Antiviral Research 95 (2012) 82–87

Contents lists available at SciVerse ScienceDirect

Antiviral Research

journal homepage: www.elsevier.com/locate/antiviral

Review

Schmallenberg virus: A new Shamonda/Sathuperi-like virus on the rise in Europe

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ARTICLE INFO

Article history:
Received 28 April 2012
Revised 21 May 2012
Accepted 25 May 2012
Available online 5 June 2012

Keywords:
Orthobunyavirus
Emergence
Arthrogryposis
Hydranencephaly
Schmallenberg

ABSTRACT

In the summer-fall of 2011, a nonspecific febrile syndrome characterized by hyperthermia, drop in milk production and watery diarrhea was reported in adult dairy cows from a series of farms located in North-West Europe. Further, in November 2011, an enzootic outbreak of abortion, stillbirth and birth at term of lambs, kids and calves with neurologic signs and/or head, spine or limb malformations emerged throughout several European countries. Both syndromes were associated with the presence in the blood (adults) or in the central nervous system (newborns) of the genome of a new Shamonda-Sathuperi reassortant orthobunyavirus provisionally named Schmallenberg virus after the place where the first positive samples were collected. The clinical, pathological, virological and epidemiological facts that were made publicly available during the first 6 months after the emergence are presented here. Current knowledge of the epidemiology of the phylogenetically closest relatives of the newcomer (Shamonda, Sathuperi, Aino and Akabane viruses) is not exhaustive enough to predict whether the current outbreak of Schmallenberg virus is the prelude to endemicity or to a 2 years long outbreak before the infection burns out when serologically naïve animals are no longer available. In the future, cyclic epizootic reemergences are a possibility too, either synchronized with a global decrease of herd immunity or due to antigenic variants escaping the immunity acquired against their predecessors. The latter hypothesis seems unlikely because of the wide array of biologic constraints acting on the genome of viruses whose life cycle requires transmission by a vector, which represses genetic drift. The remarkable stability of the Shamonda virus genome over the last forty years is reassuring in this regard.

Contents

1. Introduction

In the summer-fall of 2011, a nonspecific febrile syndrome characterized by hyperthermia, drop in milk production and watery diarrhea was reported in adult dairy cows from a series of farms located in North-West Germany and the Eastern region of the Netherlands. Herds experienced clinical signs lasting 2–3 weeks, with individual affected animals recovering over a few days (Hoffmann et al., 2012; Muskens et al., 2012).

After the presence of an array of known cattle pathogens was excluded, a metagenomic analysis conducted on blood samples of a set of clinically ill dairy cows led to the repeated detection of a new viral RNA which clusters to Shamonda-like viruses, all of which belong to the Simbu serogroup of the genus *Orthobunyavirus*

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http://dx.doi.org/10.1016/j.antiviral.2012.05.014

of the family *Orthobunyaviridae* (Hoffmann et al., 2012). The new virus, provisionally named Schmallenberg virus (SBV) after the place where the first positive samples were collected, was then isolated, successful experimental infections were carried out in calves, its genome was sequenced and specific RT-qPCR protocols were developed and disseminated by the Friedrich-Loeffler-Institut, Germany (Hoffmann et al., 2012). Using the latter, about one third of stored blood samples from clinically ill adult cows that had been drawn during the Dutch August–September outbreak also tested positive for the SBV genome (Muskens et al., 2012).

SBV's genome is phylogenetically close to that of Shamonda, Aino and Akabane viruses. These latter are transmitted by biting arthropods. Infections of serologically naïve ruminants result in few, transient and benign clinical signs (Zeller and Bouloy, 2000). Importantly, these viruses cross the ruminant placenta, replicate in the fetus and may lead to abortion and congenital malformations in offspring (Inaba et al., 1975; Kurogi et al., 1977; Charles, 1994; Noda et al., 1998; Tsuda et al., 2004). All the data made available since its emergence suggest that spontaneous infection of domestic ruminants by SBV follows a similar scenario. Indeed, since November 2011, SBV's RNA was detected in a still increasing number of aborted, stillborn or born at term lambs, kids and calves with neurologic signs and/or head, spine or limb malformations throughout several European countries.

2. The new virus and its phylogenetic relatives

Members of the *Bunyaviridae* family are enveloped single-stranded negative-sense RNA viruses of 90- to 100 nm diameter with a genome segmented in three fragments. The latter are named according to their size, with "L", "M" and "S" packages standing for *large*, *medium* and *small* segments, respectively (Schmaljohn and Nichol, 2007). The first electron micrograph of the new virus indeed confirms that its morphology reproduces the archetypal *Bunyaviridae*: a spherical virion of about 100 nm in diameter (Anonymous, 2012a). When the genomic sequences of the first SBV isolates were determined and compared with nucleotide sequence databases, it appeared that the degree of phylogenetic proximity of the newcomer with viral genomes already listed depended on the segment considered, with 97%, 82% and 92% identity with Shamonda (S segment), Sathuperi (M) and Shamonda (L) viruses, respectively (Hoffmann et al., 2012; Yanase et al., 2012). Therefore, it seems reasonable to assume that the new virus is a reassortant, with the M RNA segment derived from Sathuperi virus and the S and L segments from Shamonda virus (Yanase et al., 2012). These two viruses belong to the Simbu serogroup of the genus *Orthobunyavirus*, with Douglas, Tinaroo and Peaton viruses, all suspected to cause congenital deformities in domestic animals, mainly in Asia, Africa and Oceania (Charles, 1994). Shamonda virus was first isolated from cattle in Nigeria in 1965 (Causey et al., 1972) and recently reemerged in Japan (Yanase et al., 2005). Interestingly, the latter isolate displayed a very limited genetic drift (3% at the nucleotide level) in spite of the 40 yrs elapsed between the two isolations. As the phylogenetic distance between the Nigerian and Japanese isolates of the Shamonda virus is the same order of magnitude compared to that between this Japanese isolate and the isolates of SBV (about 3%), one can assume that SBV could ultimately prove to be a variant of the Shamonda virus (Hoffmann et al., 2012). Further genetic, virologic and epidemiologic investigations are required to enlighten this point.

3. Clinical data

Adults — As laboratory tools for large-scale detection of seroconversion to SBV were only recently made available, clinical signs associated to SBV infection are currently deduced from groups of adult animals showing similar symptoms, similar disease progression, and among which at least one tested positive for the new virus. Detection of the SBV genome by RT-qPCR has been reported in adult cattle, sheep, goat and bison (Anonymous, 2012b). Susceptibility of wild and exotic species must be determined, as specific antibodies targeting other viruses of the Simbu serogroup were already detected in the buffalo (*Syncerus caffer*), zebra (*Equus burchelli*), the greater kudu (*Tragelaphus strepsiceros*), impala (*Aepyceros melampus*), blue wildebeest (*Connochaetes taurinus*), elephant (*Loxodonta africana*), warthog (*Phacochoerus aethiopeticus),* rhinoceros (*Diceros bicornis, Ceratotherium simum*), red deer (*Cervus elaphus*) and wild boar (*Sus scrofa*) (Al-Busaidy et al., 1987; Sugiyama et al., 2009). To date, however, symptoms were reported in adult cattle only. They are typically transient and non-specific: inappetence, loss of body condition, hyperthermia (>40 °C), drop in milk production and diarrhea (Hoffmann et al., 2012; Muskens et al., 2012). Similarly, when serologically naïve 9-mo old calves were inoculated with SBV, all animals displayed these non-specific signs and some became diarrheic (Hoffmann et al., 2012). These observations contrast with the typically subclinical nature of spontaneous and experimental infections with Akabane or Aino viruses (Parsonson and McPhee, 1985; Charles, 1994), suggesting that SBV could be newly introduced in the bovine species and would thus be more likely to cause a clinical illness. Some remarkable isolates of Akabane virus were associated with encephalomyelitis in adult cattle (Kamata et al., 2009; Kono et al., 2008), but no such case has yet been reported for SBV.

Newborns — detection of the SBV genome by RT-qPCR has been reported in aborted, stillborn or newborn lambs, kids and calves (Anonymous, 2012b; Garigliany et al., 2012; van den Brom et al., 2012). An epizootic outbreak of congenital neurologic signs and malformations emerged in newborn lambs in November 2011 and in newborn calves in January 2012, throughout Germany, the Netherlands, Belgium, France, Luxembourg, Great Britain, Italy and Spain (Anonymous, 2012b). Both male and female newborns were affected and most of them were delivered near or at term. Besides head, trunk or limb malformations (see hereafter), some morphologically normal neonates displayed abnormal psychic (dullness, abnormal vocalizations), sensing (blindness), sensitive (hyperexcitability), motor (inability to stand, flaccid paralysis, exaggerated movements, ataxia or inability to suckle) or neurovegetative (excessive lacrimation) signs (Bayrou et al., submitted for publication; Garigliany et al., 2012; van den Brom et al., 2012). Taken together, the SBV-associated clinical picture is not

Fig. 1. Musculoskeletal alterations in aborted, stillborn or neonatal SBV-positive calves consist in vertebral and limb deformities, two calves with severe arthrogryposis are shown here. The SBV genome was detected by RT-qPCR as described (Hoffmann et al., 2012).

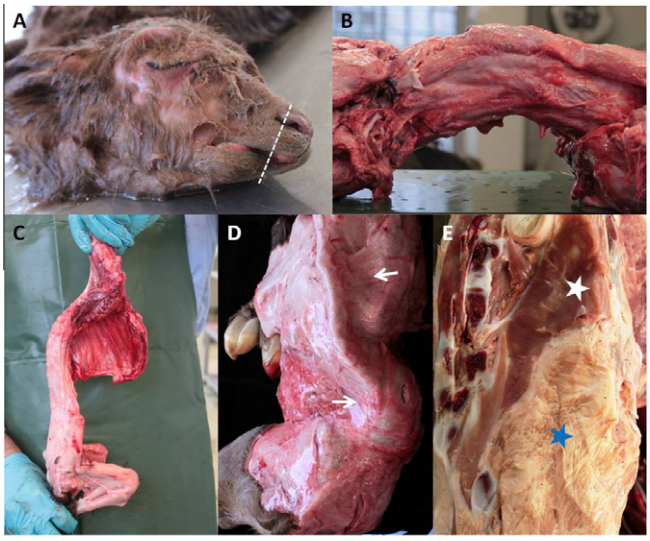

Fig. 2. Musculoskeletal alterations in aborted, stillborn or neonatal SBV-positive calves consist in jaw and vertebral deformities and chronic myositis. (A) ill-formed lower mandible; (B) torticollis; (C) scoliosis; (D) *gluteus* and *erector spinae* muscles asymmetric atrophy (arrows) and (E) severe fibrosis (blue star) and multifocal myositis (white) in *erector spinae* muscle. The SBV genome was detected by RT-qPCR as described (Hoffmann et al., 2012).

distinguishable from that reported after *in utero* infection by Akabane or Aino viruses (Parsonson and McPhee, 1985; Kirkland et al., 1988). Besides, the 20 fetuses from pregnant red and roe deer (*Capreolus capreolus*) found dead or road injured that we examined during the 2012 winter were all morphologically normal and the corresponding CNS samples were negative for SBV genome by RT-qPCR.

4. Pathological data

Musculoskeletal alterations in aborted, stillborn or neonatal lambs and calves consist of jaw, vertebral or limb deformities (Figs. 1 and 2), presenting as brachygnathia inferior, ill-formed lower mandible, torticollis, scoliosis, kyphosis or arthrogryposis (Bayrou et al., submitted for publication; Garigliany et al., 2012; van den Brom et al., 2012). At necropsy, vertebral deformities are often associated with unilateral spine muscle atrophy and/or discoloration. Articular rigidities relate to one or more limbs, to one or more joints per limb and fix the joints involved most frequently in flexion. Joints appear to be blocked by muscle–tendon contracture rather than by any articular alteration. Muscle atrophy, discolorations and petechiation are often apparent (Bayrou et al., submitted for publication). No specific lesions are noticed in thoracic and abdominal cavities, thymus edema and petechiation in some lambs being excepted. Conversely, the central nervous system almost systematically displays severe morphologic deformities, with por- or even hydranencephaly and/or severe hypoplasia of the spinal cord (Figs. 3 and 4). A hypoplastic cerebellum is frequently reported in lambs (van den Brom et al., 2012). In calves, the cerebellum is hypoplastic in some rare cases but is often distorted because of the mechanical constraints imposed by the dilated cystic cerebrum (Bayrou et al., submitted for publication). Again, SBV-associated morphologic alterations seem to replicate those typically seen after Akabane and Aino *in utero* infections (Charles, 1994). So far, no histopathological or ultrastructural description of the infection by the new virus is available.

5. Diagnostic data

In a recent study, the viral genome was always detected by RT-qPCR in lambs carrying the typical congenital malformations ($n = 15$) while all samples from animals not carrying the aforementioned lesions ($n = 17$) remained virus-negative (Bilk et al., 2012). This result suggests that the RT-qPCR protocol available could reliably confirm or refute the causal intervention of SBV in a lamb carrying an arthrogryposis–hydranencephaly complex. No trustworthy published data is available yet about this critical point in the kid and the calf. In our experience, many suspect aborted, stillborn or newborn calves combining seropositivity towards SBV's nucleoprotein and carrying of the expected lesions remain virus-negative by RT-qPCR. This is probably the consequence of a longer gestation period allowing time for viral RNA to be cleared. Interestingly, in all SBV genome-positive lambs tested, CNS, uterine placental fluid and umbilical cord were positive, which suggests that the latter two are the most pertinent sample materials for diagnostic purpose on the field where sampling the hypoplastic CNS is not feasible (Bilk et al., 2012).

6. Epidemiological data

As this new viral disease of cattle emerged only a few months ago, very limited information is available on its epidemiology. Furthermore, the number of confirmed cases by RT-qPCR most likely constitutes a significant underestimation of the number of infected herds, in particular for calves because the longer duration of gestation delays identification of suspect cases. The number of confirmed acute cases in adult ruminants with viral detection by RT-qPCR is limited to eight dairy cows in Germany (Hoffmann et al., 2012) and 18 dairy cows in the Netherlands (Muskens et al., 2012), most likely corresponding to infection during the period of viral circulation in summer/autumn 2011. With respect to

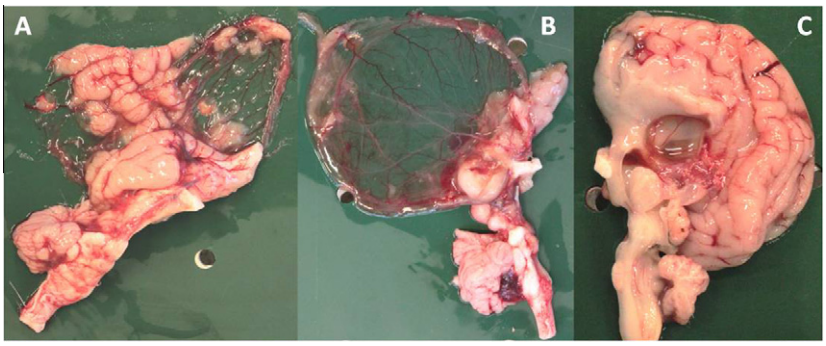

Fig. 3. Central nervous system alterations in aborted, stillborn or neonatal SBV-positive calves consist in cerebrum and cerebellum hypoplasia. (A) porencephaly; (B) hydranencephaly; (C) cerebellar hypoplasia. The SBV genome was detected by RT-qPCR as described (Hoffmann et al., 2012).

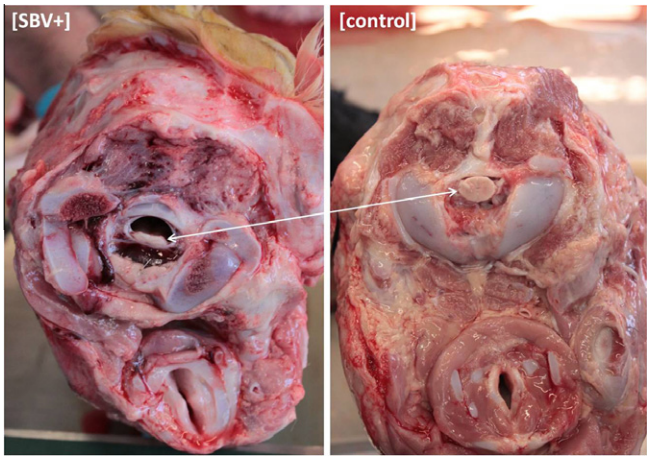

Fig. 4. Central nervous system alterations in aborted, stillborn or neonatal SBV-positive calves also consist in spinal cord hypoplasia. Double arrow points to hypoplastic (left) and normal (right) spinal cords between age- and weight-matched SBV-positive and -negative calves, respectively. Caudal view of the skull after decapitation. The SBV genome was detected by RT-qPCR as described (Hoffmann et al., 2012).

arthrogryposis/hydranencephaly syndrome in offspring, the observed temporal pattern of case detection per species is in accordance with the hypothesis that infection may have occurred during a certain period of gestation (Anonymous, 2012b). Assuming for sheep and goats a gestation period of 150 days, for cattle a gestation period of 280 days and for both a vulnerability window starting, as for Akabane virus, when the placentome is established (Kirkland et al., 1988; Parsonson et al., 1988), i.e. about 30 days after successful service/insemination, it is deduced from the data compiled by the European Food Safety Agency (Anonymous, 2012b) that viral circulation started in May 2011, then steeply increased up to the last month for which reliable deductions can be done, October 2011.

When calves from experimentally infected dams are infected with the close phylogenetic relative to SBV, Akabane virus, porencephaly develops during gestational days 62–96 (Kurogi et al., 1977). Assuming the same is true for the new virus, the porencephalitic SBV-positive calf born at term on January 12th 2012 (Garigliany et al., 2012) was probably infected between June 9 and July 13, 2011, which confirms the aforesaid deduction. When examining the spatial distribution of positive herds at the end April 2012 (Figs. 5 and 6), one is struck by the geographical spread of the emerging infection, much faster than that of BTV-8 in 2007. This suggests significant differences in the events that led to the emergence itself or in the biology of the new virus. For example, the very fast dissemination of SBV takes place in spite of a much shorter viremia than that typical of BTV-8 (weeks): about 4 days according to first experimental infection (Hoffmann et al., 2012), which fits with Akabane virus (Uchida et al., 2000).

Bunyaviruses are transmitted by hematophagous insects. Akabane virus has been isolated from *Culicoides* spp. biting midges and from mosquitoes of the *Anopheles*, *Culex* and *Ochlerotatus* genera (Kurogi et al., 1987; Bryant et al., 2005). Aino virus is transmitted by *Culex* spp. mosquitoes and *Culicoides* midges (Doherty et al., 1972; Kim et al., 2005). To date, SBV was only isolated from the salivary glands of *Culicoides obsoletus* and *Culicoides dewulfi* in Belgium (ProMED-Mail. Schmallenberg virus – Europe 26). This strongly suggests the role of these midge species in the transmission of the Schmallenberg virus. However, in the face of the

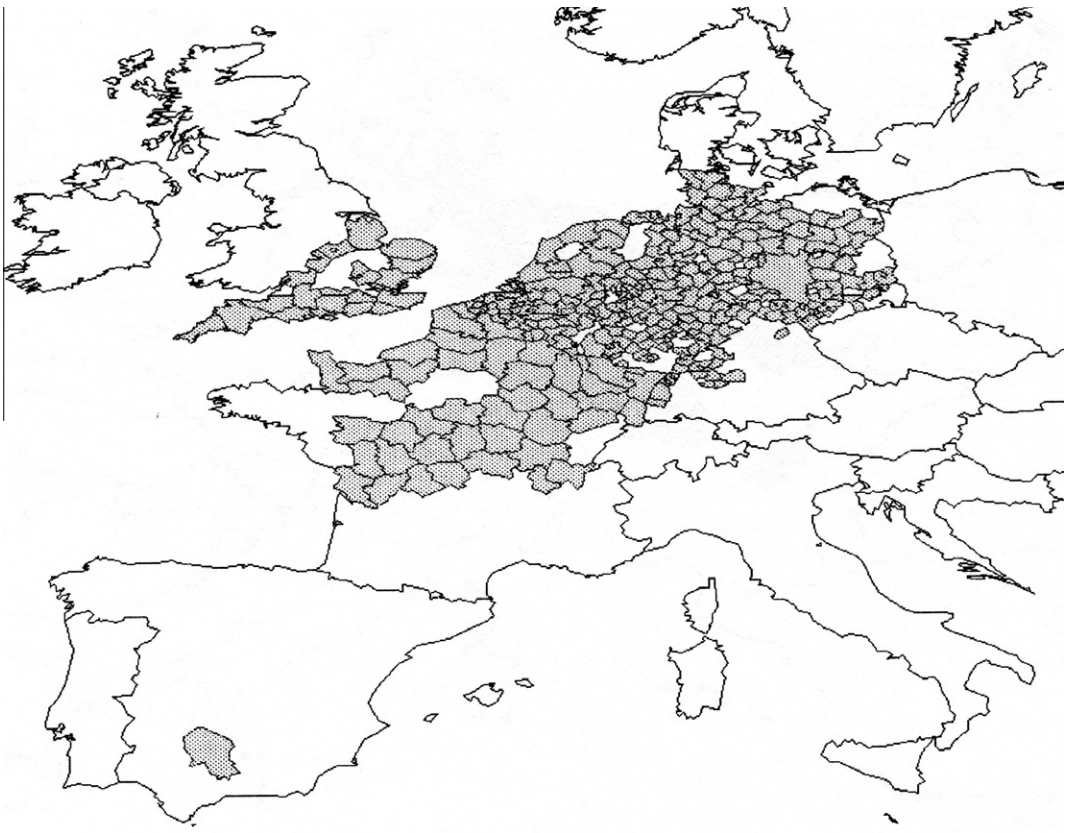

Fig. 5. Spatial distribution of regions with at least one SBV confirmed sheep herd, as reported by the European Food Safety Agency on March 30, 2012 (source: http://www.efsa.europa.eu/en/supporting/doc/261e.pdf).

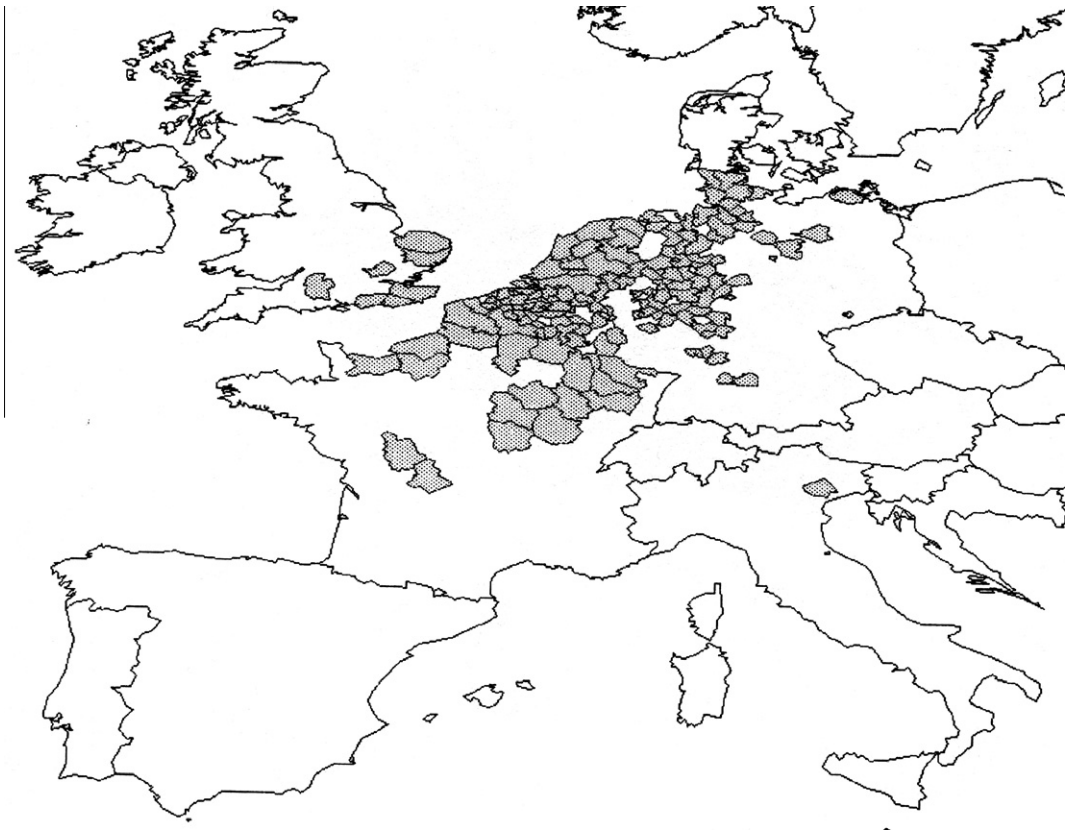

Fig. 6. Spatial distribution of regions with at least one SBV confirmed cattle herd, as reported by the European Food Safety Agency on March 30, 2012 (source: http://www.efsa.europa.eu/en/supporting/doc/261e.pdf).

explosive geographical spread of the virus, all other direct and indirect transmission ways must be prioritarily identified.

Some members of the Simbu serogroup, e.g., Oropouche virus, are zoonotic. As SBV clusters closely with Shamonda virus which only affects ruminant species and because of the absence of reports of clinical signs in humans, the risk to humans is currently assessed as very low or negligible (Anonymous, 2012b). Nevertheless, clinical and serologic surveillance in humans should be conducted in regions with infected animals and among veterinarians to update the risk assessments.

7. Scenario for the future

The remarkable geographical spread of the new infection in Europe over a few months suggests that, within the area concerned, a significant proportion of adults could already have been infected with the new virus. Although this critical point must be addressed as soon as tools become available for large-scale serological screening, preliminary data from the Netherlands suggest an apparent seroprevalence of about 70% (ProMED-Mail. Schmallenberg virus – Europe 25). In the case of Akabane virus such natural immunity prevents subsequent infections of the fetus (Anonymous, 2008). It seems likely, therefore, that the infection itself and its economic impact on farms in the regions concerned might disappear in the spring 2012. Similarly, taking into account that no vaccine will be available in 2012 and considering the 2011 propagation rate of the new infection, it is likely that, in 2012–2013, the risk of infection and its economic impact on the livestock sector will affect all European farms located in the area still "free" of the disease (Figs. 5 and 6). The infection of adult ruminants will probably rise again in the spring on the edges of the SBV-positive geographical area where herd immunity gradually decreases and the new virus will possibly spread to all European SBV-naïve farms where environmental conditions are compatible with its means of transmission, biting insects or others, which would result in an outbreak of enzootic arthrogryposis–hydranencephaly in these areas during the winter 2012–2013.

For the long term, current knowledge of the epidemiology of the Simbu serogroup orthobunyaviruses is not exhaustive enough to predict whether the current outbreak of SBV is the prelude to endemicity or to a 2 years long outbreak before the infection burns out when serologically naïve animals are no longer available. The chance for the establishment of an endemic transmission cycle of SBV in Europe despite a strong herd immunity in domestic ruminants will depend of the availability in sufficient numbers at the same time and at the same place of both competent arthropod vector species and high-level viremia-producing vertebrate species. Should these conditions be met, future cyclic epizootic reemergences among ruminants are a possibility, either synchronized with a global decrease of herd immunity or due to antigenic variants of the new virus escaping the immunity acquired against their predecessors. The latter hypothesis seems unlikely because of the wide array of biologic constraints acting on the genome of viruses whose life cycle requires transmission by a vector, which represses genetic drift. The remarkable stability of the Shamonda virus genome over the last forty years is reassuring in this regard.

Acknowledgement

The authors are grateful to Pr A. Vanderplasschen for his help in achieving this review.

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