Schmallenberg virus infection

K. Wernike (1), A. Elbers (2) & M. Beer (1)*

(1) Institute of Diagnostic Virology, Friedrich-Loeffler-Institut (FLI), Südufer 10, 17493 Greifswald – Insel Riems, Germany
(2) Department of Epidemiology, Crisis Organisation and Diagnostics, Central Veterinary Institute, Wageningen UR, Houtribweg 39, 8221 RA Lelystad, the Netherlands
*Corresponding author: martin.beer@fli.bund.de

Summary
Since Schmallenberg virus, an orthobunyavirus of the Simbu serogroup, was identified near the German–Dutch border for the first time in late 2011 it has spread extremely quickly and caused a large epidemic in European livestock. The virus, which is transmitted by Culicoides biting midges, infects domestic and wild ruminants. Adult animals show only mild clinical symptoms or none at all, whereas an infection during a critical period of gestation can lead to abortion, stillbirth or the birth of severely malformed offspring. The impact of the disease is usually greater in sheep than in cattle. Vaccination could be an important aspect of disease control.

Keywords

Introduction
Starting in late summer and autumn 2011, an unidentified disease in dairy cattle was reported by farmers and veterinarians in north-western Germany and the Netherlands. Clinical symptoms included a sudden decrease in milk production, fever and diarrhoea lasting for a few days (1, 2). A hitherto unknown orthobunyavirus was subsequently identified by metagenomic analyses in samples from acutely diseased cows on a farm near the city of Schmallenberg, Germany. In addition, using identical samples, the virus was isolated in insect and baby hamster kidney cells and subsequently named Schmallenberg virus (SBV) (1).

The virus predominantly infects domestic and wild ruminants. Thus, the viral genome and specific antibodies have been detected in cattle, sheep, goats, bison, moose, alpacas, buffalos, fallow deer, roe deer and red deer (3). Antibodies were also found in a dog in Sweden (4). Type I interferon receptor knock-out mice are susceptible to an SBV infection (5), but there is no evidence that humans can be infected (6, 7).

Aetiological agent
Schmallenberg virus is a member of the family Bunyaviridae, which is divided into the five genera Orthobunyavirus, Hantavirus, Nairovirus, Phlebovirus and Tospovirus. The genus Orthobunyavirus, to which SBV belongs, contains more than 170 viruses of differing medical and veterinary relevance (8) and is divided into 18 serogroups. Phylogenetic analyses suggested that SBV is a member of the Simbu serogroup, together with Akabane virus (AKAV), Aino virus (AINOV), Simbu virus, Douglas virus, Shamonda virus and Sathuperi virus, for example (9, 10).

Schmallenberg virions are spherical, enveloped particles approximately 80–120 nm in diameter (11). As in typical orthobunyaviruses, the negative-stranded tripartite RNA genome, which comprises a large (L), a medium (M) and a small (S) segment, encodes for six proteins. The orthobunyaviral L-segment encodes the RNA-dependent RNA polymerase, the M-segment encodes the viral glycoproteins Gn and Gc, as well as a non-structural protein, and the S-segment encodes the nucleocapsid (N) protein together with a small non-structural protein in an alternative overlapping reading frame (12, 13).
As described for related viruses such as AKAV (14), the M segment of SBV is the most variable of the three segments (15, 16, 17). A region of high sequence variability was found in field samples within the glycoprotein Gc (15, 16), and after several cell culture passages of cell culture-grown virus without immune selective pressure (16). This hypervariable region is independent of the host species or area from which the samples were derived (15); however, its relevance is unknown and needs further investigation.

As in other segmented viruses, genetic reassortment occurs between different bunyaviruses (14, 18, 19) but studies of the Simbu serogroup are very limited. It has been suggested that SBV is a reassortant between the M-segment of Sathuperi virus and the S- and L-segments of Shamonda virus (10), but in another report it was concluded that SBV is an ancestor of Shamonda virus, which is a reassortant containing the S- and L-segments of SBV and the M-segment from an unclassified virus. The latter assumption was supported by serological cross-reactivity (9).

Epidemiology

Serum samples taken during spring 2010 and in spring and summer 2011 from ruminants in Germany, the Netherlands, Belgium and France were all seronegative for SBV, suggesting the absence of the virus from central Europe before summer 2011 (20, 21, 22, 23). However, since its first detection in early autumn 2011 near the German–Dutch border, SBV has spread extremely quickly over large parts of the European continent (3, 24). After the first vector season (2011), a very high seroprevalence from approximately 70% to nearly 100% was observed in northwestern Germany, Belgium and the Netherlands (11, 20, 25), which was initially the most affected area. In general, the percentage seropositivity was higher in cattle than in small ruminants (11).

In the second transmission period (2012), SBV was still circulating in the primary affected area, but at a low level. The seroprevalence in adult Belgian cattle remained high but was only about 20% in calves between 6 and 12 months of age (26). The virus also spread from the core region of the 2011 epidemic into previously uninfected or less-affected regions; for example, eastern European countries such as Poland (27), and southern Europe as far as Spain (28) and Greece (29). Abortions caused by SBV were also reported from Turkish regions bordering European Union countries (30).

Schmallenberg virus has now been detected in northern European countries: Denmark (31), Sweden (32), Norway (33, 34) and Finland (35). The virus has even spread above the latitude of 60°N, which exceeds the distribution of bluetongue virus serotype 8, an orbivirus transmitted by the same insect vectors as SBV, during the 2006 to 2009 bluetongue epidemic (36). Cases of SBV infection, confirmed using real-time polymerase chain reaction (PCR) or antibody detection, were also reported among domestic and sympatric wild ruminants grazing alpine meadows at an altitude of more than 2,000 m in the eastern Pyrenees in Spain (28). Spreading from continental Europe, SBV reached southern England, possibly by infected midges blown across the English Channel (37), and from there spread across the British Isles to Scotland (38, 39) and Ireland (40).

As in the German–Dutch–Belgian border region in 2011, a very high seroprevalence was observed in the most-affected area after the 2012 vector season. Based on retrospective detection of antibodies or genome in archived samples, SBV was found to have reached Austria most probably in July–August 2012, the seroprevalence in Austrian cattle exceeding 98% in October of that year. The seroprevalence in small ruminants, however, was lower and differed regionally (41). An equally rapid increase of the between-herd seroprevalence in cattle was found in Switzerland: seropositivity in bulk milk samples from Swiss dairy cattle was barely 20% in July 2012, but by December that year it had increased to 99.5% (42).

Despite high seroprevalence in central European livestock, SBV was still circulating in the 2012 and 2013 vector season, but at a low level (43). As an example, seven instances of viral genome detection were reported to the German Animal Disease Reporting System (TSN) between 1 January and 24 March, 2014 (44).

Modes of transmission

Members of the Simbu serogroup to which SBV belongs are transmitted by Culicoides midges and/or mosquitoes (45, 46). Following the discovery of the introduction of SBV to European countries at the end of 2011, SBV RNA was rapidly detected in archived samples of field-caught Culicoides (47, 48, 49, 50, 51). The following Culicoides species were implicated in transmission of SBV: C. obsoletus sensu stricto, C. scoticus, C. chiopterus and C. dewulfi. A recent study has implicated C. nubeculosus for the first time as a potential field vector of SBV in France (52).

Testing of individual Culicoides specimens in the Netherlands showed that the prevalence of SBV infection was five to ten times higher than bluetongue virus infection in Culicoides species in Europe between 2002 and 2008 (50). Vector biology was positively influenced by climatological circumstances in 2011, with a prolonged vector season (several weeks as the result of higher than normal temperatures), higher survival rate and increased vector abundance (rain
in summer, higher than normal temperatures in autumn). In a Dutch field study investigating the presence of SBV in mosquitoes overwintering at 11 ruminant farms in the Netherlands, where between November 2011 and January 2012 SBV circulation had been proven based on the presence of SBV RNA in the brains of malformed newborns, no evidence was found for the presence of SBV in hibernating mosquitoes (Culex, Anopheles, Culiseta spp.) collected from January to March 2012 (53). It was therefore suggested that mosquitoes do not play an important role, if any at all, in the persistence of SBV during the winter months in north-western Europe. Recently, oral competence studies for SBV in two widespread mosquito species (Aedes albopictus, Culex pipiens) in Spain (52) demonstrated that neither species was able to replicate SBV to transmissible levels, and it was concluded that they appear unlikely to play a major role in transmission.

Experimental infection studies with laboratory-reared lines of Culicoides at the Pirbright Institute (United Kingdom [UK]) have provided evidence of successful dissemination of SBV in C. sonorensis (54). The results for C. nubeculosus were more equivocal, and the probability of developing a transmissible infection was significantly lower than in C. sonorensis. The low rate of SBV infection in laboratory-reared C. nubeculosus was confirmed in recent experimental studies in Spain (52).

No SBV could be detected in nulliparous Culicoides midges caught in Belgium in May 2012 (55), thus providing an indication that transovarial transmission is not likely to occur. Nevertheless, this should be further investigated as it was recently reported that SBV RNA was detected in midges considered as nulliparous based on visual inspection in Poland in 2012 (56).

Renewed but short-lived circulation of SBV in parous midges of the subgenus Avaritia was observed in Belgium in August 2012, but no more positive pools were found from September 2012 onwards (55). In the Netherlands, only two of 42 pools of midges of the Obsoletus complex caught in 2012 tested weakly positive, indicating a relatively low viral load (43). At the level of an individual midge, the proportion of SBV-infected Culicoides of the Obsoletus complex caught in the same area and in a comparable period of the year was significantly lower in 2012 (0.1%; 1 of 1,050 tested) than in 2011 (0.56%; 13 of 2,300 tested). It was assumed that the level of SBV circulation was lower in this area in 2012 because only a small fraction of hosts was left susceptible to infection after the massive epidemic in 2011.

Oronasal inoculation of calves with culture-grown SBV did not lead to infection (57) and in-contact cattle and sheep remained seronegative in several animal trials (57, 58, 59), therefore direct horizontal transmission of SBV is highly unlikely. In contrast, vertical transmission of the virus from the dam to the fetus by transplacental infection does occur; the rate, however, appears low in cattle (60, 61).

In addition, SBV genome has been detected in bull semen (62, 63, 64), and it was demonstrated by subcutaneous inoculation of calves (65) and interferon receptor-deficient mice (63) that a few of the tested PCR-positive semen samples contained infectious virus. Whether an infection can be induced by insemination of cows with SBV-containing semen and whether this has epidemiological relevance remain to be evaluated.

Clinical signs

Infected adult ruminants may show no clinical signs or only nonspecific mild signs such as fever, diarrhoea or reduced milk production for a few days (1, 58). As described for viruses related to SBV (66, 67), the viraemic period is short lived (maximum six days) (1, 58) but viral genome is detectable for an extended period in the lymphoreticular system, particularly in the mesenteric lymph nodes (57, 58, 59). Much more important than the effect on adult ruminants is the induction of severe congenital malformations, premature birth or stillbirth, or the birth of mummified fetuses, when the dam is infected during a critical phase of gestation. For AKAV, which is closely related to SBV, the critical period in cattle is between the third and sixth month of gestation (68, 69, 70) and in sheep between days 30 and 50 (71, 72, 73). In all probability, this critical period is similar for SBV (60). However, not every infection of the dam with SBV or other Simbu serogroup viruses during that timeframe results in an abnormal course of gestation or leads to fetal antibody response (60, 61, 74). The birth of one malformed and one healthy lamb/kid within the same litter has been reported (75, 76). Calves or lambs congenitally infected with SBV may show varying degrees of deformation in the central nervous system (Figs 1 & 2) and/or skeletal muscles (Fig. 3), which is described as arthrogryposis-hydranencephaly syndrome. The most common malformations comprise mild to severe hypoplasia of the central nervous system (Figs 1 & 2), narrow spinal cords, poliomyelitis, porencephaly, arthrogryposis (Fig. 3), torticollis, kyphosis, lordosis, scoliosis, anklylosis and brachygnathia (76, 77, 78, 79, 80).

Diagnosis

Direct virus detection is based primarily on detection of the SBV genome in real-time quantitative reverse-transcription PCR assays (RT-qPCR) targeting either the L-, M- or S-segment (1, 81, 82). Of those, the S-segment-based assay has been shown to be the most suitable system for sensitive
and specific detection of SBV genome (81). In addition, for the detection of all members of the Simbu serogroup, a pan-Simbu RT-qPCR system with the possibility of subsequent species classification via sequencing has been established (81). Further, SBV can be isolated on insect cell lines (e.g. larval cells of Culicoides variipennis), baby hamster kidney cells or African green monkey (Vero) cells (1, 58).

However, because of the short viraemia lasting only a few days in acutely infected animals (1, 57, 58), detection of specific antibodies is much more promising than RT-qPCR or virus isolation. Test systems include micro-neutralisation, indirect immunofluorescence tests and commercially available enzyme-linked immunosorbent assays (ELISAs) (57, 83, 84, 85). Of those, the neutralisation test was found to be slightly more sensitive than the applied ELISAs in a limited ring trial among European laboratories (86).

The preferred sample material for detecting acute infections in adult ruminants and for antibody detection is serum. Suitable sample materials for RT-qPCR of aborted fetuses or malformed newborns include brain samples, placenta, meconium and hair swabs (82, 87, 88). However, viral genomes cannot be detected in all lambs or calves suspected of SBV infection (88, 89), which has also been described for SBV-related viruses such as AKAV (90). In addition to RT-qPCR, the detection of antibodies in fetal heart blood samples or in serum taken before colostrum intake is a valuable tool for confirmation of congenital SBV infection (60, 88, 89).

**Impact**

In general, the impact of SBV infection on animal welfare and animal production appears limited but is greater among sheep than among cattle (2-4). Recently, the between-herd
impact of SBV was calculated as the number of herds with one or more malformed virus-positive fetuses in relation to the number of holdings in the respective region. In the countries affected by SBV between 2011 and 2013, the 75th percentile of the case intensity was below 1% for cattle (maximum 4%) and 3% for sheep herds (maximum 7%) (36).

Based on the evaluation of questionnaires sent to large-animal veterinary practitioners in Belgium, the mean cost of individual symptomatic treatment was estimated to be between €40 and €200 in cases of apparent recovery and between €50 and €80 in cases with a fatal outcome (91). In adult cattle the most frequently observed symptoms were reduced milk production, diarrhoea, fever, abortion, dystocia and a few cases of mastitis; in adult sheep and goats almost only abortion and dystocia were reported (91). In Dutch dairy herds, the average daily milk yield per cow in 2011 was slightly lower in herds with SBV cases than in control herds (defined as herds without malformations in newborns or anomalies in reproductive performance but with seropositive animals) (61). Much more important than the very low effect on adult animals is the occasional induction of abortion, stillbirth and/or fetal malformation. Lambing data on French sheep flocks affected by SBV indicate that on average about 85% of the ewes gave birth normally. However, the clinical impact varied greatly between the flocks and most probably correlates with the percentage of ewes pregnant within the susceptible phase of gestation at the time of exposure to SBV. In approximately 12% of the SBV-affected herds the course of pregnancy was normal in more than 95% of the sheep, whereas in about 10% of the monitored farms fewer than half the ewes gave birth normally (92). On British sheep farms with RT-qPCR-confirmed SBV cases, on average 10-4% of all lambs that were born died within the first week after birth, and 8–16% of the farms with confirmed or suspected SBV infections had a lamb mortality of more than 40% (93). In contrast to sheep, the percentage of vertical transmission to their fetuses from cows infected during the critical phase of gestation and a subsequent abnormal course of pregnancy appears to be low. The number of stillborn and/or malformed calves born in Dutch dairy cattle herds was combined with calving data on the respective farms and showed that only approximately 0.5% of the calves born between February and September 2012 were infected with SBV (61). The relatively low number of aborted and/or malformed calves may also be applicable at farm level.

Vaccination is a much more reliable method for acquiring immunity against the virus. It is known that inactivated vaccines against viruses closely related to SBV are able to prevent disease (95), making vaccination an adequate instrument for disease control. In Japan, for example, an inactivated, multivalent vaccine against AKAV, AINOV and the similarly teratogenic reovirus Chuzan virus is available to prevent infectious reproductive disorders in ruminants. However, this vaccine, although against viruses related to SBV, was not able to prevent an experimental SBV infection (96). In contrast to that heterologous vaccine, newly developed, inactivated, SBV-specific candidate vaccines have effectively protected cattle and sheep against an SBV infection (97). In May 2013, provisional marketing authorisation was granted for an inactivated vaccine against SBV for the UK market (98). Maternally derived antibodies, which may block the production of serum antibodies by young vaccinated animals, are detectable for a period of approximately 180 days (range 120–240) in calves (99).

Control measures

As SBV is transmitted by Culicoides biting midges, the use of repellents or insecticides could be considered as a means of reducing the risk of exposure of susceptible animals to potentially infected vectors. However, a case-control study in Germany in 2012 provided no evidence for protective effects of such treatments (11). Another possibility for prevention of transplacental transmission to the fetus may be an intelligent breeding system where, for example, the number of cows and ewes in the susceptible stage of gestation could be minimised during the season of the highest activity of insect vectors responsible for virus transmission. Furthermore, grazing management could be adapted such that young stock is kept outside and is therefore more likely to be exposed to the vector; immunity against SBV acquired before heifers conceive for the first time might prevent fetal infections. Longitudinal whole-herd serological monitoring using a virus neutralisation test indicated that 80% of adult dairy cows still had measurable anti-SBV antibodies at least 24 months after the estimated introduction of virus into the herd. This means that at least two years after natural infection, animals were probably protected against re-infection (94).

Acknowledgement

Figures 1, 2 and 3 were kindly provided by M. Peters (Staatliches Veterinäruntersuchungsamt Arnsberg, Germany).
Infection due au virus Schmallenberg

K. Wernike, A. Elbers & M. Beer

Résumé
Depuis la détection du virus Schmallenberg (un orthobunyavirus du sérogroupe Simbu) identifié pour la première fois en Allemagne, près de la frontière avec les Pays-Bas, à la fin de l’année 2011, ce virus s’est propagé à une grande vitesse, provoquant une pandémie majeure qui a affecté tout le bétail européen. Le virus, transmis par les moucherons du genre Culicoides, infecte les ruminants domestiques et sauvages. Les animaux adultes infectés ne présentent que peu ou pas de signes cliniques mais lorsque l’infection survient au cours d’un stade critique de la gestation, il peut s’ensuivre un avortement, la naissance de morts-nés ou de graves malformations congénitales chez la progéniture. L’impact de la maladie est généralement plus grave chez les ovins que chez les bovins. La vaccination pourrait jouer un rôle important dans la lutte contre cette maladie.

Mots-clés

Infección por el virus de Schmallenberg

K. Wernike, A. Elbers & M. Beer

Resumen
Desde que a finales de 2011 fue caracterizado cerca de la frontera entre Alemania y los Países Bajos, el virus de Schmallenberg, un orthobunyavirus del serogrupo Simbu, se ha extendido con suma rapidez y ha causado una gran epidemia en el ganado europeo. El virus, transmitido por el jején Culicoides, infecta a rumiantes domésticos y salvajes. Mientras que el animal adulto solo presenta signos clínicos leves, o en ocasiones ninguno, la infección en una fase crucial de la gestación puede causar aborto, mortalidad o graves malformaciones de la progenie. Las repercusiones de la enfermedad suelen ser más graves en el ganado ovino que en el vacuno. Un importante ingrediente de la lucha contra ella podría ser la vacunación.

Palabras clave
References


