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Review

The Past, Present and Future of Three-Day Sickness with Epidemiological Data

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A B S T R A C T

Three-day sickness, also known as Bovine Ephemeral Fever (BEF), is an arboviral-derived disease of cattle and water buffaloes progressing with acute, rapidly developing polyphasic fever and showing symptoms such as stiffness of muscle tissue and excessive salivation. While clinical findings generally continue between 1-3 days, it has importance due to a sudden and high decrease in milk yield in cows during lactation, infertility, loss of condition, treatment costs and sometimes serious economic losses due to death of sick animals. The possible spread mechanism is reported to be related to the inter-regional wind movement of *Culicoides*-type sandflies and various insect vectors and host feeding of these blood-fed vectors. The objective of this review is to provide information about the current situation of the three-day sickness in the light of current epidemiological data and to draw a perspective for the future.

Keywords: *Arbovirus, Bovine Ephemeral Fever, Culicoides.*

Epidemiyolojik Verilerle Üç Gün Hastalığının Dünü, Bugünü ve Geleceği

Ö Z E T

Üç gün hastalığı diğer adıyla Bovine Ephemeral Fever (BEF) hastalığı sığır ve mandaların akut, hızlı gelişen polifazik ateşle ilerleyen, kas dokusunun sertliği, aşırı salivasyon gibi bulgular gösteren arboviral kaynaklı bir hastalığıdır. Klinik bulgular genellikle 1-3 gün arasında sürerken, laktasyon döneminde bulunan ineklerde süt veriminin aniden ve yüksek oranda azalması, infertilizasyon, kondüsyon kaybı, tedavi masrafları ve bazen hastalanan hayvanların ölümü nedeniyle ciddi ekonomik kayıplara neden olması sebebiyle önem teşkil etmektedir. Muhtemel yayılım mekanizması *Culicoides* türü tatarcık ve çeşitli insekt vektörlerin bölgeler arası rüzgarla hareketi ve kan ile beslenen bu vektörlerin konakçı beslenmesi ile ilgili olduğu bildirilmektedir. Bu derlemenin amacı güncel epidemiyolojik veriler ışığında üç gün hastalığının günümüzdeki durumu hakkında bilgi vermek ve geleceğe dair perspektif çizmektir.

Anahtar kelimeler: *Arbovirus, Culicoides, Üç gün hastalığı.*

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Introduction

Three-day sickness is an acute, rapidly progressing arboviral-derived disease of cattle and buffalo characterized by polyphasic fever, excessive salivation, nasal and ocular discharge, and reluctance to move (St George 1988; Walker and Klement, 2015). While the clinical signs persist for a few days, the disease causes significant economic losses due to a sudden drop in milk production in lactating animals, infertility, loss of condition, treatment expenses, trade restrictions, and sometimes the death of affected animals (Tonbak et al., 2013; Trinidad et al., 2014; Oguzoglu et al., 2015).

The first detailed description of the disease was reported in Egypt in 1895. It was first described as "Bovine Dengue Fever" whose clinical findings were closer to the modern definition of BEF (St George, 1988). In 1907, an epidemic began in Zimbabwe. In this epidemic, the first experimental data regarding the transmission of the disease from the blood of cattle were reported (Bevan, 1907).

In 1967, the virus was isolated by Bianca Van Der Westhuizen through intracerebral inoculation in mice by obtaining the leukocyte-platelet fraction. The citrated blood samples taken by Bianca Van Der Westhuizen in 1958 were stored in dry ice, and in 1967, the leukocyte-platelet fraction was obtained and inoculated intracerebrally into mice, and the first isolation of the BEF virus was achieved. Virus isolation was also performed from cattle that were experimentally infected with these isolated viruses (Van der Westhuizen, 1967).

Etiology

Bovine fever ephemerovirus is a virus of the genus *Ephemerovirus*, which belongs to the subfamily *Alpharhabdovirinae* of the family *Rhabdoviridae* (Walker et al., 2022). *Bovine fever ephemerovirus*, which causes three-day sickness, is a single-stranded, enveloped and non-segmented negative-polarity RNA virus. *Ephemerovirus* genomes contain single-stranded and negative-polarity, non-segmented RNA ranging between 14.5 kb-16.1 kb. Virions are bullet shaped and the genome contains 5 structural and 6 non-structural proteins. There are 5 structural proteins as nucleoprotein (N), surface glycoprotein (G), RNA polymerase (L), Phosphoprotein (P) and Matrix protein (M) (Walker et al., 1991).

Epidemiology Transmission and Economics

Epidemiology

Bovine Ephemeral Fever emerges seasonally in tropical, subtropical and temperate regions of countries geographically located in Africa, Asia, Australia and the Middle East. To date, the disease has been reported in 46 countries (St George 1986; Walker and Klement, 2015). The disease has economic importance due to yield losses and deaths in fattening and dairy enterprises. Contrary to general information, the rate reported as 100% for morbidity differs. Although a low rate has been reported for mortality (1%), there are also data suggesting a higher rate (Walker et al., 2012; Pyasi et al., 2020). For instance, the mortality rate was reported to be lower than 1% in the first epidemic in Türkiye in 1986, and 15-20% in the epidemic in 2012 (Girgin et al., 1986; Tonbak et al., 2013). An average of 17% mortality was reported in Henan province of China in 2004, 2005 and 2011 (Zheng and Qiu, 2012).

In BEF infection, infected animals, asymptomatic carrier animals and insect vectors are the most important sources of infection (Akakpo, 2015). The geographical distribution and spread of BEF disease indicate vector-related diseases. The disease has been reported to be limited to the regions where insect vectors of the genus *Culicoides* are intense in farms in the countries where it is observed. It has also been reported that the disease usually starts after an intense rainy period and continues until summer or autumn months (Murray, 1970; George et al., 1977; Uren et al., 1987).

The analysis of the glycoprotein (G) gene, one of the structural proteins of the virus, led to the classification of the virus into South Africa, East Asia, Australia and the Middle East according to the isolation locations (Aziz-Boaron et al., 2012; Trinidad et al., 2014; Omar et al., 2020).

In 2020, when the last epidemic was seen in Türkiye, the provinces in the south of the country were affected. A study conducted on the envelope glycoprotein of the isolate obtained from this pandemic revealed that the isolate clustered phylogenetically in the Middle East region. It has been reported that this isolate represents a separate branch from isolates obtained during the outbreaks in 1986, 2008, and 2012. In the 2012 epidemic, it was reported that while East Asian and Middle Eastern strains were circulating in Türkiye, the 2020 isolate belonged only to the Middle East (Abayli et al., 2017; Alkan et al.,2017; Karayel-Hacioglu et al., 2021). Another finding regarding this isolate is its close similarities with the isolate obtained in India in 2018. The exact reason for this similarity cannot be explained; however, it is suggested that the geographical proximity of Middle Eastern countries to Türkiye enabled the spread of the disease between continents through vector translocation (Pyasi et al., 2020; Karayel-Hacioglu et al., 2021).

In the 2020 epidemic in Türkiye, 168 serum samples taken from BEFV suspected animals, 79 EDTA-treated blood and 2 spleen samples (Tokgoz et al., 2023) were examined in a study. While the positivity rate was determined as 69.04% in serologically examined serum, 64.20% positivity was reported in 81 samples examined molecularly. In this study conducted by (Tokgoz et al., 2023), it was determined that the phylogenetic analyses of the 2 isolates were consistent with the results of the study conducted by (Karayel-Hacioglu et al., 2021), and both isolates were in the same cluster (Tokgoz et al., 2023).

Transmission

It has been reported that direct or indirect contact has no role in the transmission of the disease. As a result of the data obtained from experimental infections in animals, it can be stated that the need for intravenous transmission of the virus in order for the infection to start, witnessing the infection from the beginning of spring until the autumn months and its geographical distribution (tropical, subtropical and temperate regions) prove the claim that the infection is transmitted through blood-fed insects (Mackerras et al., 1940; Coetzer and Tustin, 2004; Walker, 2005).

The virus has been isolated from many species of *Culicoides* and insects. These include *Culiocides imicola* in Zimbabwe and *C. coarctus*, C. *oxystoma* in Taiwan, *C. arakawae, Anopheles sinensis, Cx. tritaeniorhynchus*, *C. kingi* and *C. nivosis*, *C. bedfordi* and *C. pallidipennis* in Kenya, *C. punkticollis* in Turkmenistan, *C. brevitarsis*, *An. bancroftii, Culex, Uranotenia and Aedes* species of insects and sandflies in Australia (Davies and Walker, 1974; St George et al., 1976; Blackburn et al, 1985; Muller and Standfast, 1986; Cybinski and Muller, 1990; Lvov et al., 2015; Tzeng et al., 2023).

Simultaneous or recent disease notifications in distant regions are thought to be resulting from the transportation of vectors to the region with strong winds (Murray, 1970; Kirkland, 2002). A study conducted in Australia based on the meteorological data suggests that the winds cause BEF cases to spread in waves along a 800 km front and move 3000 km away from the region. This spreading model is supported by the fact that most animal movements are in the opposite direction to the movement in the relevant country (Murray, 1970; Newton and Wheatley, 1970). It is also argued that heavy precipitation, which promotes the emergence of large vector populations after a prolonged drought, precedes these epidemics (Walker and Klement, 2015).

Findings regarding the spread of vectors with wind are also present in BEF epidemics in Asia and the Middle East. The relationship of the BEF epidemic that started in Japan and Korea with the wind direction of a low-level airflow from China and the genetic similarity among the strains isolated from these countries were supported with evidence (Kato et al., 2009).

The fact that the isolates are clustered according to geographical regions suggests that there is another reason for the spread of the disease over long distances through animal transportation. In addition, several studies suggest that some isolates obtained from Egypt and Türkiye are phylogenetically clustered with isolates from the East Asian branch, not from the geographical regions of these countries (Aziz-Boaron et al., 2012; Trinidad et al., 2014; Oguzoglu et al., 2015). Although cattle were exported from China to the Middle East 1 year before the 2005 epidemic in Egypt, and cattle were not exported from Asia before the epidemic in Türkiye in 2012, transmission is thought to be due to neighbouring countries. Moreover, this isolate in Türkiye is thought to come through Africa by cattle transportation (Walker and Klement, 2015).

Economics

Although the low mortality of the disease and its improvement in terms of clinical findings within three days are underestimated by breeders, its economic effect is quite high. It has highly important economic effects for the industry due to serious losses in milk and meat production, its rapidly spreading character in herd, and the sequelae it causes in high yielding breeds, even if it shows improvement in terms of clinical findings. In this context, there is a study conducted with veterinarians offering service in the regions where the epidemic emerged in Türkiye in 2020 through a questionnaire on the economic effects of the disease. According to the results of this study, the cost of vaccination against infection in a herd of 50 animals was determined to be $8,10 per animal, and the cost of treatment for each unvaccinated animal was $20,2. In addition, it is stated that the cost increases to $85 depending on the milk yield lost in a dairy cow in addition to the treatment cost, and the unit cost per animal increases to $148 with the lost yield in addition to the treatment cost in livestock. It is stated that the loss is $5,381 in a dairy farm with 50 animals and $7,902 in a fattening farm. In addition, when the disease is seen as an epidemic, businesses need to spend an additional $138 in addition to all costs for fighting against insects (Ayvazoğlu and Demir, 2022).

A retrospective statistical study was conducted on the economic effects of the disease by examining the data reported by farms in the 2021 epidemic in Israel. In a study conducted on 30 dairy farms, culling rates and milk yield losses were examined. Considering the sequelae caused during infection and after healing of the loss per infected cow, the total milk yield loss was found to be $315, and it was estimated that it caused a loss of $123,000 in a herd of 300 animals due to milk yield lost during the first 40 days after infection. Depending on the culling chosen as one of the disease control methods, it was estimated that the economic loss would be $33,120 in a herd of 300 cows. When examined in terms of herd, it was estimated that the total loss of the same herd was $253,000 due to the loss of 110 cows in a herd of 700 animals, and the total loss of milk yield due to culling and death was estimated to be $275,000 (Lavon et al., 2023).

Clinical Findings

BEF disease is characterized by a sudden onset of fever in cattle and a tendency to recover quickly in uncomplicated cases. It is called “three-day sickness” because it usually shows significant improvement in animals within 3 days from the onset of the disease. The course of the disease usually begins with a sudden fever up to 41°C. Monophasic, biphasic or polyphasic fever can be seen in the disease (Kirkland, 2002).

The fever seen in the disease is usually biphasic and returns to normal levels within 1-1.5 days. Clinical findings of the disease in the first fever stage are milder than subsequent findings and may often go unnoticed. Loss of appetite, depression and behavioural abnormalities are observed 12 hours after the onset of the fever (St George, 1988). The clinical symptoms of the disease are mostly associated with secondary fever (Uren, 1989). The body temperature in the first phase is always lower than the next phase (Davis et al., 1984).

On the 2nd day of the disease, a high amount of salivation, ocular and nasal flows are observed in sick animals. Tremor may be seen in some animals, muscles may become stiff with an altered lameness, and unwillingness to move is observed in sick animals. Rumen function may stop, and constipation may develop accordingly. Animals showing symptom of paresis may be affected by dehydration due to high fever and excessive fluid loss if they remain shadowless and dehydrated in very hot weather (St George, 1988).

On the 3rd day of the disease, many animals start to stand up and feed. However, symptoms such as lameness and weakness may last for a few more days. Affected animals lose their strength rapidly, and it may take time to recover the lost weight. Abortion can be seen in approximately 5% of pregnant animals, especially in the 2-3 months of pregnancy (Uren et al., 1987). There is no evidence that disease-related venereal transmission or infection during pregnancy adversely affects the development of the foetus (Parsonson and Snowdon, 1974).

Immunity

Neutralizing antibodies that develop in infected animals were thought to be permanent (Mackerras et al., 1940). However, it has been reported that specific neutralizing antibodies can be detected in the blood for at least 422 days following infection in animals infected with the disease, and infected animals have been reported to be protected against the disease for at least 2 years (Spradbrow, 1975). In fact, the results of serological studies conducted in Taiwan between 2001 and 2013 and obtained from three major outbreaks in the country between these dates show that neutralizing antibody titers were at very low levels during the dates of BEF disease and that there is a significant relationship between outbreaks and herd immunity (Ting et al., 2014). Although it has been reported that antibodies obtained through colostrum protect the offspring, the fact that the disease is seen at certain intervals makes the protection with passive immunity insignificant (St George, 1986).

Vaccines

Vaccination has been reported to be the only effective method in the control of the BEF disease (Radostits et al., 2006). There is evidence that vaccines developed by using isolated BEF virus isolates from about half a century ago continue to be effective against strains still in circulation. The neutralization and sequence similarities between among strains isolated in different geographical regions also support this argument (Hsieh et al., 2005; Gao et al., 2017).

There are live, inactive, subunit and recombinant vaccines developed against the disease. Among all these vaccines, live attenuated vaccines have generally been reported to provide longer-lasting immunity (Radostits et al., 2006). Live, inactive and subunit vaccines are used in the field. Current vaccines are used in countries such as Australia, Japan, South Korea, China, Taiwan, Türkiye, Saudi Arabia, Israel and the Philippines. In Türkiye, there is a commercially available live attenuated vaccine and one experimental recombinant DNA vaccine developed in 2018 (Abaylı, 2018; Vetal, 2024). Although experimental and commercial vaccines have been developed in various formulations, there are few reports on their effectiveness in the field. For most of the vaccines, protective immunity seems to be a limited period of time, and due to this period, additional applications are recommended at 6-month or 1-year intervals (Walker and Klement, 2015).

Diagnosis

If the first cases of the disease are seen in regions where the disease has not been seen before, it is difficult to diagnose from the clinical findings. Furthermore, diagnosis may be difficult due to clinical findings and histories due to the presence of other diseases similar to the disease as well as its rapid onset and recovery. Symptoms such as sudden onset of fever, lameness and rapid recovery in fattening and dairy enterprises can help to diagnose the disease. (Akakpo, 2015).

However, the diagnosis should be confirmed by laboratory method due to insufficient data to make an overall estimate at times such as the presence of sporadic cases or the onset of the epidemic. For this purpose, blood and blood serum should be obtained. However, successful results are not always achieved due to difficulties such as the short viremia phase in sick animals and rapid transfer of blood samples to laboratories (Bakhshesh and Abdollahi, 2015).

Laboratory Diagnosis

Laboratory diagnosis is necessary to confirm the pre-diagnosis of the disease. For this purpose, the disease can be diagnosed virologically, molecularly and serologically from blood samples taken during the hyperthermic phase to detect the virus and specific antibodies. During the convalescent period, diagnosis can be made serologically from samples taken at that time (Akakpo, 2015).

Various molecular techniques have been developed to detect BEFV infections. These include Dot Blot, Traditional RT-PCR, RT-qPCR, RT-LAMP and LFD-RPA (Hsieh et al., 2005; Zheng et al., 2011; Zaghloul et al., 2012; Blasdell et al., 2013; Hou et al., 2018; Gao et al., 2020). Conventional RT-PCR is routinely used in real-time quantitative PCR BEFV detection (Hou et al., 2018).

Serological methods include the most commonly used methods in the diagnosis of BEF disease. Serological diagnosis aims to detect neutralizing antibodies by using viral neutralization tests, enzyme-linked immunosorbent assay (ELISA), immunoperoxidase (IP), immunofluorescence assay (IFA), dot blot hybridization and similar tests (Kirkland, 1992; Johal et al., 2008; Vorster and Mapham, 2012; Tonbak and Abaylı, 2016).

Treatment-Prevention-Control

Treatment

There is no effective treatment for the disease as in other viral diseases. However, by treating its symptoms, the disease is tried to be relieved. Resting, providing adequate shelter, feed and water to sick animals help the treatment since dehydration will be exacerbated in animals exposed to hot air. Moreover, animals raised with the pasture system move to meet their feed and water needs. This may adversely affect the course of the disease. Animals leaning on their sides should be rotated several times a day to prevent circulatory system disorders and muscle damage (Kirkland, 2002; Akakpo, 2015). When given daily during the incubation period, nonsteroidal anti-inflammatory drugs prevent the onset of clinical findings and can induce rapid recovery by relieving the symptoms after the onset of clinical disease (Uren et al., 1989).

The hypocalcaemia seen in the disease is thought to be due to hypersecretion of immunoreactive calcitonin or decreased circulating levels of vitamin D metabolites (Uren and Murphy, 1985).

Digestive disorders and increased salivation due to loss of the swallowing reflex prevent calcium absorption from the rumen (St George, 1992). Calcium borogluconate can be used in the treatment of hypocalcaemia, which is considered to be responsible for symptoms such as ruminal stasis, paresis and reflex loss. It is clear that further studies are required on the low milk production, which is presumably due to the high inflammatory response that occurs in the disease, and on the relationship between milk production and the hypocalcaemia presentation (St. George et al., 1986). In the post-infection period, animals should not be stressed for several days after clinical symptoms have subsided to ensure that biochemical functions return to normal (Coetzer and Tustin, 2004).

Prevention and Control

The use of disinfection methods in preventing the spread of the disease is relatively insignificant. The agent is rapidly inactivated in the secretions and carcass after the death of the animal. Since the disease is transmitted with vectors rather than direct or indirect contact, it is stated that the struggle should be against insects (Lvov et al., 2015). For this purpose, insecticides used in the struggle against insects are frequently preferred (Weetman et al., 2018). However, it is an important challenge to limit its effect due to the resistance to insecticides (Thomas, 2018). Quarantine measures may be beneficial in countries where the risk of spreading the bovine ephemeral fever virus from neighbouring countries is not high (Kirkland, 2002).

Future Perspective

It is clear that it is an arboviral disease due to the role of blood-fed insects and sandflies in the spread of the three-day sickness. Arboviral diseases are highly affected by ecological changes. Climate changes allow insects related to these diseases to expand and adapt to their habitats by causing them to multiply in areas where they have not been seen before. Due to deforestation caused by intense and unplanned urbanization, the nature of these insects is highly affected by reasons such as the intense contact among the habitats of different species, increasing trade between countries and socioeconomic factors that damage infrastructures (Mellor et al., 2000; Gould et al., 2006; Purse et al., 2015). Ecological changes and increasing average temperatures not only have a negative effect on insects, but also cause animals to become more susceptible to diseases due to weakening of the immune system (Lavon et al., 2023).

Although the disease has not been seen in Europe and the American continent, the risk of a sudden appearance of the disease is quite high, as in the case of the Bluetongue virus (BTV) and the Schmallenberg virus (SBV). The strong warming tendency of the climate in Europe and the change in this climate have caused the prolongation of the active periods of sandflies and increased their contact with the host by shortening their feeding and reproduction cycles. Accordingly, the transmission duration also increases. Virus detection made in common *Culicoides* species in diseases developing due to BTV and SBV is actually a striking example of how serious the risk is (Purse et al., 2005; Carpenter et al., 2009; De Regge et al., 2012; Hoffmann et al., 2012; Elbers et al., 2013). Since the animals in this region have not encountered the disease immunologically before and do not contain antibodies against the disease serologically, the result will be important for the industry if they infected with this disease (Lavon et al., 2023).

Considering the small body sizes of the *Culicoides*, which are associated with the disease, infective insects can be easily transported to overseas countries even with the effect of the wind, apart from the insect movement (Gale et al., 2015; Aguilar-Vega et al., 2019). Simultaneous or recent epidemics in distant regions in three-day sickness reports and isolate similarities in these epidemics also support this claim (Murray, 1970; Kirkland, 2002).

From an epidemiological perspective, surveillance, early warning systems and on-call animal practices will also be able to provide important information about arboviral infections for authorities, local officials and researchers. For this purpose, some practices applied in countries, where the disease is seen, may help in the struggle against the disease. In order to create a vector detection and early warning system in Türkiye, an early warning system is used by periodically scanning for many diseases, including BEFV, in insects with the light trap application applied in regions where the risk is high within the scope of the “Animal Disease Control Program”. In addition, there are antigen and antibody screening programs performed at regular intervals in sensitive areas (GKGM, 2023). Seronegative cattle, which are designated as sentinels under a program called "National Arbovirus Monitoring Program" in Australia, are periodically screened for various arboviral diseases, including BEFV. It provides importing countries with documentation of freedom from certain diseases and offers early warning capabilities to local producers regarding the onset and spread of the disease (Kirkland et al., 2016). The mentioned systems will be able to provide important information to local authorities regarding the examination of the movements of insects, the presence of existing pathogens and identification of threatened areas (ECDC, 2021).

Vaccines are an important part of the struggle against viral diseases. Vaccines have been developed in various formulations for use in the struggle against BEF (Walker, 2005). However, the low protection period of vaccines, the fact that the disease is seen every few years and requires repetition of the application, and the short-term immunity developed in the animals infected with the disease make the struggle difficult. Therefore, vaccines that provide long-term immunity are needed to obtain the desired results from vaccination practices which are indisputable in the struggle against the disease (Walker and Klement, 2015; Zheng et al., 2016).

As a result**,** vector identification in three-day sickness is an important stage of the struggle against the disease. It is important to perform this with more modern methods in order to eliminate the concerns caused by the insect struggle in terms of the environment and human health and to prevent the resistance to insecticides. There are many vaccines in various technologies and formulations developed to be used in the struggle against the disease. However, the protection duration of these vaccines is quite low considering that the disease is seen at intervals of several years due to the fact that the immunity that develops in infected and recovering animals does not protect animals for life. Accordingly, further researches should be conducted for vaccines that provide effective and long-term immunity to be used against the disease. Establishing effective surveillance and early warning systems will pave the way for more accurate and healthy information to be conveyed to local authorities and policy makers about the disease. Furthermore, the selection of these systems among the methods that can be applied in neighbouring countries, not in a single country, will allow regional struggle for diseases transmitted by insects.

Conflict of Interest

The authors declare no conflict of interests.

References

Aguilar-Vega, C., Fernández-Carrión, E., & Sánchez-Vizcaíno, J. M. (2019). The possible route of introduction of bluetongue virus serotype 3 into Sicily by windborne transportation of infected Culicoides spp. *Transboundary and Emerging Diseases*, *66*(4), 1665-1673.https://doi.org/10.1111/tbed.13201

Abayli, H., Tonbak, S., Azkur, A. K., & Bulut, H. (2017). Complete genome analysis of highly pathogenic bovine ephemeral fever virus isolated in Turkey in 2012. *Archives of Virology*, *162*, 3233-3238 https://doi.org/10.1007/s00705-017-3470-6

Abayli, H. (2018). Üç gün hastaliği virusu türkiye izolatinin tüm genom sekanslanmasi ve bu virusa karşi dna aşisi geliştirilmesi, [Doktora Tezi, Fırat Üniversitesi]. https://acikbilim.yok.gov.tr/handle/20.500.12812/403212

Akakpo A. J. (2015). Three-day fever. *Revue Scientifique Et Technique International Office Of Epizootics)*, *34*(2), 533–532.

Alkan, F., Albayrak, H., Timurkan, M. Ö., Ozan, E., & Coskun, N., (2017). Assessment of the molecular epidemiology of bovine ephemeral fever in Turkey. *Veterinarski Arhiv* , vol.87, no.6, 665-675. https://doi.org/10.24099/vet.arhiv.160711

Ayvazoğlu, C., & Demir, P. A. (2022). Bovine Ephemeral Fever in Turkey and its Economic Effect. *Van Veterinary Journal*, *33*(3), 71-75. https://doi.org/10.36483/vanvetj.1141040

Aziz-Boaron, O., Klausner, Z., Hasoksuz, M., Shenkar, J., Gafni, O., Gelman, B., David, D., & Klement, E. (2012). Circulation of bovine ephemeral fever in the Middle East--strong evidence for transmission by winds and animal transport. *Veterinary Microbiology*, *158*(3-4), 300–307. https://doi.org/10.1016/j.vetmic.2012.03.003

Bakhshesh, M., & Abdollahi, D. (2015). Bovine Ephemeral Fever in Iran: Diagnosis, isolation and molecular characterization. *Journal of Arthropod-Borne Diseases*, *9*(2), 195–203.

Bevan, L. E. (1907). Preliminary report on the so-called "stiffsickness" or "three-day-sickness" of cattle in Rhodesia. *Journal of Comparative Pathology and Therapeutics*, *20*, 104-113.

Blackburn, N.K., Searle, L., & Phelps, R. (1985). Viruses isolated from Culicoides (Diptera: Ceratopogonidae) caught at the veterinary research farm, Mazowe, Zimbabwe. *Journal of the Entomological Society of Southern Africa*, *48*(2), 331-336.

Blasdell, K. R., Adams, M. M., Davis, S. S., Walsh, S. J., Aziz-Boaron, O., Klement, E., Tesh, R. B., & Walker, P. J. (2013). A reverse-transcription PCR method for detecting all known ephemeroviruses in clinical samples. *Journal of virological methods*, *191*(2), 128–135. https://doi.org/10.1016/j.jviromet.2013.04.011

Carpenter, S., Wilson, A., & Mellor, P. S. (2009). Culicoides and the emergence of bluetongue virus in northern Europe. *Trends in microbiology*, *17*(4), 172–178. https://doi.org/10.1016/j.tim.2009.01.001

Coetzer J. A. W. & Tustin R. C. (2004). *Infectious diseases of livestock* (2nd ed.). Oxford University Press. .p: 1183-1194

Cybinski, D. H., & Muller, M. J. (1990). Isolation of Arboviruses From Cattle and Insects at 2 Sentinel Sites in Queensland, Australia, 1979-85. *Australian Journal of Zoology*, *38*(1), 25-32. https://doi.org/10.1071/zo9900025

Davies, F. G., & Walker, A. R. (1974). The isolation of ephemeral fever virus from cattle and Culicoides midges in Kenya. *The Veterinary Record*, *95*(3), 63–64. https://doi.org/10.1136/vr.95.3.63

Davis, S. S., Gibson, D. S., & Clark, R. (1984). The effect of bovine ephemeral fever on milk production. *Australian Veterinary Journal*, *61*(4), 128. https://doi.org/10.1111/j.1751-0813.1984.tb07211.x

De Regge, N., Deblauwe, I., De Deken, R., Vantieghem, P., Madder, M., Geysen, D., Smeets, F., Losson, B., van den Berg, T., & Cay, A. B. (2012). Detection of Schmallenberg virus in different Culicoides spp. by real-time RT-PCR. *Transboundary and Emerging Diseases*, *59*(6), 471–475. https://doi.org/10.1111/tbed.12000

Elbers, A. R., Meiswinkel, R., van Weezep, E., Sloet van Oldruitenborgh-Oosterbaan, M. M., & Kooi, E. A. (2013). Schmallenberg virus in Culicoides spp. biting midges, the Netherlands, 2011. *Emerging Infectious Diseases*, *19*(1), 106–109. https://doi.org/10.3201/eid1901.121054

European Centre for Disease Prevention and Control, (ECDC), (2021). *Organisation of Vector Surveillance and Control in Europe.* https://www.ecdc.europa.eu/en/publications-data/organisation-vector-surveillance-and-control-europe (accessed 05 February 2023).

Gale, P., Kelly, L., & Snary, E. L. (2015). Pathways for entry of livestock arboviruses into Great Britain: assessing the strength of evidence. *Transboundary and Emerging Diseases*, *62*(2), 115-123. https://doi.org/10.1111/tbed.12317

Gao, S., Du, J., Tian, Z., Niu, Q., Zheng, F., Huang, D., Kang, B., Luo, J., Liu, G., & Yin, H. (2017). Complete genome sequence of a bovine ephemeral fever virus JT02L strain in mainland China. *Archives of Virology*, *162*(11), 3555–3558. https://doi.org/10.1007/s00705-017-3520-0

George, T. D., Standfast, H. A., Christie, D. G., Knott, S. G., & Morgan, I. R. (1977). The epizootiology of bovine ephemeral fever in Australia and Papua-New Guinea. *Australian Veterinary Journal*, *53*(1), 17–28. https://doi.org/10.1111/j.1751-0813.1977.tb15812.x

Gıda ve Kontrol Genel Müdürlüğü, (GKGM), (2023). *2023 Yılı Hayvan Hastalıkları ile Mücadele ve Hayvan Hareketleri Kontrolü Genelgesi.* https://kms.kaysis.gov.tr/Home/Kurum/24308110#collapse8 (accessed 05 February 2024).

Girgin, H., Yonguc, A. D., Akcora, A., & Aksak, E. (1986). Türkiye'de ilk bovine ephemeral fever salgını. *Etlik Veteriner Mikrobiyoloji Dergisi*, *5*(10), 5-14.

Gould, E. A., Higgs, S., Buckley, A., & Gritsun, T. S. (2006). Potential arbovirus emergence and implications for the United Kingdom. *Emerging Infectious Diseases*, *12*(4), 549–555. https://doi.org/10.3201/eid1204.051010

Hoffmann, B., Scheuch, M., Höper, D., Jungblut, R., Holsteg, M., Schirrmeier, H., Eschbaumer, M., Goller, K. V., Wernike, K., Fischer, M., Breithaupt, A., Mettenleiter, T. C., & Beer, M. (2012). Novel orthobunyavirus in Cattle, Europe, 2011. *Emerging Infectious Diseases*, *18*(3), 469–472. https://doi.org/10.3201/eid1803.111905

Hou, P., Zhao, G., Wang, H., He, C., Huan, Y., & He, H. (2018). Development of a recombinase polymerase amplification combined with lateral-flow dipstick assay for detection of bovine ephemeral fever virus. *Molecular and Cellular Probes*, *38*, 31–37. https://doi.org/10.1016/j.mcp.2017.12.003

Hsieh, Y. C., Chen, S. H., Chou, C. C., Ting, L. J., Itakura, C., & Wang, F. I. (2005). Bovine ephemeral fever in Taiwan (2001-2002). *The Journal of Veterinary Medical Science*, *67*(4), 411–416. https://doi.org/10.1292/jvms.67.411

Johal, J., Gresty, K., Kongsuwan, K., & Walker, P. J. (2008). Antigenic characterization of bovine ephemeral fever rhabdovirus G and GNS glycoproteins expressed from recombinant baculoviruses. *Archives of Virology*, *153*(9), 1657–1665. https://doi.org/10.1007/s00705-008-0164-0

Karayel-Hacioglu, I., Duran Yelken, S., Vezir, Y., Unal, N., & Alkan, F. (2021). Isolation and genetic characterization of bovine ephemeral fever virus from epidemic-2020 in Turkey. *Tropical Animal Health and Production*, *53*(2), 276. https://doi.org/10.1007/s11250-021-02715-1

Kato, T., Aizawa, M., Takayoshi, K., Kokuba, T., Yanase, T., Shirafuji, H., Tsuda, T., & Yamakawa, M. (2009). Phylogenetic relationships of the G gene sequence of bovine ephemeral fever virus isolated in Japan, Taiwan and Australia. *Veterinary Microbiology*, *137*(3-4), 217–223. https://doi.org/10.1016/j.vetmic.2009.01.021

Kirkland, P. D. (1992, August 25-27). The epidemiology of bovine ephemeral fever in south-eastern Australia: evidence for a mosquito vector. In *Proceedings of the 1st International Symposium on Bovine Ephemeral Fever and Related Rhabdoviruses,* [Symposium Paper]. Beijing PRC.(pp. 33-37).

Kirkland, P. D. (2002). Akabane and bovine ephemeral fever virus infections. *The Veterinary Clinics of North America. Food Animal Practice*, *18*(3), 501–ix. https://doi.org/10.1016/s0749-0720(02)00026-9

Kirkland, P., Macarthur, E., Bailey, G., (2016). Bovine ephemeral fever: Three Day Sickness. *NSW Government Departmant of Primary Industries*. Erişim adresi, https://www.dpi.nsw.gov.au/__data/assets/pdf_file/0011/679106/bovine-ephemeral-fever-three-day-sickness.pdf (Accessed , 05 February 2024).

Lavon, Y., Ezra, E., Friedgut, O., & Behar, A. (2023). Economic Aspects of Bovine Ephemeral Fever (BEF) Outbreaks in Dairy Cattle Herds. *Veterinary Sciences*, *10*(11), 645. https://doi.org/10.3390/vetsci10110645

Lvov, D. K., Shchelkanov, M. Y., Alkhovsky, S. V., & Deryabin, P. G. (2015). *Zoonotic viruses of Northern Eurasia: Taxonomy and Ecology*. Academic Press.

Mackerras, I. M., Mackerras, M. J., & Burnet, F. M. (1940). Experimental Studies of Ephemeral Fever in Australian Cattle. *Bulletin of the Council for Scientific and Industrial Research, Australia*, (136).

Mellor, P. S., Boorman, J., & Baylis, M. (2000). Culicoides biting midges: their role as arbovirus vectors. *Annual Review of Entomology*, *45*, 307–340. https://doi.org/10.1146/annurev.ento.45.1.307

Muller, M. J., & Standfast, H. A. (1986, May 6-9). Vectors of ephemeral fever group viruses. In *Arbovirus research in Australia. Proceedings Fourth Symposium,*[Symposium Paper]. Brisbane, Australia. (pp. 295-298).

Muller, M. J., & Standfast, H. A. (1992, August 25-27). Investigation of the vectors of bovine ephemeral fever virus in Australia. In *Proceedings of the 1st International Symposium on Bovine Ephemeral Fever and Related Rhabdoviruses,* [Symposium Paper]. Beijing, PRC. (pp. 29-32).

Murray, M. D. (1970). The spread of ephemeral fever of cattle during the 1967-68 epizootic in Australia. *Australian Veterinary Journal*, *46*(3), 77–82. https://doi.org/10.1111/j.1751-0813.1970.tb15925.x

Newton, L. G., & Wheatley, C. H. (1970). The occurrence and spread of ephemeral fever of cattle in Queensland. *Australian Veterinary Journal*, *46*(12), 561–568. https://doi.org/10.1111/j.1751-0813.1970.tb06657.x

Oguzoglu, T. Ç., Ertürk, A., Çizmeci, Ş. G., Koç, B. T., & Akça, Y. (2015). A Report on Bovine Ephemeral Fever Virus in Turkey: Antigenic Variations of Different Strains of EFV in the 1985 and 2012 Outbreaks Using Partial Glycoprotein Gene Sequences. *Transboundary and Emerging Diseases*, *62*(5), e66–e70. https://doi.org/10.1111/tbed.12187

Omar, R., Van Schalkwyk, A., Carulei, O., Heath, L., Douglass, N., & Williamson, A. L. (2020). South African bovine ephemeral fever virus glycoprotein sequences are phylogenetically distinct from those from the rest of the world. *Archives of Virology*, *165*(5), 1207–1210. https://doi.org/10.1007/s00705-020-04568-9

Parsonson, I. M., & Snowdon, W. A. (1974). Ephemeral fever virus: excretion in the semen of infected bulls and attempts to infect female cattle by the intrauterine inoculation of virus. *Australian Veterinary Journal*, *50*(8), 329–334. https://doi.org/10.1111/j.1751-0813.1974.tb14098.x

Purse, B. V., Mellor, P. S., Rogers, D. J., Samuel, A. R., Mertens, P. P., & Baylis, M. (2005). Climate change and the recent emergence of bluetongue in Europe. *Nature reviews. Microbiology*, *3*(2), 171–181. https://doi.org/10.1038/nrmicro1090

Purse, B. V., Carpenter, S., Venter, G. J., Bellis, G., & Mullens, B. A. (2015). Bionomics of temperate and tropical Culicoides midges: knowledge gaps and consequences for transmission of Culicoides-borne viruses. *Annual review of entomology*, *60*, 373–392. https://doi.org/10.1146/annurev-ento-010814-020614

Pyasi, S., Sahu, B. P., Sahoo, P., Dubey, P. K., Sahoo, N., Byrareddy, S. N., & Nayak, D. (2020). Identification and phylogenetic characterization of bovine ephemeral fever virus (BEFV) of Middle Eastern lineage associated with 2018-2019 outbreaks in India. *Transboundary and Emerging Diseases*, *67*(5), 2226–2232. https://doi.org/10.1111/tbed.13531

Radostits, O. M., Gay, C., Hinchcliff, K. W., & Constable, P. D. (Eds.). (2006). *Veterinary Medicine E-Book: A textbook of the diseases of cattle, horses, sheep, pigs and goats*. Elsevier Health Sciences.(pp. 1177-1179).

Spradbrow P. B. (1975). Attenuated vaccines against bovine ephemeral fever. *Australian Veterinary Journal*, *51*(10), 464–468. https://doi.org/10.1111/j.1751-0813.1975.tb02380.x

St George, T. D., Standfast, H. A., & Dyce, A. L. (1976). Letter: The isolation of ephemeral fever virus from mosquitoes in Australia. *Australian Veterinary Journal*, *52*(5), 242. https://doi.org/10.1111/j.1751-0813.1976.tb00092.x

St George, T. D. (1986, May 6-9). The epidemiology of bovine ephemeral fever in Australia and its economic effect. In *Arbovirus research in Australia. Proceedings Fourth Symposium,* [Symposium Paper]. Brisbane, Australia (pp. 281-286).

St George, T. D. (1988). Bovine ephemeral fever: a review. *Tropical Animal Health and Production*, *20*(4), 194–202. https://doi.org/10.1007/BF02239980

St George, T. D. (1992, August 25-27). The Natural History of Ephemeral Fever of Cattle. In *Proceedings of the 1st International Symposium on Bovine Ephemeral Fever and Related Rhabdoviruses,* [Symposium Paper]. Beijing PRC.(pp. 13-19).

Thomas M. B. (2018). Biological control of human disease vectors: a perspective on challenges and opportunities. *BioControl (Dordrecht, Netherlands)*, *63*(1), 61–69. https://doi.org/10.1007/s10526-017-9815-y

Ting, L. J., Lee, M. S., Lee, S. H., Tsai, H. J., & Lee, F. (2014). Relationships of bovine ephemeral fever epizootics to population immunity and virus variation. *Veterinary Microbiology*, *173*(3-4), 241-248. https://doi.org/10.1016/j.vetmic.2014.07.021.

Tokgoz, B. S., Tokgoz, E. A., Sözmen, M. A., Avci, O., & Ütük, A. E. (2023). Prevalence, isolation and molecular characterization of Bovine Ephemeral Fever Virus in south and southeast regions of Turkey in the outbreak of 2020. *Journal of the Hellenic Veterinary Medical Society*, *74*(4), 6549-6558. https://doi.org/10.12681/jhvms.31543

Tonbak, S., Berber, E., Yoruk, M. D., Azkur, A. K., Pestil, Z., & Bulut, H. (2013). A large-scale outbreak of bovine ephemeral fever in Turkey, 2012. *The Journal of veterinary medical science*, *75*(11), 1511–1514. https://doi.org/10.1292/jvms.13-0085

Tonbak, Ş., & Abaylı, H. (2016). Detection of recombinant G proteins of bovine ephemeral fever virus by immunoperoxidase method. *Sağlık Bilimleri Veteriner Dergisi, Fırat Üniversitesi*, *30*(3), 217-220.

Trinidad, L., Blasdell, K. R., Joubert, D. A., Davis, S. S., Melville, L., Kirkland, P. D., Coulibaly, F., Holmes, E. C., & Walker, P. J. (2014). Evolution of bovine ephemeral fever virus in the Australian episystem. *Journal of virology*, *88*(3), 1525–1535. https://doi.org/10.1128/JVI.02797-13

Tzeng, H. Y., Ting, L. J., Chiu, C. I., Lin, N. N., Liao, K. M., & Tu, W. C. (2023). Occurrence and surveillance of Taiwanese bovine arboviruses using hematophagous insects in dairy farms during 2012-2019. *Journal of Medical Entomology*, *60*(5), 1117–1123. https://doi.org/10.1093/jme/tjad096

Uren, M. F., & Murphy, G. M. (1985). Studies on the pathogenesis of bovine ephemeral fever in sentinel cattle. II. Haematological and biochemical data. *Veterinary microbiology*, *10*(6), 505–515. https://doi.org/10.1016/0378-1135(85)90059-8

Uren, M. F., St George, T. D., Kirkland, P. D., Stranger, R. S., & Murray, M. D. (1987). Epidemiology of bovine ephemeral fever in Australia 1981-1985. *Australian Journal of Biological Sciences*, *40*(2), 125–136. https://doi.org/10.1071/bi9870125

Uren M. F. (1989). Bovine ephemeral fever. *Australian Veterinary Journal*, *66*(8), 233–236. https://doi.org/10.1111/j.1751-0813.1989.tb13577.x

Uren, M. F., St George, T. D., & Zakrzewski, H. (1989). The effect of anti-inflammatory agents on the clinical expression of bovine ephemeral fever. *Veterinary Microbiology*, *19*(2), 99–111. https://doi.org/10.1016/0378-1135(89)90076-x

Van der Westhuizen B. (1967). Studies on bovine ephemeral fever. I. Isolation and preliminary characterization of a virus from natural and experimentally produced cases of bovine ephemeral fever. *The Onderstepoort journal of veterinary research*, *34*(1), 29–40.

Vetal, (2024). Live Three-Day Disease Autovaxine. https://vetal.com.tr/en/live-three-day-disease-autovaxine (accessed 24.04.2024)

Vorster, J.H., & Mapham P.H. (2012). *Bovine ephemeral fever.* https://www.cpdsolutions.co.za/Publications/articleuploads/Bovineephemeralfever.pdf (accessed 05.02.2024)

Walker, P. J., Byrne, K. A., Cybinski, D. H., Doolan, D. L., & Wang, Y. H. (1991). Proteins of bovine ephemeral fever virus. *The Journal of General Virology*, *72 (Pt 1)*, 67–74. https://doi.org/10.1099/0022-1317-72-1-67

Walker P. J. (2005). Bovine ephemeral fever in Australia and the world. *Current Topics in Microbiology and Immunology*, *292*, 57–80. https://doi.org/10.1007/3-540-27485-5_4

Walker, P., Blasdell, K., & Joubert, A. (2012). Ephemeroviruses: arthropod-borne rhabdoviruses of ruminants, with large and complex genomes. In Dietzgen, R. G., & Kuzmin IV, R. (Eds.), *Rhabdoviruses: Molecular Taxonomy, Evolution, Genomics, Ecology, Host-Vector Interactions, Cytopathology and Control* (pp. 59 - 88). Caister Academic Press. https://doi.org/10.21775/9781912530069

Walker, P. J., & Klement, E. (2015). Epidemiology and control of bovine ephemeral fever. *Veterinary Research*, *46*, 124. https://doi.org/10.1186/s13567-015-0262-4

Walker, P. J., Freitas-Astúa, J., Bejerman, N., Blasdell, K. R., Breyta, R., Dietzgen, R. G., Fooks, A. R., Kondo, H., Kurath, G., Kuzmin, I. V., Ramos-González, P. L., Shi, M., Stone, D. M., Tesh, R. B., Tordo, N., Vasilakis, N., Whitfield, A. E., & Ictv Report Consortium (2022). ICTV Virus Taxonomy Profile: *Rhabdoviridae* 2022. *The Journal of General Virology*, *103*(6), 10.1099/jgv.0.001689. https://doi.org/10.1099/jgv.0.001689

Weetman, D., Kamgang, B., Badolo, A., Moyes, C. L., Shearer, F. M., Coulibaly, M., Pinto, J., Lambrechts, L., & McCall, P. J. (2018). Aedes Mosquitoes and Aedes-Borne Arboviruses in Africa: Current and Future Threats. *International Journal of Environmental Research and Public Health*, *15*(2), 220. https://doi.org/10.3390/ijerph15020220

Zaghloul, A. H., Mahmoud, A., Hassan, H. Y., Hemeida, A. A., Nayel, M. A., & Zaghawa, A. A. (2012). Establishment of dot-blot hybridization for diagnosis of bovine ephemeral fever virus in Egypt. *International Journal of Virology*, *8*(3), 271-278. 10.3923/ijv.2012.271.278

Zheng, F., Lin, G., Zhou, J., Wang, G., Cao, X., Gong, X., & Qiu, C. (2011). A reverse-transcription, loop-mediated isothermal amplification assay for detection of bovine ephemeral fever virus in the blood of infected cattle. *Journal of Virological Methods*, *171*(1), 306–309. https://doi.org/10.1016/j.jviromet.2010.10.028

Zheng, F., & Qiu, C. (2012). Phylogenetic relationships of the glycoprotein gene of bovine ephemeral fever virus isolated from mainland China, Taiwan, Japan, Turkey, Israel and Australia. *Virology Journal*, *9*, 268. https://doi.org/10.1186/1743-422X-9-268

Zheng, F. Y., Chen, Q. W., Li, Z., Gong, X. W., Wang, J. D., & Yin, H. (2016). Experimental infection with bovine ephemeral fever virus and analysis of its antibody response cattle. *Research in Veterinary Science*, *104*, 146–151. https://doi.org/10.1016/j.rvsc.2015.12.018