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Clinical and epidemiological investigation of bovine ephemeral fever outbreaks in the Jordan Valley (1999–2001)

Клиническое и эпидемиологическое изучение вспышек эфемерной лихорадки крупного рогатого скота в долине реки Иордан в 1999–2001 гг.

Israel Yeruham [1], Hagai Yadin [2, 3] & Yehuda Braverman [2, 4]
Исраэль Иерухам, Хагай Ядин, Иехуда Браверман

[1] "Hachaklait", Gedera and the Koret School of Veterinary Medicine, the Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76100, Israel (deceased).
[2] The Kimron Veterinary Institute, Bet Dagan 50250, Israel.
[3] The Koret School of Veterinary Medicine, The Hebrew University of Jerusalem, P.O. Box 12, Rehovot 76100, Israel.
[4] Ha'Gesher Street 10, Hod Ha'Sharon 45266, Israel. E-mail: ronab@bezeqint.net

KEY WORDS: bovine ephemeral fever, outbreaks, Jordan Valley, 1999–2001, morbidity.

КЛЮЧЕВЫЕ СЛОВА: эфемерная лихорадка крупного рогатого скота, вспышки заболевания, долина р. Иордан, 1999–2001 гг., заболеваемость.

ABSTRACT. The patterns of bovine ephemeral fever (BEF) spread over cattle herds in the Jordan Valley were similar in 1999, 2000 and 2001. The incidence rates of the disease were 100, 85 and 93.7% in 1999, 2000 and 2001, respectively. Morbidity rates were 38.6, 4.6 and 13.6%, and mortality rates were 8.6, 0.3 and 14.8% of affected animals in 1999, 2000 and 2001, respectively. The values of the three parameters are very high compared to those reported in earlier publications. An average of 2.7% of the affected animals experienced a second attack of the disease after 2 to 6 weeks. All the affected cattle were over the age of three months. The vectors are not known for certain but the available evidence indicates that Culicidae and not *Culicoides* are the natural vectors of BEF virus.

РЕЗЮМЕ. Картина распространения эфемерной лихорадки крупного рогатого скота (BEF) по стадам коров в долине реки Иордан была сходной в 1999, 2000 и 2001 гг. Доля животных, заболевших BEF, впервые составила 100, 85 и 93,7% в 1999, 2000 и 2001 гг., соответственно. Доля заболевших особей составила 38,6, 46 и 13,6% от общего числа животных, а смертность – 8,6, 0,3 и 14,8% от общего числа заболевших особей (в 1999, 2000 и 2001 гг., соответственно). Значения всех трёх показателей оказались очень высокими по сравнению с ранее опубликованными данными. В среднем, 2,7% заболевших животных заболевали повторно через 2–6 недель после первого случая болезни. Все заболевшие особи были старше 3 месяцев. Переносчики заболевания достоверно не известны, но, по всем имеющимся данным, кровососущие комары (Culicidae), а не мокрецы (*Culicoides*) являются векторами вируса BEF в природе.

Introduction

Bovine ephemeral fever (BEF) is an arthropod-borne acute viral disease of cattle and buffaloes. It is caused by an arbovirus of the family Rhabdoviridae, a member of the genus *Ephemerovirus*. The BEF virus life cycle is maintained through a vector-host system probably involving bloodsucking dipterans and cattle [Walker & Boreham, 1976]. The virus agent has been isolated from various species of midges and mosquitoes, which probably act as vectors [Davies & Walker, 1974; Blackburn et al., 1985; Mellor, 1996; Venter et al., 2003]. Nevertheless there is no evidence as to which vector species can transmit the BEF virus [Braverman, 2001].

BEF is spread by movement of the host or by vectors [Murray, 1977; St George, 1988]. Long-distance carriage of infected insects by wind has most likely been responsible for the spread of BEF in various countries [Murray, 1970; Newton & Wheatley, 1970; Sellers, 1980; Sellers & Pedgley, 1985; St George, 1988; Al-Busaidy & Mellor, 1991]. According to Sellers [1980], Israel and the rest of the Mediterranean area are in zone "C", where pathogens are introduced by infected vectors carried by warm winds. Outbreaks of BEF probably occur when vector populations increase, resulting in high rates of virus transmission to susceptible cattle.

BEF is an inflammatory disease of short duration, affecting cattle [Uren et al., 1992].

It is becoming increasingly apparent that BEF occurs as a direct result of disruption of the normal functioning of both the physiological and immunological systems of the host [Uren et al., 1992]. There is some evidence to suggest that BEF is immunogenic in nature [Burgess & Spradbrow, 1977; Uren & Murphy, 1985; Uren et al., 1989] and that the clinical characteristics of the disease are the expression of mediators of inflammation common to a number of acute febrile diseases with a secondary hypocalcaemia [Uren et al., 1992; St George et al., 1995]. Clinical signs and pathological changes are reflections of the effects of virus replication on the host and the host's response to the infection [Burgess & Spradbrow, 1977].

BEF was described in 1924 in Egypt [Sen, 1931] and in the Jordan Valley in Palestine in 1931 [Rosen, 1931]. Since then the disease has occurred at irregular and long intervals over the years, and the last outbreaks, before the ones discussed in the present paper, occurred in 1990–1991. The disease has been reported in Jordan, Syria, Iraq, Saudi Arabia [Burgess, 1971; Abu-Elzein, 1997], and in Israel [Yeruham et al., 2002].

Significant economic losses in dairy cattle herds may result from mortality, reduced milk production, increase in somatic cell count [Morgan & Murray, 1969; Newton & Wheatley, 1970; Uren et al., 1989; Yeruham et al., 2003].

There is paucity of information on the clinical and epidemiological aspects of the disease in high-yielding dairy cattle under a subtropical climate. The present study was therefore aimed at investigating the clinical and epidemiological aspects of bovine ephemeral fever outbreaks in the Jordan Valley during 1999–2001.

Material and methods

Field observations, virological and serological investigations were made on 10 dairy cattle herds located in the region where the BEF epizootic occurred.

GEOGRAPHY AND CLIMATE. The affected dairy herds were located in the Jordan Valley (33°15'N 35°37'E to 31°45'N 35°27'E), which is a part of the Rift Valley and forms a part of the lee-side dry lands to the east of the hill region. Those regions are semiarid with mean annual precipitation of 270 mm. Appropriate weather charts were obtained from the Israel Meteorological Service at Bet Dagan and from publications [Jaffe, 1988; Bitan & Rubin, 1994; Goldreich, 1998].

THE HERDS. The 10 dairy cattle herds included in this survey comprised 5081 animals. The herd included an average of 250 lactating individuals, which were divided into three groups: heifers, first-calvers and cows. Dry cows and heifers were kept in separate sheds. All herds (Holstein-Israeli) were kept under a zero-grazing management system, and each lactating cow produced an average milk yield of 10,000 to 12,000 kg/year. Each herd was visited twice weekly by the attending veterinarian. Epidemiological and clinical data relating to the morbidity, mortality, fertility, abortions, milk production, and somatic cell counts were recorded by computerized dairy management systems.

We used the following terms in this paper. Incidence is the percentage of newly-affected animals in the herds under study. It includes the animals which exhibited BEF symptoms for the first time in their life. Morbidity is the percentage of affected animals in the herd. Mortality is the ratio the number of succumbed animals to the number of affected animals in the herd (in %). Cattle which exhibited clinical signs consistent with BEF infection were included in the morbidity records, and those which succumbed to the infection were included in the mortality records. The cause of death was confirmed by pathological examination of randomly selected carcasses. Morbidity and mortality rates were averaged for all the affected herds in the study.

LABORATORY INVESTIGATIONS. The presence of BEF was assessed clinically and confirmed serologically. Viruses were isolated from cattle which had severe disease incursions, at the Viral Diagnosis Laboratory, within the Kimron Veterinary Institute, Bet Dagan, Israel. A serological survey was conducted in all 10 herds, and it served as an indicator of the prevalence of BEF virus during the 1999–2001 outbreaks.

Forty blood samples were collected from each herd from randomly selected cattle in various age groups: nine samples from heifers up to one year of age, eight samples from heifers up to calving, six from first-calvers and 17 from mature cows. This technique was used in 1999 and 2001. Serological reaction rates were averaged for the affected herds in the study.

BEF infection elicits neutralizing antibodies in sera of infected cattle. The titres of antibodies were assessed by a serum neutralization (SN) test in a micro-assay system of Vero cells cultured against 100 TCID50 [Cybinski & Zakrzewski, 1983] of the BEF virus strain BB7721 passage 12 on BHK [Burgess, 1971]. All sera were titrated in duplicate. After 96 hours the plates were stained with 0.2% Amidoblack (an acid diazo dye) and read for cytopathogenic effect (CPE) under the microscope. The SN titre was expressed as the negative $\log_2$ of the highest serum dilution. Sera that showed a titre of 1 in 16 or higher were considered positive. Five sero-conversions were considered to be positive when the differences between the titres of paired sera were twice as high as $\log_2$ or higher.

Heparinized whole blood samples for virus isolation were collected from cattle which had severe disease incursions, at the Viral Diagnosis Laboratory, of the Kimron Veterinary Institute, Bet Dagan, Israel. The buffy coat was collected in phosphate-buffered saline (PBS) pH 7.4 and washed three times, sonified at low temperature and high amplitude for 1 minute, in an ultrasonic vibrator, and then inoculated on to Vero cell cultures.

PROPHYLAXIS AND TREATMENT. Once the disease was confirmed, the movement of cattle from infected regions was banned. Treatment with non-steroidal anti-inflammatory and supportive medication proved beneficial. Spraying or pour-on treatments of the animals with repellents were also recommended.

STATISTICS. Comparison of regressions between affected and unaffected cows was performed by means of the Primer of Biostatistics software, version 4.0 [Glantz, 1996]. The PROC GENMOND Software from SAS [SAS, 2001] was used to analyze involuntary culling and mortality rates in the affected and unaffected herds. The involuntary culling rate and mortality rate were compared with data from the same herds and from the same season in the three years prior to the BEF

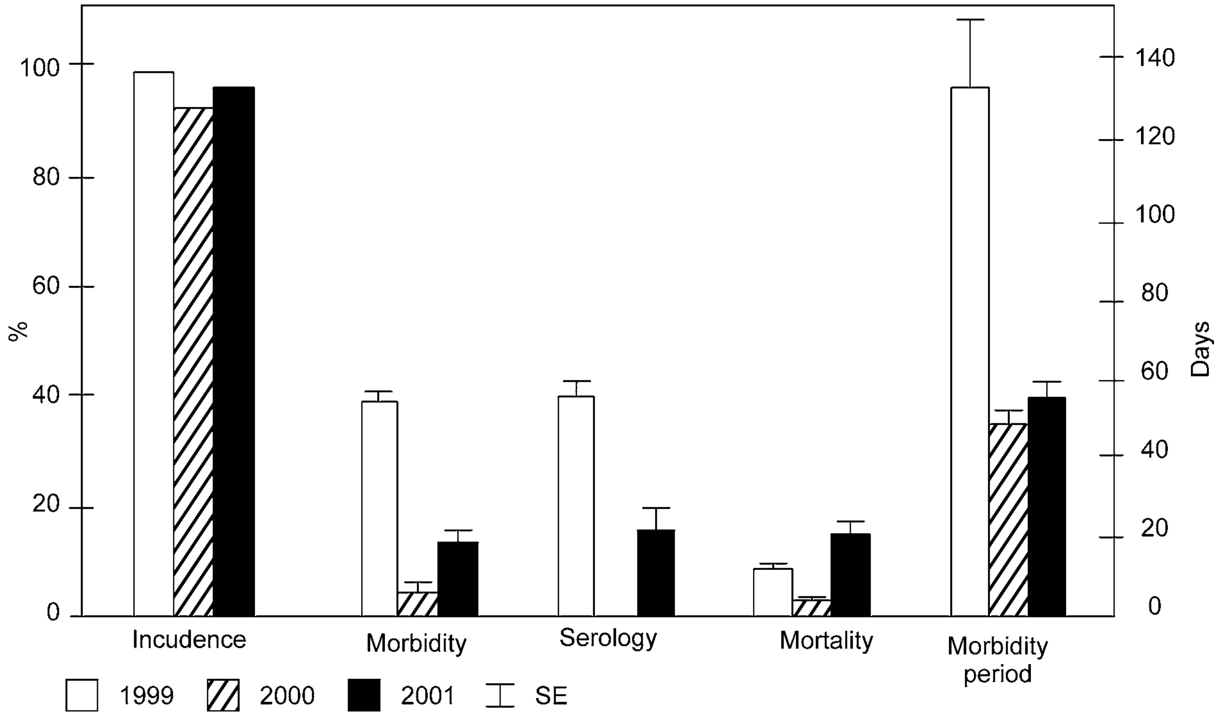

Fig. 1. Bovine ephemeral fever epizootics in the Jordan Valley (1999–2001): incidence of outbreaks (%); average rates of positive serological reaction (%); morbidity (%); mortality (%); average duration of morbidity period (days). SE – standard error. See text for details.

Рис. 1. Эпизоотии эфемерной лихорадки крупного рогатого скота в долине реки Иордан (1999–2001): доля животных, заболевших эфемерной лихорадкой впервые (%); заболеваемость (средняя доля заболевших от общего числа особей, %); смертность (средняя доля погибших от общего числа заболевших, %); средний уровень положительной серологической реакции (%); средняя продолжительность заболевания (дни). SE – стандартная (среднеквадратичная) ошибка. Подробности см. в тексте.

outbreak (1996–1998), and with data from eight unaffected herds which were BEF free in a southern district of the country (monthly data for the years 1998–2000). The odds ratio is abbreviated as OR.

Results

The patterns of BEF spread in the Jordan Valley in the 1999–2001 outbreaks were similar. The epizootic spread from the primary focus in the Jordan Valley on a front of 15 km and advanced about 30 km weekly. The disease spread northwards along the Jordan Valley to Upper Galilee and southwards to the Dead Sea area. The epizootic of BEF in 1999 commenced in May and terminated in December. In 2000 the disease had an epizootic course from April to December, while in 2001 it commenced in August and terminated in December. During all three years (1999–2001) the epizootic terminated in December, soon after the daily average ambient temperature decreased below 16°C.

The disease broke out under optimal epidemiological conditions among a vulnerable cattle population. The clinical signs were consistent with BEF virus infection. The first cases occurred sporadically, but after 7–10 days morbidity increased and the disease became an epizootic.

The incidence rates of the disease in the affected area were 100, 85 and 93.7% in 1999, 2000 and 2001, respectively. The average morbidity rates were 38.6, 4.6 and 13.6% in 1999, 2000 and 2001, respectively. The average mortality rates among affected animals were 8.6, 0.3 and 14.8% in 1999, 2000 and 2001, respectively. The average rates of positive serological reaction were 39.5 and 18.8% in 1999 and 2001, respectively (Fig. 1).

An average of 2.7% of the affected animals experienced a second attack of the disease two to six weeks after the first attack. About 12.3% in 2000 and 2.7% in 2001, of the sick animals had previous exposure to the disease in the preceding year.

All the cattle affected were over the age of three months (Fig. 2). The lowest morbidity rates were noted in the youngest age group (heifers up to one year): 3.6, 0.08 and 4.3%, respectively, during the three consecutive years of the epizootics, while the highest were in cows: 35.7, 8.6 and 14.7%, respectively. In heifers from one year to calving the rates were 14.9, 1.8 and 15.6%, and in first-calvers 31.6, 7.7 and 19.9%, respectively (Fig. 2). The mortality rates in 1999 and 2001 ranged from 5 to 11.6%, while the mortality rates in 2000 were very low, ranging from 0.4 to 0.6% in all age groups, except for heifers up to one year, among which no mortality occurred (Fig. 2).

The involuntary culling and mortality rates in the affected herds were significantly higher than those in the unaffected herds and during the three years before the outbreak in the affected herds: $p < 0.0001$ (OR = 2.5) and $p < 0.005$ (OR = 2.4), respectively.

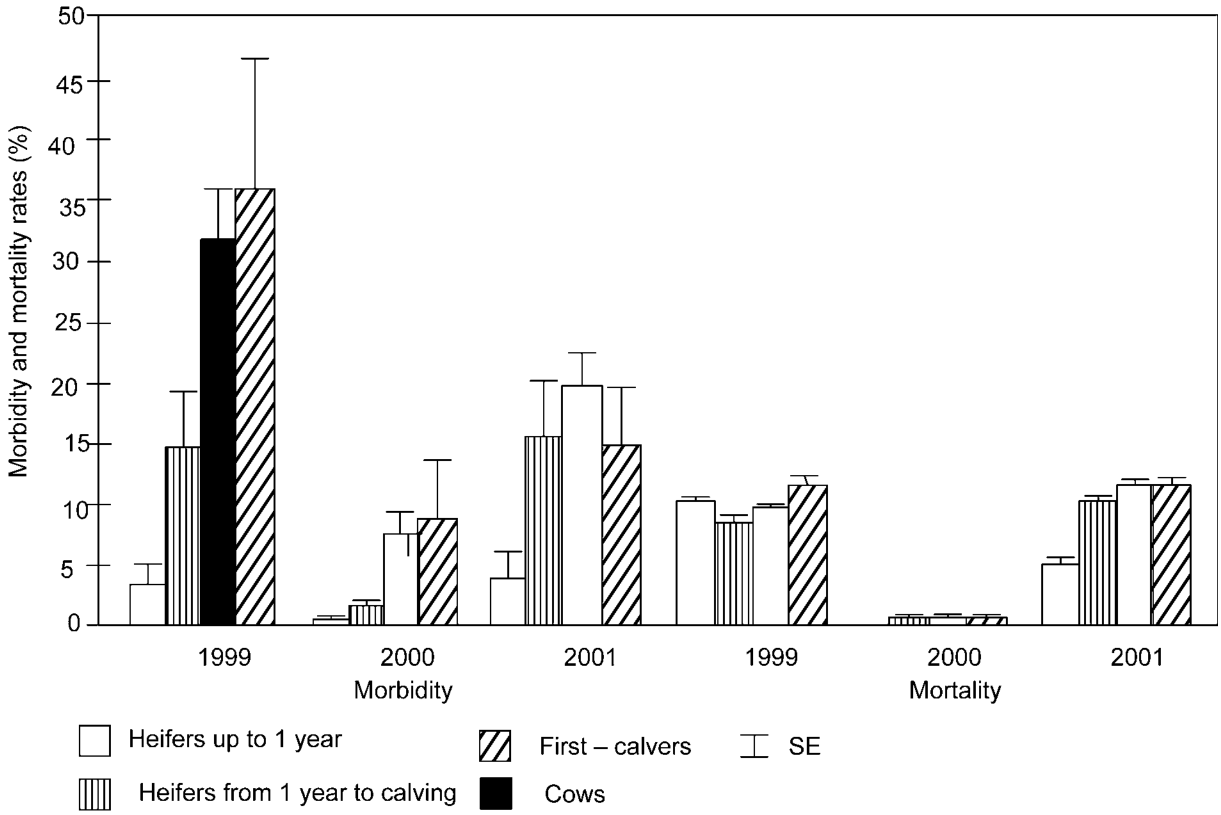

Fig. 2. Bovine ephemeral fever epizootics in the Jordan Valley (1999–2001): Average rates of morbidity and mortality (%) among different age groups. SE – standard error. See text for details.

Рис. 2. Эпизоотии эфемерной лихорадки крупного рогатого скота в долине реки Иордан (1999–2001): средняя заболеваемость и смертность (%) среди различных возрастных групп. SE – стандартная (среднеквадратичная) ошибка. Подробности см. в тексте.

In addition, the epizootics in 2000 and 2001 had a shorter duration of morbidity period (48.2 and 55.6 days on average, respectively) than in 1999 (133.3 days on average) (Fig. 1).

Discussion

There is very little information as regards to the epidemiology of ephemeral fever in the Middle East that translates into limited knowledge of its incidence in the region. Eight years elapsed between the end of the 1990 outbreak of BEF and its reappearance in 1999. In both cases the disease reappeared among cattle in the following years.

The 1999 to 2001 BEF epizootic caused considerable economic losses to the dairy cattle industry in Israel [Yeruham et al., 2003].

The incidence, morbidity and mortality rates in the 1999 outbreaks in the Jordan Valley were higher than reported elsewhere [Newton & Wheatley, 1970; Davies et al., 1984; St George, 1988; Abu Elzein et al., 1997; Yeruham et al., 2007], seemingly because this region was the longest lasting primary focus of the disease. Moreover, it seems that the duration of the disease outbreaks within any herd were influenced essentially by the susceptibility of the cattle, the size of the herd, crowding of the animals in the herd, intensity of the epizootics, and density of probable vectors.

The average duration of morbidity periods in 1999–2001 and the highly significant increase in the involuntary culling rate and in the mortality rate in the affected herds, compared with those in the same herds in the previous years and in unaffected dairy herds in other region in the same period, indicate that the cattle were susceptible to BEF virus, and probably that the virus strain involved in the 1999 epizootic was highly virulent. Interestingly, all the cattle affected were over the age of three months. This may indicate that calves younger than three months possess natural resistance to the BEF virus. The morbidity rates in the Jordan Valley in 1999 and 2001 matched the serologically determined infection rates (Fig. 1).

One infection usually confers lifelong immunity [St George, 1988], and the occurrence of double or triple bouts of illness from one to six weeks after the first [Seddon, 1938; Macfarlane & Haig, 1954; Newton & Wheatley, 1970; St George, 1985] has been attributed to the existence of different strains of the BEF virus [Macfarlane & Haig, 1954]. Another possible explanation for double bouts of the disease is that if the first episode is mild, with insufficient antigenic stimulus to produce adequate antibody levels, immunity may last only one or two weeks, thus allowing a second infection during the same epizootic [St George, 1994]. Newton & Wheatley [1970] also reported that certain animals known to have been affected in one outbreak were affected again in a subsequent one, as was noted in the present study.

BEF is principally a summer disease, and it has been diagnosed in a wide range of ecological zones corresponding to the geographical distribution and the peak activity of the arthropod vectors. There were no attempts to isolate the virus from possible vectors. The suspected vectors were mosquitoes (Culicidae), biting midges (Ceratopogonidae: mostly *Culicoides* Latreille, 1809) and sand flies (Psychodidae: *Phlebotomus* Rondani & Berté, 1840). *Phlebotomus* and biting midges were trapped frequently in suction light traps installed in dairy cattle herds in this region. The main Culicidae species in the study area are: *Anopheles claviger* (Meigen, 1804), *A. sergentii* (Theobald, 1907), *A. superpictus* Grassi, 1899, *Culex perexiguus* Theobald, 1903, *C. pipiens* Linnaeus, 1758, and *Ochlerotatus caspius* (Pallas, 1771). These dipteran vectors which could be potential vectors of arboviruses of animals have been identified in the areas in Israel where BEF has occurred [Braverman & Galun, 1973; Braverman et al., 1981; Pener & Kitron, 1985; Kitron & Pener, 1986; Braverman & Chechik, 1996; Braverman et al., 1996].

The seasonality of various species of mosquitoes has been described [Margalit & Tahori, 1974; Pener & Kitron, 1985; Kitron & Pener, 1986]. The outbreaks reported in the present paper occurred between May and December, and in the Mediterranean basin, most of this period comprises the driest and the hottest months in the year and corresponds with the activity period of Culicidae. This contrasts with the observations reported by Davies et al. [1990] in Kenya, where an association between epizootics of BEF and prolonged rainfall was observed.

Climatic and environmental factors govern the survival and distribution of insect vectors and the pathogens they may transmit [Thomson & Connor, 2000], and the substantial role of mosquitoes in the perpetuation and dissemination of BEF virus has been assumed by many authors [Davies & Walker, 1974; Blackburn et al., 1985; Standfast & Muller, 1985; Muller & Standfast, 1986; Kaneko et al., 1986; St George, 1988; Braverman, 1992a, 1992b]. The fact that the outbreaks of 1999–2001 started early in the season, in April and May, is not typical of diseases vectored by *Culicoides*, which generally start in July and are associated with the air current of the Persian trough. The BEF virus has been assumed to survive by transovarial transmission through the mosquito vector, as was suggested also by Kirkland [1982] and St George [1988]. This phenomenon cannot occur in *Culicoides* midges. Apparently the insect vectors play crucial roles in the transmission of the BEF virus and also as a reservoir during the winter months and during interepizootic periods. This mode of transmission maintains the biological cycle of the BEF virus. The continuous presence of adult vectors seems to be essential for persistence of the virus [Mellor, 1996]. All these arguments support the hypothesis that BEF was probably transmitted by mosquitoes and not by *Culicoides* spp.

It seems that the eastern basin of the Mediterranean is a fringe region of the geographical distribution of BEF, into which the disease makes irregular but often spectacular spring and summer incursions. Nevertheless, the origin of and reasons for these occurrences of epizootics of BEF have been the subject of much speculation. The spread of the disease apparently followed the prevailing winds [Gat & Karni, 1995], and mostly hot and dry weather prevailed in these regions during the BEF morbidity period. The Red Sea trough is probably responsible for the carriage of infected vectors in the spring and late autumn [Braverman & Chechik, 1996]. Retrospective analysis of the patterns of spread of the epizootics in 1999–2001 found similarities that could indicate that vectors infected with BEF virus could have been brought into the Jordan Valley on seasonal winds blowing over relatively long distances from eastern or southern regions where the disease is endemic [Al-Busaidy & Mellor, 1991; Abu Elzein et al., 1997; Abu Elzein et al., 1999]. It can be concluded that the rapid spread to north and south of outbreaks in the dairy cattle herds in the Jordan Valley, was clearly supported by dense populations of susceptible cattle, dense vector populations, and ecological conditions suitable for propagation and dispersal of massive numbers of vectors.

The spread of BEF both by actively flying vectors and by wind-borne vectors is thought to be possible. There is no evidence of the spread of BEF from cow to cow [Mackerras et al., 1940]. The time for the disease to progress from herd to herd ranged between two and three weeks, somewhat shorter than was reported by Murray [1970]. Mechanical transmission via insect vectors or by direct contact does not occur, and the virus does not persist much beyond the fourth day after subsidence of the fever [Nandy & Negi, 1999]. Thus, the BEF virus is unlikely to be maintained by subclinical infections in cattle during interepizootic periods, as was postulated by St George et al. [1977] and Knott et al. [1983]. No evidence of carrier animals has been found experimentally or indicated by epizootic outbreaks [Mackerras et al., 1940].

The major factor contributing to the abatement of the Israeli epizootics was the onset of cold weather in December, when the daily average ambient temperature decreased below 16°C, a level which suppresses vector activity and is not conducive to virus transmission [Braverman, 1992b]. In this region BEF epizootics appear to have developed a periodic pattern in the last decade and, in spite of the above-mentioned favourable conditions, BEF is still not endemic in Israel. However, the long intervals between the epizootic occurrences of the disease have resulted in a cattle population highly susceptible to BEF.

Quite often the main wave of the disease in Israel has occurred several days after the first clinical cases were recorded. Thus, the presence of the appropriate vector(s), together with introduction of the virus, and a susceptible cattle population could have led to the rapid spread of the disease over a wide area. Incrimination studies to identify the insect vectors involved in the transmission of BEF in Israel and to characterize the behaviour of the BEF virus in the vectors would help in the development of novel and effective management strategies for the control of the disease.

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