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EPIDEMIOLOGY AND CONTROL OF BOVINE EPHEMERAL FEVER OVER CENTRAL ASIA REGION

Mengliyev Ali Saykonovich
Doctor of Philosophy of Veterinary Sciences.Termez institute of agro technologies and innovative development
Bobomurodov Urol Chorievich
Assistant of the Department of Veterinary and Silkworm Breeding.Termez institute of agro technologies and innovative development
Abdullayev Baxtiyor Ismatovich
Assistant of the Department of Veterinary and Silkworm Breeding.Termez institute of agro technologies and innovative development

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Abstract. *Bovine ephemeral fever (or 3-day sickness) is an acute febrile illness of cattle and water buffaloes. Caused by an arthropod-borne rhabdovirus, bovine ephemeral fever virus (BEFV), the disease occurs seasonally over a vast expanse of the globe encompassing much of Africa, the Middle East, Asia and Australia. Although mortality rates are typically low, infection prevalence and morbidity rates during outbreaks are often very high, causing serious economic impacts through loss of milk production, poor cattle condition at sale and loss of traction power at harvest. There are also significant impacts on trade to regions in which the disease does not occur, including the Americas and most of Europe. In recent years, unusually severe outbreaks of bovine ephemeral fever have been reported from several regions in Asia and the Middle East, with mortality rates through disease or culling in excess of 10–20%.*

Keywords*: ephemer Ephemerovirus. genome, KOTV amino acid sequence identity YATV Mansoniauniformis, Colostralantibody, mepizootiology, viraema, clinical a specific neutralizing, antibody response, neutrophils, induction, humoral immune response.*

ЭПИДЕМИОЛОГИЯ И БОРЬБА С ЭФЕМЕРНОЙ ЛИХОРАДКОЙ КРУПНОГО РОГАТОГО СКОТА В РЕГИОНЕ ЦЕНТРАЛЬНОЙ АЗИИ

Аннотация. *Эфемерная лихорадка крупного рогатого скота (или трехдневная болезнь) — острое лихорадочное заболевание крупного рогатого скота и водяных буйволов. Вызванное членистоногими рабдовирусом, вирусом эфемерной лихорадки крупного рогатого скота (BEFV), заболевание возникает сезонно на обширных территориях земного шара, включая большую часть Африки, Ближнего Востока, Азии и Австралии. Хотя уровень смертности, как правило, низок, распространенность инфекций и заболеваемость во время вспышек часто очень высоки, что приводит к серьезным экономическим последствиям из-за потери производства молока, плохого состояния скота при продаже и потери тяговой силы при уборке. Имеются также значительные последствия для торговли с регионами, в которых болезнь не встречается, включая Америку и большую часть Европы. В последние годы в нескольких регионах Азии и Ближнего Востока были зарегистрированы необычайно тяжелые вспышки эфемерной лихорадки крупного рогатого скота, при этом уровень смертности от болезни или выбраковки превышал 10–20%.*

Ключевые слова: *эфемерный эфемеровирус. геном, аминокислотная последовательность KOTV, идентичность YATV Mansoniauniformis, колостральные*

антитела, мепизоотология, вирема, клиническая специфическая нейтрализация, гуморальный иммунный ответ, нейтрофилы, индукция, гуморальный иммунный ответ.

INTRODUCTION

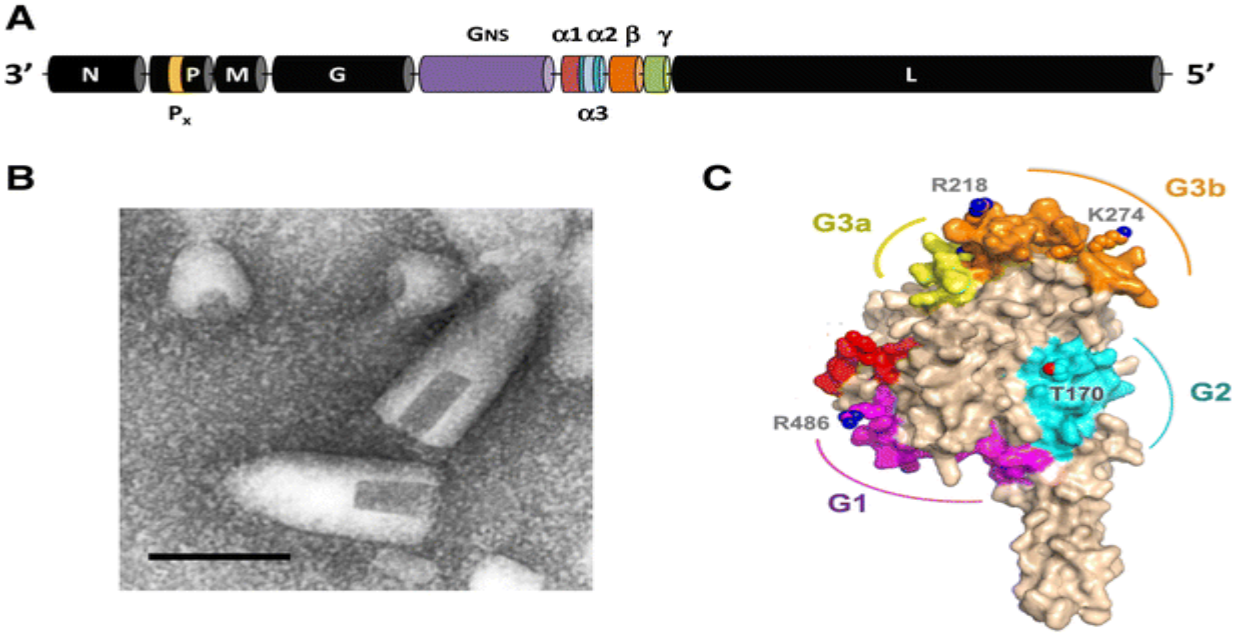
Bovine ephemeral fever virus (BEFV) an arthropod-borne rhabdoviruswhich is classified as the type species of the genus *Ephemerovirus*. It causes an acute febrile illness of cattle and water buffalo known as bovine ephemeral fever (BEF) or various other local names such as 3-day sickness, bovine enzootic fever, bovine influenza or stiffseitke. It occurs over a vast expanse of the globe from the southern tip of Africa to the Nile River Delta, across the Middle East through South and South-East Asia, into northern and eastern Australia, and throughout most of China, extending into Taiwan, the Korean Peninsula and southern Japan (Figure 1). BEFV does not occur in the islands of the Pacific, Europe (other than in the western regions of Turkey) or in the Americas where, for quarantine purposes, it is considered as an important exotic pathogen. Infection may be clinically unapparent or result in mild to severe clinical signs including a bi-phasic fever, salivation, ocular and nasal discharge, recumbency, muscle stiffness, lameness and anorexia. Sternal and lateral recumbency in cattle with clinical BEF are shown in Additional file 1. Usually, the disease is characterised by rapid onset and rapid recovery, lasting only 1–3 days, but there are reports of prolonged paralysis and ataxia in some animals following the acute phase of infection. The most severe cases can result in mortality which may be due to exposure, starvation or pneumonia, but little is currently known about the direct cause of death. Morbidity rates can be very high (approaching 100%) and mortality rates are typically low (<1%). However, in recent years there have been reports from several countries of alarmingly high case-fatality rates, sometimes exceeding 20% .

Molecular structure

METHOD AND METHODOLOGY

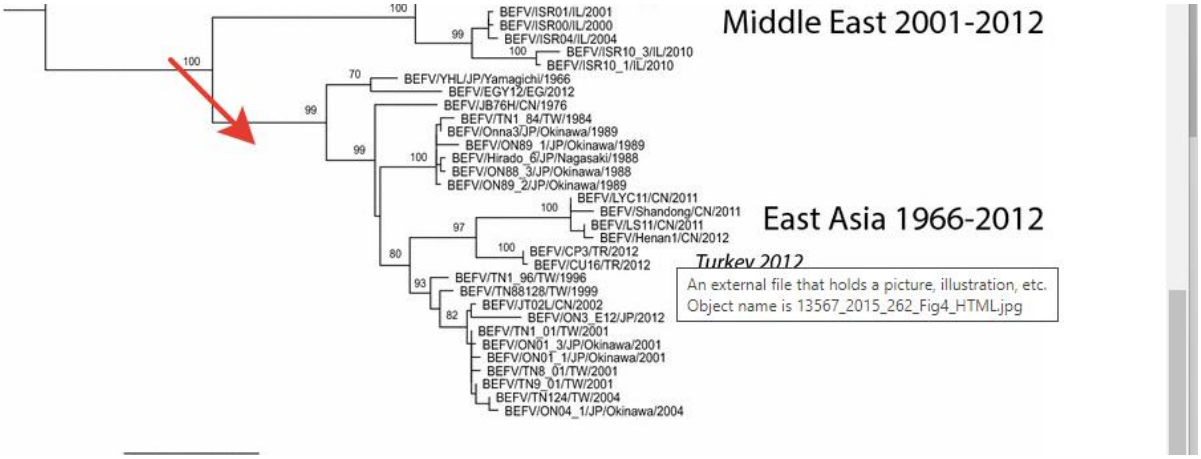
BEFV displays typical rhabdovirus bullet-shaped morphology (Figure 2), although virions (~185 nm × ~75 nm) appear to be more tapered at one end than the rounded forms that are observed for vesicular stomatitis virus (VSV) or rabies virus (RABV) . Helical nucleocapsids comprise the negative-sense, single-stranded RNA genome tightly associated with the 52 kDa nucleoprotein (N) which, together with the 43 kDaphosphoprotein (P) and the large multi-functional enzyme (L) form a ribonucleoproteincomplex .Nucleocapsids are encased in the 29 kDa matrix protein (M) and a lipid envelope through which an 81 kDa class 1 transmembrane glycoprotein (G) protrudes to form surface projections . Defective-interfering particles with truncated cone-shaped morphology are commonly present in purified virus preparations

(Figure 2



Central Asia

There is little published information readily available on the occurrence of BEF in Central Asia. Chunikhin and Alekseev referred to the presence of BEFV in the former Soviet Union. Sporadic outbreaks have been reported in the Amu Darya, Pyandzh and Vahsh Valleys in Tajikistan and Uzbekistan, and two BEFV isolates have been reported from midges (*Culicoidespuncticollis*) collected in 1980 from camels in Turkmenistan . There is also a report of a BEFV isolate, apparently obtained from Mongolia in 1993, which has been used for vaccine production in response to disease in territories bordering Russia, including Central Asia and Mongolia . A BEF outbreak was also reported in Tajikistan in 2002, affecting the Moskva, Pyandzh and Parkhar districts bordering Afghanistan . Epidemiologically, this vast region could link the Middle East to China and South Asia and so viral sequence data and further information on the status of the disease would be highly valuable.



Several other viruses that have been isolated from cattle or biting insects are antigenically related to BEFV, some of which have been classified as members of the genus *Ephemerovirus*. From a clinical perspective, the most significant of these is kotonkan virus (KOTV) which was isolated from biting midges (*Culicoides* spp.) in Nigeria in 1967 .Seroconversion to KOTV neutralising antibody has been associated with an ephemeral fever-

like illness in cattle in Nigeria and mild signs of the disease have been observed following experiment infection of calves with a mouse brain-adapted strain of the virus . Based primarily on antigenic cross-reactions with Mokola virus in complement-fixation and indirect immunofluorescence tests , KOTV was originally classified as a lyssavirus but sequence analysis has clearly established its classification as a species (*Kotonkan virus*) in the genus *Ephemerovirus* . Other established ephemerovirus species include *Berrimah virus* (BRMV), *Adelaide River virus* (ARV) and *Obodhiang virus* (OBOV). BRMV was isolated in 1981 from a healthy sentinel steer in the Northern Territory of Australia .Antigenically, it is the most closely related ephemerovirus to BEFV, cross-reacting weakly in virus-neutralisationtests.

RESEARCH RESULTS

Kimberley virus (KIMV), Malakal virus (MALV), Koolpinyah virus (KOOLV), Yata virus (YATV) and Puchong virus (PUCV) have not yet been classified formally but are likely to be assigned to the genus *Ephemerovirus* based on serological and phylogenetic relationships, and similarities in genome organisations and host/vector associations. KIMV was first isolated from mosquitoes (*Culexannulirostris*) collected in Western Australia in 1973 and then subsequently on several occasions from biting midges (*Culicoidesbrevitarsis*) and healthy sentinel cattle in the Northern Territory and Queensland. KIMV is indistinguishable in virus neutralisation tests from MALV which was isolated from mosquitoes (*Mansoniauniformis*) in Sudan in 1963, and these are now considered to be variants of the same virus species . KIMV antibodies have been detected in cattle in China and in cattle, water buffalo, goats and horses in Indonesia KOOLV was isolated in 1985 and 1986 from healthy sentinel cattle in the Northern Territory and shown to cross-react in virus-neutralisation tests with KOTV. At the time of the isolations, there was evidence of sero-conversion to KOOLV antibody in other cattle at the same site and in sheep infected experimentally with the virus. Subsequent sequence analysis of the KOOLV genome has established that it is indeed closely related to KOTV with a similar genome organisation and high levels of amino acid sequence identity between cognate proteins . YATV was isolated in 1969 from mosquitoes (*Mansoniauniformis*) collected in the Central African Republic. Recent studies have established that YATV clusters phylogenetically with the ephemeroviruses and shares a similar genome organization .

Control and treatment of BEF and Protective immunity

Natural BEFV infection has been reported to result in durable immunity . There have been observations of multiple episodes of clinical ephemeral fever in the same cattle , but it is not known if other ephemeroviruses may have been responsible for the disease. A strong neutralising antibody response follows natural or experimental BEFV infection, developing by the third day of clinical disease with titres increasing during recovery It has been reported that specific neutralising antibodies last for at least 422 days following natural BEFV infection and that previously infected animals resist challenge for at least 2 years . There are conflicting reports on the role of neutralising antibodies in protection against the disease. Tzipori and Spradbrow observed that cattle developing a neutralising antibody response following vaccination with mouse-brain-adapted virus were not consistently resistant to challenge. Della-Porta and Snowdon found no correlation between the magnitude of the neutralising antibody response to vaccination and protection, and suggested that cell-mediated responses may also be required. However, others have observed a correlation between BEFV-specific neutralising antibody titer and

protection and effective protection has been demonstrated using purified preparations of the G protein split from virions. Inclusion of N protein in the purified G protein vaccine, although stimulating a T-lymphocyte proliferative response, did not improve protective efficacy .Colostral antibody has also been shown to protect cattle against BEFV infection and neutralising G protein monoclonal antibodies injected intraperitoneally protect suckling mice from paralysis and death . Therefore, it appears that the G protein delivered in an appropriately folded form and with a suitable adjuvant is sufficient to induce protective immunity. A key role for neutralising antibodies in protection is also consistent with the short incubation period, rapid onset of disease and rapid recovery that coincides with the first appearance of neutralisingantibody . However, it is plausible that cell-mediated immunity is also involved in protection, particularly for the longer termsequelae that occur in some animals.

DISCUSSION

There is also evidence that innate immunity is involved in both the immune response to infection and the pathology of disease. In an elegant experiment, Young and Spradbrow[challenged calves with BEFV after depletion of neutrophils with a specific anti-bovine neutrophil serum of equine origin. Although becoming viraemic, the calves did not develop clinical signs and no BEFV-neutralising antibodies were detected. However, virus challenge following restoration of neutrophils resulted in viraema, clinical signs and a specific neutralising antibody response. It appears, therefore, that neutrophils are important in the induction of clinical signs and in the development of the humoral immune response. This is consistent with evidence that the pathology associated with BEFV infection is primarily due to vascular permeability and the cytokine storm resulting from the associated inflammatory response .

Vaccines

Four types of BEF vaccine have been developed to date: (1) live-attenuated vaccines; (2) inactivated vaccines; (3) sub-unit G protein-based vaccines; and (4) recombinant vaccines. Live-attenuated, inactivated and subunit vaccines are being used in the field. Vaccination has been adopted to varying extents in Australia, South Africa, Namibia, Japan, South Korea, Taiwan, mainland China, the Philippines, Turkey, Israel, Kuwait, Oman, Bahrain, Saudi Arabia and Egypt. The vaccines differ in the seed virus from which they are prepared, the method of attenuation or inactivation, and the adjuvant formulation.

Live-attenuated vaccines have been prepared by serial passage of BEFV in suckling mice and/or in cell cultures, including baby hamster kidney (BHK-21), hamster lung (HmLu-1) or African green monkey kidney (Vero) cells Many of these live-attenuated vaccines have been administered with aluminium hydroxide or Freund’s incomplete adjuvant and require volumes of up to 12 mL/dose. A live-attenuated vaccine employing Freund’s incomplete adjuvant has been adopted for commercial use in South Africa .Vanselow et al. have reported that two 1 mL doses of an attenuated BEF vaccine mixed with Quil A (a purified saponin derivative) induced higher neutralising antibody titers than when using aluminium hydroxide or dextran sulphate as adjuvants. Inactivated BEF vaccines have been prepared by treatment with formalin, β-propriolactone binary ethyleneimineor ultraviolet light . Heat-inactivation of the virus resulted in failure to induce a neutralising antibody response after vaccination .. Most early inactivated vaccines used either aluminium gel or Freund’s incomplete adjuvant [. A formalin-inactivated, aluminium phosphate gel-adsorbed vaccine developed in Japan was shown to elicit a strong antibody response after two doses but immunity waned rapidly and neutralising antibody was no

longer detected in most animals 4 months after vaccination . More recently, inactivated vaccines have used water-in-oil-in-water adjuvant .Such a vaccine developed in Israel was shown to elicit a stronger and longer lasting neutralising antibody response after two vaccinations and showed a significant booster effect 9 months after the second vaccination.

CONCLUSIONS

BEF is a disease for which the economic and social impacts are not always obvious and are frequently underestimated. Epizootics are now occurring more frequently in some parts of the world, there are increasing reports of alarmingly high case-fatality rates, and there is potential, under the influence of climate change and through the livestock trade, for spread of the disease to regions that are presently free. Although the epizootiology has been studied extensively in some regions, little is known of the distribution, prevalence and impacts over vast areas of Africa and Asia, relatively few virus isolates have been recovered and sequenced, and the specific vectors are not clearly defined anywhere in the world. Additional files 10.1186/s13567-015-0262-4 **Sternal and lateral recumbency in cattle with clinical BEF**. Movie showing cattle displaying sternal and lateral during the clinical phase of BEFV infection. video file.(7.7M, mp4) 10.1186/s13567-015-0262-4 **Isolate details and Genbank accession numbers of the BEFV sequences used for phylogenetic analysis.** Table providing isolation details (number/country/location/date) of viruses and Genbank accession numbers of L protein sequences that were used for the phylogenetic analysis displayed in Figure 4.

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