What can Akabane disease teach us about other arboviral diseases

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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,
Malformazione,
Sierogruppo Simbu.

Riassunto
I virus del sierogruppo Simbu causano lesioni al feto visibili alla nascita, correlate con lo stadio di gravidanza in cui viene contratto il virus. Il sierogruppo Simbu comprende i virus di Akabane (AKAV), Aino, della valle di Cache Valley e di Schmallenberg. Questi sono arbovirus noti per causare disturbi della sfera ripoduttiva in ruminanti domestici caratterizzati da: aborto, morte fetale e malformazioni congenite. Recentemente sono state riportate manifestazioni cliniche come: diarrea, febbre e riduzione della produzione di latte in vacche di aziende europee dove sono state osservate anche malformazioni dei feti. Due episodi di parti anomali in aziende bovine causati da due arbovirus del sierogruppo Simbu si sono verificati in Israele a 35 anni di distanza l'uno dall'altro. All'inizio di gennaio 2012 è stata registrata un'ondata di nuovi episodi clinici dovuti a un nuovo ceppo di AKAV. Ricerche eseguite nel 2011-2012 hanno evidenziato anomalie del sistema nervoso centrale associate a presenza del ceppo israeliano di AKAV in bovini da latte. Tutte queste indagini hanno rivelato la mancanza di uniformità clinica/epidemiologica tra le infezioni determinate da AKAV. In questo articolo vengono descritte e discusse le differenze cliniche e di distribuzione spaziale dell'infezione in 3 epidemie e analizzati gli aspetti sugli animali target della malattia.

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 Whittman 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 I. *Comparison of the major clinical-epidemiological features reported during three distinct, different Akabane disease episodes in Israel (1969/1970, 2001/2003, 2011/2012).*

Episode	1969/1970	2001/2003	2011/2012
Species affected	Clinical manifestations observed in cattle, sheep and goat neonates (Markusfeld-Nir and Mayer 1971, Nobel *et al.* 1971)	Clinical manifestations observed only in bovine neonates	Clinical manifestations observed in sheep, goat neonates, and adult cattle
AD: the syndromes reported	Arthrogryposis hydranencephaly syndrome (AHS) (Markusfeld-Nir and Mayer 1971, Nobel *et al.* 1971, Shimshony 1980)	Blind calf syndrome - hydranencephaly syndrome	AHS and LDS (T). Central nervous symptoms in adult cattle. Hypofertilty in apparently healthy cattle
Spatial distribution	Reported only above 31° latitude North (Markusfeld-Nir and Mayer 1971)	Reported above 31° latitude North in 2002 only. Spread to the southern regions in 2003	Reported in the north and central Coast Plain
How the 1st episode was reported and diagnosed	Reports of malformed (ML) neonates from multiple locations (Kalmar *et al.* 1975, Markusfeld-Nir and Mayer, 1971, Shimshony 1980)	Pursuit of an unsolved episode of BVDV	Investigation of putative rabies episode in adult cattle led to a visit to a cattle farm exhibiting ML calf and hypofertilty.

LDS (T) = Lymphocytes depletion syndrome (thymus).

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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, 2001/2012)*

1969/1970	2001/2003	2011/2012
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)	Adopting the AKAV/AINO-SNT and investigating the seroreactivity of affected and the unaffected farms and zones	Adopting a novel AKAV-PCR for S, M and L segments carried out on sera, EDTA-blood, and pathological material
Description of macro- and micro-pathology of congenital malformation (Nobel *et al.* 1971)	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).	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
Adopting AKAV-SNT and investigating the seroreactivity of affected and unaffected farms and zones (Kalmar *et al.* 1975, Nobel *et al.* 1971)	Adopting a novel AKAV/AINOV-PCR for the S segment only	Cooperation with an international arbo laboratory (Germany)
Analyzing sera by AKAV-SNT of animals that were alive during the epidemics in the affected zones and of animal that were born 3 years after the end of the epidemic, to clarify where and when the vector was active (Kalmar *et al.* 1975)	Cooperation with an international reference arbo laboratory (Japan)	
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)		
Cooperation with an international reference arbo laboratory (Japan) (Trainin and Meirom 1973)		

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.*

Animal age	Sampling period/date	Deformity type /hypofertilty	AKAV-RNA fragments detected in...
Adult milking cow [4*]	Sep-Nov/2011	Abortions	Sera and/or EDTA-blood
Neonate[a]	Jan/15/2012	Arthrogryposis and cleft palate	Brain/Thymus/ EDTA-blood
Adult milking cow[a]	Jan/16/2012	Dystocia	EDTA-blood/ Brain#
Neonate	Jan/17/2012	Arthrogryposis	Brain
Neonate[b]	Jan/17/ 2012	Arthrogryposis	EDTA-blood
Adult milking cow[b]	Jan/17/2012	Apparently healthy	EDTA-blood
Neonate	Feb/15 2012	Apparently healthy	EDTA-blood
Adult milking cow	Feb/16/2012	Abortion	EDTA-blood
Adult milking cow	Feb/16/2012	Abortion	EDTA-blood
Neonate[c]	Feb/22/2012	Small size	EDTA-blood
Adult milking cow[c]	Feb/27/ 2012	Dystocia	Brain #
Fetus[d]	Feb/27/2012		Brain
Fetus[d]	Feb/27/2012		Brain
Adult milking cow[d]	Feb/27/2012	Abortion	EDTA-blood/ Brain

[*] of 4 cows, two died or culled; [#] in Hippocampus; [a,b,c,d] pairs of dams and their offspring.

reported in 1969/1970, 2002/2003, and 2011/2012 (Brenner *et al.* 2004 a, b, 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.

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, Nobel *et al.* 1971, Shimshony 1980, Trainin 1971, Trainin and Meirom 1973).

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.

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

Species	Sample type	N total
Bovine adult	Blood EDTA (n = 7), Sera (n = 4)	11
Bovine neonates	Brain (n = 1 healthy), Blood EDTA (n = 3), Thymus (n = 1)	5
Bovine fetus	Brain (n = 1), Thymus** (n = 1 & brain)	2
Ovine fetuses	Brain	2
Goat fetuses	Brain	2
Camel fetus	Brain	1
Elk fetus*	Brain	1
N Total		24

* *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.* 2004 a, 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 hypo fertility, 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).

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.

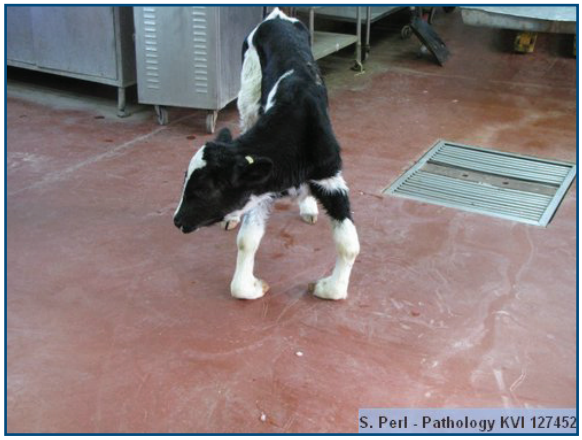

Figure 1. *Typical posture of a ruminant neonate infected with the Israeli strain of Akabane virus and born with musculo-skeletal malformations (arthrogryposis), on experimental cattle farm.*

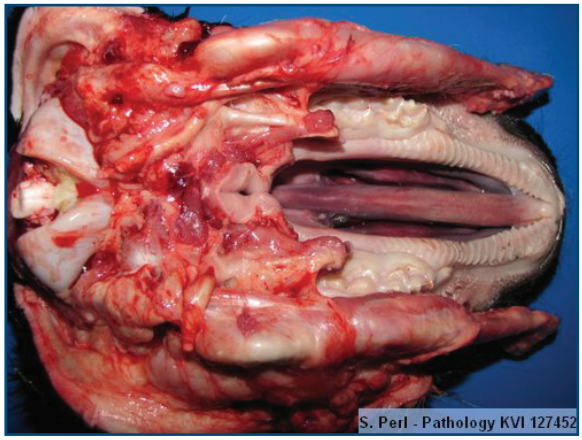

Figure 2. *A newborn calf, with colostral regurgitation, born on experimental cattle farm infected with the Israeli strain of Akabane virus.* Post mortem revealed imperfect genesis of the palate.

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).

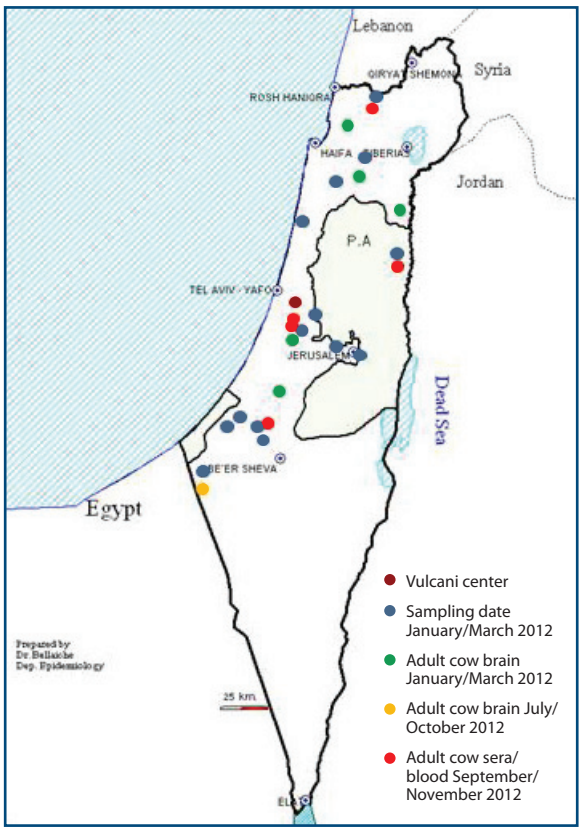

Figure 3. *Map showing all the Akabane disease-infected sites.* In addition, the map indicates time and location of 'cerebral Akabane disease' diagnosis events.

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 Meirom 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.* 2014), where it was demonstrated that the teratogenic AKAV-Iriki strain of Simbu serogroup was capable of causing cerebral 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

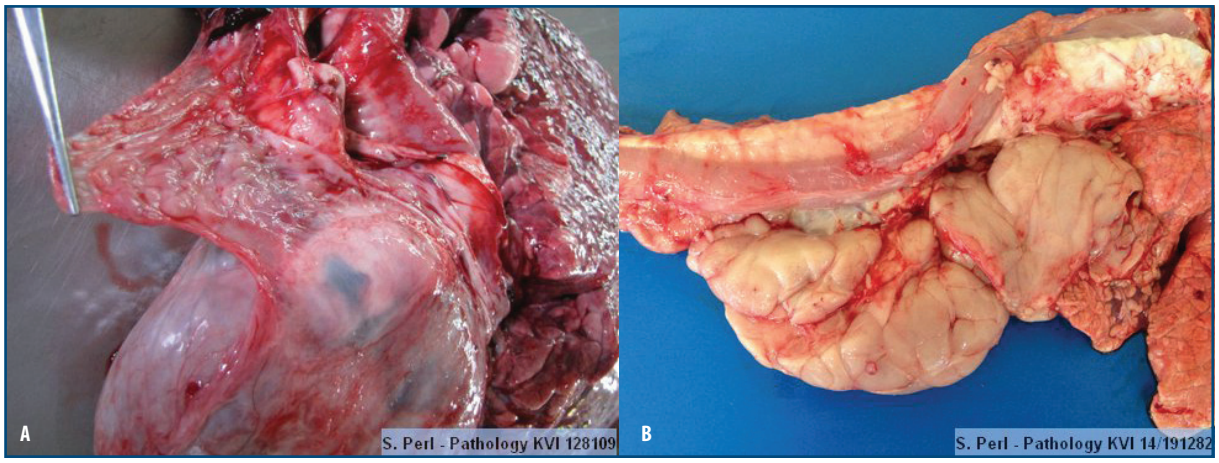

Figure 4. *A neonate calf, born on experimental cattle farm infected with the Israeli strain of Akabane virus (AKAV), it was described by the breeder as 'dummy calf' (*i.e., *weak calf syndrome).* On post mortem examination, the thymus was 'empty' - lymphocyte depletion syndrome. Akabane disease fragments were found in that organ (**A**). Part **B** shows a normal thymus of a calf which died from causes not related to AKAV infection.

obtained from field investigations carried out during the AKAV outbreak in 2001/2003 (Brenner *et al.* 2004 a, b), when AKAV activity was observed and confirmed by specific serum-neutralizing tests (SNT) on serum samples taken from cattle in the North of the country.

Instead all sera tested from the South that were regarded as uninfected controls, tested AKAV negative in 2002 (Brenner *et al.* 2004a). However, AKAV SNT-negative sera that were taken as controls, tested positive for another Simbu virus, AINOV. This virus was probably active in the group of sampled cattle some years before. In light of the maximum life span of the average Israeli dairy cow, it appears that the initial AINOV infection occurred in 1996/1997.

A particular feature that drew the investigators' attention was the finding of AKAV genetic fragments in the hippocampus of 2 clinically healthy lactating cows that gave birth to malformed AKAV PCR-positive calves (Table III) (Brenner *et al.* 2013). In addition, AKAV genetic material was detected in the peripheral blood of 2 healthy neonates (Tables III and IV). These findings raised suspicions regarding the existence of AKAV carriers, which hide the virus during the inter-endemic period. The absence of AKAV infections from the Israeli ruminant population during the interim quiescent period was proven in the course of the analysis of sera from animals born 3 years after disappearance of the syndromes related to the 1969/1970 AKAV episode (Kalmar *et al.* 1975). All sera tested negative for AKAV-SNT.

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 findings 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, Orbi 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).

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 5-0°C (day and night, respectively) - not considered suitable for *Culicoides* reproduction.

The discoveries of BTV-26 (Batten *et al.* 2013), and of its ability to infect naïve goats by direct contact and of chronic AKAV infection in apparently healthy cattle (Brenner *et al.* 2013) indicate that these diseases might be losing the strict seasonality that was one of their distinctive characteristic epidemiological features. Adult cattle that were sent to slaughter from farms affected by AKAV in the Far East were found to harbor AKAV in their cerebral tissues (Miyazato *et al.* 1989) but were culled from the farm only at the end of their economic life span. These examples conflict with the 'seasonal arbo concept'.

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 semiarid 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).

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

Figure 6. *A camel-calf presenting musculo-skeletal malformations (courtesy of Dr Ahmad Junes).*

described as "the cluster phenomenon" (Brenner *et al.* 2011). It is plausible to envision further novel clinical manifestations in the future.

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).

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