Clinical Commentary

Controlling EVA in the 21st century: ‘zero tolerance’ or ‘live and let live’?

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Introduction

At the time of writing in August 2007, when foot and mouth disease virus (FMDV) has apparently escaped from biologically secure research or vaccine production facilities to nearby cattle in the UK and bluetongue virus (BTV) continues to infect livestock in its second season after over-wintering in northern Europe, the importance of controlling infectious diseases of animals through measures such as ‘heightened surveillance’, ‘optimal biosecurity’ and ‘vaccination’ is firmly in the dual spotlights of scientific and public scrutiny.

Although they may not obviously or directly affect horses, these latest livestock disease outbreaks should act as an important alarm call to the equine veterinary and research communities for vigilance and preparedness to deal with equivalent situations in the equine species. To this end, since March 2007 the UK equine welfare charity, The Horse Trust, has been campaigning to raise awareness and develop contingency planning for the threat to the UK and Europe from African horse sickness virus, a highly fatal midge-borne infection of horses that is closely related to BTV.

At the same time as we have seen the re-emergence of these high profile outbreaks of infection by FMDV and BTV, the potentially economically and clinically important infectious disease equine viral arteritis (EVA) (Timoney and McCollum 1990) has been recognised since late June 2007 among non-Thoroughbred horses in France (International Collating Centre, Newmarket). At the time of writing 16 equine premises in Normandy had been identified with infection with equine arteritis virus (EAV), with many of the cases being clinically apparent and clear epidemiological links between most outbreaks identified. The EVA outbreak currently unfolding in France acts as a timely backdrop for this commentary, which in considering approaches to control of EVA hopes that, as with all outbreaks, lessons can be learned so that not only are diseases dealt with effectively when they occur but that they may actually be prevented through measured and affordable actions.

EVA epidemiology: necessary understanding for effective control

Before considering possible approaches to control of EVA it is worth refreshing on the salient epidemiological features of the disease as effective control of any infectious disease is only possible with as full an understanding of the way that it behaves in the population i.e. its epidemiology.

EVA can be transmitted either venereally from a stallion with infected semen through natural covering or artificial insemination (AI) or through the respiratory route through close contact between horses (Fig 1) (Timoney and McCollum 1985; 1993; Collins et al. 1987; Chirnside 1992; Timoney et al. 1992).

After initial infection, most animals excrete virus in all bodily secretions, including semen, nasal and ocular discharges, urine and faeces for up to 3 weeks (Chirnside 1992; Timoney et al. 1992; Timoney and McCollum 1993). After this time, the virus is cleared by the immune system, (apart from the accessory sex glands in stallions). Aborted fetuses are also a potentially important source of virus (Doll et al. 1957; Cole et al. 1986). All horses can be infected by the respiratory route and mares can also be infected by the venereal route by stallions shedding virus in their semen (natural covering and AI are both effective) (Timoney et al. 1986, 1987a,b, 1992). Respiratory spread of infection is not usually particularly efficient or rapid and usually requires some degree of direct contact, but spread between nursing mare and foal appears to be efficient (Wood et al. 1995).
In a stallion infected with EAV, after the initial 3 week period, the virus is cleared by the immune system from the horse’s organs, with the important exception of the accessory sex glands (Timoney et al. 1986, 1987a, b, 1992; Neu et al. 1988). In general, the length of time that a stallion will shed virus in its semen can be categorised as either i) short term (2–5 weeks), ii) medium term (3–8 months) or iii) long term (many years). The proportion of animals that fall into the different categories varies fairly widely between different scientific reports. The majority of animals seem to fall into categories i) or iii). The most widely accepted figure for category iii), the long-term shedders, is approximately 30% (Timoney et al. 1987a; Wood et al. 1995). Semen shedding of EAV in stallions is testosterone dependent and there are 2 main implications of this. Firstly, immature males generally do not become long-term semen shedders and secondly, castration of stallions invariably allows them to eliminate the virus.

Shedding stallions and chilled semen are the most common ways that infection spreads long distances and across international borders (Timoney and McCollum 1993). In the UK it has been recognised that importation of shedding stallions (or their semen) poses the biggest risk of EVA, as some stallions remain potentially infectious through their semen for many years (Wood et al. 1995; Newton et al. 1999)

Although respiratory spread of EAV infection contributes to infectious transmission in some outbreaks, infected horses are usually only potentially infectious to other animals for several weeks and close contact is usually required.
An important feature of EVA is that in a significant proportion of infections, animals do not show obvious clinical signs (so-called subclinical infections), although infected horses are still able to transmit the infection to other animals with which they are in contact (McCollum and Bryans 1973; Timoney and McCollum 1985). It is possibly that EVA is predominantly subclinical in some horse breeds that precipitates the attitude in some quarters that the need for control of EVA is unnecessary and financially unjustified.

Current approaches to control of EVA: the UK model

The annually updated Horserace Betting Levy Board Code of Practice (http://www.hblb.org.uk/sndFile.php?fileID=3) continues to be the practical means by which prevention of EVA is implemented in the UK and some other parts of Europe, which is done particularly, but not exclusively, by the Thoroughbred breeding industry. This is based on annual prebreeding serological screening of both stallions and mares and use of a killed vaccine (Artervac) in stallions only. This approach has shown its worth on at least 2 occasions when previously infected mares have been detected following subclinical outbreaks among Thoroughbreds in France in 2000 and Ireland in 2003 and highlights the importance of sero-surveillance to detect infected animals in the absence of clinical signs (Newton et al. 1999). This has subsequently led to heightened control measures among imported animals on some UK Thoroughbred stud farms.

In the event that EVA is confirmed, the Code of Practice recommends that the local Divisional Veterinary Manager of the Department for the Environment, Food and Rural Affairs (Defra) be immediately notified in accordance with The EVA Order 1995 (http://www.opsi.gov.uk/si/si1995/Uksi_19951755_en_1.htm). In addition, all movements and breeding is stopped, all cases and contacts are traced, sampled and isolated and all other horses on the affected premises are screened and grouped according to infectious status. It is also important that good communication exists between interested parties including premises that have received animals (and semen if relevant) from the infected stud, those that are due to send animals and the breeder’s association. Testing and screening should continue on all possible affected premises until the end of the outbreak, seropositive animals and pregnant mares should be isolated for 4 weeks after first sampling and stallions must have their shedding status investigated.

The most important aspect of control programmes after an outbreak of EVA has been diagnosed on a stud is to stop covering immediately. If a stallion is not infected, then attempts must be made to prevent infection of all stallions. If a stallion has already been infected, then it will be the most efficient means of maintaining the spread of the infection around the stud. The rates of infection on the index stud in the 1993 outbreak in the UK closely followed the rate of covering in the preceding week (Fig 2) (Wood et al. 1995).

All horse and semen movement should be stopped on and off the stud and recently departed animals should be traced, placed in isolation and tested. The control of outbreaks of EVA can be based on the fact that virus is most unlikely to be present in the horses (other than stallions) for more than 3 weeks after exposure. It is sometimes impossible to determine the precise day of infection during an outbreak. Thus, horses should be kept in isolation for at least 3 weeks after their first positive blood test. They then are likely to be free from infection. As EVA usually spreads poorly between animals via the respiratory route, it should be possible to stop the spread of infection around a stud once covering has ceased.

Use of vaccination in control of EVA

Vaccination strategies for EVA are based on use of formalin inactivated and live attenuated (also referred to as modified live) vaccines, with a geographical split in their use between Europe and Japan (inactivated) and North America (live attenuated) (Barquero et al. 2007). Some concern exists for both types of vaccines regarding absence of their ready differentiation from natural infection and as such future marker vaccines based on a range of technology such as subunits, DNA or viral vectors would be useful, especially if they provided rapid onset and long lasting immunity.

Following the outbreak in the UK in 1993, a formalin inactivated vaccine (Artervac) has been in use. In order to provide protection from the commercially devastating effects that long-term EAV shedding would incur, vaccination has almost exclusively been restricted to breeding stallions, with the majority of Thoroughbred stallions receiving vaccine. However, although an archive of data exists to demonstrate that the vaccine is capable of inducing long lasting neutralising antibody levels in animals receiving repeated booster vaccinations, no definitive direct evidence from its use in the field is available on which to assess its efficacy in preventing the establishment of the carrier state in infected stallions. As EAV infection has not been widely associated with abortion in Europe, no data are available as to the safety of this inactivated vaccine during pregnancy or its effectiveness in preventing EVA-related abortion. The decision not to adopt EAV vaccination among breeding mares, in which the carrier state does not occur, in combination with requirements for routine prebreeding serological screening has effectively provided a sentinel population in which on-going surveillance for EVA can be conducted. As described previously this has proved valuable on several occasions for alerting to new subclinical infections.

Sero-surveillance of stallions vaccinated using Artervac conducted at the Animal Health Trust (J. Cardwell, personal communication) demonstrates that to achieve and maintain levels of immunity required to protect against developing semen shedding, stallions require several boosters in addition to the 2 or 3 dose primary course (Fig 3). This indicates that many first season sires are probably inadequately protected against EVA infection by use of killed vaccine. This could be overcome by vaccination and subsequent boosting of.
potential stallions whilst they are still racing. This was particularly highlighted in the 2003 breeding season when there were problems with availability of Artervac in Europe. The consequence of this was that first season sires were left completely susceptible to EAV infection, whereas previously well vaccinated stallions had good levels of residual immunity as evidenced by high virus neutralisation antibody levels. The outbreak in Ireland resulted in infection of a first season sire, which did not subsequently shed virus in its semen.

It has been shown that virulent EAV can be attenuated by repeated passage through various different cell lines whilst at the same time retaining the viruses ability to stimulate long lasting immunity for several years following vaccination (Doll et al. 1968; McCollum et al. 1988). Minimal side effects including short lasting abnormal sperm morphology in stallions and mild fever have been reported for this live attenuated vaccine, although EAV can be recovered transiently from the blood and nasopharynx in some animals that receive the vaccine (Timoney et al. 1988; Timoney and McCollum 1993). The live attenuated vaccine protects against clinical disease and reduces viral shedding and animals in contact with and mares covered by vaccinated stallions are not infected by EAV (McKinnon et al. 1986; Timoney et al. 1996). However, the use of this vaccine has not been widely recommended in pregnant mares because occasional fetal infections have been described (Moore et al. 2003). It is this specific issue that is covered by an accompanying paper in this issue by Timoney et al. (2007) in their description of the inadvertent but ultimately non-detrimental administration of a live attenuated EAV vaccine to 5 pregnant mares in the last trimester of pregnancy. The authors make the observation that the same vaccine has been periodically used without adverse effect in pregnant mares in the face of EVA outbreaks on stud farms in the USA in the past 20 years. This small scale but detailed study provides some scientifically robust evidence to support the previous decisions that off-label use of the live attenuated vaccine in specific circumstances may be justified in pregnant mares.

Attitudes to control of EVA: a European dichotomy?

Attitudes to control of EVA within Europe could simplisticly be thought of as being polarised between those that effectively have ‘zero tolerance’ of it and therefore all reasonable measures are taken to maintain infection/disease freedom and those that do not recognise a clinical problem and are satisfied to ‘live and let live’. It is important to note, however, that such polarisation of views is not necessarily along national or regional lines but more likely represents different strata of the European equine industry. This complexity is probably best evidenced by the differences in level of EVA control adopted for example between the UK, with its statutory EVA Order and Thoroughbred predominance, and elsewhere in Europe where other breeds predominate that do not employ such powers. Closer examination shows that the Thoroughbred breeding industry across Europe vigorously adopts a Common Code of Practice for the disease, whereas other breeds do not. It may be argued that this difference in attitude is evidenced through the breed specific seroprevalence data from a cross sectional surveillance study conducted in the UK in the mid 1990s (Fig 4) (Newton et al. 1999).

Results show that the highest EAV seroprevalence (25%) was amongst Standardbred breeding animals, which was related to a particularly high prevalence (41%) in American-bred shedding stallions but did not apparently result in clinical signs of EVA. There was also an increased prevalence of EAV seropositivity in some nonindigenous breeds that were imported from mainland Europe. There was a very low level of seropositivity (<0.3%) among Thoroughbreds. The study demonstrated that 18 of 50 seropositive stallions that were identified in the UK in 1994 and 1995, and 5 of 9 confirmed EAV shedding stallions, were non-Thoroughbreds that originated from European Union countries. This has been supported in recent years in that several non-Thoroughbred stallions that have been transiting the UK during export from mainland Europe to destinations outside the European Union have been detected as positive for EAV during quarantine in England and this has invoked statutory powers of control through the EVA Order 2005.

Conclusions

Although EVA may remain subclinical it is capable of causing significant clinical and financial problems as has been seen in France during 2007.

- There are examples of statutory and voluntary measures for the effective control of EVA:
  - Voluntary measures such as those outlined in the HBLB Codes of Practice provide effective surveillance and early detection and may be considered to be preventive
  - Statutory measures such as those outlined in the UK’s EVA Order 1995 may be considered to be effective in implementing control of confirmed infection and/or disease.
  - Vaccination strategies for EVA are available based on inactivated or modified live vaccines.
  - Inactivated vaccines are used mainly in Europe and Japan and are targeted particularly at protecting stallions against becoming semen virus shedders
  - Modified live vaccines are used mainly in the USA and have been shown to protect against development of the carrier state in stallions.
  - Some data now exist to show in certain situations that the benefits of using modified live vaccines to protect pregnant mares against abortion are likely to outweigh the theoretical adverse risks.
  - Differences in attitudes as to the necessity for control of EVA still exist between different breeds and regions where different breeds predominate.
  - Outbreaks of clinically and financially significant EVA and constraints on national and international travel and trade may precipitate future changes in attitudes to control of EVA.
Manufacturer's address

1Fort Dodge Animal Health, Fort Dodge, Iowa, USA.

References


