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Schmallenberg virus in Europe—a review
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Abstract
Schmallenberg virus has spread all over Europe since late summer 2011. It belongs to the family of the Orthobunyaviruses and is transmitted through biting midges and vertical infection. Horizontal transmission is improbable. The virus was mainly detected in ruminants and only in two other species, but typical symptoms such as abortions, stillbirths and malformed newborns only occur in ruminants. Antibodies were also detected in several non-ruminants. There are no indications for pathogenicity in humans. The virus can be diagnosed by real-time PCR, virus isolation or serologically by virus neutralization, indirect immunofluorescence test and ELISA. Two vaccines have been made commercially available in Europe. This review will briefly summarize the current knowledge on the Schmallenberg virus and its disease.

Keywords: Schmallenberg virus, ruminants, Europe

Introduction
In August 2011, there was the first report on an unknown disease that was observed in dairy cows in North Rhine-Westphalia (Germany). A similar case was reported from the Netherlands at the same time. Clinical signs that were associated with the disease were non-specific such as fever, diarrhea and decreased milk production. Later on, lambs were born that showed different degrees of malformation. Laboratory tests were all negative for classical bovine endemic and emerging viruses such as pestivirus (BDVD), bovine herpesvirus 1 (BHV1), foot and mouth disease virus (FMDV), bluetongue virus (BTV), epizootic hemorrhagic disease virus (EHDV), Rift Valley fever virus (RVFV), and bovine ephemeral fever virus (BEFV). At the same time, comprehensive investigations performed at the Federal Research Institute for Animal Health in Germany that also included a metagenomic analysis revealed that the disease was caused by a new virus belonging to the family of Orthobunyaviruses. Because the virus was found in a pooled blood sample obtained from three sick cows from a dairy farm near the German town Schmallenberg, North Rhine-Westphalia, the new virus was named “Schmallenberg virus”. Since its first detection, the virus quickly spread all over Europe. In Germany, for instance, Schmallenberg virus-associated disease which is considered a notifiable animal disease in ruminants, was observed on 1,478 cattle farms as well as 973 sheep and 53 goat flocks until March 2014. This contribution will briefly review the disorder.

Epidemiology
Schmallenberg virus is part of the Simbu serogroup of the genus Orthobunyavirus within the family Bunyaviridae. Akabane virus, Aino virus and Shamonda virus cause similar symptoms as Schmallenberg virus (see below) and are widespread in Oceania, Australia, Africa, and Asia. Clinical signs have not been reported in non-pregnant adults with the exception of one report of sudden astasia and leukopenia in a naturally infected dairy cow. In naturally infected pregnant cattle and sheep, Aino virus has been associated with stillbirths, premature births, and birth defects including arthrogryposis, scoliosis, sunken eyes, cataracts, maxillary retraction, and dental irregularities. Some calves may have a domed head from hydranencephaly and cerebellar hypoplasia. Schmallenberg virus is relatively liable in the environment or the vectors, as it does not survive outside its natural hosts for a long time. Also, it is susceptible to standard disinfectants such as 70 % ethanol.

It seems that Schmallenberg virus is almost completely adapted to domestic ruminants, as the virus itself was almost exclusively found in cattle, sheep and goats by either PCR or virus isolation. There are only two reports on virus positivity in other than the aforementioned species, i.e. in a dead elk calf and in one dead puppy.
There are a number of other ruminants and also non-ruminant species that were found serologically positive including roe deer, fallow deer, red deer, sika deer, chamois, bison, moufflon as well as alpaca, dog and wild boar.\textsuperscript{11-20} Schmallenberg virus spread all over Europe within a very limited time period i.e. 2 1/2 years.\textsuperscript{4} The list of countries that are positive includes Germany,\textsuperscript{3} the Netherlands,\textsuperscript{2} France,\textsuperscript{21} Belgium,\textsuperscript{22} Luxembourg, Austria, Switzerland,\textsuperscript{23} Italy,\textsuperscript{2} Poland,\textsuperscript{11} Czech Republic, Spain,\textsuperscript{25} Denmark,\textsuperscript{26} the UK,\textsuperscript{27} Ireland,\textsuperscript{29} Norway, Finland, Sweden, Estonia, Latvia, Hungary, Slovenia, Romania, Croatia, Serbia, Turkey,\textsuperscript{30} and Greece.\textsuperscript{31} Other neighboring countries are most likely also positive, but have yet not been sampled.

The prevalence of Schmallenberg virus infection in dairy herds is high. Studies conducted in the Netherlands and Belgium in 2012 revealed a prevalence at farm level of 95.5 % and 99.76 %, respectively, in 2012.\textsuperscript{32,33} Moreover, the intra-herd-prevalence was 86.3 % in the Dutch study.\textsuperscript{32} A high prevalence of 97.1% was also found in sheep flocks in the Netherlands.\textsuperscript{34} Within a flock, 58.7-84.31% of the sheep were found seropositive.\textsuperscript{34,35} Goats were found less often infected; the intra-herd-prevalence was 40.68 % in Belgium, 36.7 % in the northwest part of Germany and 43.8 % in Lower Saxony, Germany.\textsuperscript{34-36} Schmallenberg virus is transmitted by biting midges (\textit{Culicoides} spp.). The virus was found in several \textit{Culicoides} spp. (i.e. \textit{C. obsoletus complex}, \textit{C. dewulfi}, \textit{C. chiopterus}, \textit{C. scoticus}, \textit{C. punctatus}) in Denmark, the Netherlands, Belgium and Poland.\textsuperscript{26,37-40} A horizontal transmission through animal contact is unlikely. For instance, in one experiment where two cows were orally inoculated with virus did not result in an infection. Also, sentinel cattle kept in the same compartment remained virus- and seronegative.\textsuperscript{41} Schmallenberg virus can also be detected in semen of infected bulls.\textsuperscript{32-44} In a recent study performed by Wim van der Poel et al,\textsuperscript{44} two bulls were inoculated subcutaneously with a Schmallenberg virus isolate. Virus RNA was then isolated from blood samples two to four days after inoculation. In semen, the highest amounts of virus were observed on days four to seven after inoculation, followed by intermittent shedding during the next two to three weeks. However, the clinical relevance of virus transmission by semen and artificial insemination still needs to be determined.\textsuperscript{43}

\textbf{Clinical signs and pathology}

Generally, there are only weak clinical signs in the adult animal that are associated with the infection. In adult cows signs are rather inconspicuous or nonspecific such as fever (up to 41°C), decreased milk production and diarrhea.\textsuperscript{1} The signs last for up to six days (concurrent with the time period of viremia that also lasts for up to six days).\textsuperscript{45} Infections occur seasonally with higher incidences in summer and autumn when midges are most active. Up until now, no clinical signs have been described in goats and sheep. An infection experiment performed with 30 adult sheep resulted in a mild or subclinical disease course in only a few animals (diarrhea in one sheep; snotty nose in two sheep).\textsuperscript{46} Overall, the situation resembles that of Akabane virus infection which also causes only mild clinical signs or is subclinical in ruminants.\textsuperscript{5}

Vertical transmission of Schmallenberg virus and infection of the fetuses can lead to embryonic mortality, malformed newborns, abortions and stillbirths. Virus has been isolated from mummies.\textsuperscript{2} However, there is a critical or susceptible window in gestations where an infection has to happen for malformations to occur. In sheep this window is between days 28 and 60 of gestation;\textsuperscript{47} for cattle it is between day 80 and 150.\textsuperscript{6} For Schmallenberg virus it is yet not known what happens to the embryos or fetuses if an infection occurs prior to, or after the aforementioned windows. However, assuming that the pathogenesis of Schmallenberg virus infection is similar to Akabane virus infection, infections outside the aforementioned windows may still lead to embryonic/fetal death, but malformations may then be rare or absent.\textsuperscript{48}

The predominant malformation in calves, lambs and kids is the “arthrogryposis-hydranencephalia-syndrome”. Generally affected newborns do show one or more of the following malformations: arthrogryposis, vertebral malformations, brachygnathia inferior, ankylosis, torticollis, and scoliosis. In addition, malformations of the central nervous system (CNS) can occur, including
hydramencephaly, porencephaly, hydrocephalus, cerebellar hypoplasia, and micromyelia.⁴⁹-⁵¹ Most of the malformed newborns are dead at birth. Those that are born alive are usually nonviable and have to be euthanized immediately. Furthermore, especially malformations of the limbs can cause dystocia that then require obstetrical intervention. Also, due to limb malformations perforations of the uterine wall during labor are possible.⁵² If the CNS is additionally affected, newborns may also show a decreased or missing sucking reflex and develop locomotion problems.

**Diagnosis**

The Schmallenberg virus can be detected by real-time RT-PCR or by virus isolation using different cell lines.³ The best time to isolate the virus is during the period of viremia (i.e. within the first week of infection) using EDTA-blood or serum. Also, different tissue specimens such as brain, spleen, meconium and amniotic fluid from stillborn or malformed newborns are feasible.⁵³ Virus specific antibodies can be detected by virus neutralization, indirect immunofluorescence test or by ELISA (there a several commercial antibody ELISA-Kits available).

**Zoonotic potential**

Susceptibility of Schmallenberg virus for humans is still patchy. Available data suggest, however, that the risk of a transmission from animals to man is unlikely. For instance, there are two recent studies conducted in Berlin, Germany, by the Robert Koch Institute, and in Bilthoven, The Netherlands, by the National Institute for Public Health and the Environment.⁵⁴,⁵⁵ In these studies, personnel working in infected sheep and goat flocks and cattle barns, as well as the responsible veterinarians, were tested for antibodies against the virus. None of the tested people were positive for virus specific antibodies.

**Control and prophylaxis**

There is currently no specific treatment against the Schmallenberg virus. There are two vaccines (Bovilis® SBV [Intervet UK Ltd, Milton Keynes, Buckinghamshire, United Kingdom], SBVvax [Merial SAS, Lyon, France]) that are available in two European countries, i.e. in the United Kingdom and in France, to be used in sheep and cattle. Both vaccines contain inactivated virus. According to the labels, sheep at four months or older are to be vaccinated only once while in cattle, two vaccinations are required at an age ≥2 months and again three weeks later. A clear antibody response can be usually observed three weeks after first (sheep) or second (cattle) vaccination. While it is not yet known how long protection may last, the general assumption is for at least 12 months. To the author’s knowledge there is no commercial vaccine available for use in goats.

Another preventative measure is to use repellents and pyrethroids directed against the vector, i.e. biting midges, thus reducing the risk of an infection with the virus. Another but probably only theoretical approach is to breed the animals in colder times of the year (i.e. in the late autumn or winter time) to avoid having the dams pregnant during the time of gestation when the fetuses are susceptible to an infection.

**Summary and conclusion**

Up until now clinical disease caused by Schmallenberg virus has only been seen in ruminants. Main economic losses result from the infection of pregnant animals leading to stillbirths, abortions, malformations and embryonic death. Since the virus is transmitted by biting midges, preventive measures that would completely protect from an infection are almost impossible to be implemented. Currently, vaccination is the best and only effective way to reduce clinical disease and thus reduce economic losses due to an infection. In addition, repellents and pyrethroids may help as a vector control measure.
References


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