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Advances in Schmallenberg Virus Research: A Review

Shahin Nekoei[1], Arezoo Fattahian[2]*, Hossein Momeni[3] and Abed Raki[3]

[1]Department of Clinical Sciences, Faculty of Veterinary Medicine,
Shahrekord Branch, Islamic Azad University, Shahrekord, Iran.
[2]MSc of Food Hygiene and Quality Control, Faculty of Veterinary Medicine,
Shahrekord University, Shahrekord, Iran.
[3]Young Researchers and Elite Club, Shahrekord Branch, Islamic Azad University, Shahrekord, Iran

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After the emergence of the Bluetongue virus serotype eight (BTV-8), which was unexpected, in 2006 in northern Europe, another *Bunyaviridae* family, referred to as the Schmallenberg virus (SBV) also emerged in 2011 in Europe resulting to a new disease in ruminants which proved to be economically significant. This SBV virus, grouped in the genus *Ortobunyavirus* and the family of *Bunyaviridae*, initially detected in Germany, Belgium, and the Netherlands in the year 2011. It later spread to France, Great Britain, Spain, Denmark, Italy, Luxembourg, Switzerland, Sweden, Norway, Finland, Irleand, Austria, Poland, Estonia.

Key words: Schemallenberg virus, Pathogenesis, Epidemiology, fetal malformations, *Ortobunyavirus* genus, *Bunyaviridae*.

In 2011, during autumn, a virus that was previously unknown but was common among ruminants known as "Schemallenberg" virus (SBV) was discovered in dairy cows, in the Netherlands around the eastern regions and in the north western side of Germany (Beer *et al*., 2012; Dominguez *et al*., 2014; Raboisson *et al*., 2014).

The virus was classified under the Simbu serogroup that falls under the *Orthobunyavirus* genus of the *Orothobunyaviridae* family. Just like the rest of the *Orothobunyaviruses*, the virus is transmitted through arthropod vectors, mainly by the biting midges (Beer *et al*., 2012; Elbers *et al*., 2014; Koenraadt *et al*., 2014). In regions facing temperate climate, such biting result in a seasonal spread pattern. Acute SBV infection common in mature ruminants has been identified to be the cause of transient and mild disease or in some cases remain clinical unapparent. Transplacental SBV infection on pregnant ruminants during a delimited gestation stage can result to giving birth of offspring that are severely damaged such as stiff neck, sever brain malformations and arthrogryposis. The malformation type typically caused by Simbu serogroup virus is known as 'arthrogryposis hydranencephaly syndrome' (Goller *et al*., 2012; Koenraadt *et al*., 2014).

Following the fact that there is lack of specific knowledge on SBV, it is generally assumed by Akabane virus analogy that the vulnerability

* To whom all correspondence should be addressed.
E-mail: fattahianpasport@yahoo.com

gestation stage, when the foetal infection of SBV is likely to lead to AHS, is the gestation second month for small ruminants and between the third to the sixth month of their gestation period for cattle (Goller *et al*., 2012).

AHS affecting ruminant offspring following SBV foetal infections was initially reported in Europe in the winter season of 2011 to 2012. In accordance to the European Food Safety Agency (EFSA) as of 2013, more than 9,000 cases of SBV infections had already been confirmed affecting ruminant herds all over Europe, and about half of these cases were reported in France (Goller *et al*., 2012; Doceul *et al*., 2013; Koenraadt *et al*., 2014).

In some of the cases, transient diarrhea symptoms were also witnessed in Netherlands. Some of the observed symptoms in these areas were similar to those of Bluetongue virus (BTV) and a re-emergence of the same virus that resulted in a major epizooty in Europe between 2006 and 2008 was feared. The Friedrich –Loeffler Institute (FLI) in November 2011, in Germany identified viral RNA related to a new virus in blood samples from dairy cows that are clinically affected using a meteganomic approach (Conraths *et al*., 2013).

This paper is going to look at Schmallenberg virus genetics advances, Schmallenberg virus pathogenesis infection on host, environmental factors that trigger the transmission of Schmallenberg virus, Schmallenberg virus vaccine development advances and Schmallenberg virus epidemiological spread. It will be achieve through analysis of already existing literature on SBV.

Significance of the study

Previous studies have shown milk drop and fever in adult dairy cows. However, in animals that are pregnant, the virus has been observed to infect the developing fetus, attacking the spinal cord and the brain, resulting to damage of such organs and deformation of the spine, legs, and head. In most cases, most viruses do not result in diseases in non-pregnant animals so the SBV virus can be slightly different. This implies that careful examination and studies are needed in areas that are affected to determine how important such information is. Through the efficient surveillance on the spread of the virus across Europe is essential to describe further the epidemic progression as well as its impact in the breeding industry. This calls for the need for more studies to determine the areas where SBV is present, to understand its genetic and geographical origin as well as indentify the putative reservoirs of the disease. More information on pathogenesis related to SBV infection and the SBV antibodies ability to protect animals against associated diseases is useful in controlling the disease.

Review

Timeline of SBV infection in Europe

SBV was initially detected in 2011 in the Netherlands and in Germany. By December 2011, the Netherlands had reported a teratogenic SBV effect in sheep that resulted to the birth of malformed lambs which had crooked neck, stiff joints, and hydrocephalus. The SBV presence was then reported at the end of December 2011 in Belgium and on January 2012 in the United Kingdom (Bilk *et al*., 2012; De Regge *et al*., 2012a; Conraths *et al*., 2013).

The first SBV case in France was reported in January 2012 after the detection of virus genome by RT-qPCR in brain samples that had been removed from malformed lambs from farms located in the Meurthe et Moselle and Moselle territorial divisions in north-eastern France (Bilk *et al*., 2012; De Regge *et al*., 2012a; Conraths *et al*., 2013).

The SBV presence was later reported in 16th of February in Luxembourg. In the same month, SBV was then confirmed in north-east Italy in a case that involved a malformed goat and there after a newborn lamb was detected to have SBV in Andalusia, Spain (Bilk *et al*., 2012; De Regge *et al*., 2012a; Conraths *et al*., 2013).

By April 2013, SBV cases had been detected involving more than 3628 herds across Europe. Holding infected by SBV recorded up to this period corresponded to infections detected in 2011. In 2012, May, acute SBV infections were also detected in south west France involving a cattle in the Pyrennes-Antlantiques territorial division. This latest detection indicated that SBV could re-circulate following the winter period. Similar conclusions were reached at after the detection of SBV in the United Kingdom involving newborn lambs in May and June the same year and in Germany where a sample of sheep, cattle and goat holdings were taken. In early 2012, the assays were developed in an effort to detect anti-SBV

antibodies, offered a useful tool that showed the presence of SBV infection after viraemia is transient (Conraths *et al*., 2013).

In June, the presence of antibodies that could fight SBV was reported in Denmark involving two cattle is southern Jutland and on July, the first case of acute SBV infection was reported in Switzerland involving cows from two farms around canton of Berne. By the end of August 2012, approximately more than 55000 SBV infection cases in ruminants had been reported across northern Europe (Conraths *et al*., 2013).

Anti-SBV antibodies were detected in mid-September in Australia in sheep and cattle (Conraths *et al*., 2013). Add the start of October 2012, the antibodies presence to SBV was recorded in western Poland involving goats which had been sampled at the end of July and also in Sweden involving cows (Kaba *et al*., 2013). Anti-SBV antibodies were detected in mid-October in northern Scotland in two cows and a tup from Finland that had been sampled in September 2012 (Kaba *et al*., 2013).

More studies on the same show that the virus spread during the summer as well as in early autumn to South Finland in 2012 (Kaba *et al*., 2013) The presence of SBV was reported at the end of October in 2012 in Ireland involving a bovine foetus and a few days after another incident, in Northern Ireland involving a malformed calf (Bilk *et al*., 2012; De Regge *et al*., 2012a; Kaba *et al*., 2013). SBV infection was confirmed by the end of October the same year using RT-qPCR and or/and serology in more than 6000 holdings across Europe (Bradshaw *et al*., 2012).

In November the same year, antibodies to fight the virus were reported in milk samples from cattle herds in Norway and a SBV outbreak was reported in Sardinia, Italy involving a sheep flock having cases of foetal malformations and abortion (Bradshaw *et al*., 2012). The first case of SBV was also detected in December 2012 in the Czech Republic after the birth of malformed lambs. The first cases of SBV were reported in mid-January in Estonia in a case involving sheep fetuses and the presence of SBV was conformed in January in sheep in Slovenia (Bilk *et al*., 2012; De Regge *et al*., 2012a; Bradshaw *et al*., 2012).

Advances in Schmallenberg Virus Genetics

The *Bunyavirus* genome is made up of 3 segments of single-stranded RNA that is negatively sensed. The segments include (S) small, (M) Medium and L (large). *Tospoviruses* and *Phleboviruses* are different from other forms of *Bunyaviruses* as their S segment takes on an ambisense coding strategy (Bouloy *et al*., 2003).

The L segment codes with the RNA-dependent RNA polymerase (RdRp) L, the M segment codes with the precursor polyprotein which is co- translationally sliced into the glycoprotein Gc and Gn envelope and the protein NSm that is non structural. The S segment codes with the non-structural protein NSs and the nucleoprotein in an open frame that is overlapping (Bouloy *et al*., 2003).

The three SBV genome segments have been completely sequenced but the different encoded proteins and its structure are not yet well-characterized and the only chance they have of being predicated is from the data provided on related viruses (Elliott *et al*., 2013).

There have been a number of works at the laboratories in the recent past to reverse the genetic system for the Orthobunyavirus prototype, *Bunyamwera* virus (BUNV), by the use of the bacteriophage T7 RNA polymerase system (Bouloy *et al*., 2003). In this process, the infectious virus could be entirely from cDNA clones. The system has been subsequently applied to the the *Phlebovirus* Rift Valley fever virus (RVFV) and *Orthobunyavirus* La Crosse virus (LACV) (Elliott *et al*., 2013).

To add on this development, Akabane virus recovery has been accomplished by the use of the RNA polymerase I approach. One of the reverse genetics exploitation is the coming up with the genetically engineered recombinant viruses which have the ability as candidate vaccines. Hence, a tool to be used in future in developing SBV vaccine strains can be used in the establishment of a reverse genetic system that is efficient (Bouloy *et al*., 2003)

Pathogenesis of schmallenberg virus infection on host

The *Orthobunyaviruses* pathogenicity depends on several viral factors that are encoded by the three segments of genomic. For example, the neuroinvasive La Crosse virus ability, another *Orthobynyavirius* from the California serogroup, can be determined using glycoproteins or/and

polymerase as the host immune response can be inhibited using NSs that antagonizes the type I interferon (IFN-I) expression and the transcription mediated using RNA polymerase II (Bouloy *et al*., 2003).

The **NSs** proteins of Bunyamwera serogroup, the Orothobunyavirus prototype virus and the *Bunyaviridae* family, also takes part in viral pathogenesis and has been identified as a major virulence factor. The non-structural protein prevents the synthesis of protein and the response of the host cell antiviral through interfering with the dependent transcription of the RNA polymerase II, apoptosis mediated using IRF-3 and IFN-I production (Walter and Barr, 2011).

Despite the fact that there exists no sequence of the conservation, NSs coming from other *Bunyaviruses* also take part in the inhibition and pathogenesis of the antiviral response of the host cell. A good example is the Rift Valley's NSs fever virus represses host transcription through interfering with the transcription factor II H (TFIIH) complex subunits, reduces dsRNA that are protein kinase which have been activated and suppresses the promoter IFN activation through its association with the Sin3A complex subunit (Walter and Barr, 2011).

However, little is known with regards to the viral factors that take part in the viruses pathogenicity involved in veterinary medicine like Shamonda virus, Akabane virus and SBV. Recent studies have indicated that IFN-I receptor knock-out mice are vulnerable to SBV infection and may lead to fatal diseases as it has been reported in the past for La Crosse virus and that SBV intracerebral injection is lethal when it comes to NIH-Swiss mice (Walter and Barr, 2011). In addition, another study has shown that infectious serum coming from cattle is suitable for SBV infection model standardized compared to culture-grown virus (Humphries and Burr, 2012).

The above models could be applied in future in the study of SBV pathogenesis and positively to vaccines design. Reverse genetic systems have over the years been developed for SBV and offer a powerful tool in the characterization of the virus. Recombinant viruses that lack NSs have been generated already to be used in the study of the viral protein role as a virulence factor (Humphries and Burr, 2012).

It has been proved that NSs is not important for this virus for it to replicate to become vitro, but a virus that is without the viral protein is assuaged in newborn mice. NSs has been identified to block protein synthesis as well as interfere with IFN production suggesting that, as the case of *Bunyaviruses*, SBC NSs is in a position to modulate the innate immune response of the host (Dominguez *et al*., 2012).

Potential Environmental Factors That Encourage/ Trigger Spread Of Schmallenberg Virus

Most of the *Bunyaviruses* are spread by arthropod vectors and, in particular, phlebotoms, ticks, mosquitoes, culiciodes and thrips. The only exception is the hantaviruses that are transmitted through rodents. Different researchers have reached to the conclusion that the Simbu serogroup are in most cases transmitted through culicoides, but also some cases of transmission by mosquitoes from the Culex and Aedes genus and by various species of ticks (Dominguez *et al*., 2012; Elbers *et al*., 2013)

Recent studies have reported cases of the presence of the SBV genome located in a group of culicoides that include, *C. obsoletus complex*, *C. dewulfi*, and *C. chiopterus* in Belgium trapped in 2011 from July to October (Dominguez *et al*., 2012). Culicoides that is caused by *C. obsoletus* group reported in Denmark during the same period of time it was also found to contain SBV RNA (Dominguez *et al*., 2012; Elbers *et al*., 2013).

In addition, SBV RNA was reported in *C. chiopterus* and *C. obsoletus* with samples collected in the Netherlands between August and September where the SBV prevalence among culicoides during this period was estimated to be approximately 0.25% (Elbers *et al*., 2013; Varela *et al*., 2013).

The virus was also reported in biting midges in Poland, Norway and Sweden. The above studies indicate that the culicoides species that was identified as BTV vectors also serve as vectors for SBV transmission. Up to now, there are studies that have been conducted to examine the ability of other types of arthropods, such as ticks and mosquitoes, to serve as vectors for SBV transmission (Walter and Barr, 2011; Elbers *et al*., 2013; Larska *et al*., 2013).

SBV infection cases were reported following the beginning of the 2012 vector season in the United Kingdom, France, Germany, Italy, and

Switzerland. It is not yet clear how SBV was able to survive considering the conditions in the winter season. It has been explained by some researches that the virus survived as a result of the vector population in the cold season or the virus might have persisted in the cattle population as well as in other reservoirs (Walter and Barr, 2011).

It was reported that some of the culicids species were recorded in the farm buildings in the winter and were able to complete their life cycle in different animals' enclosures. The above findings indicate that SBV has the ability to persist from one year to another in the vector population regardless of the winter temperatures (Walter and Barr, 2011).

The main transmission route of SBV is through arthropod vectors. Schmallenberg virus has been identified in the semen bulls but the venereal transmission has not yet been scientific demonstrated. Vertical transmission across hosts has been reported but has not yet been considered as being important in the spread of the disease (Murphy *et al*., 2003).

The midge vectors reliance for disease transmission implies that the spread of the virus is limited seasonally. It has been proved that vector transmission can take place even when the affected animals have been housed indoors. The exiting evidence that the virus was able to spread during 2011, 2012, and 2013 show that the disease contain mechanisms for overwintering through the low vector activity period (Hahn *et al*., 2012; Ducomble *et al*., 2012).

The overwintering mechanism has not yet been scientifically determined but it is strongly believed that the virus could have survived through vertical transmission, vertical survival in animals housed indoor, or some other form of mechanism (Walter and Barr, 2011).

Advances in Vaccine Development

Vaccination has been applied in individual livestock with the intention of protecting them from being infected by Schmallenberg virus. The significance of vaccination on cattle has increased over the years as a result of the preference for the feeding of culicoides in cattle has been incorporated in the current vaccine developments. This approach narrows the transmission chain as the vector is made to feed preferentially on animals which are likely to be protect (Murphy *et al*., 2003).

The cattle feeding preference cuts down in the number of sheep that are infected, but also in several infected cattle. This is because of the need to break the transmission chain through infected vectors over and over feeding on animals that have been infected previously. Following the greater infection force at higher temperatures, the impact of feeding preference reduces at higher temperatures (Wernike *et al*., 2012).

As in the case of other forms of midge borne pathogens, vector feeding preferences has had a significant effect on the transmission of SBV. The emphasis on the significance of the field studies is offering data to refine the model parameters. Past modeling BTV studies also included a feeding preference, however, the studies did not consider its impact explicitly, and only one study outside Great Britain considered BTV and feeding preferences (Wernike *et al*., 2012).

In the case of Horse Sickness virus infections, there are several demonstration of feeding preferences and the results indicate a large effect on disease transmission. While some of the studies have indicated a midge feedings preference among cattle, evidence on host feeding researches is variable, usually showing that species associated with livestock are opportunistic and are likely to feed on any large mammals that are available in the vicinity. Several livestock that are associated with species from Europe feed on domestic ruminants and wild deer particularly in extensive pasture and woodland contexts (Ducomble *et al*., 2012; De Regge *et al*., 2012b).

As SBV has been identified as being an insect-transmitted pathogen, vaccination is one of the most significant aspects when it comes to the control of the disease. In this case, mutant viruses that lack one or more proteins which significantly lead to viral pathogenicity were examined in the form of live vaccines in cattle (De Regge *et al*., 2012b).

It is easily shown that a novel recombinant deletion mutation is efficacious and safe vaccine candidate (Williamson *et al*., 2012). This is the initial description of a live vaccine that is putative modified for the genus *Orthobunyavirus* that is complete and to add on that, such kind of vaccine has never been examined in cattle for the presence of viruses of the entire family *Bunyaviridae*. Therefore, the vaccine that has been

described above also represents a first model for a wide range of related viruses and is of great significance in the prevention of Schmallenberg virus (Calisher, 1996; De Regge *et al*., 2012b).

Epidemiological Spread of Schmallenberg Virus

Samples taken from malformed or stillborn ruminant offspring were taken particularly from the spleen and brain. The samples showed clinical signs such as torticolis, arthrogryposis, branchygnathia, scoliosis, or hydranencephaly. RT-qPCR was conducted on them to detect the presence of virus and SBV RNA and the samples were isolated using protocols (De Regge *et al*., 2012b).

Different laboratories were set aside across Europe for SBV testing. The network of these laboratories was similar to the one put up for BTV genome detection using RT-qPCR and the laboratories considerably increased the capacity of testing samples from animals that were suspected. The structure allowed the testing of thousands of blood samples by ELISA or RT-qPCR using automats (De Regge *et al*., 2012b).

The experience that was gained earlier in 2006 during the BTV-8 facilitated the rapid construction of a laboratory network that was used in the diagnosis of SBV at a national level. By August 2012, more than 3100 cases of SBV infected farms in France has been reported and this included 2019 cattle farms, 1143 sheep farms, and 35 goat farms (De Regge *et al*., 2012b; Garigliany *et al*., 2012).

Farms reported to have been infected by SBV were localized mostly in the central-west and north-east of France as well as other affected areas across Europe. Following the new SBV cases reported in different areas in France after September 2012, surveillance measures were initiated in a move to monitor the congenital SBV forms (Garigliany *et al*., 2012).

The Surveillance took into account the SBV cases that had been reported from September 2012. Up to now, France has been identified as the nation that has recorded the highest number of SBV infected farms (Steukers *et al*., 2012).

The four main epidemiological parameters include duration of viraemia, latent period, virus replication, and transmission probability from host to vector. Changes in these epidemiological parameters are an enough account for the differences witnessed in SBV transmission between and within farms in comparison to BTV-8 (Steukers *et al*., 2012).

The above conclusion is a suggestion that alternative mechanisms for transmission such as additional vector species and direct transmission are not required in the explanation of the observed patterns of SBV spread, although they can still be considered for a minor role (Steukers *et al*., 2012).

The enhanced transmission of SBV between farms, relative to BTV, caused by the changes in these four epidemiological factors is such that the movement restrictions application, even a total ban to animal movement, has minimal effect on the final results (Steukers *et al*., 2012).

The SBV emergence at the end of 2011 across Europe is a reminder that the new disease introduction remains a threat for countries in Europe. The rapid response of the SBV emergence established by different countries from Europe has indicated that an efficient laboratories network is in place to counter any emergence of new animal viruses. This new virus was referred to as Schmallenberg virus (SBV) after the area where the origin samples were found. Viral genomic sequences analysis revealed similarities with Aino, Akabane, and Shamonda viruses, all classified under the *Orthobunyavirus* genus falling under the *Bunyaviridae* family. Sathupari, Shamonda, and Douglas viruses were identified later as closely related to SBV. A quantitative reverse transcription on a specific real time was consequently developed by FLI in an effort to detect the SBV genome and the protocol used was then shared to several European partners (van der Poel, 2012).

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