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Epidemiology of Equine Influenza Viruses

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Abstract

The equine influenza virus (EIV) is a major pathogen of respiratory diseases in horses, donkeys and mules. Equine influenza (EI) is characterized by a very rapid spread and remains a disease with high economic stakes for the equine industry. A large-scale outbreak caused by equine influenza virus of the H3N8 subtype has occurred in each decade since an H3N8 was first isolated from horses in 1963. Each epidemic, and some minor outbreaks, has influenced equine influenza surveillance and vaccination policies in the world. The use of the molecular tools is of a high interest in epidemiology. The interest of the association of these techniques and the classical epidemiological analyses will be illustrated by taking the example of equine influenza viruses. The determination and the comparison of the nucleotide sequences allow to characterize the virus strains more precisely than the classical methods and are useful to analyze the evolution of the equine influenza viruses. These methods are also useful to select the relevant strains that will be used in the vaccines. The possible reasons for the infection of horses despite intensive vaccination are currently being investigated and may shed new light on the epidemiology of equine influenza.

Keywords: equine influenza virus, epidemiology, pathogen, vaccination, vaccine strains selection

1. Introduction

Equine influenza (EI) is an important equine respiratory pathogen and a high-priority disease for the equine industry globally. It is highly contagious and spreads rapidly in horse population by direct contact; clinical signs associated with the infection are characterized by pyrexia, dyspnoea, dry hacking cough and serous nasal discharge that can become mucopurulent in the case of secondary bacterial infections [1]. The causative agent, equine influenza virus (EIV), has a global distribution; it is endemic in many countries and there are occasional incursions in

Japan, South Africa and Hong Kong, with only Australia, New Zealand and Iceland being considered free.

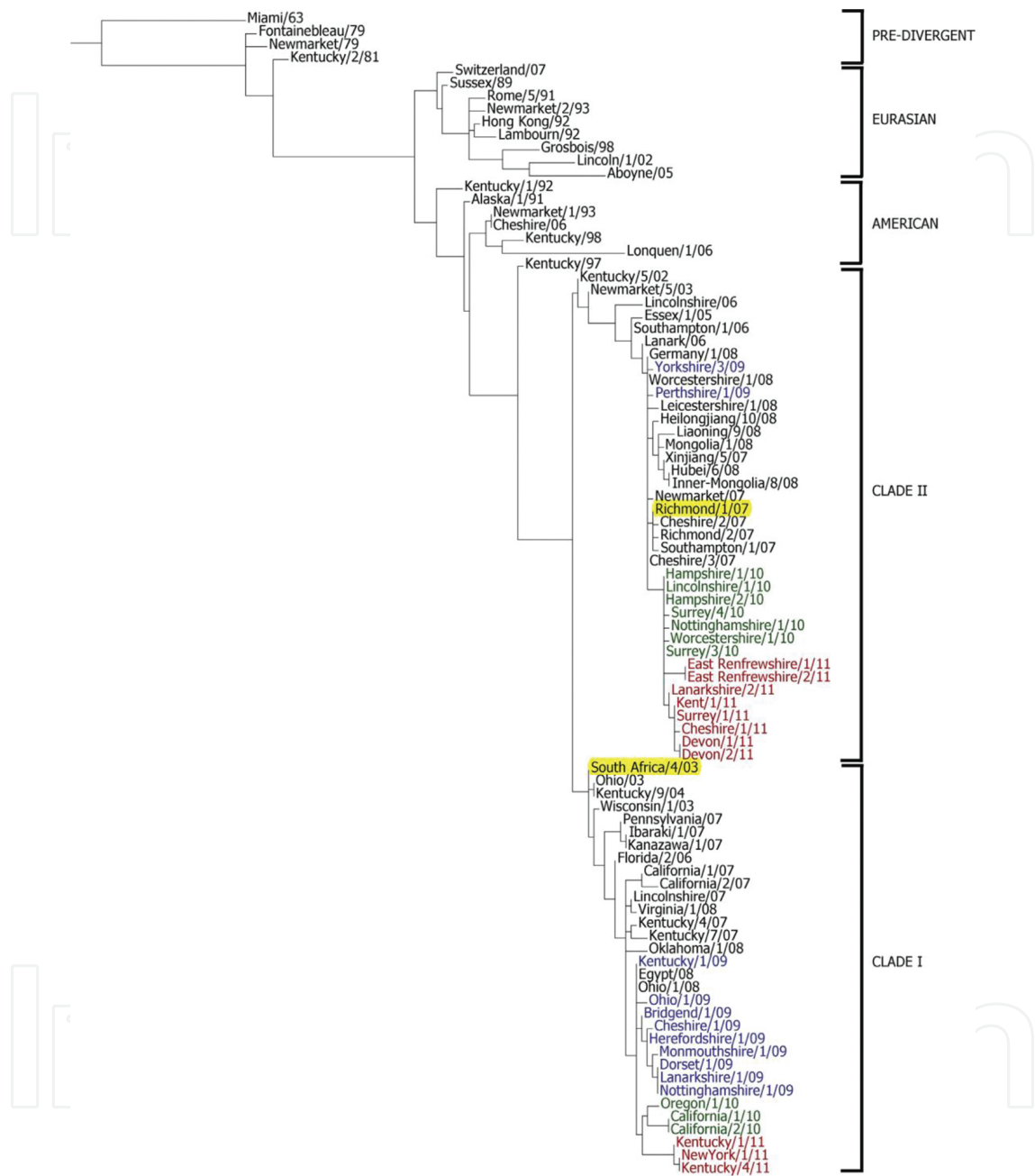


Figure 1. Phylogenetic analysis of the HA1 nucleotide sequences encoded by 90 EIV, subtype H3N8 isolated since 1963 and prototype strains of the different lineages and clades. Sequences are coloured by date of isolation for the years 2011 (red), 2010 (green) and 2009 (blue), with older strains in black. Current OIE recommended vaccine strains are highlighted in yellow [1].

EIV is belonging to the family of the *Orthomyxoviridae*, genus *Influenzavirus*, type A and is a major cause of respiratory diseases in horses. Only two antigenic subtypes of EIV (H7N7 and H3N8) have been isolated from horses, although highly pathogenic avian influenza virus

(H5N1) was isolated from donkeys in Egypt [2]. The equine H7N7 virus first isolated in Prague (Czechoslovakia) in 1956 [3] and has not been isolated in horses since 1979 [4], but serological evidence for its circulation in unvaccinated horses has been recorded at the end of the 1980s in India [5] and at the beginning of the 1990s in Croatia and USA [6, 7]. Since then, the equine H3N8 virus, first isolated in 1963 after an important outbreak in Miami (Florida, USA) [8], has persisted [9, 10] and only has been isolated from sick horses [11–15]. Phylogenetic studies have shown that H3N8 virus evolved in the late 1980s, into the American and the Eurasian lineages [16]. The Eurasian lineage strains, were almost exclusively isolated from horses in Europe and Asia, represented by Newmarket/2/93, continue to form a single clade, but have rarely been isolated in recent years [17]. The American lineage strains, were predominantly isolated from horses on the continent of America, further evolved into three sublineages, South American, Kentucky and Florida [18]. The original American lineage strains, represented by Newmarket/1/93 and Kentucky/1994, have not been completely superseded, with isolations of strains from this clade in the United Kingdom [17] and Chile [19] in 2006. The evolution of the Florida sublineage resulted in the emergence of two groups of viruses that differ in their HA sequences referred as Clade 1 viruses that have been isolated in North America since 2003 (e.g. Ohio/2003) and are distinct from the Florida Clade 2 strains that spread to Europe (Newmarket/5/03) [17]. Clade 1 viruses predominate on the American continent; nevertheless, they have caused large outbreaks in Africa, Asia, Australia, Europe and South America [20–27]. Similarly, Clade 2 viruses predominate in Europe but also have been isolated in Asia and North Africa [15, 28–32]. The phylogenetic analysis points to sporadic incursions of virus from North America into Europe and other regions, as happened around 1993 and 2003, followed by a period of more localized divergent evolution (**Figure 1**).

The use of the molecular tools is of a high interest in epidemiology. The interest of the association of these techniques and the classical epidemiological analyses will be illustrated by considering the example of equine influenza viruses. The determination and the comparison of the nucleotide sequences allow to characterize the virus strains more precisely than the classical methods and are useful to analyze the evolution of the equine influenza viruses. These methods are also useful to select the relevant strains that will be used in the vaccines. The possible reasons for the infection of horses despite intensive vaccination are currently being investigated and may shed new light on the epidemiology of equine influenza [33].

Influenza is a classic example of a (re-)emerging infection. Vaccines against influenza have been used in man since the 1940s [34] and became available for use in horses 20 years later. However, the existence of a reservoir of virus in aquatic birds and the highly variable nature of the virus mean that influenza defies worldwide eradication. The prevention and control of influenza are closely related measures of vaccination and livestock management. Vaccination is to date the most average usual to limit the spread of the virus in the horse population. Vaccines against equine influenza must contain subtypes and, inside thereof, the antigenic variants circulating in the horse population. Every year, the expert surveillance panel (ESP) of the World Organization for Animal Health (OIE) recommends influenza virus strains to be contained equine vaccines. The fact that H7N7 viruses and Eurasian H3N8 viruses are no longer required, current vaccines should include the antigenic variants of viruses representing

each of Clades 1 and 2 of the Florida sublineage. The Clade 1 is represented by A/equine/South Africa/4/2003-like or A/equine/Ohio/2003-like viruses. The Clade 2 is represented by A/equine/Richmond/1/2007-like viruses.

2. Epidemiology

2.1. Incubation period

EI is characterized by an incubation period of 5 days a maximum and an infective period of 14 days. An incubation period of 2–3 days has been observed in susceptible horse populations during severe epidemics in the field. In naive horses, the incubation period can be less than 24 h [35] and virus excretion may persist for 7–10 days [36]. Most shedding occurs in the early stages of clinical disease when coughing is most pronounced. In partially immune horses showing no clinical signs or mild clinical signs, virus shedding may occur.

2.2. Interspecies transmission of equine influenza viruses

There are three types of influenza viruses: A, B and C, but only the first has a very high propensity to crossing species barrier, the two others being found almost exclusively in humans. Influenza A viruses met in several species including birds, humans, swine, horses, marine mammals and dogs. Only a restricted number of sub-type combinations have become established in mammalian species (H7N7 and H3N8 in horses; H1N1, H3N2 and H2N2 in humans) [37]. Recently, two distinct lineages (H17N10 and H18N11) of influenza A virus have been derived from bats. This discovery provided novel insights into the origin and evolution of influenza A viruses beyond the predominant hypothesis of waterfowls/shorebirds as the primary natural reservoir.

The equine influenza virus infects horses and other equids (such as donkeys, mules and zebras) can, but rarely affects other species (such as dogs) [38]. Studies have shown that the H3N8 sub-type was introduced into horses a long time ago and the lack of exchange of virus genes between the equine viruses and viruses from other species [39] led to the suggestion that horses may be a 'dead-end' host. However, in Florida (US) at the beginning of 2004, equine influenza virus has been associated with outbreaks of respiratory disease in dogs (primarily but not exclusively, greyhounds) in North America, quarry hounds in England and dogs on premises with horses affected by influenza in Australia in 2007 [40–44]. Interspecies transmission of equine influenza virus to dogs upon close contact with experimentally infected horses was demonstrated [45]. To date, there is no documented evidence on the transmission of equine influenza virus from dogs to horses [46].

During 2004–2006 swine influenza surveillance in central China, two equine H3N8 influenza viruses were isolated from pigs [47]. Pigs have both sialic acid (SA) α 2-3 galactose and α 2-6 galactose containing receptors on cell surfaces. However, in vivo infection experiments on mini-pigs demonstrated that equine influenza virus failed to induce pyrexia, appreciable histopathological lesions or virus shedding [1]. The H3 HA has broad pathogenic potential but

analysis of the HA genes of influenza A viruses suggests that the equine and canine H3 have evolved separately to the H3 of avian, human and swine viruses [48].

It is generally accepted that there is a correlation between receptor binding characteristics and host specificity of equine influenza viruses. For influenza viruses to enter host cells, the HA glycoprotein must bind to sialic acid receptors on the cell surface. Viruses isolated from wild aquatic birds bind strongly to SA in a 2,3-linkage (SA 2,3). The same linkage is recognised by equine influenza virus and is the predominant linkage found on cells lining the equine upper respiratory tract. In contrast, human-adapted influenza viruses recognise and bind SA 2,6 receptors, and these are the receptors that predominate in the human respiratory tract [37]. Virus shedding and seroconversions were recorded in human volunteers inoculated with equine influenza virus [49] but although the potential for such transmission is demonstrable, there is no evidence that horses are reservoirs of virus for humans.

It is equally possible that a new influenza sub-type could emerge in horses from the avian reservoir. Although it did not replace the current equine H3N8 virus that has been circulating in horses for many years [39], cross-species transmission of avian H3N8 influenza virus into horses occurred in Jilin Province in China during 1989. The genetic analysis of the strain responsible of this outbreak (A/equine 2/Jilin 89) indicated was more closely related to avian influenza viruses than to other equine H3N8 influenza viruses [50, 51]. This strain (A/equine 2/Jilin 89) did not appear to persist in the horse population after 1990 or to spread beyond China to other countries. This transient re-emergence of the H3N8 subtype rather than any other may reflect the fact that this sub-type is commonly isolated from the avian reservoir [52]. More recently, avian H5N1 has been associated with respiratory disease in donkeys in Egypt [2]. This detection described a new subtype of highly contagious avian influenza virus as an equine infectious agent, and raises questions about the role of donkey in the spread of H5N1 virus to birds, humans and other mammals including equines.

2.3. Spread and transmission of equine influenza viruses

Influenza is primarily a seasonal disease usually occurring in epidemic form, often rampant in waves, followed by periods of relative calm. EIV is highly contagious and is primarily spread by the respiratory route through direct contact between infectious and susceptible horses in close proximity. In unvaccinated, susceptible horses, the short incubation period and persistent coughing which releases large amounts of virus into the environment contribute to the rapid spread of the infection. Personnel and fomites also contribute to virus spread. In the absence of release of horses from the quarantine station, it was concluded that the virus escaped on the person, clothing or equipment of a groom, veterinarian, farrier or someone else who had contact with the infected horses and left the station without implementing adequate biosecurity measures. The contaminated vehicles were implicated in the spread of the virus [20, 53]. Severe outbreaks of equine influenza occur in unimmunized populations of horses or when a new strain infects a vaccinated population. In a susceptible group of horses, morbidity can be as high as 100%. Horses stabled under intensive conditions are at risk from a build-up of infective virus in the common airspace. The global distribution of the EIV is associated with increased movement of horses participating in competitions or for breeding or sale. In the first

outbreak of equine influenza in Australia in 2007, the initial spread of the virus in the general horse population, then spread to the Thoroughbred population, it was estimated that over 75,000 horses had been infected. In the Japanese outbreak, in the same year, the reverse situation pertained, the initial outbreaks were in racehorses and the virus then spread to the non-Thoroughbred population. In the second confirmed outbreak of respiratory disease in Algeria in 2011 since 1972, the disease occurred in a variety of locations and stud farms among Thoroughbred and non-Thoroughbred horse populations. Around 900 horses have been affected during this outbreak which led to race cancellation in the whole country for 2 months [15]. During the outbreak in Uruguay in 2012, which affected over 2000 horses, race meetings were cancelled for several weeks and movement of horses out of the country was prohibited. Equine influenza outbreaks also resulted in the cancellation of equestrian events in Brazil [27].

2.4. Mortality to EIV

Mortality is very rarely associated with equine influenza but a small number of fatalities have been reported in young foals from non-vaccinated mares; thus, inadequate passive transfer of antibodies, due to poor-quality colostrum or inadequate intake, is likely to be a major factor. All mares should be vaccinated adequately to ensure that there are sufficient maternally derived antibodies in colostrum [54, 55]. Deaths of those foals as a result of acutely viral pneumonia, and in affected donkeys and horses that are not adequately rested. In northeastern China in 1989, a mortality rate of up to 20% in some herds was associated with a large outbreak of equine influenza. More than 40 horses died during an outbreak affecting over 74,000 horses in Mongolia in 2011 [32]. Disconcertingly, several foal deaths were also reported during EI outbreaks in France during 2012 [56].

2.5. Factors influencing transmission

Although equine influenza virus spread is frequently explosive in naïve populations, the majority of outbreaks in endemic populations are contained with limited spread between premises. Outbreaks are often associated with the introduction of new horses to premises [17], and seronegative horses are frequently the index cases [57]. Although the index cases may not be the source of the virus, they act to amplify the virus and serve as a source of infection to other horses in the cohort. The severity of the disease depends on the immune status of the horse (naïve, partially immunized or immunosuppressive), on the infecting viral dose, virulence of the virus strain and to the inoculation route. However, antigenic variants can give rise to large-scale disease epidemics such as occurred in 1979–1981 in Europe and in North America [58, 59]. Mismatch between vaccine and infecting strains requires higher levels of antibodies to prevent infection and significantly increases the risk of an outbreak at the population level [60, 61]. Introduction of subclinical affected vaccinated horses in a susceptible population is also a major contributing factor to influenza outbreaks, in South Africa in 1986, India in 1987, Europe in 1989, Croatia in 2004, Italy in 2005 and also suspected in Australia in 2007. In general, young horses, horses with low serum antibody titres and those that are highly mobile and mix with large groups of horses are considered most at risk [15, 62]. However, in the 2003 outbreak in Newmarket, 2-year-old horses were less susceptible than older horses

despite having accounted for any differences in antibody levels [63]. Finally, a few studies demonstrated that the sex as a risk factor for influenza infection.

2.6. Survival and persistence of EIV

The equine influenza virus has a lipid envelope and does not survive for long outside the horse. It is fragile and easily inactivated by exposure to ultraviolet light for 30 min, by heating at 50°C for 30 min, by ether and by acid (pH 3). Exposure to sunlight for 15 min at 15°C also inactivates the virus. The virus will not survive long in the environment in conditions of high humidity [64].

The virus can however survive on skin, fabrics and the surfaces of contaminated equipment for some time. The periods of survival are shorter in conditions of higher humidity. Studies have also shown that the virus may be transferred from stainless steel surfaces to hands and from paper tissues to hands.

Equine influenza is a self-limiting disease and the virus does not persist in recovered horses. It is thought that influenza persists in endemic populations by low-grade circulation with occasional small outbreaks [65]. In countries where equine influenza appears not to be endemic and quarantine measures are implemented, there is no evidence of long-term persistence following sporadic incursions. In Australia in 2007, the disease was eradicated within 4 months following the implementation of an extensive control programme [66].

No information is available about the persistence of EI virus in horse carcasses. Virus could be expected to be present in the carcasses of animals that die during the viraemic phase of infection.

3. Conclusion

Equine influenza A H3N8 viruses continue to cause serious diseases in horses despite control measures, including quarantine and vaccination, and the international spread of the virus occurs during exchanges and participation horses in competitions. Moreover, monitoring antigenic drift and emergence of new strains that allow the production of effective vaccines is critical. Finally, the vaccination of horses by modern and effective vaccines will be considered to be a new weapon to control this disease.

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