



Tarlinton, Rachael E. and Daly, Janet M. and Dunham, Stephen P. and Kydd, Julia M. (2012) The challenge of Schmallenberg virus emergence in Europe. *Veterinary Journal*, 194 (1). pp. 10-18. ISSN 1090-0233

**Access from the University of Nottingham repository:**

[http://eprints.nottingham.ac.uk/3167/1/Tarlinton\\_et\\_al\\_2012\\_2.pdf](http://eprints.nottingham.ac.uk/3167/1/Tarlinton_et_al_2012_2.pdf)

**Copyright and reuse:**

The Nottingham ePrints service makes this work by researchers of the University of Nottingham available open access under the following conditions.

- Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners.
- To the extent reasonable and practicable the material made available in Nottingham ePrints has been checked for eligibility before being made available.
- Copies of full items can be used for personal research or study, educational, or not-for-profit purposes without prior permission or charge provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.
- Quotations or similar reproductions must be sufficiently acknowledged.

Please see our full end user licence at:

[http://eprints.nottingham.ac.uk/end\\_user\\_agreement.pdf](http://eprints.nottingham.ac.uk/end_user_agreement.pdf)

**A note on versions:**

The version presented here may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the repository url above for details on accessing the published version and note that access may require a subscription.

For more information, please contact [eprints@nottingham.ac.uk](mailto:eprints@nottingham.ac.uk)



## Review

# The challenge of Schmallenberg virus emergence in Europe

Rachael Tarlinton\*, Janet Daly, Stephen Dunham, Julia Kydd

School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington Campus, Loughborough LE12 5RD, UK

## ARTICLE INFO

Article history:  
Accepted 27 August 2012

Keywords:  
Orthobunyavirus  
Schmallenberg virus  
Teratogenic infection  
Vector-borne  
Cattle  
Sheep

## ABSTRACT

The large-scale outbreak of disease across Northern Europe caused by a new orthobunyavirus known as Schmallenberg virus has caused considerable disruption to lambing and calving. Although advances in technology and collaboration between veterinary diagnostic and research institutes have enabled rapid identification of the causative agent and the development and deployment of tests, much remains unknown about this virus and its epidemiology that make predictions of its future impact difficult to assess. This review outlines current knowledge of the virus, drawing comparisons with related viruses, then explores possible scenarios of its impact in the near future, and highlights some of the urgent research questions that need to be addressed to allow the development of appropriate control strategies.

© 2012 Elsevier Ltd. All rights reserved.

## Introduction

The first record of the town of Schmallenberg in the state of North Rhine-Westphalia, Germany dates from 1243. Over 700 years later, its name is now linked with the latest vector-borne viral disease to pose a threat to livestock in Northern Europe. Schmallenberg virus (SBV) was originally identified in clinical samples from cattle in Germany presenting with fever and milk drop syndrome (with occasional reports and diarrhoea and abortion), that were submitted for investigation to the Friedrich Loeffler Institute (FLI) in October 2011.

Following elimination of the usual causes of such clinical signs in cattle, blood samples from three cattle were subjected to the new technology of deep sequencing known as metagenomic analysis, which allows the sequencing of all nucleic acid present in a sample. As is typical with this approach, a large amount of host genomic and known bacterial sequences were identified, the latter most likely as a consequence of prolonged sample storage. However, present within the samples were genetic sequences from a novel Bunyavirus of the genus *Orthobunyavirus* which were most similar to viruses of the Simbu serogroup including Akabane and Shamonda virus (Hoffmann et al., 2012). This group of viruses produce a syndrome in ruminants referred to as arthrogryposis hydranencephaly syndrome (AHS), resulting in abortions, stillbirths and congenital defects in neonatal cattle, sheep and goats following infection during pregnancy.

Outbreaks of diarrhoea, fever and milk drop syndrome had also been reported in The Netherlands over the late summer and early

autumn of 2011. Retrospective testing of blood samples from these cases at the Central Veterinary Laboratories, Lelystad demonstrated SBV RNA in 36% of animals indicating that the same causative agent was responsible for the disease outbreaks in both countries (Muskens et al., 2012).

This review describes what is currently known about SBV (based on published data up to 19th June 2012) compared with related *Bunyaviridae*. Our knowledge of this virus is rapidly expanding as many research groups are actively working in this area, and the situation changes as the outbreak progresses. Useful websites that provide the most up-to-date information are listed in Table 1.

## Schmallenberg virus: What is currently known?

Following its initial detection using molecular methods, it was not clear whether SBV was anything more than an incidental finding. However, the teratogenic nature of genetically similar viruses, and the fact that orthobunyaviruses of the Simbu serogroup had not previously been reported in Europe, was enough to warrant increased vigilance for malformed ruminant fetuses and neonates and the development of a primer- and probe-based reverse-transcriptase quantitative PCR (qRT-PCR) test for the 'S' segment of the virus by the FLI (Hoffmann et al., 2012). These steps proved prudent, as large numbers of malformed lambs were reported from the start of the 2011–2012 lambing season in continental Europe. The first clinical report described lambs born in The Netherlands during November and December 2011 with malformations consistent with the AHS syndrome (van den Brom et al., 2012). Twenty-two of 54 lambs with such distinct malformations tested positive by qRT-PCR for SBV RNA (van den Brom et al., 2012).

\* Corresponding author. Tel.: +44 150 9516273.

E-mail address: [rachael.tarlinton@nottingham.ac.uk](mailto:rachael.tarlinton@nottingham.ac.uk) (R. Tarlinton).

**Table 1**

A selection of useful websites providing information on Schmallenberg virus (SBV) infection in Europe.

Website	Comment
<a href="http://www.fli.bund.de/en/startseite/current-news/animal-disease-situation/new-orthobunyavirus-detected-in-cattle-in-germany.html">http://www.fli.bund.de/en/startseite/current-news/animal-disease-situation/new-orthobunyavirus-detected-in-cattle-in-germany.html</a>	Friedrich Loeffler Institute, Germany: current distribution and publications listed
<a href="http://agriculture.gouv.fr/maladies-animales,11003">http://agriculture.gouv.fr/maladies-animales,11003</a>	Ministry of Agriculture, France
<a href="http://www.izs.it/IZS/Engine/RAServePG.php/P/357410010300/M/250010010303">http://www.izs.it/IZS/Engine/RAServePG.php/P/357410010300/M/250010010303</a>	Istituto Giuseppe Caporale, Italy
<a href="http://www.vva.nl/onderwerpen/dierziekten/dossier/schmallenbergvirus">http://www.vva.nl/onderwerpen/dierziekten/dossier/schmallenbergvirus</a>	Food and Consumer Product Safety Authority, The Netherlands
<a href="http://www.defra.gov.uk/animal-diseases/a-z/schmallenberg-virus">http://www.defra.gov.uk/animal-diseases/a-z/schmallenberg-virus</a>	Department for the Environment Food and Rural Affairs (DEFRA) provides official statements on current UK status of SBV
<a href="http://www.defra.gov.uk/ahvla/tag/Schmallenberg/">http://www.defra.gov.uk/ahvla/tag/Schmallenberg/</a>	Animal Health and Veterinary Laboratories Agency (AHVLA) lists UK outbreaks of SBV chronologically
<a href="http://www.oie.int/for-the-media/press-releases/detail/article/oie-scientists-review-knowledge-on-schmallenberg-virus/">http://www.oie.int/for-the-media/press-releases/detail/article/oie-scientists-review-knowledge-on-schmallenberg-virus/</a>	World Animal Health Organisation (OIE). Includes link to 'Technical Factsheet' on SBV
<a href="http://www.promedmail.org/?p=2400:1000">http://www.promedmail.org/?p=2400:1000</a>	Internet-based reporting system of the International Society for Infectious Diseases dedicated to the rapid dissemination of information on outbreaks of infectious diseases occurring worldwide

The initial publication by Hoffmann et al. (2012) described the genetic identification of SBV, its culture in the laboratory, and the experimental infection of cattle with the virus. Blood samples from a cow with milk drop and fever were ultrasonically disrupted and incubated for 10 days on a mosquito cell line (KC cells), before being passaged onto a baby hamster kidney cell line (BHK21). Cytopathic effects were visible after 5 days of incubation and viral RNA was detected in the supernatant by qRT-PCR. Reproduction of

the acute disease in cattle was demonstrated by IV and/or SC inoculation of the isolated virus into three 9-month old calves. Viral genetic material was detected in the blood of all three animals between days 2 and 5 post infection: one calf developed fever on day 4 post infection and a further animal developed diarrhoea. All animals had seroconverted to the virus by 3 weeks post infection. This study went some way towards satisfying Koch's postulates as to SBV being the causative agent of the disease, although

Stillbirths, premature births, mummified fetuses and dysfunctions of fetuses or neonates with two or more of the following:
Arthrogryposis (joint stiffness and tendon shortening)
Hydranencephaly
Ataxia
Paralysed limbs
Muscle atrophy
Joint malformations
Torticollis (overstretched neck)
Scoliosis (curvature of the spine)
Kyphosis (over curvature of the thoracic vertebrae causing a hunch-back appearance)
Brachygnathia inferior (undershot jaw or "parrot mouth")
Behavioural abnormalities
Blindness

(a)



(b)

**Fig. 1.** (a) To facilitate the identification of potential cases of Schmallenberg virus infection, the European Food Safety Authority (EFSA) produced this checklist of clinical features for fetuses and neonates. (b) Photograph of a lamb exhibiting kyphosis.

demonstration of congenital malformations following experimental infection during pregnancy has yet to be confirmed.

In order to facilitate identification of potential cases of SBV infection, the European Food Safety Authority (EFSA) has issued a 'case definition' for fetuses and neonates as evidence of AHS (Fig. 1).

### Structure of Schmallenberg virus

Electron microscopy confirms that the morphology of SBV is typical of the *Bunyaviridae* (Table 1). These viruses are approximately 100 nm in diameter, with surface glycoproteins projecting from an outer envelope. The genetic structure of the virus is also typical for *Bunyaviridae*, containing three segments of single-stranded negative-sense RNA, called the large (L; 6865 nucleotides), medium (M; 4415 nucleotides) and small (S; 830 nucleotides) segments (Fig. 2; Hoffmann et al., 2012). On the basis of phylogenetic analysis of the S segment (Fig. 3a), SBV is most like Shamonda virus (Hoffmann et al., 2012).

The segmented genome of *Bunyaviridae* creates a potential for re-assortment, which can lead to rapid genetic change in the virus population. This is the process by which new subtypes of influenza A viruses may emerge through the exchange of gene segments, in a host simultaneously infected with viruses of more than one subtype, and is the major mechanism underlying the generation of new pandemic influenza viruses. Indeed, several examples of re-assortment in orthobunyaviruses have been reported (Yanase et al., 2010; Aguilar et al., 2011; Blitvich et al., 2012). There has been some suggestion that SBV is a 're-assortant' (Fig. 3b and c; Hoffmann et al., 2012). Recent work re-sequencing Japanese isolates of Sathuperi and Shamonda virus and the Douglas isolate of Sathuperi virus from Australia support this idea, with the S and L segments of SBV most closely related to Shamonda virus isolates and the M segment most similar to that of Sathuperi virus, respectively (Yanase et al., 2012).

### What can we infer from our knowledge of similar viruses?

#### Host range

Viruses of the genus *Orthobunyavirus* are divided into 18 serogroups (International Committee on Taxonomy of Viruses, 2011), of which the Simbu serogroup is one of the largest. Most of these viruses have not been well characterised. Some are associated with cattle and transmitted by biting midges (*Culicoides* spp.), though this may merely reflect bias in the sentinel monitoring programmes that have detected these viruses. Shamonda virus was

initially identified in Nigeria in the 1960s, and was subsequently identified in Japan in 2002, indicating that this virus probably has an extensive geographic range (Causey et al., 1972; Yanase et al., 2005).

Viruses from these serogroups have also been found in other ruminants, pigs and horses (Kessell et al., 2011) with a recent report of Shuni virus in horses with encephalitis (van Eeden et al., 2012) and reports of Akabane virus in horses (Yang et al., 2008), pigs (Huang et al., 2003) and adult cattle (Lee et al., 2002; Kono et al., 2008) with neurological disease.

While none of the Simbu serocomplex of viruses has been demonstrated to cause disease in humans, the wider Simbu serogroup includes Oropouche and Iquito viruses, which cause a severe febrile syndrome in humans in South America (Aguilar et al., 2011). As the most closely related viruses do not cause disease in humans, most authorities have concluded that the likelihood of SBV being zoonotic is minimal, though the potential for rare infections cannot be ruled out.

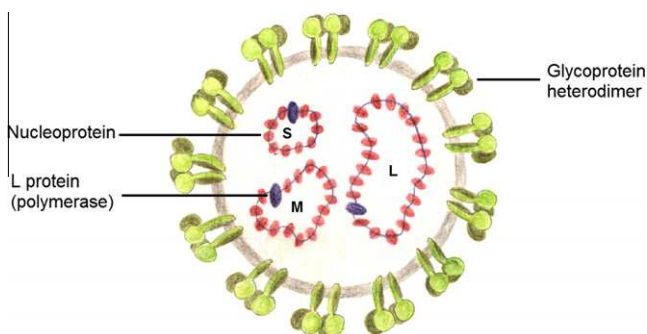
The Robert Koch Institute in Germany issued a questionnaire to sheep farmers in North Rhine Westphalia which raised no suspicion of human disease as a result of SBV and all farmers were seronegative for antibodies against SBV as monitored by an immunofluorescence antibody test (IFAT) or virus neutralisation (VN) assay. Furthermore, no viral RNA was detected when sera from these farmers were tested using qRT-PCR. A similar serological survey of 301 farmers and veterinarians with known exposure to SBV-affected herds in The Netherlands, using a VN assay, also found no antibodies against SBV (European Centre for Disease Prevention and Control, 2012), leading The European Centre for Disease Prevention and Control to declare the zoonotic risk of SBV as 'very unlikely'.

#### Pathogenesis of viral infection

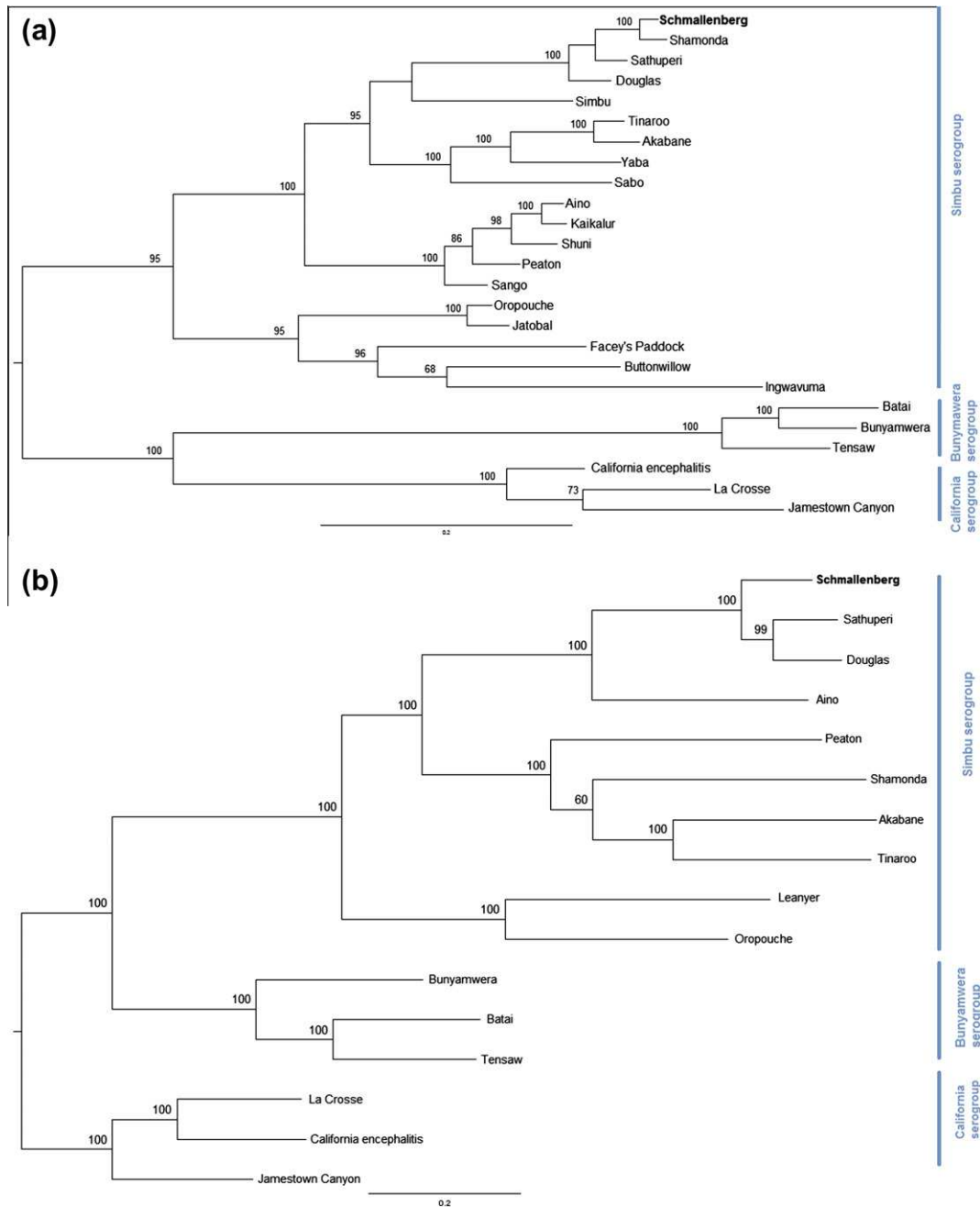
Although a full description of the pathogenesis of Akabane virus infection is likely to be provided in a forthcoming review of the Simbu viruses (P.D. Kirkland and D.S. Finlaison, unpublished data), several points of interest in comparison with SBV are highlighted here. Clinical studies have identified a pattern of malformations in Akabane outbreaks in cattle which suggest that the lesions in fetuses are dependent on the developmental stage of the fetus at the time of infection. Fetuses aborted at around 4–6 months of gestation are often the first indication of an outbreak, followed by dead, full-term fetuses with severe arthrogryposis (infected between 103 and 174 days of gestation), then live-born animals with less severe arthrogryposis but with neurological deficits due to hydranencephaly (infected between 79 and 104 days of gestation) (Kirkland et al., 1988).

Histopathological lesions also vary depending on the age of fetus when infected. Calves infected late in gestation are born at the start of an outbreak and may have non-suppurative encephalomyelitis accompanying their neurological deficits. Calves born mid-outbreak show varying degrees of neurological deficits and arthrogryposis with encephalitis, and Wallerian-type degeneration of the spinal cord with degeneration and loss of the ventral horn neurones and spinal nerves. Calves born towards the end of outbreaks (i.e. those infected in early gestation) tend to display hydranencephaly, with or without arthrogryposis, and very few other lesions, with occasional calves exhibiting spinal cord hypoplasia (Hartley et al., 1977).

The incidence of lesions in affected herds can be very high with up to 50% of calves and 80% of lambs malformed, respectively (Kirkland, 2002). In addition, recent outbreaks in Japan and Korea have demonstrated that some strains of Akabane virus cause encephalitis in adult cattle (Kamata et al., 2009; Oem et al., 2012). The disease can have considerable economic impact: an



**Fig. 2.** Schematic diagram illustrating a Schmallenberg virus particle with glycoproteins (Gn and Gc) projecting from the lipid bilayer as heterodimers and the three segments of RNA (small, S; medium, M; and large, L) in circular form in association with nucleoprotein and the 'L' polymerase protein.



**Fig. 3.** Phylogenetic trees illustrating the: (a) small; (b) medium; and (c) large segments of the Simbu serogroup viruses along with representatives from the Bunyamwera and California serogroups. Trees were generated by maximum likelihood (DNAML) in PHYLIP. Bootstrap values > 50% (1000 replicates) are given. Scale bar indicates the estimated number of nucleotide substitutions/site.

estimated 42,000 abnormal calves were born during the 1972–1975 disease outbreak in Japan (Kono et al., 2008).

Experimental infection of pregnant sheep with Akabane virus (Parsonson et al., 1977, 1988) suggests that a 'time-window' exists during which infection results in fetal abnormalities, with abnormalities less frequently seen when infection occurs after day 40 of gestation. Lesions in affected ovine fetuses include hydranencephaly, porencephaly, hypoplasia of the spinal cord and lungs, arthrogryposis, brachygnathia, and scoliosis. Histopathological changes described include skeletal muscle degeneration and oedema and perivascular cuffing, gliosis and mineralised plaques in the brain and spinal cord (Parsonson et al., 1981b). Due to the shorter gestation period in sheep and goats, infected fetuses of these spe-

cies do not display as distinct a pattern of malformations as described in bovine fetuses.

In comparison to Akabane virus, initial pathology reports indicated that SBV typically caused hydranencephaly, porencephaly, hydrocephalus, cerebellar hypoplasia and micromyelia (shortening of the spinal cord). Micromyelia particularly affected the ventral horn of the spinal cord in calves. Histologically, affected animals displayed a lymphohistiocytic meningo-encephalomyelitis with glial nodules in lambs and goats and neuronal degeneration and necrosis in the brain-stem of calves. Additional lesions included arthrogryposis, vertebral malformations and brachygnathia inferior, with myofibrillar hypoplasia of skeletal muscle in both calves and lambs (Herder et al., 2012). Other pathological features in full-

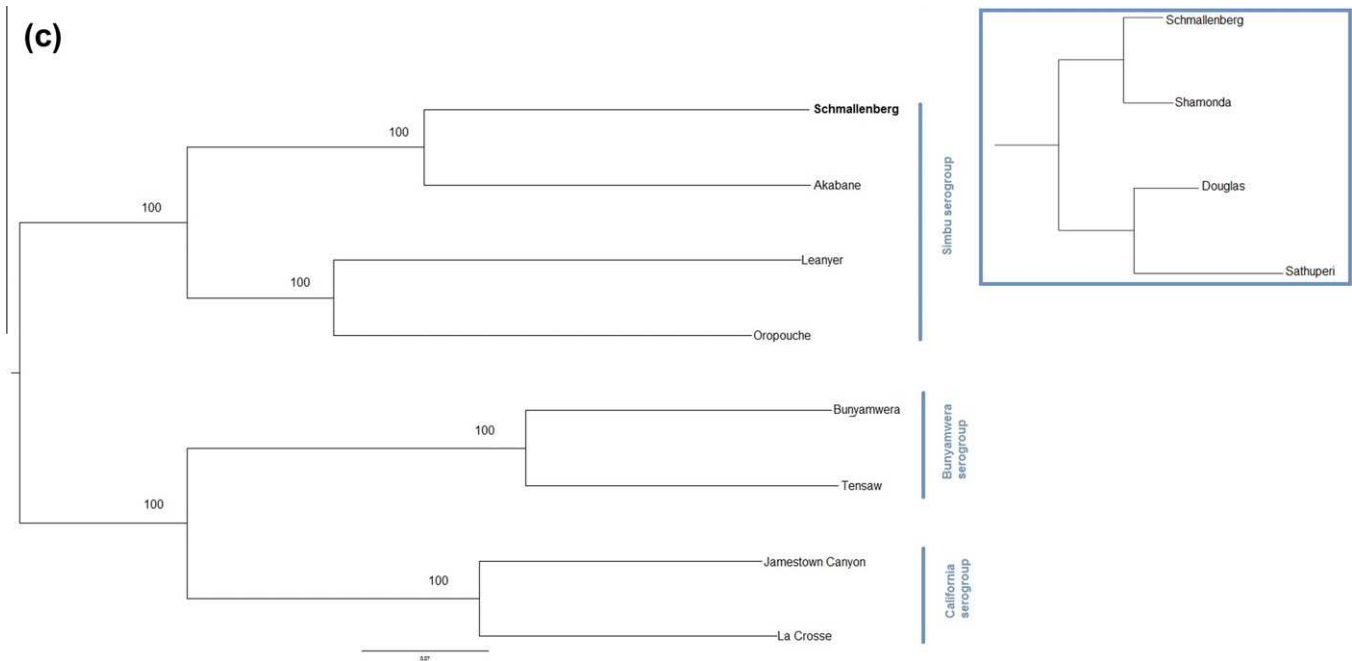


Fig. 3. continued

term calves include severe hydranencephaly (Garigiany et al., 2012), and non-suppurative meningoencephalitis and poliomyelitis with neuronophagia (Peperkamp et al., 2012). These lesions are very similar to those of AHS in Akabane-infected animals. The distinct timescale of occurrence of the different lesions in cattle has not been reported in the current SBV outbreak, but this may be because of the low numbers of affected cattle to date, and possibly, the protracted period of transmission.

One critical difference between the SBV outbreak and historical Akabane virus outbreaks is that a large number of affected full-term fetuses contain 'PCR detectable' SBV RNA (Bilk et al., 2012; van den Brom et al., 2012). However, the sensitive qRT-PCR based methods of detection were not available when much of the historical work on Akabane virus was performed, and there have been few reports of the isolation of this virus from full-term lambs and calves (Levin et al., 2008). However, Akabane virus was successfully isolated from a variety of tissues from ovine fetuses at an earlier stage of gestation (up to 70 days) as well as from placentomes and chorioallantoic membranes up to 100 days of gestation (Parsonson et al., 1981a) in the face of virus neutralising antibody in both dam and fetus. These findings are consistent with reports that SBV RNA can be detected in a variety of tissues from affected lambs and calves, particularly the cerebrum, spinal cord, external placental fluid and umbilical cord (Bilk et al., 2012).

#### Epidemiology of virus infection

The epidemiology of Akabane and Aino viruses has been best described following outbreaks in Australia and Japan. In Australia, Akabane is known to be present in the northern (tropical and subtropical) areas of the country, limited by the range of the primary vector, *Culicoides brevitarsis* (Bishop et al., 2000). In these regions, virus circulates annually, most animals become infected pre-puberty and develop immunity which is thought to be long-lasting. In these endemic zones, fetal malformations are rare. Virus transmission in endemic zones is heavily dependent on midge abundance, with transmission beginning in summer and reaching a peak in autumn. There is also usually a lag phase between the ini-

tial detection of the vector and the circulation of the virus. The onset of frosts typically ends viral transmission.

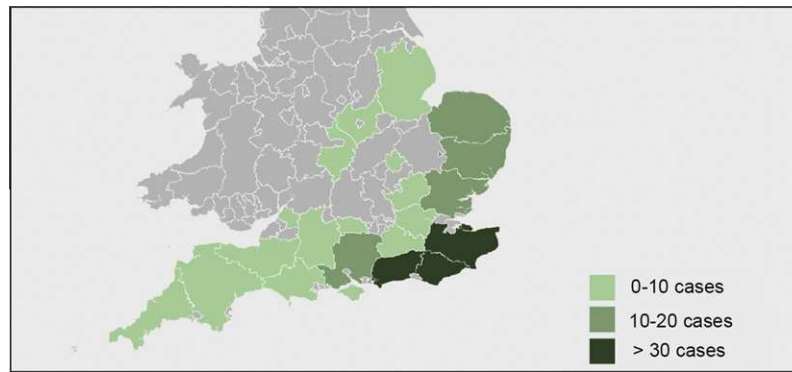
Large-scale outbreaks occur where unusual climatic conditions substantially alter the host vector range, either carrying the virus to new areas populated by naive hosts or back into previously affected areas populated by young, naive and older, previously exposed hosts (Kirkland, 2002). These situations result in large numbers of naive animals becoming exposed and attendant large-scale outbreaks of fetal malformation. It is worth noting that this can occur over a large geographical area: outbreaks were reported in Northern Victoria, almost 1000 km from the recognised endemic zone (Della-Porta et al., 1976; Bishop et al., 2000), with seroconversion rates as high as 80–100% (Della-Porta et al., 1976). Infection returning to a previously endemic area results in a typical pattern of malformation in the offspring of young cows and heifers, while older animals with pre-existing immunity give birth to unaffected calves (Kirkland, 2002).

The situation in Japan and Korea is slightly different as the Akabane virus does not appear to be endemic in these temperate climates. In Japan, the virus is typically detected in the south of the country in spring and summer before spreading northward. It is thought that the virus is probably endemic in China and that outbreaks in Japan are due to wind-borne spread of the main vector *Culicoides oxystoma* (Yanase et al., 2010).

#### Issues requiring research

##### Origins and transmission

It is unclear where SBV originated. One theory is that it may have come with insects imported with an infected animal or with 'cut flowers' from Africa. It is also possible that the virus was circulating latently, perhaps in a reservoir host, and only causing disease when expansion of its vectors' range gave rise to infection of fully susceptible hosts. It is worth considering in this context that Akabane outbreaks spread by *Culicoides imicola* have been recorded in Israel in 2002–2003 (Brenner et al., 2004; Stram et al.,



**Fig. 4.** Map of England and Wales indicating the initial spread of Schmallenberg virus. Figures represent numbers of cases reported by the UK Animal Health Veterinary Laboratories Agency as of 26th of March 2012.

2004) as well as in Turkey and Cyprus in 1980 (Taylor and Mellor, 1994). Thus Simbu serocomplex viruses have been present historically in the Mediterranean basin.

As of June 19th 2012, there had only been sporadic reports of SBV infection in Southern European countries (one herd in Italy and one in Spain, respectively) compared to the large numbers reported in Northern Europe. This may indicate either that the virus is spreading southwards after being introduced into Northern Europe, or that it has been an endemic, subclinical infection in Southern Europe for some time. Initial serological surveys in Germany, France and The Netherlands suggest a decreasing incidence of infection spreading out from a point near the Dutch–German border, a finding that corresponds with the initial reports of milk-drop and fever syndrome in adult cattle (European Commission, 2012).

It is presumed, as for the other viruses in the Simbu serogroup, that the insect vector for SBV is biting midges (*Culicoides* spp.), however work to identify the actual vector species is ongoing. Data from the Antwerp Institute of Tropical Medicine would appear to confirm this assumption (ProMED-mail, 2012b). Midges have been trapped at several locations in Belgium as part of an ongoing blue tongue virus (BTV) surveillance programme. Returning to stored samples, SBV genetic material has been detected in three species of midge (*C. obsoletus*, *C. dewulfi* and *C. pulicaris*) trapped in September and October of 2011. There are similar reports of SBV genetic material in *C. obsoletus* collected in September–November 2011 in Italy and in *Culicoides* spp. in Denmark in October 2011 (ProMED-mail, 2012c,d): both countries have only reported single herds affected by SBV infection to date.

Although these findings do not prove these midges are the primary vectors, all three species are associated with the transmission of BTV and, in the Belgian study, only the heads of these insects were tested for the presence of virus in order to minimise the possibility of detecting virus ingested in a blood meal from an infected animal (suggesting that virus is present in the midge salivary glands). Studies are on-going to determine whether SBV replicates in midges, i.e. to demonstrate their 'vector capacity'. It is noteworthy that funding for the BTV surveillance programme carried out in Antwerp is due to end soon and without this kind of monitoring, the swift resolution of such critical questions in any future emerging disease outbreak will be difficult.

Knowledge of the ecology of the vector species is important in predicting the likelihood of the virus continuing to circulate. As orthobunyaviruses do not replicate well at temperatures <15 °C, over-wintering strategies are important, particularly in temperate countries. Survival of some of the proposed vector species indoors during periods of low temperatures in Europe has been demonstrated and is thought to contribute to the over-wintering of BTV

(Napp et al., 2011). Lambing times in Europe vary from December through to late April which does overlap with the 'midge season' in the UK (April to October). However midge numbers are generally low until the warmer months of June–September, so that most pregnant sheep will have lambed before the midge numbers rise substantially (assuming no prolonged, unseasonably warm periods), and it is unlikely that the disease would be perpetuated by midges feeding on surviving viraemic lambs or their placental fluid.

However, calving occurs throughout the year including during the peak vector season, providing a potential mechanism by which the virus may persist from year to year. SBV RNA was detected in lambs and calves born 'at-term' in 2012 (Bilk et al., 2012; van den Brom et al., 2012) but, as yet, attempts to isolate infectious virus have been unsuccessful. One recent report of a full-term calf with polioencephalomyelitis and detectable SBV RNA and Simbu group viral proteins (Peperkamp et al., 2012), as well as reports of affected lambs since April 2012 (indicating infection in early 2012) (DEFRA, 2012) suggest SBV was circulating in cattle and sheep in Europe in the spring of 2012.

The mechanism by which SBV arrived and became disseminated within the UK remains unknown. Both the pattern of farms affected by SBV in the UK to date (Fig. 4) and the modelling of midge 'plumes' using weather data from the UK Meteorological Office support the theory that the virus first arrived in southern counties, with infected midges blown over from continental Europe by prevailing winds. The very high density of cases on individual farms infers either local spread or that a high proportion of midges were infected. It is unknown whether SBV can be transmitted via contact with infected fomites, although this seems unlikely based on the evidence to date.

If dissemination is due to large numbers of infected vectors, this may result in efficient *de novo* infection of large numbers of naïve cattle and sheep, which would be in keeping with data from outbreaks of other Simbu virus infections (P.D. Kirkland and D.S. Finlaison, unpublished data). This is in marked contrast to the infection of UK livestock with BTV, which caused infection of a smaller proportion of animals.

To address the question of whether SBV had been previously circulating in some European countries, it would be useful to compare the density of cases occurring in the UK with that on mainland Europe, and the ages of the mothers of affected lambs and calves. There is some anecdotal evidence from Germany that younger animals are more likely to have affected fetuses than older animals (ProMED-mail, 2012a), though initial serological surveys in The Netherlands have not found any evidence to support this (European Commission, 2012).

Unfortunately, these data may be difficult to acquire. Typically in the UK, samples from a single case may be submitted to confirm SBV on the farm, so there is relatively little information as to the exact proportion of infected animals. There is also debate as to whether it is better to encourage reporting by offering free testing or alternatively to make the disease notifiable, and different approaches have been adopted in different countries across Europe (e.g. SBV is notifiable in The Netherlands but not in the UK).

#### *Current epidemiological data*

The EFSA has produced a summary of the current epidemiological data up to the 19th of March 2012 ([European Food Safety Authority, 2012](#)). This report lists SBV cases confirmed in Germany, Holland, Belgium, France, Luxembourg, Italy, Spain and England. Denmark was added to this list in June 2012 ([ProMED-mail, 2012e](#)). The distribution follows that of BTV-8 outbreaks in Northern Europe in 2006–2008. Affected animals include cattle, sheep, goats and one bison, with the recent addition of roe deer and llamas ([ProMED-mail, 2012f](#); [Jack et al., 2012](#)), although clinical diarrhoea syndrome has only been confirmed in eight cattle. The vast bulk of the reported cases in the early part of the outbreak was in sheep, partly because cattle have a much longer gestation period and calves infected in utero at the same time as lambs are born later. Most of the cases born later in the outbreak (after April) were in cattle.

Several countries have declared the current SBV outbreak resolved with the total number of affected premises in Europe as of 31st May, 2012 standing at 2062 cattle, 2482 sheep and 77 goat farms ([ProMED-mail, 2012g](#)). Extrapolation of the estimated date of infection of lamb fetuses from their birth date would indicate that the virus circulated from May to November 2011 with the peak of viral circulation occurring in October 2011. This would indicate that virus was circulating in sheep well before the initial disease outbreak was reported in cattle in August. These dates are also significant in that lambs and calves born in spring and summer 2012 have qRT-PCR detectable viral RNA at a time when potential vectors are becoming active.

Given that some of the midge species identified to date are present over most of Northern Europe, this makes further viral transmission in 2012 and the establishment of endemic infection a real possibility. The total number of herds affected compared with the total number of herds in the reporting countries is low with morbidity and mortality estimates of <3% in affected countries ([ProMED-mail, 2012g](#)). However, as the EFSA report indicates, there is likely to be serious under-reporting of cases, and few EU countries have provided morbidity rates for individual herds.

#### *Prevention and control*

Management of outbreaks of Akabane and Aino viral disease in Japan and Australia is largely dependent on sentinel monitoring of vectors and cattle. In Japan, strategic deployment of vaccines is applied if it is apparent that virus is circulating (vaccines are not currently available in Australia). Suggestions have been made that restricting the timing of mating in cattle and sheep to outside of the vector season may be an option to reduce SBV cases in future years ([Anon, 2012](#)). However, the distinctive seasonality of the reproductive cycle in sheep in Europe renders this strategy economically impractical in most instances. Although delaying the insemination of cattle may be a management option, such a change may be problematic, necessitating significant changes in husbandry and potentially resulting in substantial economic losses.

Recommendations for control of bunyavirus infections in humans include avoidance of mosquito exposure by staying indoors at dusk, the peak mosquito biting period, and through the use of

mosquito nets and insecticides. Such an approach remains impractical for all but very valuable livestock. Clearly transporting naïve animals to endemic areas for mating or during pregnancy is to be avoided.

Discussions about the testing of animals, semen and embryos for trading purposes are complicated by the fact that serological tests do not indicate when an animal was infected so do not indicate the likelihood that that animal will give birth to an affected fetus. There has also not yet been time to assess the risk of infection via semen, although this seems unlikely as experimental infection of bulls with Akabane virus results in viraemia, but does not produce detectable virus in semen ([Parsonson et al., 1981c](#)). Infection of embryos recovered from subclinically infected animals is an unknown risk at present.

Several non-European countries have placed movement bans on EU livestock due to the risk of SBV transfer, although the Chief Veterinary Officers within the EU have issued a joint statement indicating that SBV-affected animals and regions should only be subject to the same controls that apply to other viruses of the Simbu group ([European Commission, 2012](#)). The widespread nature of the potential vector species for SBV within Europe and the speed and range over which Simbu viruses can spread probably renders vector control, or the placement of movement restrictions on animals, relatively futile. From a pragmatic perspective, until a vaccine becomes available there is little that can currently be done to reduce the impact of SBV.

#### *Diagnostic assays*

The qRT-PCR developed by the FLI is the primary diagnostic assay used by laboratories in affected countries, and it is currently recommended that brain, blood, spleen and placental samples are tested. This assay does have limitations in detecting infected individuals based on blood samples, as it only detects viral RNA when the animal is viraemic. The report by [van den Brom et al. \(2012\)](#) indicated that only 40.7% of lambs with typical malformations from known affected flocks tested positive for viral RNA in brain tissue. A high proportion of calves have SBV antibodies 'at term' and serum or pericardial fluid may be used for the detection of antibodies by ELISA or VNT (P.D. Kirkland, personal communication). Serology is a reliable method of detecting Akabane virus infection in non-endemic areas in the dams of affected calves, and this approach is beginning to be used in Europe to detect SBV ([Jack et al., 2012](#)). There is currently a critical need for serological testing of adult animals to establish what proportion of national flocks and herds remain susceptible should SBV continue to circulate.

Use of a VN assay in The Netherlands indicates that 70% of the dairy cattle in the country have seroconverted with a higher prevalence in the east of the country and a within-flock/herd seroprevalences of 70–95% (sheep) and 70–100% (dairy cattle), respectively. Initial results using an IFAT test in Germany indicate that there is a higher prevalence in the north-west than in the south-east of the country. Initial VN assays in some French herds indicate 32–100% seropositivity in affected herds in the north of the country, compared with only 7.5% on an affected farm in the central region ([European Commission, 2012](#)). Ongoing research is focused on developing SBV-specific serological tests for high-throughput screening, with the first commercial ELISA made available by French company IDvet.

#### *Vaccine development*

Research is also directed at developing a SBV vaccine. Numerous vaccination strategies have been deployed against zoonotic bunyaviruses such as Rift Valley fever virus ([Ikegami and Makino,](#)



2009), and a number of these have been proposed in the context of developing a SBV vaccine. Regulatory approval is more likely to be obtained for a non-replicating vaccine, as one of the major risks of a live virus vaccine is the potential teratogenic effects in livestock accidentally inoculated while pregnant.

Several Akabane vaccines have been deployed in Australia and Japan. Inoculation with formalin-inactivated aluminium phosphate-adjuvanted viral preparations resulted in the production of VN antibody in animals following two doses given 4 weeks apart (Kurogi et al., 1978). In Japan, live attenuated and killed adjuvanted vaccines against Akabane virus are currently registered for use in cattle. To date, there are no reported trials assessing if there is cross protection by these vaccines against SBV infection. Furthermore, the situation pertaining with SBV is quite different to that of the recent BTV-8 outbreak in Europe, where rapid deployment of a monovalent inactivated vaccine was facilitated by the availability of existing efficacy and safety data for this vaccine from countries where BTV-8 is endemic.

## Conclusions

The outcome of the emergence of SBV in Europe remains hard to predict. However, with the UK being the largest producer of sheep meat in Europe, and the fifth largest producer worldwide, there is the potential for a considerable economic impact on farmers, the meat industry and food supply, both in the UK and on mainland Europe. Yet there remains reason for optimism. The experience gleaned from the study of closely related viruses may result in more rapid progress towards the control of SBV infection, and it is clear that through the expeditious research of many groups, the next 12 months will provide a further wealth of information about this previously unknown disease. Forging and strengthening international collaborations will enable existing expertise on related viruses to be used constructively and decisions about how to proceed to be evidence-based.

At the time of its initial isolation, it was not clear if SBV was a coincidental finding or the cause of this novel disease. The early sharing of information about the virus by the FLI via a press release on 21st November 2011 proved vital to the rapid identification of the first malformed lambs and calves in the spring of 2012. The FLI also facilitated the rapid establishment of a diagnostic capability in the veterinary laboratories of other EU states by making the details of their qRT-PCR test available. On occasions in the past, researchers have delayed announcing new findings until they had sufficient data for submission to a high impact journal. The timely release of information regarding SBV has not only facilitated its rapid diagnosis but has also promoted healthy competition to develop new diagnostic assays and vaccines. This provides an exemplar of a coordinated international response to future emergent disease threats.

Unfortunately, given factors such as climate change and increased globalisation, SBV is unlikely to be the last 'exotic' vector-borne disease to affect European livestock. However, the experience of this outbreak of SBV infection should assist in the development of systems that facilitate the rapid identification and notification of emerging diseases and streamline government responses in areas such as disease control and reactive research funding.

## Conflict of interest statement

None of the authors of this paper has a financial or personal relationship with other people or organisations that could inappropriately influence or bias the content of the paper.

## Acknowledgements

The photograph of a Schmallenberg virus-affected lamb was kindly provided by Amanda Straughton. Thanks to Brian Cloak for preparing this photograph for publication. The authors wish to thank Dr. Peter Kirkland for his critical appraisal of the manuscript.

## References

- Aguilar, P.V., Barrett, A.D., Saeed, M.F., Watts, D.M., Russell, K., Guevara, C., Ampuero, J.S., Suarez, L., Cespedes, M., Montgomery, J.M., Halsey, E.S., Kochel, T.J., 2011. Iquitos virus: A novel reassortant *Orthobunyavirus* associated with human illness in Peru. *PLoS Neglected Tropical Diseases* 5, e1315.
- Anon, 2012. Scenarios for the future spread of Schmallenberg virus. *Veterinary Record* 170, 245–246.
- Bishop, A.L., Barchia, I.M., Spohr, L.J., 2000. Models for the dispersal in Australia of the arbovirus vector, *Culicoides brevitarsis* Kieffer (Diptera: Ceratopogonidae). *Preventive Veterinary Medicine* 47, 243–254.
- Bilk, S., Schulze, C., Fischer, M., Beer, M., Hlinak, A., Hoffman, B., 2012. Organ distribution of Schmallenberg virus RNA in malformed newborns. *Veterinary Microbiology* 159, 236–238.
- Blitvich, B.J., Saiyasombat, R., Dorman, K.S., Garcia-Rejon, J.E., Farfan-Ale, J.A., Lorono-Pino, M.A., 2012. Sequence and phylogenetic data indicate that an orthobunyavirus recently detected in the Yucatan Peninsula of Mexico is a novel reassortant of Potosi and Cache Valley viruses. *Archives of Virology*. <http://dx.doi.org/10.1007/s00705-012-1279-x>.
- Brenner, J., Tsuda, T., Yadin, H., Chai, D., Stram, Y., Kato, T., 2004. Serological and clinical evidence of a teratogenic Simbu serogroup virus infection of cattle in Israel, 2001–2003. *Veterinaria Italiana* 40, 119–123.
- Causey, O.R., Kemp, G.E., Causey, C.E., Lee, V.H., 1972. Isolations of Simbu-group viruses in Ibadan, Nigeria 1964–69, including the new types Sango, Shamonda, Sabo and Shuni. *Annals of Tropical Medicine and Parasitology* 66, 357–362.
- Della-Porta, A.J., Murray, M.D., Cybinski, D.H., 1976. Congenital bovine epizootic arthrogryposis and hydranencephaly in Australia. Distribution of antibodies to Akabane virus in Australian Cattle after the 1974 epizootic. *Australian Veterinary Journal* 52, 496–501.
- DEFRA, 2012. Update 9 on Schmallenberg Virus in Northern Europe. <http://www.defra.gov.uk/animal-diseases/files/poa-schmallenberg-update-120618.pdf> (accessed 19 June 2012).
- European Centre for Disease Prevention and Control, 2012. New *Orthobunyavirus* Isolated from Infected Cattle and Small Livestock – Potential Implications for Human Health. [http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC\\_DispForm.aspx?ID=881](http://www.ecdc.europa.eu/en/publications/Publications/Forms/ECDC_DispForm.aspx?ID=881) (accessed 01 June 2012).
- European Commission, 2012. Schmallenberg Virus. [http://www.ec.europa.eu/food/animal/diseases/schmallenberg\\_virus/scientific\\_seminar\\_en.htm](http://www.ec.europa.eu/food/animal/diseases/schmallenberg_virus/scientific_seminar_en.htm) (accessed 19 June 2012).
- European Food Safety Authority, 2012. 'Schmallenberg' Virus: Analysis of the Epidemiological Data. <http://www.efsa.europa.eu/en/supporting/pub/261e.htm> (accessed 04 April 2012).
- Garigiany, M.M., Hoffman, B., Dive, M., Sartelet, A., Bayrou, C., Cassart, D., Beer, M., Deschmect, D., 2012. Schmallenberg virus in calf born at term with porencephaly, Belgium. *Emerging Infectious Diseases* 18, 1005–1006.
- Hartley, W.J., Della-Porta, A.J., Snowdon, W.A., Shepherd, N.C., 1977. Pathology of congenital bovine epizootic arthrogryposis and hydranencephaly and its relationship to Akabane virus. *Australian Veterinary Journal* 53, 319–325.
- Herder, V., Wohlsein, P., Peters, M., Hansmann, F., Baumgartner, W., 2012. Salient lessons in domestic ruminants infected with the emerging so called Schmallenberg virus in Germany. *Veterinary Pathology* 49, 588–591.
- Hoffmann, B., Scheuch, M., Hoper, D., Jungblut, R., Holsteg, M., Schirmer, H., Eschbaumer, M., Goller, K.V., Wernike, K., Fischer, M., Breithaupt, A., Mettenleiter, T.C., Beer, M., 2012. Novel orthobunyavirus in cattle, Europe, 2011. *Emerging Infectious Diseases* 18, 469–472.
- Huang, C.C., Huang, T.S., Deng, M.C., Jong, M.H., Lin, S.Y., 2003. Natural infections of pigs with Akabane virus. *Veterinary Microbiology* 94, 1–11.
- Ikegami, T., Makino, S., 2009. Rift Valley fever vaccines. *Vaccine* 27, 69–72.
- International Committee on Taxonomy of Viruses, 2011. *Virus Taxonomy: 2011 Release*. <http://www.ictvonline.org/virusTaxonomy.asp?version=2011> (accessed 04 April 2012).
- Jack, C., Anstaett, O., Adams, J., Noad, R., Brownlie, J., 2012. Evidence of seroconversion to SBV in camelids. *Veterinary Record* 170, 603.
- Kamata, H., Inai, K., Maeda, K., Nishimura, T., Arita, S., Tsuda, T., Sato, M., 2009. Encephalomyelitis of cattle caused by Akabane virus in southern Japan in 2006. *Journal of Comparative Pathology* 140, 187–193.
- Kessell, A., Finnie, J., Windsor, P., 2011. Neurological diseases of ruminant livestock in Australia. IV: Viral infections. *Australian Veterinary Journal* 89, 331–337.
- Kirkland, P.D., 2002. Akabane and bovine ephemeral fever virus infections. *Veterinary Clinics of North America: Food Animal Practice* 18, 501–514.
- Kirkland, P.D., Barry, R.D., Harper, P.A., Zelski, R.Z., 1988. The development of Akabane virus-induced congenital abnormalities in cattle. *Veterinary Record* 122, 582–586.

- Kono, R., Hirata, M., Kaji, M., Goto, Y., Ikeda, S., Yanase, T., Kato, T., Tanaka, S., Tsutsui, T., Imada, T., Yamakawa, M., 2008. Bovine epizootic encephalomyelitis caused by Akabane virus in southern Japan. *BioMed Central Veterinary Research* 4, 20.
- Kurogi, H., Inaba, Y., Takahashi, E., Sato, K., Goto, Y., Satoda, K., Omori, T., Hatakeyama, H., 1978. Development of inactivated vaccine for Akabane disease. *National Institute of Animal Health Quarterly (Tokyo)* 18, 97–108.
- Lee, J.K., Park, J.S., Choi, J.H., Park, B.K., Lee, B.C., Hwang, W.S., Kim, J.H., Jean, Y.H., Haritani, M., Yoo, H.S., Kim, D.Y., 2002. Encephalomyelitis associated with Akabane virus infection in adult cows. *Veterinary Pathology* 39, 269–273.
- Levin, A., Rubinstein-Guini, M., Kuznetsova, L., Stram, Y., 2008. Cleavage of Akabane virus S RNA in the brain of infected ruminants. *Virus Genes* 36, 375–418.
- Muskens, J., Smolenaars, A.J., van der Poel, W.H., Mars, M.H., van Wuijckhuise, L., Holzhauser, M., van Weering, H., Kock, P., 2012. Diarrhea and loss of production on Dutch dairy farms caused by the Schmallenberg virus. *Tijdschrift voor Diergeneeskunde* 137, 112–115.
- Napp, S., Gubbins, S., Calistri, P., Allepuz, A., Alba, A., Garcia-Bocanegra, I., Giovannini, A., Casal, J., 2011. Quantitative assessment of the probability of bluetongue virus overwintering by horizontal transmission: Application to Germany. *Veterinary Research* 42, 4.
- Oem, J.K., Yoon, H.J., Kim, H.R., Roh, I.S., Lee, K.H., Lee, O.S., Bae, Y.C., 2012. Genetic and pathogenic characterization of Akabane viruses isolated from cattle with encephalomyelitis in Korea. *Veterinary Microbiology*. <http://dx.doi.org/10.1016/j.vetmic.2012.02.017>.
- Parsonson, I.M., Della-Porta, A.J., Snowdon, W.A., 1977. Congenital abnormalities in newborn lambs after infection of pregnant sheep with Akabane virus. *Infection and Immunity* 15, 254–262.
- Parsonson, I.M., Della-Porta, A.J., O'Halloran, M.L., Snowdon, W.A., Fahey, K.J., Standfast, H.A., 1981a. Akabane virus infection in the pregnant ewe 1. Growth of virus in the fetus and the development of the fetal immune response. *Veterinary Microbiology* 6, 197–207.
- Parsonson, I.M., Della-Porta, A.J., Snowdon, W.A., 1981b. Akabane virus infection in the pregnant ewe. 2. Pathology of the fetus. *Veterinary Microbiology* 6, 209–224.
- Parsonson, I.M., Della-Porta, A.J., Snowdon, W.A., O'Halloran, M.L., 1981c. Experimental infection of bulls with Akabane virus. *Research in Veterinary Science* 31, 157–160.
- Parsonson, I.M., McPhee, D.A., Della-Porta, A.J., McClure, S., McCullagh, P., 1988. Transmission of Akabane virus from the ewe to the early fetus (32 to 53 days). *Journal of Comparative Pathology* 99, 215–227.
- Peperkamp, K., Dijkman, R., van Maanen, C., Vos, J., Wouda, W., Holzhauser, M., van Wuijckhuise, L., Junker, K., Greijdanus, S., Roumen, M., 2012. Polioencephalomyelitis in a calf due to infection with Schmallenberg virus. *Veterinary Record* 170, 570.
- ProMED-mail, 2012a. Schmallenberg Virus – Europe (24): Update, Request for Information. <http://www.promedmail.org> (accessed 04 April 2012).
- ProMED-mail, 2012b. Schmallenberg Virus – Europe (26): Vector, Morphology. <http://www.promedmail.org> (accessed 04 April 2012).
- ProMED-mail, 2012c. Schmallenberg Virus – Europe (35): Update, Italy, Vector. <http://www.promedmail.org> (accessed 18 June 2012).
- ProMED-mail, 2012d. Schmallenberg Virus – Europe (41): Serosurvey, Vector. <http://www.promedmail.org> (accessed 18 June 2012).
- ProMED-mail, 2012e. Schmallenberg Virus – Europe (46): Denmark, Bovine. <http://www.promedmail.org> (accessed 18 June 2012).
- ProMED-mail, 2012f. Schmallenberg Virus – Europe (43): Update, Deer. <http://www.promedmail.org> (accessed 18 June 2012).
- ProMED-mail, 2012g. Schmallenberg Virus – Europe (44): Germany Update, OIE, Resolved. <http://www.promedmail.org> (accessed 18 June 2012).
- Stram, Y., Brenner, J., Braverman, Y., Banet-Noach, C., Kuznetsova, L., Ginni, M., 2004. Akabane virus in Israel: A new virus lineage. *Virus Research* 104, 93–97.
- Taylor, W.P., Mellor, P.S., 1994. The distribution of Akabane virus in the Middle East. *Epidemiology and Infection* 113, 175–185.
- van den Brom, R., Lutikholt, S.J., Lievaart-Peterson, K., Peperkamp, N.H., Mars, M.H., van der Poel, W.H., Vellema, P., 2012. Epizootic of ovine congenital malformations associated with Schmallenberg virus infection. *Tijdschrift voor Diergeneeskunde* 137, 106–111.
- van Eeden, C., Williams, J.H., Gerdes, T.G., van Wilpe, E., Viljoen, A., Swanepoel, R., Venter, M., 2012. Shuni virus as cause of neurologic disease in horses. *Emerging Infectious Diseases* 18, 318–321.
- Yanase, T., Aizawa, M., Kato, T., Yamakawa, M., Shirafuji, H., Tsuda, T., 2010. Genetic characterization of Aino and Peaton virus field isolates reveals a genetic reassortment between these viruses in nature. *Virus Research* 153, 1–7.
- Yanase, T., Kato, T., Aizawa, M., Shuto, Y., Shirafuji, H., Yamakawa, M., Tsuda, T., 2012. Genetic reassortment between Sathuperi and Shamonda viruses of the genus *Orthobunyavirus* in nature: Implications for their genetic relationship to Schmallenberg virus. *Archives of Virology*. <http://dx.doi.org/10.1007/s00705-012-13>.
- Yanase, T., Maeda, K., Kato, T., Nyuta, S., Kamata, H., Yamakawa, M., Tsuda, T., 2005. The resurgence of Shamonda virus, an African Simbu group virus of the genus *Orthobunyavirus*, in Japan. *Archives of Virology* 150, 361–369.
- Yang, D.K., Kim, B.H., Kweon, C.H., Nah, J.J., Kim, H.J., Lee, K.W., Yang, Y.J., Mun, K.W., 2008. Serosurveillance for Japanese encephalitis, Akabane, and Aino viruses for Thoroughbred horses in Korea. *Journal of Veterinary Science* 9, 381–385.