirisuthigul, T., Kalayanarooj, S., Ubol, S., 2007. Dengue virus (DENV) antibody-dependent enhancement of infection upregulates the production of anti-inflammatory cytokines, but suppresses anti-DENV free radical and pro-inflammatory cytokine production, in THP-1 cells. J Gen Virol 88, 365–375.
Cheng, I.C., Liang, S.M., Tu, W.J., Chen, C.M., Lai, S.Y., Cheng, Y.C., Lee, F., Huang, T.S., Jong, M.H., 2006. Study on the porcinophilic foot-and-mouth disease virus I. production and characterization of monoclonal antibodies against VP1. J Vet Med Sci 68, 859–864.
Christensen, L.S., Normann, P., Thykier-Nielsen, S., Sorensen, J.H., de Stricker, K., Rosenorn, S., 2005. Analysis of the epidemiological dynamics during the 1982-1983 epidemic of foot-and-mouth disease in Denmark based on molecular high-resolution strain identification. J Gen Virol 86, 2577–2584.
Chung, W.B., Liao, P.C., Chen, S.P., Yang, P.C., Lin, Y.L., Jong, M.H., Sheu, T.W., 2002. Optimization of foot-and-mouth disease vaccination protocols by surveillance of neutralization antibodies. Vaccine 20, 2665–2670.
Cottam, E.M., Haydon, D.T., Paton, D.J., Gloster, J., Wilesmith, J.W., Ferris, N.P., Hutchings, G.H., King, D.P., 2006. Molecular epidemiology of the foot-and-mouth disease virus outbreak in the United Kingdom in 2001. J Virol 80, 11274–11282.
Cottam, E.M., Wadsworth, J., Shaw, D.A.E., Rowlands, J., Goatley, L., Maan, S., Maan, N.S., Mertens, P.P.C., Ebert, K., Li, Y., 2008. Transmission Pathways of Foot-and-Mouth Disease Virus in the United Kingdom in 2007. PLoS Pathog 4 .
Dawe, P.S., Flanagan, F.O., Madekurozwa, R.L., Sorensen, K.J., Anderson, E.C., Foggin, C.M., Ferris, N.P., Knowles, N.J., 1994. Natural transmission of foot-and-mouth disease virus from African buffalo (Syncerus caffer) to cattle in a wildlife area of Zimbabwe. Vet Rec 134, 230–232.
de Freitas, R.B., Durigon, E.L., Oliveira Dde, S., Romano, C.M., de Freitas, M.R., Linhares Ada, C., Melo, F.L., Walshkeller, L., Barbosa, M.L., Huatuco, E.M., Holmes, E.C., Zanotto, P.M., 2007. The "pressure pan" evolution of human erythrovirus B19 in the Amazon, Brazil. Virology 369, 281–287.
DEFRA. Department for Environment, Food and Rural Affairs, UK- Foot and Mouth Disease. 2008. http://www.defra.gov.uk/animalh/diseases/fmd/default.htm.
del Rio Vilas, V.J., Guitian, J., Pfeiffer, D.U., Wilesmith, J.W., 2006. Analysis of data from the passive surveillance of scrapie in Great Britain between 1993 and 2002. Vet Rec 159, 799–804.
Domingo, E., Escarmis, C., Baranowski, E., Ruiz-Jarabo, C.M., Carrillo, E., Nunez, J.I., Sobrino, F., 2003. Evolution of foot-and-mouth disease virus. Virus Res 91, 47–63.
Domingo, E., Escarmis, C., Lazaro, E., Manrubia, S.C., 2005a. Quasispecies dynamics and RNA virus extinction. Virus Res 107, 129–139.
Domingo, E., Escarmis, C., Sevilla, N., Moya, A., Elena, S.F., Quer, J., Novella, I.S., Holland, J.J., 1996. Basic concepts in RNA virus evolution. FASEB J 10, 859–864.
Domingo, E., Gonzalez-Lopez, C., Pariente, N., Airaksinen, A., Escarmis, C., 2005b. Population dynamics of RNA viruses: the essential contribution of mutant spectra. Arch Virol Suppl 19, 59–71.
Domingo, E., Pariente, N., Airaksinen, A., Gonzalez-Lopez, C., Sierra, S., Herrera, M., Grande-Perez, A., Lowenstein, P.R., Manrubia, S.C., Lazaro, E., Escarmis, C., 2005c. Foot-and-mouth disease virus evolution: exploring pathways towards virus extinction. Curr Top Microbiol Immunol 288, 149–173.
Domingo, E., Ruiz-Jarabo, C.M., Sierra, S., Arias, A., Pariente, N., Baranowski, E., Escarmis, C., 2002. Emergence and selection of RNA virus variants: memory and extinction. Virus Res 82, 39–44.
Domingo, E., 2006. Quasispecies: Concepts and Implications for Virology. Springer, Berlin.
Donaldson, A.I., 1972. The influence of relative humidity on the aerosol stability of different strains of foot-and-mouth disease virus suspended in saliva. J Gen Virol 15, 25–33.
Donaldson, A.I., 1997. Risks of spreading foot and mouth disease through milk and dairy products. Rev Sci Tech 16, 117–124.
Donaldson, A.I., Gibson, C.F., Oliver, R., Hamblin, C., Kitching, R.P., 1987. Infection of cattle by airborne foot-and-mouth disease virus: minimal doses with O1 and SAT 2 strains. Res Vet Sci 43, 339–346.
Drake, J.W., 1993. Rates of spontaneous mutation among RNA viruses. Proc Natl Acad Sci U S A 90, 4171–4175.
Duarte, E.A., Novella, I.S., Weaver, S.C., Domingo, E., Wain-Hobson, S., Clarke, D.K., Moya, A., Elena, S.F., de la Torre, J.C., Holland, J.J., 1994. RNA virus quasispecies: significance for viral disease and epidemiology. Infect Agents Dis 3, 201–214.
Enami, M., Kohama, T., Sugiura, A., 1989. A measles virus subgenomic RNA: structure and generation mechanism. Virology 171, 427–433.
Enserink, M., 2007. Biosecurity. Reports blame animal health lab in foot-and-mouth whodunit. Science 317, 1486.
Escarmis, C., Lazaro, E., Manrubia, S.C., 2006. Population bottlenecks in quasispecies dynamics. Curr Top Microbiol Immunol 299, 141–170.
EUFMD, 2007. EUFMD—The European Commission for the Control of Foot-and-Mouth Disease. Report of the 37th Session of EUFMD, Rome 2007. Ref type: internet communication.
Fan, X., Zhu, J., Schadt, E.E., Liu, J.S., 2007. Statistical power of phylo-HMM for evolutionarily conserved element detection. BMC bioinform 8, 374.
Gibbens, J.C., Sharpe, C.E., Wilesmith, J.W., Mansley, L.M., Michalopoulou, E., Ryan, J.B., Hudson, M., 2001. Descriptive epidemiology of the 2001 foot-and-mouth disease epidemic in Great Brita: the first five months. Vet Rec 149, 729–743.
Gibbens, J.C., Wilesmith, J.W., 2002. Temporal and geographical distribution of cases of foot-and-mouth disease during the early weeks of the 2001 epidemic in Great Britain. Vet Rec 151, 407–412.
Gloster, J., Freshwater, A., Sellers, R.F., Alexandersen, S., 2005. Re-assessing the likelihood of airborne spread of foot-and-mouth disease at the start of the 1967-1968 UK foot-and-mouth disease epidemic. Epidemiol Infect 133, 767–783.
Goldman, N., 1993. Statistical tests of models of DNA substitution. J Mol Evol 36, 182–198.
Gonzalez-Lopez, C., Gomez-Mariano, G., Escarmis, C., Domingo, E., 2005. Invariant aphthovirus consensus nucleotide sequence in the transition to error catastrophe. Infect Genet Evol 5, 366–374.
Goodman, R.A., Buehler, J.W., 2002. Field epidemiology defined. In: Gregg, M.B., Dicker, R.C., Goodman, R.A. (Eds.), Field Epidemiology. Oxford University Press, pp. 3–7.
Grubman, M.J., Baxt, B., 2004. Foot-and-mouth disease. Clin Microbiol Rev 17, 465–493.
Gulbahar, M.Y., Davis, W.C., Guvenc, T., Yarim, M., Parlak, U., Kabak, Y.B., 2007. Myocarditis associated with foot-and-mouth disease virus type O in lambs. Vet Pathol 44, 589–599.
Hartnett, E., Adkin, A., Seaman, M., Cooper, J., Watson, E., Coburn, H., England, T., Marooney, C., Cox, A., Wooldridge, M., 2007. A quantitative assessment of the risks from illegally imported meat contaminated with foot and mouth disease virus to Great Britain. Risk Anal 27, 187–202.
Haydon, D.T., Bastos, A.D., Awadalla, P., 2004. Low linkage disequilibrium indicative of recombination in foot-and-mouth disease virus gene sequence alignments. J Gen Virol 85, 1095–1100.
Haydon, D.T., Woolhouse, M.E., 1998. Immune avoidance strategies in RNA viruses: fitness continuums arising from trade-offs between immunogenicity and antigenic variability. J Theor Biol 193, 601–612.
Holmes, E.C., 2007. Viral evolution in the genomic age. PLoS Biol 5, e278.
Holmes, E.C., Drummond, A.J., 2007. The evolutionary genetics of viral emergence. Curr Top Microbiol Immunol 315, 51–66.
Holzhauer, M., Verhoeff, J., van Wuijckhuise, L.A., 2001. The clinical symptoms of foot and mouth disease in the first confirmed cases at five different farms in the Netherlands. Tijdschr Diergeneeskd 126, 282–285.
Horsington, J., Zhang, Z., 2007. Analysis of foot-and-mouth disease virus replication using strand-specific quantitative RT-PCR. J Virol Methods 144, 149–155.
Hutber, A.M., Kitching, R.P., Conway, D.A., 1999. Predicting the level of herd infection for outbreaks of foot-and-mouth disease in vaccinated herds. Epidemiol Infect 122, 539–544.
Islam, M.A., Rahman, M.M., Adam, K.H., Marquardt, O., 2001. Epidemiological implications of the molecular characterization of foot-and-mouth disease virus isolated between 1996 and 2000 in Bangladesh. Virus genes 23, 203–210.
Jackson, A.L., O'Neill, H., Maree, F., Blignaut, B., Carrillo, C., Rodriguez, L., Haydon, D.T., 2007. Mosaic structure of foot-and-mouth disease virus genomes. J Gen Virol 88, 487–492.
Jarvis, T.C., Kirkegaard, K., 1992. Poliovirus RNA recombination: mechanistic studies in the absence of selection. EMBO J 11, 3135–3145.
Kirkegaard, K., Baltimore, D., 1986. The mechanism of RNA recombination in poliovirus. Cell 47, 433–443.
Kitching, R.P., 2005. Global epidemiology and prospects for control of foot-and-mouth disease. Curr Top Microbiol Immunol 288, 133–148.
Kitching, R.P., 2002. Clinical variation in foot and mouth disease: cattle. Rev Sci Tech 21, 499–504.
Kitching, R.P., Alexandersen, S., 2002. Clinical variation in foot and mouth disease: pigs. Rev Sci Tech 21, 513–518.
Klein, J., Hussain, M., Ahmad, M., Afzal, M., Alexandersen, S., 2008. Epidemiology of foot-and-mouth disease in Landhi Dairy Colony, Pakistan, the world largest Buffalo colony. Virol J 5, 53.
Klein, J., Hussain, M., Ahmad, M., Normann, P., Afzal, M., Alexandersen, S., 2007. Genetic characterisation of the recent foot-and-mouth disease virus subtype A/IRN/2005. Virol J 4, 122.
Klein, J., Parlak, U., Ozyoruk, F., Christensen, L.S., 2006. The molecular epidemiology of foot-and-mouth disease virus serotypes A and O from 1998 to 2004 in Turkey. BMC Vet Res 2, 35.
Knipe, D.M., Howley, P.M., Griffin, D., Lamb, R., Martin, M.A., 2006. Fields Virology. Lippincott Williams & Wilkins, p. 3312.
Knowles, N.J., Samuel, A.R., 2003. Molecular epidemiology of foot-and-mouth disease virus. Virus Res 91, 65–80.
Knowles, N.J., Samuel, A.R., Davies, P.R., Midgley, R.J., Valarcher, J.F., 2005. Pandemic strain of foot-and-mouth disease virus serotype O. Emerg Infect Dis 11, 1887–1893.
Konig, G.A., Palma, E.L., Maradei, E., Piccone, M.E., 2007. Molecular epidemiology of foot-and-mouth disease virus types A and O isolated in Argentina during the 2000-2002 epizootic. Vet Microbiol 124, 1–15.
Kuge, S., Kawamura, N., Nomoto, A., 1989. Genetic variation occurring on the genome of an in vitro insertion mutant of poliovirus type 1. J Virol 63, 1069–1075.

Lee, K.N., Oem, J.K., Park, J.H., Kim, S.M., Lee, S.Y., Tserendorj, S., Sodnomdarjaa, R., Joo, Y.S., Kim, H., 2009. Evidence of recombination in a new isolate of foot-and-mouth disease virus serotype Asia 1. Virus Res. 139, 117–121.

Lemey, P., Van Dooren, S., Van Laethem, K., Schrooten, Y., Derdelinckx, I., Goubau, P., Brun-Vezinet, F., Vaira, D., Vandamme, A.M., 2005a. Molecular testing of multiple HIV-1 transmissions in a criminal case. AIDS 19, 1649–1658.

Lemey, P., Van Dooren, S., Vandamme, A.M., 2005b. Evolutionary dynamics of human retroviruses investigated through full-genome scanning. Mol Biol Evol 22, 942–951.

Lemey, P., Vandamme, A.M., 2005. Exploring full-genome sequences for phylogenetic support of HIV-1 transmission events. AIDS 19, 1551–1552.

Loeffler F and Frosch P., (1897). Summarischer Bericht ++ber die Ergebnisse der Untersuchungen zur Erforschung der Maul und Klauenseuche. Centralbl Bakteriol.

Lunter, G., Hein, J., 2004. A nucleotide substitution model with nearest-neighbour interactions. Bioinformatics 20 (Suppl. 1), i216–i223.

Malirat, V., de Barros, J.J., Bergmann, I.E., Campos Rde, M., Neitzert, E., da Costa, E.V., da Silva, E.E., Falczuk, A.J., Pinheiro, D.S., de Vergara, N., Cirvera, J.L., Maradei, E., Di Landro, R., 2007. Phylogenetic analysis of foot-and-mouth disease virus type O re-emerging in free areas of South America. Virus Res 124, 22–28.

Mao, Q., Ray, S.C., Laeyendecker, O., Ticehurst, J.R., Strathdee, S.A., Vlahov, D., Thomas, D.L., 2001. Human immunodeficiency virus seroconversion and evolution of the hepatitis C virus quasispecies. J Virol 75, 3259–3267.

Martin, V., Perales, C., Abia, D., Ortiz, A.R., Domingo, E., Briones, C., 2006. Microarray-based identification of antigenic variants of foot-and-mouth disease virus: a bioinformatics quality assessment. BMC genomics 7, 117.

Martinez, M.A., Carrillo, C., Gonzalez-Candelas, F., Moya, A., Domingo, E., Sobrino, F., 1991. Fitness alteration of foot-and-mouth disease virus mutants: measurement of adaptability of viral quasispecies. J Virol 65, 3954–3957.

Martinez, M.A., Dopazo, J., Hernandez, J., Mateu, M.G., Sobrino, F., Domingo, E., Knowles, N.J., 1992. Evolution of the capsid protein genes of foot-and-mouth disease virus: antigenic variation without accumulation of amino acid substitutions over six decades. J Virol 66, 3557–3565.

Martinez, M.A., Verdaguer, N., Mateu, M.G., Domingo, E., 1997. Evolution subverting essentiality: dispensability of the cell attachment Arg-Gly-Asp motif in multiply passaged foot-and-mouth disease virus. Proc Natl Acad Sci U S A 94, 6798–6802.

Mason, P.W., Grubman, M.J., Baxt, B., 2003. Molecular basis of pathogenesis of FMDV. Virus Res 91, 9–32.

Mattion, N., Konig, G., Seki, C., Smitsaart, E., Maradei, E., Robiolo, B., Duffy, S., Leon, E., Piccone, M., Sadir, A., Bottini, R., Cosentino, B., Falczuk, A., Maresca, R., Periolo, O., Bellinzoni, R., Espinoza, A., Torre, J.L., Palma, E.L., 2004. Reintroduction of foot-and-mouth disease in Argentina: characterisation of the isolates and development of tools for the control and eradication of the disease. Vaccine 22, 4149–4162.

Meier, E., Harmison, G.G., Keene, J.D., Schubert, M., 1984. Sites of copy choice replication involved in generation of vesicular stomatitis virus defective-interfering particle RNAs. J Virol 51, 515–521.

Miralles, R., Moya, A., Elena, S.F., 1999. Effect of population patchiness and migration rates on the adaptation and divergence of vesicular stomatitis virus quasispecies populations. J Gen Virol 80 (Pt 8), 2051–2059.

Mohapatra, J.K., Sanyal, A., Hemadri, D., Tosh, C., Sabarinath, G.P., Manoj Kumar, R., Venkataramanan, R., Bandyopadhyay, S.K., 2004. Sequence variability in the structural protein-encoding region of foot-and-mouth disease virus serotype Asia1 field isolates. Res Vet Sci 77, 153–161.

Mohapatra, J.K., Sanyal, A., Hemadri, D., Tosh, C., Sabarinath, G.P., Venkataramanan, R., 2002. Sequence and phylogenetic analysis of the L and VP1 genes of foot-and-mouth disease virus serotype Asia1. Virus Res 87, 107–118.

Monaghan, P., Gold, S., Simpson, J., Zhang, Z., Weinreb, P.H., Violette, S.M., Alexandersen, S., Jackson, T., 2005. The alpha(v)beta6 integrin receptor for Foot-and-mouth disease virus is expressed constitutively on the epithelial cells targeted in cattle. J Gen Virol 86, 2769–2780.

Muthuchelvan, D., Venkataramanan, R., Hemadri, D., Sanyal, A., Tosh, C., 2001. Sequence analysis of recent Indian isolates of foot-and-mouth disease virus serotypes O, A and Asia 1 from clinical materials. Acta Virol 45, 159–167.

Nunez, J.I., Fusi, P., Borrego, B., Brocchi, E., Pacciarini, M.L., Sobrino, F., 2006. Genomic and antigenic characterization of viruses from the 1993 Italian foot-and-mouth disease outbreak. Arch Virol 151, 127–142.

O'Rourke, K.H., Williamson, J.G., 2002. From Malthus to Ohlin: Trade, Growth and Distribution Since 1500. Centre for Economic Policy Research, London, p. 36.

OIE. WAHID Interface - OIE World Animal Health Information Database. 2008. https://www.oie.int/wahis/content.php?page=home&sslcheck=true.

Paton D., 2006. Report of the annual meeting of EU national Foot-and-Mouth Disease Laboratories. Conference Proceeding.

Paton, D.J., de Clercq, K., Greiner, M., Dekker, A., Brocchi, E., Bergmann, I., Sammin, D.J., Gubbins, S., Parida, S., 2006. Application of non-structural protein antibody tests in substantiating freedom from foot-and-mouth disease virus infection after emergency vaccination of cattle. Vaccine 24, 6503–6512.

Penny, D., Lockhart, P.J., Steel, M.A., Hendy, M.D., 1994. The role of models in reconstructing evolutionary trees. In: Scotland, R.W. (Ed.), Models in Phylogenetic Reconstruction. Clarendon Press, Oxford, pp. 211–230.

Perez, A.M., Konig, G., Spath, E., Thurmond, M.C., 2008. Variation in the VP1 gene of foot-and-mouth disease virus serotype A associated with epidemiological characteristics of outbreaks in the 2001 epizootic in Argentina. J Vet Diagn Invest 20, 433–439.

Posada, D., 2001. The effect of branch length variation on the selection of models of molecular evolution. J Mol Evol 52, 434–444.

Posada, D., Crandall, K.A., 2001. Selecting the best-fit model of nucleotide substitution. Syst Biol 50, 580–601.

Pro MED m., 2007. PRO/AH> Foot & mouth disease (type A) (03)—Jordan, Middle East. Archive Number 20070129.0380. 29-1-2007.

Rott, R., Siddell, S., 1998. One hundred years of animal virology. J Gen Virol 79 (Pt 11), 2871–2874.

Rzhetsky, A., Nei, M., 1995. Tests of applicability of several substitution models for DNA sequence data. Mol Biol Evol 12, 131–151.

Sa-Carvalho, D., Rieder, E., Baxt, B., Rodarte, R., Tanuri, A., Mason, P.W., 1997. Tissue culture adaptation of foot-and-mouth disease virus selects viruses that bind to heparin and are attenuated in cattle. J Virol 71, 5115–5123.

Saffron, C.M., Park, J.H., Dale, B.E., Voice, T.C., 2006. Kinetics of contaminant desorption from soil: comparison of model formulations using the Akaike information criterion. Environ Sci Technol 40, 7662–7667.

Sahle, M., Venter, E.H., Dwarka, R.M., Vosloo, W., 2004. Molecular epidemiology of serotype O foot-and-mouth disease virus isolated from cattle in Ethiopia between 1979-2001. Onderstepoort J Vet Res 71, 129–138.

Salemi, M., Vandamme, A.M., Desmyter, J., Casoli, C., Bertazzoni, U., 1999. The origin and evolution of human T-cell lymphotropic virus type II (HTLV-II) and the relationship with its replication strategy. Gene 234, 11–21.

Salt, J.S., 1993. The carrier state in foot and mouth disease—an immunological review. Br Vet J 149, 207–223.

Sangare, O., Bastos, A.D., Venter, E.H., Vosloo, W., 2004. A first molecular epidemiological study of SAT-2 type foot-and-mouth disease viruses in West Africa. Epidemiol Infect 132, 525–532.

Sanyal, A., Gurumurthy, C.B., Venkataramanan, R., Hemadri, D., Tosh, C., 2003. Antigenic characterization of foot-and-mouth disease virus serotype Asia1 field isolates using polyclonal and monoclonal antibodies. Vet Microbiol 93, 1–11.

Sanyal, A., Hemadri, D., Tosh, C., Bandyopadhyay, S.K., 2004a. Emergence of a novel subgroup within the widely circulating lineage of foot-and-mouth disease virus serotype Asia 1 in India. Res Vet Sci 76, 151–156.

Sanyal, A., Mohapatra, J.K., Kumar, R.M., Biswas, S., Hemadri, D., Tosh, C., Sabarinath, G.P., Gupta, S.K., Mittal, M., Giridharan, P., Bandyopadhyay, S.K., 2004b. Complete nucleotide sequence analysis of a vaccine strain and a field isolate of foot-and-mouth disease virus serotype Asia1 with an insertion in VP1 genomic region. Acta Virol 48, 159–166.

Seghouane, A.K., Amari, S., 2007. The AIC criterion and symmetrizing the Kullback-Leibler divergence. IEEE Trans Neural Networks 18, 97–106.

Sellers, R., Gloster, J., 2008. Foot-and-mouth disease: a review of intranasal infection of cattle, sheep and pigs. Vet J 177 (2), 159–168.

Simmonds, P., 2006. Recombination and selection in the evolution of picornaviruses and other Mammalian positive-stranded RNA viruses. J Virol 80, 11124–11140.

Sitia, G., Cella, D., De Mitri, M.S., Novati, R., Foppa, C.U., Perackis, K., Bianchi, C., Lazzarin, A., Morsica, G., 2001. Evolution of the E2 region of hepatitis C virus in an infant infected by mother-to-infant transmission. J Med Virol 64, 476–481.

Sole, R.V., Sardanyes, J., Diez, J., Mas, A., 2006. Information catastrophe in RNA viruses through replication thresholds. J Theor Biol 240, 353–359.

Sutmoller, P., Casas, O.R., 2002. Unapparent foot and mouth disease infection (subclinical infections and carriers): implications for control. Rev Sci Tech 21, 519–529.

Sutmoller, P., McVicar, J.W., Cottral, G.E., 1968. The epizootiological importance of foot-and-mouth disease carriers.I. Experimentally produced foot-and-mouth disease carriers in susceptible and immune cattle. Arch Gesamte Virusforsch 23, 227–235.

Thalmann, G., Nockler, A., 2001. Occurrence of foot and mouth disease—a historical survey. Dtsch Tierarztl Wochenschr 108, 484–494.

Thiermann A., 2008. OIE Terrestrial Animal Health Code. OIE. 2008. http://www.oie.int/eng/normes/Mcode/en_sommaire.htm.

Thompson, D., Muriel, P., Russell, D., Osborne, P., Bromley, A., Rowland, M., Creigh-Tyte, S., Brown, C., 2002. Economic costs of the foot and mouth disease outbreak in the United Kingdom in 2001. Rev Sci Tech 21, 675–687.

Thompson, R.C.A., 2000. Molecular Epidemiology of Infectious Diseases. Arnold, London, p. 326.

Tosh, C., Hemadri, D., Sanyal, A., 2002a. Evidence of recombination in the capsid-coding region of type A foot-and-mouth disease virus. J Gen Virol 83, 2455–2460.

Tosh, C., Sanyal, A., Hemadri, D., Venkataramanan, R., 2002b. Phylogenetic analysis of serotype A foot-and-mouth disease virus isolated in India between 1977 and 2000. Arch Virol 147, 493–513.

Valarcher, J.F., Knowles, N.J., Ferris, N.P., Paton, D.J., Zakharov, V., Sherbakov, A., Shang, Y.J., Liu, Z.X., Liu, X.T., Sanyal, A., Hemadri, D., Tosh, C., Rasool, T.J., 2005. Recent spread of FMD virus serotype Asia 1. Vet Rec 157, 30.

Van Brussel, M., Salemi, M., Liu, H.F., Goubau, P., Desmyter, J., Vandamme, A.M., 1999. The discovery of two new divergent STLVs has implications for the evolution and epidemiology of HTLVs. Rev Med Virol 9, 155–170.

Vandamme, A.M., Bertazzoni, U., Salemi, M., 2000. Evolutionary strategies of human T-cell lymphotropic virus type II. Gene 261, 171–180.

Vandamme, A.M., Salemi, M., Desmyter, J., 1998. The simian origins of the pathogenic human T-cell lymphotropic virus type I. Trends Microbiol 6, 477–483.

Vercauteren, J., Vandamme, A.M., 2006. Algorithms for the interpretation of HIV-1 genotypic drug resistance information. Antiviral Res 71, 335–342.

Villaverde, A., Martinez, M.A., Sobrino, F., Dopazo, J., Moya, A., Domingo, E., 1991. Fixation of mutations at the VP1 gene of foot-and-mouth disease virus. Can quasispecies define a transient molecular clock? Gene 103, 147–153.

Waldmann D, Kobe K, and Pyl G., (1937). Die aktive Immunisierung des Rindes gegen Maul-und Klausenseuche. Zentralbl Bakteriol.
Waldmann O and Pape J., (1920). Die kuenstliche Uebertragung der Maul-und Klauenseuche auf das Meerschweinchen. Berl Tierarztl Wochenschr.
Wijnker, J.J., Haas, B., Berends, B.R., 2007. Removal of foot-and-mouth disease virus infectivity in salted natural casings by minor adaptation of standardized industrial procedures. Int J Food Microbiol 115, 214–219.
Wright, W.C., 1930. Hieronymi Fracastorii De Contagione et Contagiosis Morbis et Eorum Curatione. Putnams sons, New York and London.
Yadin, H., Brenner, J., Chai, D., Oved, Z., Hadany, Y., Kusak, A., Haimovich, M., 2007. The NSP immune response of vaccinated animals after in-field exposure to FMDV. Vaccine 25 (49), 8298–8305.
Yang, Z., 2002. Likelihood and Bayes estimation of ancestral population sizes in hominoids using data from multiple loci. Genetics 162, 1811–1823.