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Reconstruction of the *Schmallenberg virus* epidemic in Belgium: Complementary use of disease surveillance approaches

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ABSTRACT

Schmallenberg virus (SBV) emerged across Europe in 2011 and Belgium was among the first countries affected. In this study, published findings are combined with new data from veterinary surveillance networks and the Belgian reference laboratory for SBV at the Veterinary and Agrochemical Research centre (CODA-CERVA) to reconstruct the epidemic in Belgium.

First retrospective cases of SBV were reported by veterinarians that observed decreased milk yield and fever in dairy cattle in May 2011. The number of SBV suspicions subsequently increased in adult cattle in August 2011. That month, first SBV positive pools of *Culicoides* were detected and extensive virus circulation occurred in Belgium during late summer and autumn 2011. As a consequence, most pregnant ruminants were infected and their fetuses exposed to the virus. This resulted in an outbreak of abortions, still-births and malformed new-borns observed between January and April 2012. The number of cases drastically diminished in 2012–2013, although multiple lines of evidence obtained from cross-sectional serological surveys, analyses on aborted foetuses, sentinel herd surveillance and surveillance of SBV in vectors prove that SBV was still circulating in Belgium at that time. Virus circulation was then probably strongly reduced in 2013–2014, while increasing evidence indicates its recirculation in 2014–2015 in Belgium.

Based on the experience gathered with the closely related Akabane virus, recurrent outbreaks of congenital events can be expected for a long period. Vaccination of seronegative animals before the first mating could be used to prevent the deleterious effects of SBV. During this epidemic, different surveillance approaches including syndromic surveillance, sentinel herd surveillance, cross-sectional seroprevalence studies and pathogen surveillance in vectors have proven their utility and should be considered to continue in the future.

1. Introduction

During summer 2011, several dairy cattle herds in Germany presented high fever, decreased milk yield and severe diarrhea from unknown origin. In September 2011, blood samples were collected from cattle showing these symptoms in Schmallenberg, a small city located in Western Germany nearby the Dutch and Belgian borders. Metagenomic analysis identified a virus that was probably responsible for this unspecific syndrome and the newly emerged virus was named *Schmallenberg virus* (SBV) (Hoffmann et al., 2012). Starting from November 2011, a wide outbreak of aborted, stillborn and malformed new-borns due to transplacental infection with SBV was observed in cattle, sheep and goat (Garigliany et al., 2012b).

The teratogenic effects due to SBV are mostly reported to affect the musculoskeletal system: arthrogryposis, hydranencephly, brachygnathia, scoliosis, kyphosis or lordosis were malformations frequently reported during the epidemic (Herder et al., 2012). Also morphologically normal SBV infected animals were born presenting central nervous system alterations, mostly porencephaly and

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hydranencephaly (Hahn et al., 2013). Lesions due to SBV in peripheral organs were only demonstrated in muscle and consisted in myofibrillar hypoplasia (Seehusen et al., 2014). It remains unclear if the muscular alterations are the consequence of primary myositis or due to the central nervous loss inducing denervation and alteration of muscle development (Herder et al., 2012).

Sequencing analysis classified SBV in the family *Bunyaviridae*, genus *Orthobunyavirus* (Hoffmann et al., 2012). *Orthobunyaviruses* are enveloped RNA viruses with a negative sense, single-stranded genome. The genome is divided in 3 segments named after their size small (S, 1 kb), medium (M, 4.5 kb) and large (L, 6.9 kb) respectively (Elliott and Blakqori, 2011). The S-segment encodes a non-structural protein (NSs) and the nucleocapsid protein (N) that together with the viral RNA forms the ribonucleoprotein complex (Elliott and Blakqori, 2011; Yanase et al., 2012). The M-segment encodes a non-structural protein (NSm) and a polyprotein precursor that is cleaved in 2 glycoproteins forming the basis of the virus envelope (Gn and Gc) (Doceul et al., 2013). Finally, the L-segment encodes a RNA-dependent RNA polymerase, also called the L-protein (Elliott and Blakqori, 2011).

SBV is a member of the Simbu serogroup to which Aino virus (AINO), Akabane virus (AKAV), Douglas virus (DOUV), Oropouche virus (ORO), Sathuperi virus (SATV) and Shamonda virus (SHAV) belong (Hoffmann et al., 2012). Contradictory results have been published on the origin of SBV. First sequencing analysis conducted by Hoffmann et al. (2012) identified a high degree of homology between SBV and SHAV S- segment, AINO M-segment and AKAV L-segment. Another study suggests that SBV is a reassortant between SATV M-segment and SHAV S and L-segments (Yanase et al., 2012), while a third study suggested that SBV belongs to the species SATV and is likely to be the ancestor of SHAV (Goller et al., 2012).

AKAV is probably the most studied virus within the Simbu serogroup. Since its first isolation in 1958, evidence of virus presence was reported in four continents: Asia, Oceania, Europe (Cyprus) and East-Africa (Sellers and Herniman, 1981; Al-Busaidy et al., 1987; Kono et al., 2008). The last known emergence of the more restricted SATV and SHAV took place in Japan back in 1999 and 2002, respectively (Yanase et al., 2004, 2005). SBV was therefore the first *Orthobunyavirus* of veterinary importance to emerge in continental Europe (Saeed et al., 2001).

After the first identification in Germany in August 2011, SBV spread rapidly and widely over a large part of Europe. SBV infection was confirmed in at least one herd in Belgium, Denmark, England, France, Italy, Luxembourg, the Netherlands, Poland, Sweden, Spain and Switzerland by August 2012 (EFSA, 2013). The *Culicoides*, also known as biting midges, are small hematophagous insects belonging to the order *Diptera*, family *Ceratopogonidae* (Mellor et al., 2000). *Culicoides* can be transmitted over long distance by wind (Hendrickx et al., 2008) what most probably explains the virus expansion from its place of emergence which precise location remains currently unknown. Much indirect evidence supports the role of the *Culicoides* in this wide expansion. SBV RNA was found in field-caught *Culicoides* in many countries (EFSA, 2014). In this context, *Culicoides obsoletus*, *Culicoides scoticus*, *Culicoides chiopterus* and *Culicoides* dewulfi midges have been proposed to be putative vectors while the role of *Culicoides pulicaris*, *Culicoides-nubeculosus*, *Culicoides punctatus* and *Culicoides imicola* remains to be clarified (De Regge et al., 2012; Rasmussen et al., 2012; Elbers et al., 2013a,b; Goffredo et al., 2013; Larska et al., 2013; Balenghien et al., 2014; De Regge et al., 2014, 2015).

Different seroprevalence studies carried out in Europe show that Belgium was one of the first and most SBV affected countries (Elbers et al., 2012; EFSA, 2013; Gache et al., 2013; Helmer et al., 2013; Méroc et al., 2013a,b; Veldhuis et al., 2013; Astorga et al., 2014; Méroc et al., 2014; Veldhuis et al., 2014). The goal of this manuscript is to reconstruct the SBV outbreak in Belgium using information gathered via different monitoring approaches that were simultaneously conducted. Published findings will be combined with unpublished data. Perspectives for future SBV circulation will be discussed and recommendations for different surveillance strategies and preventive measures will be addressed.

2. Material and methods

2.1. Syndromic surveillance

The 'Veterinary technical Network: Milk Objective' (RTVOL) is an organization hosted by the Professional Union of Veterinarians (UPV) in southern Belgium. It was founded in 2007 in order to increase communication among veterinarians dedicated to milk production and udder health. It consists of a free mailing list, a social network group and two annual forums. Membership is voluntary, but controlled through verification of the professional status of the participants. The members are mostly field practitioners, but the network also includes regional lab veterinarians, specialists working at the veterinary faculty, and technical veterinarians working in the pharmaceutical industry. Sending messages and questions via the mailing list is free, and can be commented by all members on a voluntary basis. The coordinator, originating from the veterinary faculty of Liège, keeps track of the exchanges in order to keep in touch with the needs and aspirations of field practitioners, leading to educational and scientific proposals. Between 260 and 430 emails are exchanged each year with a seasonal peak between January and May.

2.2. Diagnostic surveillance at the Belgian reference laboratory

CODA-CERVA is the Belgian reference laboratory responsible for SBV diagnosis since the first suspected cases in fetuses and neonates appeared from mid-December 2011 in Belgium. Following the case definition of EFSA (2013) this means fetuses and neonates with congenital anomalies classified as arthrogryposis hydranencephaly syndrome (AHS) (stillbirth, premature birth, mummified fetuses, arthrogryposis, hydranencephaly, ataxia, paralysis, muscle atrophy, joint malformations, torticollis, kyphosis, scoliosis, behavioral abnormalities and blindness). Although SBV has never been declared as a notifiable disease, samples were sent to us in the context of an existing mandatory notification of all aborted fetuses in cattle (abortion protocol). All samples were analysed in rRT-PCR following methods described in De Regge et al. (2013).

Since June 2012, CODA-CERVA also regularly received serum that was tested for the presence of SBV specific antibodies via a virus neutralization test (VNT). Details on this test can be found in De Regge et al. (2013). Most samples originated from adult cattle present in artificial insemination centres in order to follow-up their status, or from cattle meant to be exported. Adult animals that are found positive in VNT (or ELISA, IFAT or PCR) are considered as confirmed cases (EFSA, 2013).

2.3. Cross-sectional seroprevalence studies

Three large scale cross-sectional seroprevalence studies for SBV at the Belgian level have been supervised by CODA-CERVA: two after the first vector season (end 2011-beginning 2012) and one after the second vector season (beginning 2013). In 2011–2012, 11.635 cattle sera from 422 herds stratified by province and following the average age distribution of Belgian cattle herds (max. 40 samples per farm: 10 animals of 6–12 months of age; 10 animals of 12–24 months of age; and 20 animals >24 months of age) were tested. Furthermore 1.082 sheep sera and 142 goat sera of animals