What can Akabane disease teach us about other arboviral diseases

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Veterinaria Italiana 2016, 52 (3-4), 353-362. doi: 10.12834/VetIt.547.2587.2
Accepted: 01.03.2016 | Available on line: 30.09.2016

Keywords
Arbovirus,
Cerebral akabane,
Malformation,
Simbu serogroup.

Summary
Viruses of the Simbu serogroup cause lesions to foetuses that are seen at birth and that correlate with the stage of pregnancy at which the dam first contracts the virus. The Simbu serogroup comprises arboviruses known to cause outbreaks of abnormal parturitions in domestic ruminants; these abnormalities include abortion, stillbirth, and congenitally deformed neonates. Simbu serogroup members include: Akabane virus (AKAV), Aino virus, Cache Valley virus, and Schmallenberg virus. Lately, dairy herds calf malformations have been observed in Europe, where there have been reports of clinical manifestations such as diarrhoea, fever, and reduced milk yield in adult lactating cows. The Israeli dairy cattle industry has experienced 2 major episodes of abnormal parturitions that resulted from 2 arboviral Simbu serogroup episodes, which occurred 35 years apart. A wave of apparently newly introduced AKAV was noted from the beginning of January 2012. Investigations carried out throughout the period of late Summer 2011 to early Winter 2012, associated the Israeli AKAV strain with central nervous system manifestations in lactating cows. A lack of clinical/epidemiological ‘uniformity’ among the AKAV infections was noted during these investigations. Here we describe and discuss the clinical and spatial distribution differences found among the 3 above-mentioned outbreaks. Comparable features in the clinical presentation, spatial distribution, and target-animal issues relating to Akabane disease are discussed.

Analogie e differenze tra malattia di Akabane e altre arbovirosi

Parole chiave
Akabane,
Arbovirus,
Malformation,
Sierogruppo Simbu.

Riassunto
Introduction

The Simbu serogroup viruses and their relation to ruminant pathology

Simbu viruses, which infect ruminants, are transmitted by blood-sucking insects – midges of the Culicoides spp. complex (Mellor et al. 2000, Mellor and Whitman 2002). The genus Bunyavirus includes 90 virus serogroups, of which Simbu viruses represent 1 of the largest groups. It comprises at least 24 viruses, among which a serological cross-reaction occurs (Kinney and Calisher 1981, Parsonson and McPhee 1985). Members of the Simbu serogroup are arboviruses known to cause outbreaks of abnormal parturition in domestic ruminants, which include abortion, stillbirth, and deformed neonates (Edwards 1994, Kinney and Calisher 1981). Simbu serogroup members include: Akabane virus (AKAV) (Inaba et al. 1975, Kono et al. 2008, Miura et al. 1974), Aino virus (ANIV) (Nada et al. 1998, Uchinuno et al. 1998), Cache Valley virus (Edward 1994), and Schmallenberg virus (SBV) – a provisional name given to the novel Simbu ‘European’ virus strain (Hoffmann et al. 2011). The complex of symptoms is known as the congenital arthrogryposis-hydranencephaly syndrome (AHS), and it affects the musculo-skeletal and/or nervous system(s) (Brenner 2004, Brenner et al. 2004 a, b, Kurogi et al. 1975, Markusfeld-Nir and Mayer 1971, Nobel et al. 1971). However, other clinical manifestations attributed to this group of viruses have been recently reported in adult cattle. These include diarrhoea, fever, reduced milk yield (Goller et al. 2012, Hoffmann et al. 2011), and cerebral Akabane (Oem et al. 2012, Oem et al. 2014).

The Orbiviruses and the haemorrhagic complexes in ruminants

The genus Orbivirus, within the family Reoviridae, contains several viruses that might be pathogenic to all domestic and wild ruminant species. Viruses that infect ruminants have been shown to be transported by blood-sucking midges of the genus Culicoides (Mellor et al. 2000, Mellor and Whitman 2002). Bluetongue disease (BT) is a consequence of systemic arteritis, BT is also characterised as haemorrhagic disease. To date, several serotypes of the BT viruses (BTV) (serotypes 2, 4, 5, 8, 12, 15, 16, and 24) (Brenner et al. 2010, Brenner et al. 2011, Bumbarov et al. 2012) and 1 serotype of the Epizootic haemorrhagic disease virus (EHDV serotype 7) have been identified in Israel (Yadin et al. 2008).

The 2 above-mentioned arboviral entities – the teratogenic Simbu serogroup and orbiviruses – share the same insect vector, show the same spatial distribution, and affect the same animal species concurrently (Brenner et al. 2004b, Kalmar et al. 1975, Kedmi et al. 2011b, Thompson et al. 1988). However, they cause different syndromes: BT is observed mainly in adult ruminants, whereas the Akabane disease (AD) mainly affects embryogenesis and development, resulting in the presentation of clinical manifestations in different seasons. Although ruminant infection occurs during the period of midge activity, the clinical manifestations related to BT (Brenner et al. 2011, Shimshony 2004) and to AD (Brenner et al. 2004 a, b, Shimshony 1980) appear in late Summer/early Winter, and Autumn/winter/early Spring, respectively.

The article describes the clinical/epidemiological changes observed in Simbu serogroup outbreaks in Israel in the last 40 years. These outbreaks were

<table>
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<tbody>
<tr>
<td>Species affected</td>
</tr>
<tr>
<td>Spatial distribution</td>
</tr>
<tr>
<td>How the 1st episode was reported and diagnosed</td>
</tr>
</tbody>
</table>

LDS (T) = Lymphocytes depletion syndrome (thymus).
Table II. Epidemiological and laboratory methods used to link Akabane virus with the syndromes reported for three distinct, different Akabane disease outbreaks in Israel (1969/1970, 2001/2003, 2011/2012)

<table>
<thead>
<tr>
<th>Year</th>
<th>2001/2003</th>
<th>2011/2012</th>
</tr>
</thead>
<tbody>
<tr>
<td>Collecting demographic and meteorological data and investigating spatial distribution of the affected zones as well as the clinical features in ruminants (Kalmar et al. 1975, Markusfeld-Nir and Mayer 1971, Shimshony 1980)</td>
<td>Adopting the AKAV/AINO-SNT and investigating the seroreactivity of affected and unaffacted farms and zones</td>
<td>Adopting a novel AKAV-PCR for S, M and L segments carried out on sera, EDTA-blood, and pathological material</td>
</tr>
<tr>
<td>Description of macro- and micro-pathology of congenital malformation (Nobel et al. 1971)</td>
<td>Demonstrating for the first time the presence of AKAV in C. imicola and in pathological material from an aborted fetus (Stram et al. 2004 a, b).</td>
<td>For the first time, analyzing samples and pathological materials from unsolved episodes of hypofertilty and from adult cows with CNS manifestations, formerly tested negative for rabies</td>
</tr>
<tr>
<td>Adopting AKAV-SNT and investigating the seroreactivity of affected and unaffected farms and zones (Kalmar et al. 1975, Nobel et al. 1971)</td>
<td>Adopting a novel AKAV/AINO-PCR for the S segment only</td>
<td>Cooperation with an international arbo laboratory (Germany)</td>
</tr>
<tr>
<td>Analyzing sera by AKAV-SNT of animals that were alive during the epidemics in the affected zones and of animals that were born 3 years after the end of the epidemic, to clarify where and when the vector was active (Kalmar et al. 1975)</td>
<td>Cooperation with an international reference arbo laboratory (Japan)</td>
<td></td>
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<tr>
<td>Showing that 150-day-old fetuses are able to mount specific responses and that specific Abs of a pre-colostral ruminant enable allow identification of the causative agent (Trainin 1971, Trainin and Meirom 1973)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cooperation with an international reference arbo laboratory (Japan) (Trainin and Meirom 1973)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

SNT = sera neutralizing test; Abs = antibodies; CNS = Central nervous system.

Table III. Akabane genetic fragments in aborted fetuses, neonates, and adult milking cows, found from October 2011 onward in one affected dairy farm.

<table>
<thead>
<tr>
<th>Animal age</th>
<th>Sampling period/date</th>
<th>Deformity type /hypofertilty</th>
<th>AKAV-RNA fragments detected in...</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult milking cow a</td>
<td>Sep-Nov/2011</td>
<td>Abortion</td>
<td>Sera and/or EDTA-blood</td>
</tr>
<tr>
<td>Neonate a</td>
<td>Jan/15/2012</td>
<td>Arthrogryposis and cleft palate</td>
<td>Brain/Thymus/EDTA-blood</td>
</tr>
<tr>
<td>Adult milking cow a</td>
<td>Jan/16/2012</td>
<td>Dystocia</td>
<td>EDTA-blood/Brain#</td>
</tr>
<tr>
<td>Neonate a</td>
<td>Jan/17/2012</td>
<td>Arthrogryposis</td>
<td>Brain</td>
</tr>
<tr>
<td>Neonate a</td>
<td>Jan/17/2012</td>
<td>Arthrogryposis</td>
<td>Brain</td>
</tr>
<tr>
<td>Adult milking cow a</td>
<td>Jan/17/2012</td>
<td>Apparently healthy</td>
<td>EDTA-blood</td>
</tr>
<tr>
<td>Neonate a</td>
<td>Feb/15/2012</td>
<td>Apparently healthy</td>
<td>EDTA-blood</td>
</tr>
<tr>
<td>Adult milking cow</td>
<td>Feb/16/2012</td>
<td>Abortion</td>
<td>EDTA-blood</td>
</tr>
<tr>
<td>Adult milking cow</td>
<td>Feb/16/2012</td>
<td>Abortion</td>
<td>EDTA-blood</td>
</tr>
<tr>
<td>Neonate a</td>
<td>Feb/22/2012</td>
<td>Small size</td>
<td>EDTA-blood</td>
</tr>
<tr>
<td>Adult milking cow a</td>
<td>Feb/27/2012</td>
<td>Dystocia</td>
<td>Brain #</td>
</tr>
<tr>
<td>Fetus a</td>
<td>Feb/27/2012</td>
<td>Brain</td>
<td></td>
</tr>
<tr>
<td>Fetus a</td>
<td>Feb/27/2012</td>
<td>Brain</td>
<td></td>
</tr>
<tr>
<td>Adult milking cow a</td>
<td>Feb/27/2012</td>
<td>Abortion</td>
<td>EDTA-blood/Brain</td>
</tr>
</tbody>
</table>

a of 4 cows, two died or culled; * in Hippocampus; a, a, a pairs of dams and their offspring.

Materials, methods and results

The relevant data regarding the first 2 Simbu serogroup outbreaks (1969/1970, 2001/2003) have been reported in detail elsewhere (Brenner 2004, Brenner et al. 2004 a, b, Brenner et al. 2013, Kalmar et al. 1975, Markusfeld-Nir and Mayer 1975, Shimshony 1980). In addition, certain parallel features are noted between these 3 AKAV outbreaks and other arboviral diseases (Radostits et al. 2007), such as the BT and the EHD (Brenner et al. 2010, Brenner et al. 2011, Yadin et al. 2008), which occurred from 2006 to 2013 both in Israel and Europe.

Tables I and II summarise the major clinical/epidemiological features reported in the literature and the laboratory methods used to associate AKAV infection with 3 AD episodes in Israel (1969/1970, 2001/2003, and 2011/2012). Table III summarises the clinical features of AKAV infections and laboratory findings from 1 of the affected farms. Table IV describes the AKAV laboratory findings from additional regions during the 2011/2012 seasons only.
Polymerase chain reaction

RNA was extracted and served as a template for amplification, which was performed in a single tube with 3 pairs of primers targeting a different genome segment. For the first amplification, the primers for the S, M, and L segments were AKAS1 and AKAR41, respectively. For the nested reaction AKAS10, and AKAR411 (for S segment), AKAM2132 and AKAM2853; and AKAM2239, and aka1F380 and AKAM2853 (for segment M); and AKAL380, AKAL829, AKAL381, AKAL829 (for segment L) were used. Each of the nested reaction was carried out for 25 cycles (Brenner et al. 2013, Stram et al. 2004a).

Collection of samples

Samples from the affected farm comprised sera, blood in ethylenediaminetetraacetic acid, and brain tissues from 16 lactating cows and 20 neonates or foetuses (Table III). All the samples were taken between late Autumn, i.e., September 2011, and mid-Spring, i.e. March 2012.

A total of 16 of the 20 affected animals and 1 apparently healthy neonate were positive to polymerase chain reaction (PCR) for AKAV-RNA. These included 10 cows that aborted, out of which 4 died, 5 neonates, and 2 foetuses (Table III). Brain tissue from 2 of the 10 adult cows was tested and found positive; 1 of the 2 tissue samples was of the dam of a malformed neonate, while the other had been found empty for 3 consecutive lactations. In both of these cows AKAV-RNA was detected only in the hippocampus (Table IV).

Four of the affected animals probably were not infected with AKAV.

Table IV. More regional Akabane virus identifications (Figure 3) during the 2011/2012 activity.

<table>
<thead>
<tr>
<th>Species</th>
<th>Sample type</th>
<th>N total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bovine adult</td>
<td>Blood EDTA (n = 7), Sera (n = 4)</td>
<td>11</td>
</tr>
<tr>
<td>Bovine neonates</td>
<td>Brain (n = 1 healthy), Blood EDTA (n = 3), Thymus (n = 1)</td>
<td>5</td>
</tr>
<tr>
<td>Bovine fetus</td>
<td>Brain (n = 1), Thymus* (n = 1 &amp; brain)</td>
<td>2</td>
</tr>
<tr>
<td>Ovine fetuses</td>
<td>Brain</td>
<td>2</td>
</tr>
<tr>
<td>Goat fetuses</td>
<td>Brain</td>
<td>2</td>
</tr>
<tr>
<td>Camel fetus</td>
<td>Brain</td>
<td>1</td>
</tr>
<tr>
<td>Elk fetus</td>
<td>Brain</td>
<td>1</td>
</tr>
<tr>
<td>N Total</td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

* Addax nasomaculatus; ** Figure 4.

Case history of the 2011/2012 AKAV episode

Increased rates of abortions and periparturient deaths were noted in a herd of 170 lactating cows. The first case of malformation was reported on January 15, 2012 (Figures 1 and 2), and it triggered a retrospective/prospective investigation into probable AKAV infection at this farm from September 2011 through March 2012. Retrospectively, sera from 4 adult milking cows that aborted in September/October 2011 were found AKAV-PCR positive.

During the follow-up, AKAV was also identified in the brain tissue (Stram et al. 2004a, b) of 3 apparently healthy adult cows, which showed reproductive abnormalities. The findings of circumstantial association between AKAV infections and clinical disease in adult cattle triggered an investigation to confirm whether AKAV could be involved in central nervous system (CNS) infection and in hypothalamic dysfunction, as reported in connection with other AKAV outbreaks elsewhere (Haughey et al. 1988, Inaba et al. 1975, Kurogi et al. 1975, Lee et al. 2002, Oem et al. 2012, Oem et al. 2014).

Collection of samples

Samples from the affected farm comprised sera, blood in ethylenediaminetetraacetic acid, and brain tissues from 16 lactating cows and 20 neonates or foetuses (Table III). All the samples were taken between late Autumn, i.e., September 2011, and mid-Spring, i.e. March 2012.

A total of 16 of the 20 affected animals and 1 apparently healthy neonate were positive to polymerase chain reaction (PCR) for AKAV-RNA. These included 10 cows that aborted, out of which 4 died, 5 neonates, and 2 foetuses (Table III). Brain tissue from 2 of the 10 adult cows was tested and found positive; 1 of the 2 tissue samples was of the dam of a malformed neonate, while the other had been found empty for 3 consecutive lactations. In both of these cows AKAV-RNA was detected only in the hippocampus (Table IV). Four of the affected animals probably were not infected with AKAV.
Additional evidence of regional AKAV and its identification in brain samples from adult cows

In order to assess whether AKAV activity had occurred in other regions known to be at risk for arboviruses during the same period, from the end of September 2011 through mid-March 2012, 40 EDTA-blood samples were collected on the field or taken from a storage of abortive material at the Kimron Veterinary Institute (KVI). All of these samples were associated with reproductive disorders. The stored samples included sera and brain tissue from aborted foetuses or malformed neonates collected during January-February 2012. Additional brain samples from adult cows with central nervous system (CNS) manifestations, all from 2012, were sent to the KVI for rabies diagnosis, 5 in February/March and 11 in August-October 2012 (Figure 3).

Half of the tested serum samples were RNA-AKAV positive (Table IV). Six out of the 16 brain samples from adult cows tested positive for AKAV RNA using nested PCR (Brenner et al. 2013, Stram et al. 2004 a, b). Surprisingly, all of the 5 brain samples collected during February/March 2012 were positive, whereas only 1 of the 11 samples collected from August to October 2012 was found positive (Figure 3).

Discussion

Akabane disease was first named and described 4 decades ago (Inaba et al. 1975). The disease can be regarded as an array of clinical manifestations and syndromes attributed to infections by the teratogenic Simbu serogroup in ruminants. During this long period, however, in Israel and elsewhere, the clinical condition(s) was/were thought to concern only foetuses and new-borns (Brenner 2004, Brenner et al. 2004 a, b, Brenner et al. 2013, Edwards 1994, Haughey et al. 1988, Inaba et al. 1975, Markusfeld-Nir and Mayer 1971, Miura et al. 1974, Nada et al. 1988, Nobel et al. 1971, Oem et al. 2014, Shimshony 1980, Trainin 1971, Trainin and Meirion 1973, Uchinuno et al. 1988, Zentis et al. 2012), and the clinical manifestations in adult animals were almost excluded or clinically neglected. This interpretation has been revised by the extant literature focusing on the spreading of SBV in Europe, especially in cattle from autumn 2011 onward (Hoffmann et al. 2011). The findings were added to those regarding another relatively rare adult AD, ‘cerebral Akabane’. So far this disease has been reported only in the Far East (Miyazato et al. 1989, Oem et al. 2012, Oem et al. 2014). The Israeli AKAV strain, found in brains of adult cows (Brenner et al. 2013) adds a new aspect to the potential virulence of the set of viruses within the teratogenic Simbu serogroup. In light of the data presented here, and in respect to the involvement of AKAV in hypofertilty and cerebral AKAV infections in adult milking cows (Lee et al. 2002, Miyazato et al. 1989, Oem et al. 2012, Oem et al. 2014). The Israeli AKAV strain, found in brains of adult cows (Brenner et al. 2013) adds a new aspect to the potential virulence of the set of viruses within the teratogenic Simbu serogroup. In light of the data presented here, and in respect to the involvement of AKAV in hypofertilty and cerebral AKAV infections in adult cows with and without clinical symptoms (Tables III and IV), we conclude with reasonable confidence that the Israeli AKAV strain (Stram et al. 2004 a, b) should be considered as the causal agent of the syndrome in adult cattle in Israel. Therefore, the prospective case of an outbreak of cerebral AD in Europe has to be considered.

It seems probable that the AKAV activity occurred in Israel at the end of 2011 (Tables III and IV, Figure 3). However, from the clinical point of view, AD is considered endemic in Israel, whereas syndromes related to AKAV infection have been reported, diagnosed, and confirmed by field observations and laboratory findings approximately every 15 years (1969/1970, 1985, 2001/2003 and 2011/2012) (Brenner et al. 2004 a, b, Brenner et al. 2013, Markusfeld-Nir and Mayer 1971, Shimshony et al. 1980, Factsheet Israeli veterinary services annual report 1985, personal communication). These syndromes appeared as cyclic waves of this particular virus. Therefore, the question arises as to which of the viruses belonging to the teratogenic Simbu serogroup was active in the periods attributed to AKAV activity. A partial answer was
foundings which show similar features. These concern the following studies.

**Seasonality**

Orbiviruses and teratogenic Simbu serogroup members are both transmitted by flying insects. The activities of these vectors are influenced by major topographical climatic variations, and by human factors such as decisions on where and how to breed domestic and other animals. Suitable microenvironments, climate and the presence of animal populations promote the progression of the vectors’ sexual reproductive cycle (Mellor et al. 2000). Theoretically, any virus belonging to these two viral entities, namely, Orbivirus and Simbu serogroup viruses (Yanase et al. 2010, Yanase et al. 2012), might infect insect swarms. Therefore the identification of ‘novel’ viruses or serotypes amongst viruses within each group, as a consequence of the occurrence of reassortments, should not be surprising. These ‘novel variants’ might appear at any time, and may occur during seasons they were formerly not expected in (Braverman and Chechic 1996). Moreover, the spread of arboviruses has reached climatic zones in Northern Europe, that have been thought of as unsuitable for SBV (Rasmussen et al. 2012). The appearance of SBV in unexpected seasons (Zentis et al. 2012, Figure 5) represents another good example of potential future developments. The isolation of Shuni virus (SHUV) from pathological ruminant tissues in Israel (Golender et al. 2015), exemplifies the situation where an agent causes various pathological syndromes in different animal species. SHUV caused pathology in South African horses, whereas it caused malformations in cattle, sheep and goats, in Israel (Golender et al. 2015).

Parallels encountered between AD in Israel and other arboviral diseases in Israel and elsewhere

Some of the arboviral epidemiological studies carried out in Israel and lately also in Europe yielded
Syndromes and clinical manifestations based on field and laboratory observations

The AD was first described in 1975 (Inaba et al. 1975). Subsequently, disease syndromes were identified and described during the 2001-2003 episode in Israel (Brenner 2004, Brenner et al. 2004 a, b). However, little attention was paid to studies performed in the Far East, which claimed that additional clinical manifestations might be attributed to the Simbu infections (Miyazato et al. 1989, Lee et al. 2002, Oem et al. 2012, Oem et al. 2014). This attitude changed, and scientifically oriented attention focused on this possibility only after SBV had emerged in Europe (Hoffmann et al. 2011).

A similar attitude prevailed regarding BT and Epizootic haemorrhagic diseases, and it changed dramatically only during the last decade. Bluetongue has been considered a disease affecting sheep alone, therefore, very little attention was focused on BTV’s infections in cattle. However, recently an entire supplement of the scientific journal Virus Research (vol. 182, March 2014, 1-94) was dedicated to BT. Epizootic haemorrhagic disease virus is a disease of cattle. Serotype 7 of EHDV was identified in Israel (Yadin et al. 2008) and serotype 6 around the Mediterranean Basin (Temizel et al. 2009). Moreover, BT in cattle has been documented in a number of different reports that addressed both the serotype and the geographical region of occurrence. At the same time, BT has been

Spatial distribution

From the clinical point of view, manifestations that are associated with infections with the Simbu serogroup viruses frequently appear in areas located on the fringes of endemic regions (Parsonson and McPhee 1985). In contrast, AD seems to appear cyclically in regions distant from recognised endemic zones (Parsonson and McPhee 1985). Laboratory analyses raise questions about the possible occurrence of new invasive diseases, or sporadically seen agents becoming endemic. In both cases predictions are difficult.

Southern Israel, which includes the desert and the semi-arid Arava region, was considered free from vectors such as Culicoides, and was therefore declared free from BT (and AKAV) for 50 years (Shimshony 1980). The AKAV activity in these regions in 2002/2003 (Brenner et al. 2004 a, b) shattered this perception. Moreover, after BT has appeared in this area, its presence has continued to this date (Brenner et al. 2010, Bumbarov et al. 2012).

Figure 5. A deformed calf born at the beginning of May 2012 in Germany (Zentis et al. 2012), which tested positive for Schmallenberg virus (SBV). Its dam was probably infected with SBV in December 2011. The environmental temperature range was about -5ºC (day and night, respectively) - not considered suitable for Culicoides reproduction.

Figure 6. A camel-calf presenting musculo-skeletal malformations (courtesy of Dr Ahmad Junes).
and found no epidemiological evidence that sheep were involved. However, in a second publication (Kedmi et al. 2011a), the authors reported that EHDV and BTV were both clinically apparent in the same geographical regions as a result of their transmission by a common insect vector.

Etiology/viral evolution

Viral reassortment, including the description of cases in orbiviruses, is well documented in the literature (Allison et al. 2010, Stott et al. 1987). The finding that SBV is probably composed of at least 2 viruses, Shamonda and Sathuperi (Goller Yanase et al. 2012, Garigliany et al. 2012), may improve our understanding of possible Simbu reassortments (Yanase et al. 2010, Yanase et al. 2012). Kedmi and colleagues (Kedmi et al. 2011b), documented various aspects of a single EHD outbreak in cattle in 2006, and found no epidemiological evidence that sheep were involved. However, in a second publication (Kedmi et al. 2011a), the authors reported that EHDV and BTV were both clinically apparent in the same geographical regions as a result of their transmission by a common insect vector.

Although no clinical cases of AKAV infection in small ruminant were reported during the 2002/03 outbreak in cattle, both clinical and laboratory experience shed doubt on the accuracy of the documentation.

The importance of other ruminants – domestic, wild, semi-wild, and captive – in the epidemiological chain should be taken into consideration for the evaluation of epidemiological aspects of AD and BT/EHD diseases (Table IV, Figure 6).
References


