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Role of evolutionary epidemiology in the determination of the risk factors associated with some equine viral diseases

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Abstract

The evolutionary epidemiology is crucial as it does not only help in tracking the origin, spreading, prediction, and control of viruses but also explains the failure causes of some vaccines and serological diagnostic tools. To keep animal welfare, it is essential to raise awareness of the multiple risk factors associated with the different epidemics. Arthropod-borne viruses like African horse sickness virus (AHSV) and equine infectious anaemia virus (EIAV) are related to vectors multiplication. Accordingly, their seasonal occurrence was attributed to the environmental climatic conditions. While equine influenza virus (EIV) and equine herpes virus (EHV) were found to occur in winter and spring (foaling seasons), respectively. The management risk factors resulted in the occurrence and reactivation of latently infected cases. The RNA viruses are characterized by genetic assortment which results in increasing pathogenicity, and failure of the used vaccines. The EHVs able to establish infection in different host tissues adding to their immune evasion strategies. Most of the diseases occurred at the age over 2 years although the EIAV takes long time to appear. The hard work of males and other stress factors render them more liable for infection with equine viral arteritis (EVA), EIAV, and EHV. Genetically, some breeds of horses were at risk of AHSV, EVA, and EHV infection. Most of the donkeys, mules, and zebra develop subclinical forms that magnifies their role in the epidemiological situation. Different phenomena like overwintering in AHSV, hard work in EIV, virus hidden nature and latency in EHV should be more analysed.

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Introduction

Horses have great economic importance. So, any infectious threat happens not only affects the endemic areas but also affects other regions at risk of epidemics from importation. Emerging viral diseases outbreaks have grown rapidly in the recent years and a great impact on human life was recorded (1,2). Tran's boundary animal diseases have a great potentiality to threaten food security, through serious loss of animals, and increasing poverty levels. Due to the lack of adequate resources, surveillance does not cover these infectious diseases, and therefore the movement of pathogens in animals and the environment is likely to be seriously underestimated (3,4).

Using serological methods in diagnosis of the different microorganisms is very common due to its availability and easiness (5,6). Molecular detection and phylogeny were not only used to determine positive and negative cases, but it also becomes essential in monitoring the source of infection, spreading, and prevalence, of the different pathogens (7-10). Therefore, the sound of "evolutionary epidemiology" becomes as clear as it also investigates the impact of vaccination on the evolution of pathogen's virulence, the emergence of new infectious diseases and whole-genome analysis (11). The role of phylogenetic analysis was developed to assist in the determination of the pathogen's sources and its geographical distribution patterns. Recently, many viruses passed over its origin places (12,13). Different

risk factors including environmental, and managemental ones adding to those related to the host and causative agents were found to modulate the occurrence and spreading of equine viruses (14).

Different infectious diseases are only exclusive to the *Equidae* family, and they have a tremendous economic impact on the equine industry. However, some viruses may cross the species barrier and affect humans, representing an imminent risk to public health (15). African horse sickness virus (AHSV), equine influenza virus (EIV), equine viral arteritis (EVA), equine infectious anaemia virus (EIAV), and equine herpesvirus (EHV) which are listed in the OIE Terrestrial Animal Health Code are the most important ones and should be notified (16). So, the aim of the current review was highlighting the role of molecular epidemiology in realizing the different aspects of these diseases and the understanding of their related risk factors.

Evolutionary epidemiology

Molecular epidemiological studies were carried out to monitor the spreading, prevalence, and genetic lineages of the different pathogens between the countries (17). Also, phylogeny could be used for typing and characterisation of the insect vector, it helped in providing information about genes associated with pathogen transmission or midge reproduction (18). Accordingly, the role of phylogenetic analysis was evolved to help in detecting the origin of virus's evolutions and their relation to geographical distribution, recent phylogenetic analyses of many viruses demonstrated their overlap in their geographic regions (19). On the same side, the field of evolutionary epidemiology becomes so important as it is not only focusing on analyses of multivariate datasets that encompass genetic and phenotypic data but also correlates with geographic and ecological information, which helps in the prediction and control of infectious diseases (12).

Role in classification and variant's identification

Recently, the molecular techniques were widely used to characterise and classify the different viruses. Molecular identification of the EIV revealed the presence of two recognized subtypes namely H7N7 (subtype 1) and the prototype H3N8 (subtype 2) which was isolated in 1963 and named A/eq/Miami/63 that predominantly circulates till now, it has two antigenic variants namely Eurasian and American lineages (20). According to the Open Reading Frames 5 (ORF5), all EVA isolates have 85 to 99% nucleotide identity and are characterised into 2 major clades; the North American group which was divided into clades 1 and 2 and the European one which was divided into two subgroups 1, and 2 (21). Sequence analysis of different EIAV field isolates revealed identification of more than 80 % with each comprising a separate clade, suggesting their evolving independently since diverging from a common ancestor. On the other side, phylogeny based on gag gene sequence revealed presence of 13 clades from just 23 samples which explains the complex epidemiological situation of this virus, adding to the inability to develop an efficient vaccine (22). Analysis of virus isolates from 3 French districts confirmed their clustering together suggesting a common origin whereas districts were 50 km apart and the collected isolates were different from European strains described before (23). Recently, the Brazilian genome sequences of EIAV showed 75-88 % nucleotide identity with other field strains, such as EIAV Liaoning, Wyoming, belonging to Ireland, and Italy respectively. This high genetic variability was attributed to a long time since disease entrance and not all positive animals were euthanized which allowed mutation, maintenance, and amplification of the virus over the years (24). Phylogenetic study about the current circulating EIAV strains in America revealed that all isolates shared around 77-84 % identity with genetic diversity exists and comprised a single monophyletic group completely different from the Asian ones (25). Regarding the 7 EHV Egyptian isolates detected in 2017, they were 95.7 to 100% identical and similar to European abort-genic isolates with some mutations in nucleotide sequences especially in Egypt/ EHV- 1/Cairo/ 3K and Egypt/ EHV-1/Cairo/ 12L isolates. The effect of these amino acid substitutions on the pathogenesis of the strains needs further investigation (26).

Determination of the geographic distribution

The origin of many outbreaks was determined using phylogeny. Analysis of the recent AHSV outbreak in Thailand (THA2020/01 isolate) showed its classification under serotype 1 and was genetically related to South African strains. This was the first occurrence of AHVS in South East Asia and of serotype 1 outside of Africa (27). Passive surveillance and phylogenetic analysis of Namibian strains isolated in the AHSV outbreaks between 2006 and 2013 revealed their presence in the same clusters of those circulating in South Africa in recent years (28). Phylogenetic assessment of previous EIV outbreaks declared its continuous occurrence passed over its original geographic barriers. Evaluation of the EIV outbreaks in West and Central Africa in 2019 showed that the identified viruses belonged to clade 1 of the Florida sublineage and were very similar to viruses identified in Nigeria in the same year and similar to strains in recent outbreaks in South America than those in Europe (29). Phylogeny of the obtained EVA Serbian strains declared its relatedness to isolates from the neighbouring Hungary adding to UK and USA. These strains were recently clustered together to form a new distinct group of viruses originating in the central European region (30). A recent study explained that Hungary was the origin for EIAV disease occurrence in different directions, starting with its neighbouring European countries. Also, a spread occurred first toward the Americas (∼1950), followed by a dispersion through Asian countries

(~2000) which might be due to the intensive movement of animals between these continents (12). The high nucleotide identity between most of the isolated strains within the same country may be due to an intra-nuclear self-proofing system of the herpes DNA. Therefore, genetic diversity among them is low (31). Many of the recent research focused on studying the functional characterization of many genes at the cellular level to explore their role in the pathogenesis and the potentiality of created mutants to develop vaccines (7).

Genetic changes and re-assortments

A big analytical study on AHSV field isolates obtained during the last 100 years confirmed genetic recombination through re-assortment with the vaccinal strains (32). On the same side, genomic analysis of strains isolated from South Africa 1961-2014 cleared that many outbreaks were due to virulent reverting of AHSV type 1 live attenuated vaccine (LAV). This result showed that despite the beneficial protective effect of the LAV, but it places susceptible horses at risk for AHSV (33). EVA genetic changes were determined at a rate of approximately 10 nucleotide substitutions per 1 kb every year in the carriers. These changes resulted in the emergence of novel genotypic and phenotypic variants (34). The sequence of the new two isolated EIAV strains in France showed no relatedness between them and both are different than those recorded in Europe confirming their belonging to 2 different phylogenetic groups (35).

New strains evolving, vaccine, and diagnostics failure

Genetic analysis of the obtained isolates helped in explaining some diseases' occurrence as in the Chinese EIV outbreak in 2017. The virus was found to belong to the Florida sub lineage clade 2. Amino acid sequence comparison with the vaccine strain showed substitutions at different antigenic regions (7). In Morocco, Phylogeny of one of the EIV obtained isolate revealed its relation to A/equine/Fontainebleau/1/1979 and exhibited 12 substitutions in NS1 protein when compared with the reference A/equine/Miami/1963 strain (36). The EIAV showed antigenic drift occurrence with the formation of "immunologic escape mutant" after each febrile episode usually in the envelope encoding genes. Sequence analysis of the P26 encoding gene revealed its high conservation between the different isolates. Accordingly, most of the commercially available serologic tests depend on this antigen (22). Although a recent study determined amino acid changes in the p26 protein and its molecular modelling cleared surface amino acid alterations in some epitopes which give an explanation for the failure of some serological tools used for detection antibodies against this protein (24). A molecular epidemiology study in Uruguay explained that a single nucleotide polymorphism (A2254/G2254) in the EHV genome region of open reading frame 30 which results in an amino acid variation (N752/D752) is significantly associated with the neuropath genic potential of naturally occurring strains (26).

Risk factors: Factors related to the environment

The spreading of arbovirus diseases including AHSV is affected by several factors including, host migration, climatic conditions mainly temperature, and humidity that control vector like *Culicoides* midges' multiplications (Figure 1). so, the most AHSV sero-conversions cases happened during the rainy season (37). The highest rates of AHSV sero-positivity were detected in the wet areas near the irrigation projects in Sudan while the low sero-positivity rate was recorded in other areas having dry climate conditions and high variations in temperatures (17). In South Africa, the temperature was the important factor that influenced the AHSV outbreaks occurrence, while in Namibia, humidity and precipitation were the main drivers. A large number of diseased cases occurred at temperatures of 20-22°C and relative humidity between 50-70%. Temperature is so important not only for vector multiplication in nature, but it also affects the rate of the AHSV replication within the insect mainly through the activity of the viral RNA polymerase (37). Regarding the EIAV, the painful vector bites induce defensive behaviour and interrupt blood feeding, this makes *tabanids* is the favourable vector in comparing to other insects because of its mouthpart anatomy, it is essential to have the blood meal from the infected host without interruption followed by feeding another horse within a short time (38). Animals in wet lands especially after flooding were at high risk to be infected with the EIAV in comparing with those in dry areas, this may be attributed to the presence of *tabanids* (*Tabanus* sp.) in a high number in the swamps (39). Presence of wind especially with high speed originated from the infected areas increased the risk for EIV infection for horses downwind e.g., Australian outbreak in 2007. Also, multiple epidemiological analyses of several outbreaks declared the role of humidity and temperature in EIV transmission. Especially that colder temperatures and dry conditions were found to be correlated with the disease incidence (20).

Risk factors: Factors related to management behaviour

Human's actions are an important component in the risk chain. Different outbreaks of the EIV disease were recorded previously in the UK, and Dubai due to the absence of strict precautions and inadequate quarantine measures to facilitate the international movement of horses for racing, competition, and breeding purposes (40). In 1992, an EIV outbreak occurred in thoroughbred horses in Hong Kong. It originated after the importation of horses 1 month before any clinical sign's appearance. It resulted in the delaying of seven race meetings for a period of 1 month (41). Some country's laws allowed the horse owners to keep EIAV seropositive animals in the endemic areas without

euthanization which hardens the disease control due to the uncontrolled movement (42). The higher epidemiological survey of the outbreak in France in 2009 declared that the three premises that had the outbreak were related to organizing events like the markets, shows, and using of shared or nearby pastures (23). Equine instruments were found to keep EHV-1 viable for 2 days and virus particles were successfully obtained with persistence decreasing over time (Figure 1). so, sharing of these utilities should be prohibited during any outbreak to facilities disease control (43). Any stress factors could result in reactivation of latent cases with subsequent horizontal spreading, but a recent study indicated that transportation alone is not enough stress factor to ease reactivation (38).

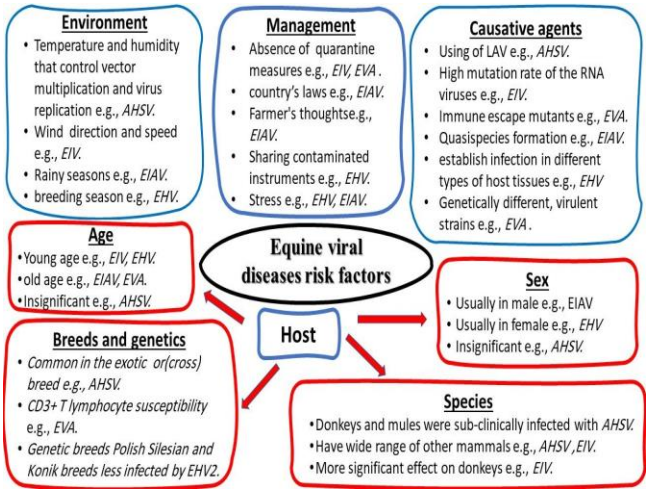

Figure 1: Risk factors associated with occurrence of equine viral diseases.

Risk factors: Factors related to the causative agent

Using of live attenuated vaccines helped in the persistence of many viruses. Many studies proved genetic recombination through re-assortment with the vaccinal strains (32), or due to virulent reverting of AHSV type 1 live attenuated vaccine (LAV) (33). This theory was strongly confirmed by the finding that Sequence analysis of the isolated AHSV-9 strain in Gambia was100% identical to Seg-2 of the used reference vaccinal strain (44). Tissue culture attenuation to produce AHSV vaccines was expected to diminish its ability to multiplication in the natural vector. The high mutation rate of the RNA viruses including the EIV resulted in evolutionary change mainly antigenic drift, shift, and sometimes recombination which could influence the host specificity and pathogenicity of newly generated viruses. Recently, there are nine substitutions in the sequences of HA of Brazilian EIV isolates in comparison to the vaccine strain (32). Unfortunately, vaccination only could help in decreasing morbidity and severity of clinical signs but did not prevent infection (41). Although the abort genic potentiality of different isolates was not adequately researched, the severity of the clinical response to infection, the difference in establishment of short- or long-term infertility clear this assumption (45). Many new variants recognized as *quasi* species were reported due to replication errors of the EIAV genome and frequent recombination take place between two copies of the genomic RNA (Figure 1). Also, virus virulence was found to be increased after multiple passages in vivo (38). Although the EHV-1 and EHV-4 viruses share a high degree of antigenic criteria and vaccines are affordable. The disease is ubiquitous all over the world due to the capability of the virus to establish infection in different types of host tissues adding to its immune evasion strategies (7). The neuro-pathogenic phenotype of EHV-1 could result from a single nucleotide substitution within ORF30 (26).

Factors related to the host: Age

Sudanese and Ethiopian studies cleared that; age had no relation to the percentage of AHSV positive cases (17). Also, Oura *et al.* (44) confirmed that the majority of the tested horses and donkeys were seropositive from any age over 2 years. Although Equine influenza usually occurs mainly in the age between 2- to 3-year-old in raced horses (46). However, during the 2003 EIV outbreak in the UK, fewer infected cases among younger horses in comparing with the older ones were recorded, despite their having similarly high levels of vaccinal antibody (47). A Brazilian sero-survey showed that, adult horses over 5 years have a high level of antibodies against the EIV 52% in comparison younger ones 38% (48). Many serological surveys revealed that most of the positive cases 34.21% were older than 11 years' old which proves that EVA could circulate for several years without detection (30). An increased number of EIAV seropositive cases was recorded in consistent with the age especially in older animals over 8 years. This is because of the nature of the virus adding to a longer time of exposure to potential transmission factors (39). The EHV-1 disease was more prevalent in young horses less than 3 years, but older horses are likely to be sub-clinically infected (26). Infection with EHV-2 and EHV-5 was common in young horses in comparing with the old ones, a different study cleared those horses > 5 years of age were at significant risk of getting EHV-1 infection in comparison with those < 1-year-old (2).

Factors related to the host: Sex

Many previous studies cleared the insignificant role of the sex as a risk factor correlated with the sero-prevalence of the AHSV (17). A Brazilian study declared that, sex had no significant effect on EIAV sero-prevalence. Although a previous study involved 3767 horses, males were at higher risk of infection than females (14.3% and 10.6%) respectively (39). Moreover, male horses are mainly used

as working animals more often than females, which means they are more exposed to viral infection adding to the stress and immunosuppression from the work nature (42). Although, some reports showed no significant association between sex and EHV-1 infection (31). But females were found to be significantly lower than males in getting the EHV-1 infection (7). While mares were 2.8 times more likely than male horses to be EHM cases, and other factors including physical condition, immune status were included. Pregnancy is a physiological status that was found to be a stress factor that could reactivate latent EHV1 carrier. Accordingly, pregnant mare's separation should be a regimen for abortion prevention. But Ata *et al.* (49), reported that seropositive pregnant mares were insignificantly lower than non-pregnant ones.

Factors related to the host: Breed and genetics

The exotic (cross) breed of horses was at risk of AHSV infection compared to the local breed in Sudan which may be attributed to their high susceptibility to insect's bites. Racehorses were 3 times more likely to be at risk in comparison with other drought ones. As the racing ones were usually Arabian horses that were imported from outside (17). An earlier experimental infection study in Nigeria confirmed that the imported breeds were highly susceptible to AHSV infection while the local breeds exhibited a high degree of resistance with mild clinical manifestation with complete recovery (50). There was a relation between the long-term persistence of EVA infection with the in vitro susceptibility of a subpopulation of $CD3^+$ T lymphocytes. So, stallions with the $CD3^+$ T lymphocyte susceptibility phenotype were at high risk of long-term persistency (51). A correlation between the EqCXCL16 gene and the establishment of carrier status was proved. Animals with one copy of the dominant allele (EqCXCL16Sa or EqCXCL16Sb) associated with in-vitro susceptibility of $CD3^+$ T lymphocytes to EVA infection are more likely to become long-term shedders in comparing with the (EqCXCL16R) resistant phenotype (21). In Serbia, horses used for breeding were found to be positive for EVA infection than other species (30). Also, the Friesian horses were more likely to shed EHV-4 than the European warm bloods. A recent study excluded the involvement of a recessive genetic factor in the susceptibility to develop this status. Also, there was no relation with genes on equine chromosome 6 as previously recorded (52).

Factors related to the host: Species

Most of the donkeys and mules were sub-clinically infected with AHSV but they can multiply and shed the virus. Accordingly, they have a significant role in the epidemiology of the disease. It was thought that the presence of Zebra animals is considered the natural reservoir for the virus in South Africa. A recent study proved that this risk was low, and a large number of zebras was needed for the long-term persistence (53). Although mortalities due to EIV infection are uncommon, the virus may have a great influence on the donkeys and colostrum-deprived foals that may be died (32). Introduction of horses that travel from a population to another one has been repeatedly shown to be the major risk factor for epidemics occurrence especially when it enters a large, previously unexposed herd (8). The EIV could have "host-jump" or "cross-species spread" causing extensive outbreaks of respiratory disease in other species. The new hosts could play a role in the epidemiology and persistence of the diseases (46). Although the interspecies transmission route is still unclear many reports declared transmission of EIV to dogs, and a Canine influenza in Australia occurred simultaneously with the 2007 EIV outbreak in horses (54). A strain of influenza was determined in camels in Mongolia was directly related to a circulating equine H3N8 strain, but horizontal transmission in camels was not detected (55). Serological assay in the USA showed that antibodies against EIV were detected in people regularly exposed to horses especially the smoker ones which may be due to oral contamination or because of a compromised immune system (56).

Factors related to the host: Latency and carrier status

It is a non-replicative, non-immunogenic stage and one of the main EHV-1 infection criteria, by which the genome is maintained in the trigeminal ganglia or in lymphoid tissues, without expression of structural genes and without production of infectious viruses (2,7). The latently infected cells are not recognised by the host immune system, these animals are the keys importance in the epidemiology of EHV-1 as they are a source of infectious virus to other susceptible animals and many sporadic cases of abortion and encephalomyelitis happened due to reactivation of the virus within the blood vessels of the pregnant uterus or the central nervous system (57). Detecting latent cases is crucial from the both epidemiological and disease-control aspects but this is a great challenge. The presence of antibodies in unvaccinated animals is an indicator of the previous infection. So, latency could be expected but latent infection cannot be precluded in horses that are sero-negative. Many reports exhibited the role of donkeys and mules as silent carriers in the face of a neurological EHV-1 outbreak among horses and should be considered in outbreak control strategies (58). The persistently infected animals are the key epidemiological challenge in the control and eradication of the EVA as they serve as a source of infection for all susceptible individuals. The virus was found to be in the ampulla and to a lesser extent other accessory sex glands of the stallion's reproductive tract. The carrier state was found to be androgen dependent. Furthermore, persistently infected stallions that are castrated stopped shedding the virus in semen, whereas those supplemented with testosterone after castration

continue to shed the virus (45). The presence of in apparent carriers is the real threat to disease persistence, as they remain a source of infection for other horses. It was one cause of the outbreak reoccurrence in horse schools in France in 2009 although they were suffering from the disease before in 2000 (23). There is a shortage of data about mule's natural infection and their epidemiological importance in the transmission. Some studies showed no difference between disease prevalence in the 2 host species (39,59,60).

Conclusion

The field of molecular epidemiology is so important in the characterisation of equine viruses adding to the detection of the new linages. Continuous updating of the sequence of circulating viruses is mandatory to develop an efficient vaccine and diagnostic tools. RNA viruses including AHSV, EIV, and EIAV are characterised by genetic changes either through recombination with the live attenuated vaccines strains and this was the main cause of vaccine and/ or diagnostic tools failure. Carriers and sub-clinically infected donkeys and mules could exhibit some clinical manifestations of diseases. So, their role in disease's circulation must not be excluded. Most of the epidemics were due to the importation of sub-clinically infected animals or mutation of the circulating local strains as in EIV. Management strategies that cause immunosuppression help in virus reactivation in the carriers.

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Conflict of interest

The authors of the current work declare that they have no conflicts of interest in this work.

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دور علم الأوبئة التطوري في تحديد عوامل الخطر المرتبطة ببعض الأمراض الفيروسية للخيول

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الخلاصة

يعد مجال علم الأوبئة التطوري أمرًا بالغ الأهمية لأنه لا يساعد فقط في تتبع أصل الأمراض الفيروسية للخيول والتنبؤ بها ومكافحتها، ولكنه يشرح أيضًا أسباب فشل بعض اللقاحات وأدوات التشخيص المصلي. لذلك للحفاظ على رفاهية الحيوان، من الضروري زيادة الوعي بعوامل الخطر المتعددة المرتبطة بالأوبئة المختلفة. وترتبط الفيروسات التي تولدها المفصليات مثل حمة مرض الخيول الأفريقي وحمة فقر الدم المعدي بتكاثر هذه النواقل. وعليه فإن الحدوث الموسمي لهذه الأمراض يعزى إلى الظروف المناخية البيئية. فقد وجد أن حمة الأنفلونزا الخيلي وحمة الهربس الخيلي يحدثان في فصلي الشتاء والربيع (موسم ولادة الأمهار) على التوالي. وتؤدى عوامل الخطر إلى حدوث وإعادة تنشيط الحالات المصابة بالعدوى الكامنة. حيث تتميز فيروسات الحمض النووي الريبوزى بإعادة التجميع الجيني مما يؤدي إلى زيادة الإمراضية وفشل اللقاحات المستخدمة. وفيروسات الهربس الخيلي قادرة على إنشاء عدوى في أنواع مختلفة من أنسجة العائل إضافة إلى استراتيجيات التهرب المناعي. حدثت معظم الأمراض في سن أكثر من عامين على الرغم من أن ظهور حمة فقر الدم المعدي يستغرق وقتًا طويلاً. فضلا عن ذلك فإن العمل الشاق للذكور وعوامل الإجهاد الأخرى يجعلهم أكثر عرضة للإصابة بالتهاب الشرايين الفيروسي للخيول وفقر الدم المعدي ومرض الهربس الخيلي. ووراثيا، كانت بعض سلالات الخيول معرضة لخطر الإصابة بعدوى مرض الخيول الأفريقي وفقر الدم المعدي ومرض الهربس الخيلي. وتأخذ العدوى على معظم الحمير والبغال والحمار الوحشي أشكالًا تحت السريرية والتي تزيد من دورها في الوضع الوبائي. لذلك يجب تحليل الظواهر المختلفة مثل شدة برودة الشتاء في مرض الخيول الأفريقي، والعمل الشاق في مرض فقر الدم المعدي، والطبيعة الخفية وكمون الفيروس في مرض الهربس الخيلي.