1 **Review**

2
3 **How is Europe positioned for a re-emergence of Schmallenberg virus?**

4
5 Anastasios Stavrou^{a,b}, Janet Daly^a, Ben Maddison^a, Kevin Gough^a, Rachael Tarlinton^{a,*}

6
7 *^a School of Veterinary Medicine and Science, University of Nottingham, Sutton Bonington Campus,*
8 *Leicestershire, LE12 5RD*

9 *^b Department of Molecular and Cell Biology, University of Leicester, LE1 7RH- current address*

10
11
12 *Corresponding author. Tel.: +44 115 9516273.

13 Email address: rachael.tarlinton@nottingham.ac.uk (R.Tarlinton).

14 **Abstract**

15 The Schmallenberg virus (SBV) caused a large scale epidemic in Europe from 2011–2013
16 infecting ruminants and causing fetal deformities after infection of pregnant animals. The main
17 impacts of the virus were financial losses due to animal, meat and semen trade restrictions.
18 Even though effective vaccines were produced, their uptake was never high. This along with the
19 subsequent decline in new SBV infections and natural replacement of previously exposed livestock
20 has resulted in a drop in the number of protected animals. Recent surveillance has found a large
21 population of naïve animals currently present in Europe and the virus circulating at a low level.
22 These changes in animal status in combination with favourable conditions for the insect vectors
23 may open the door to the re-emergence of the virus and another large-scale outbreak in Europe.
24 This review details the potential and preparedness for SBV re-emergence in Europe, discusses
25 possible co-ordinated sentinel monitoring programmes both for ruminant seroconversion and the
26 presence of virus in the insect vectors and provides an overview of the economic impact associated
27 with diagnosis, control and the effect of non-vaccination.

28
29
30
31 *Keywords:* Schmallenberg virus; Monitoring; Re-emergence, Surveillance

32 **Introduction**

33 Schmallenberg virus (SBV) is an Orthobunyavirus of the Simbu serogroup that was
34 responsible for a large-scale outbreak of fetal deformities in lambs and calves in Northern Europe in
35 2011–13 (Hoffmann et al., 2012). The virus causes little or no disease in adult animals but displays
36 a distinct tropism for the central nervous system of lambs and calves infected *in utero* leading to a
37 range of distinctive deformities including hydrocephalus and arthrogryposis (Bayrou et al., 2014;
38 Peperkamp et al., 2015). In the years since its initial emergence, SBV appears to have settled to a
39 low-level endemic circulation. Considerable research into SBV and its epidemiology (Helmer et al.,
40 2013; Luttikholt et al., 2014; Veldhuis et al., 2014) has been conducted since its discovery,
41 including the development of commercial vaccines (Kraatz et al., 2015). However, several years of
42 little or no clinical disease and a lack of clarity about the economic impacts have resulted in very
43 poor uptake of the vaccine. It is also unclear what conditions could result in a further large scale
44 outbreak, but it is likely that herd-level immunity to the virus at a European and a local level has
45 decreased, creating the potential conditions for another outbreak of fetal deformities. This review
46 summarises the current state of preparedness for further SBV outbreaks in Europe.

47

48 **First detection and initial spread of SBV**

49 SBV was first detected in Europe in the beginning of September 2011. Infections appeared
50 near simultaneously in 2011 in neighbouring countries Germany, the Netherlands and Belgium. By
51 February 2012 and May 2012 peaks in infections in sheep and cattle respectively had been
52 identified. At the height of the outbreak in 2013, SBV cases were reported in 13,846 herds in 29
53 countries, with 8730 being laboratory confirmed. It is difficult to calculate the actual numbers of
54 animals affected as only herd level data were collected and reported in many countries (Afonso et
55 al., 2014). In the UK, seroprevalence in the most affected counties by the end of 2013 was 73%.
56 However, in other UK areas, this figure was less than 50% suggesting there were a large number of
57 animals still at risk (King et al., 2015). Circulation re-occurred the next winter and spring, though at

58 a lower peak than in 2011/12, probably due to large numbers of animals with pre-existing immunity
59 (EFSA, 2012a).

60

61 SBV spreads extremely rapidly, estimated from EU Nomenclature of Territorial Units for
62 Statistics (NUTS) to be 6 days from region to region (Sedda and Rogers, 2013). It has been reported
63 in climate ranges from the Mediterranean basin (Italy and Spain) to more than latitude 60 ° north
64 (Norway) (Balseiro et al., 2015; Monaco et al., 2013; Wisløff et al., 2014). Spread of the virus has
65 tended to be from close-by infected regions to the next region, rarely exceeding 200 km at a time
66 (Afonso et al., 2014). Interestingly, modelling the spread of SBV using mathematical methods has
67 replicated the spread of SBV across Europe, uncovering a high vector competence and high
68 replication rate for temperatures common in Europe (16-34°C) (EFSA, 2014; Gubbins et al.,
69 2014a).

70

71 It is still unclear where the virus originated from but at least two studies have demonstrated
72 SBV cross reactive antibodies (along with several other Simbu group viruses) in cattle in Africa
73 prior to or after the European outbreak. In the Middle East a Simbu serogroup virus related to Aino
74 virus was found recently, causing clinical signs similar to SBV in infected ruminants (Abutarbush et
75 al., 2015). Several historical and recent reports have highlighted that viruses from the Simbu group,
76 many of which have teratogenic potential, circulate within the Mediterranean basin (Lievaart-
77 Peterson et al., 2012; Azkur et al., 2013; Chaintoutis et al., 2014; Yilmaz et al., 2014).
78 At the height of the original outbreak in Europe, herds in Northern Europe were reporting
79 essentially all animals seroconverting to the virus, 98.5–99.8% in adult cattle and 89% in sheep
80 (Méroc et al., 2013; Veldhuis et al., 2013) at herd level.

81

82 **Virus transmission**

83 SBV, like many other Bunyaviruses, is an arbovirus, i.e. it is transmitted via arthropod

vectors. The fact that the virus relies on vector transmission limits antigenic drift as mutations that could confer advantages in final host replication could be disadvantageous in the vector. This bottleneck has also been seen in other RNA viruses that depend on mosquito vectors, such as Venezuelan equine encephalitis virus (Forrester et al., 2012). SBV has also been found to have a low mutation rate both *in vitro*, even when passaged 10 times, and *in vivo* (Hoffmann et al., 2015). Several field studies of virus variability have also demonstrated that the virus is relatively stable over time (Coupeau et al 2016; Izzo et al., 2016).

Direct horizontal transmission by contact has not been detected, even when infected cows were kept in close proximity to uninfected cows (Wernike, 2013a). The presence of different species of insects might determine the speed and pattern of infection in different farms (Ayllón et al., 2014; Bessell et al., 2014). The main vectors are thought to be species in the *obsoletus* complex of *Culicoides*, or biting midges, including *Culicoides chiopterus*, *dewulfi* and *scoticus* (Balenghien et al., 2014; De Regge et al., 2012). Experimental studies with *C. sonorensis* (Veronesi et al., 2013), a known vector of bluetongue virus, have shown that these midges can also produce a competent infection and could act as a reservoir of the virus. Importantly, midges are most abundant between April and October, with a ‘peak midge season’ between July to September, which coincides with the peak of SBV seroconversion in 2012/2013 (Mellor et al., 2000; EFSA, 2012b; Larska et al., 2013; Veldhuis et al., 2013).

It is probable that SBV can overwinter in midges. Viral RNA has been detected in midges belonging to the *obsoletus* complex over-winter in north Italian farms 3 months after the SBV outbreak (Goffredo et al., 2013). Furthermore, these midges can become active at temperatures as low as 3.5°C (Sprygin et al., 2014). In Germany, it was reported that midges could be trapped during warmer (~9°C) winter days (Wernike et al., 2013c). SBV spread in winter does occur (Davies and Daly, 2013), but is likely to be limited as the threshold for replication of the virus

110 appears to be between 12 and 13°C (Gubbins et al., 2014b).

111

112 Wind also plays an important role in the transmission of the virus, as midges are easily
113 carried on air currents. (Sedda et al., 2012; Sedda and Rogers, 2013). UK Meteorological office
114 atmospheric dispersion models proved accurate at predicting SBV outbreaks due to midge spread.
115 South-east, south and south-west counties in the UK were found at increased risk of outbreaks
116 (Met-Office, 2012), from ‘midge plumes’ from mainland Europe. Wind models for midge dispersal
117 in mainland Europe have also been used and have found that 70% of the spatial and temporal
118 distribution of affected farms could be explained by wind movements (Sedda and Rogers, 2013).

119

120 **Clinical disease**

121 The main clinical disease seen in adult animals is fever, diarrhoea and, in the case of
122 lactating animals, ‘milk drop’ syndrome. This is usually mild and self-limiting (Wernike et al.,
123 2012, 2013a, 2013b), however during the initial SBV outbreak due to the numbers of animals
124 involved, there was a significant effect on farm level milk production (Toson et al., 2015; Veldhuis
125 et al., 2014). Interestingly, neither field nor experimental infections produced clinical signs in adult
126 sheep, goats or alpacas (Wernike et al., 2012, 2013a, 2013b; Poskin et al., 2014; Laloy et al., 2015;
127 Schulz et al., 2015). The virus however readily crosses the placenta and has been isolated from the
128 cerebrum, nerve and astroglial cells and spinal cords of lambs (Bilk et al., 2012; Varela et al.,
129 2013). After crossing the placenta, the virus infects and attacks the fetal central nervous system and
130 the cerebral cortex, possibly causing necrosis (Agerholm et al., 2015).

131

132 Since SBV targets these critical cells, the level of CNS development, and therefore the
133 susceptible period of infection, determines the severity of lesions. Consistent with infection with
134 other *Bunyaviridae* (Kurogi et al., 1977; Kirkland et al., 1988), infection in mid-gestation appears to
135 be the defining factor causing these abnormalities. SBV infection from 60–180 days in cattle

136 (Wernike et al., 2014) leads to severe dysplastic CNS lesions (Peperkamp et al., 2015). Infection
137 during late pregnancy, when the CNS and the fetuses own immune system responses are more
138 developed results in less severe clinical signs such as non-suppurative inflammation in the brain and
139 spinal cord (Peperkamp et al., 2015). The typical arthrogryposis is thought to be a secondary
140 clinical sign indicative of neuronal loss, leading to a muscle activity imbalance and a failure of
141 normal muscle and joint development. This is supported by the fact that the virus is not found in the
142 skeleton or muscle in fetuses (Bayrou et al., 2014; Peperkamp et al., 2015).

143

144 Reports of early pregnancy loss (presenting as a failure to conceive) were a feature of the
145 SBV outbreak. SBV infected sheep during the SBV outbreak in Belgium, had a doubling of
146 abortions compared to non-infected flocks (Saegerman et al., 2014). Similarly, SBV infected flocks
147 from Ireland to Germany also had a 10–50% reduction in weaning rates reflecting both increased
148 abortions and increased mortality during early lamb life (Helmer et al., 2013; Wernike et al.,
149 2013b; Dominguez et al., 2014; Luttikholt et al., 2014; Barrett et al., 2015; Martinelle et al., 2015;
150 Toson et al., 2015; Wüthrich et al., 2016). Some studies of affected dairy cattle herds have also
151 demonstrated a detrimental impact in fertility parameters (including an increase in animals failing to
152 conceive) during SBV outbreaks (Veldhuis et al., 2014) whereas others did not (Luttikholt et al.,
153 2014).

154

155 **Diagnosis**

156 The European Food Safety Authority released case definitions and diagnostic standards for
157 SBV, which have been widely adopted by member states of the European Union (EFSA, 2012a,
158 2012b). Suspect clinical cases include fetuses with two or more signs of arthrogryposis,
159 hydranencephaly, spinal abnormalities such as kyphosis and scoliosis, joint malformation, limb
160 paralysis and muscle atrophy (Afonso et al., 2014). Blindness and abnormal behaviour in neonates
161 are also suspect signs. In adult animals, fever >40 °C, reduced appetite and milk drop (with no other

162 apparent reason) can lead to suspicion of viral infection.

163

164 Virus can be isolated in cell culture. However, RT-qPCR to detect viral RNA was generally
165 used during the outbreak to confirm viral infection in fetuses or neonates. In adult animals,
166 seropositivity has been detected by a variety of ELISA-based methods or with virus neutralisation
167 tests (Loeffen et al., 2012; Breard et al., 2013; Afonso et al., 2014). Problems exist with either
168 method for confirmation of the causality of the disease. For RT-qPCR assays, there is a narrow
169 window of time where the virus can be detected in tissue/blood; fetuses with typical clinical signs of
170 the disease may have cleared the virus before birth and therefore test negative on RT-qPCR. Most
171 ELISA tests are not able to distinguish between different members of the Simbu serogroup of
172 viruses, therefore serum neutralisation tests are required to definitively identify which virus an
173 animal has been exposed to in regions where multiple viruses are circulating (Abutarbush et al.,
174 2015; Mathew et al., 2015). Although serum neutralisation tests are more specific than ELISA,
175 they are time consuming to perform and require cell culture facilities. These serological tests can
176 confirm past infection but cannot give an indication of the timing of that infection in relation to the
177 birth of an affected fetus (Bouwstra et al., 2013). Testing of the antibody response of the fetus (via
178 fetal thoracic fluid testing) has been suggested as a more useful test for confirmation of SBV
179 infection in deformed calves and lambs (De Regge et al., 2013).

180

181 Herd level testing via bulk milk tank sampling was widely used at the height of the outbreak
182 to confirm the geographical spread of the virus. There are, however, reports of herds with high
183 values when bulk tank milk was tested by ELISA where the within-herd prevalence of antibodies is
184 actually low (Tarlinton and Daly, 2013). Individually-sampled milk shows a strong correlation with
185 serum results from the same animal, potentially providing a non-invasive method of determining
186 within-herd exposure for dairy farms (Daly et al., 2015). Furthermore, detection of antibodies in
187 saliva by ELISA provides another non-invasive, fast method to determine prevalence of antibodies

188 (Lazutka et al., 2015).

189

190 **Control**

191 Attempts were made during the initial outbreak to limit midge numbers through
192 environmental controls (insecticide dipping of animals, breaking up of manure from midge breeding
193 sites). Chemical treatment of sheep has shown some promise in reducing numbers of midges
194 (Weiher et al., 2014) however environmental control of midge breeding sites on farms has so far
195 failed to impact on insect numbers (Harrup et al., 2014). The seemingly high replication efficiency
196 and spread of SBV in *Culicoides spp.* especially when compared with bluetongue virus (BTV),
197 (spread by the same main vectors) also limits the use of insect control methods in the control of
198 SBV (EFSA, 2014; Veronesi et al., 2013)

199

200 There have been three commercial vaccines released against the virus, all of which are
201 adjuvanted inactivated ('killed') virus vaccines. The first vaccine available was brought to market in
202 record time under a provisional registration, however the speed of introduction and licencing route
203 has meant that comprehensive data on efficacy and safety in pregnant animals (a crucial group to
204 protect) has not been available. In a study of prototype killed virus vaccines, onset of immunity in
205 cattle and sheep was demonstrated three weeks after the second of two doses given three weeks
206 apart (Wernike et al., 2013d). This type of vaccine appears to be effective in preventing viral
207 replication in animals, with sheep protected when challenged 3 weeks after a single dose
208 (Hechinger et al., 2014). Natural infection has been shown to induce persistent antibodies in
209 infected cows, lasting at least 36 months (Elbers et al., 2014; Méroc et al., 2015, Wernike et al
210 2015b).

211

212 Anecdotal reports and the author's observations have indicated that uptake of the
213 commercial SBV vaccines has been low and the fact that none of the released vaccines are currently

214 available (March 2017) would attest to this. Recent data in England showed that even though half of
215 124 farmers surveyed suspected cases of SBV on their farm, only 13.7% had vaccinated in 2013,
216 with that figure falling to 1.6% in 2014. One farm had vaccinated cattle but not sheep (Stokes et al.,
217 2016). There are a number of potential reasons for a lack of interest from farm managers in
218 vaccinating against SBV. In our own unpublished data from surveys of UK farms in 2013 only one
219 farm in 20 was planning on vaccinating for SBV. A recurrent theme in responses was the perception
220 that SBV “would disappear like bluetongue” usually indicating that European farmers did not feel it
221 was economically viable to maintain vaccination programmes for intermittent vector borne diseases.
222 Indeed, in the Netherlands the circulation of the virus in 2013 was <1% with a low number of
223 seropositive animals (Veldhuis et al., 2015).

224

225 The two non-structural proteins (NSs, NSm) may play a role in viral pathogenesis (Eifan et
226 al., 2013; Hart et al., 2009). Experimental trials of live virus vaccines with the viral NSs and NSm
227 protein genes deleted have demonstrated the efficacy and safety of such vaccines (Kraatz et al.,
228 2015). A crucial advantage of knockout mutants like this includes the ability to develop tests against
229 the missing proteins to differentiate infected from vaccinated animals, an important issue in
230 international trade considerations. These vaccines have however not been taken through to full
231 commercialisation.

232

233 The main other control method that has been advocated, apart from vaccinating before first
234 mating, has been the moving of mating of sheep flocks and cattle herds to later in the autumn when
235 midge numbers and virus circulation are lower. This should be effective in limiting reproductive
236 effects in sheep flocks and cattle herds but is only practical in production systems that practice
237 block matings (Helmer et al., 2013; Dominguez et al., 2014; Luttikholt et al., 2014; Poskin et al.,
238 2016).

239

240 **Economic impact of SBV**

241 The impact of the initial SBV outbreak on the overall European economy was low (EFSA,
242 2012a). The cost to individual farm businesses shows great variation depending on whether their
243 mating practices result in the at-risk gestation period overlapping with peak midge season. Several
244 recent studies have considered the overall economic impacts of the virus (Dominguez et al., 2014;
245 Martinelle et al., 2014; Veldhuis et al., 2014; Barrett et al., 2015) and there have been several
246 economic models produced from this data (Alarcon et al., 2014; Raboisson et al., 2014). The main
247 impacts of the virus on farm economics can be summed up as milk production losses, reproductive
248 losses due to abortion and fetal deformity, the cost of purchase of replacement stock to compensate
249 for reproductive losses, replacement animals not sold, as well as veterinary costs and movement
250 restrictions (Alarcon et al., 2014).

251

252 One factor the current models have not included is the impact of early reproductive losses as
253 firm data is still not available on this. The inclusion of these losses would of course add to the
254 economic impact of the virus for producers. These impacts need to be considered in the light of the
255 very high variation in impact on individual farms, ranging from negligible to over 50% of losses of
256 new-born animals (Helmer et al., 2013). It also needs to be considered in the light of the range of
257 production systems for ruminants in Europe which vary from high genetic value, intensively
258 managed, indoor housed year round reproduction dairy herds to extensively grazed, low stocking
259 density, block mated in autumn, sheep flocks.

260

261 One of the main economic impacts of the initial SBV outbreak was the loss of export
262 markets for bovine genetics (semen, embryos and breeding stock) due to the introduction of trade
263 barriers from countries free of SBV (60% of countries trading with Europe imposed restrictions). A
264 decline of 10-20% in trade was observed in addition to the value of pure-bred breeding animal
265 exports dropping by 20% from 2011 to 2012 (EFSA, 2014). The remaining outcome of economic

significance has been the finding that potentially infectious virus is shed intermittently in semen for up to 3 months after initial infection in a small number of bulls (Hoffmann et al., 2012, 2013; Ponsart et al., 2014; Schulz et al., 2014; Van Der Poel et al., 2014). This has not been reported for rams or bucks, however only small numbers of sheep and goats have been examined compared with cattle. Sexual transmission of the virus has not been reported, however given the importance of artificial insemination in cattle breeding in developed countries the risk of virus introduction has resulted in trade bans or testing requirements on semen or embryos from SBV-affected areas (Hoffmann et al., 2012).

274

In the light of the concerns of producers over vaccination cost and benefit and the current risk and uncertainty over future SBV outbreaks it is worth considering recent data on the economic impacts of the virus and the cost-benefits of vaccination as a control measure. Vaccination experience with bluetongue virus has shown that a high rate of vaccination can significantly reduce virus circulation and reduce the economic impact of the loss of animals (Lazutka et al., 2015). A brief summary of the range of the costs of the disease versus the cost of vaccination for the main production types in Europe is presented in Table 1 below.

282

These figures would indicate that vaccination would be warranted in most beef cattle herds and dairy sheep flocks, however in other production systems only those herds in “high risk” categories, such as a herd of low seropositivity, management systems where gestation and pasture availability overlaps with peak midge season (Baylis et al., 2010; Alarcon et al., 2014) would accrue an overall benefit from vaccination against SBV.

288

289 **Potential for SBV re-emergence**

Other viruses that infect ruminants, such as BTV in Europe, and related *Bunyaviridae* in Japan and Australia, have shown a pattern of re-emergence when certain conditions are met. It is

292 therefore anticipated that SBV might follow the same pattern of re-emergence. In Japan there are
293 epidemics of Aino virus every 3-6 years (Tsuda et al., 2004; Kono et al., 2008) as naïve animals
294 become available. For Akabane virus in Australia there are predictable annual transmission patterns
295 and outbreaks every 10-15 years, due to expansion or temporary contraction of the vector or
296 movement of naïve animals.

297

298 Bluetongue virus serotype 8 (BTV-8), which shares the same vector species as SBV,
299 recently re-emerged in Europe after a period of absence of clinical disease of several years and
300 declining seropositivity in the resident ruminant population (Sailleau et al., 2015; Bréard et al.,
301 2016). Loss of SBV immunity has already been seen in Germany with only about 20% of newborn
302 animals having antibodies (Wernike et al., 2015a). In animals born since the initial outbreak, the
303 numbers seroconverting have been much lower, 58–65.7% in adult animals and as low as 20.6% in
304 heifers (Meroc et al., 2015; Wernike et al., 2015b), resulting in a drop of seropositivity (and
305 presumably immunity). In the UK and Ireland no seroconversions were detected in 2014–15
306 indicating a presumed absence of the disease there in those years (Collins et al., 2016a; Stokes et
307 al., 2016).

308 The virus has continued to circulate at a low level in continental Europe with detection in
309 Germany (Wernike et al., 2015a) and Belgium (Delooz et al., 2016). Evidence of increased
310 circulation has recently been seen in the Netherlands with outbreaks of diarrhoea in cattle linked to
311 SBV reported (Promed Mail 2016). Similarly, virus re-circulation has been evident in the UK in
312 2016 with a number of reports of clinical cases and seroconversion (Unknown, 2016). It is possible
313 that large scale resurgence could occur when a combination of the number of naïve replacement
314 stock reaches a critical level together with favourable conditions for the vectors.

315

316 It has also been proposed that local wild ruminant populations may be a reservoir for
317 arboviruses as BTV virus was detected in red deer in Spain, while livestock was disease free (Ruio-

318 Fons et al., 2014). Similarly, SBV virus has also been found in roe deer (Diaz et al., 2015), the
319 European bison (Krzysiak et al., 2016) and other species (reviewed in Tarlinton et al., 2013) raising
320 the prospect of a wild-life SBV reservoir in Europe.

321

322 SBV is not notifiable at the European level, however several individual countries have made
323 it notifiable (including Germany, France, the Netherlands and Ireland) and hence have maintained
324 active monitoring programmes. Using milk yield to monitor disease state has been suggested as
325 syndromic surveillance for several diseases that affect ruminants (Madouasse et al., 2013,2014). In
326 combination with testing milk for virus-specific antibodies, this could help identify areas where
327 infection is occurring (Veldhuis et al., 2016).

328

329 In both Australia and Japan arbovirus monitoring programmes of sentinel animals and
330 midge trapping and testing are in place as early warning systems (Kirkland, 2004; Geoghegan et al.,
331 2014; Kato et al., 2015) and we, as well as others (Regge, 2016) would suggest that such a system
332 in Europe would be warranted. In Ireland and France, which have instituted surveillance using
333 *Culicoides* monitoring and sentinel herds or reporting by sentinel veterinarians this approach has
334 been successful in detecting circulating virus and new cases in the recent re-emergence (Collins et
335 al., 2016b, Gache et al., 2017).

336

337 In Japan, sentinel herds are employed in the southernmost islands where the outbreaks are
338 more likely to begin due to the warmer climate. Several vaccines are available and are deployed
339 pro-actively if circulation is detected (Kurogi et al. 1979, Kono et al 2008; Kim et al. 2011, Kato et
340 al., 2015). In Australia, even though there is no currently registered vaccine, the information gained
341 from the early monitoring and warning systems allows the farmers to make decisions about moving
342 their herds or delaying mating to avoid the teratogenic consequences of infection (reviewed in
343 Kirkland, 2015).

344

345 Such a programme Europe-wide would alert livestock holders of the potential for SBV
346 disease impacts in advance of the main seasonal ruminant breeding activities in summer and autumn
347 giving producers the opportunity to assess whether vaccination or delay of mating would be
348 necessary for their herds and flocks. Ideally, improved data on midge abundance, virus circulation
349 in midges and modelling of long term climate and land use variables that affect midge abundance
350 would be necessary for advanced warning of the risk of disease, however without a substantial body
351 of data from long term sentinel monitoring programmes on a continent wide basis such as that
352 available in Australia (Bishop et al., 2000; Eagles et al., 2014) this cannot happen.

353

354 In addition, the detection of numerous different Simbu-group viruses in the Mediterranean
355 and Africa has made it clear that there are numerous viruses circulating in the regions where SBV is
356 likely to have come from. This, combined with the well-studied propensity of this group of viruses
357 to swap genetic segments (antigenic shift), makes it quite likely that there will be outbreaks of
358 viruses with similar pathogenesis and epidemiology to SBV in Europe in the near future, making
359 preparation of diagnostic and vaccine platforms transferrable across this virus group a priority.

360

361 **Conclusions**

362 While we now know much more about SBV than when it was initially reported, there are
363 still a number of long-term uncertainties about the impact of the virus on the European ruminant
364 herd. Chief among these is the long-term endemic stability of the viruses. From the currently
365 available data, it is clear that the initial epidemic front of the virus in 2011–12 was the worst case
366 scenario, with immunologically-naïve animals being exposed for the first time to the virus resulting
367 in almost 100% seroconversion in some regions. Since 2013–14, there has been continuing low
368 level circulation of SBV in Western Europe and overall herd immunity (variable to begin with) has

369 dropped. This unfortunately increases the likelihood of repeated epidemic outbreaks, particularly in
370 years when high midge numbers and susceptible ruminants coincide.

371

372 **Conflict of interest statement**

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

375

376 **Acknowledgements**

377 AS was supported by a BBSRC tools and resources development fund grant BB/M018822/1
378 Held by JD, KG and RT. The funding body had no involvement in the preparation of this paper.

379

380 **References**

- 381 Abutarbush, S.M., La Rocca, A., Wernike, K., Beer, M., Al Zuraikat, K., Al Sheyab, O.M., Talafha,
382 A.Q., Steinbach, F., 2015. Circulation of a Simbu serogroup virus, causing Schmallerberg
383 virus-like clinical signs in northern Jordan. *Transboundary and Emerging Diseases*. Epub 2015
384 Dec 30. doi:10.1111/tbed.12468
- 385
- 386 Afonso, A., Abrahantes, J.C., Conraths, F., Veldhuis, A., Elbers, A., Roberts, H., Stede, Y. Van der,
387 Méroc, E., Gache, K., Richardson, J., 2014. The Schmallerberg virus epidemic in Europe—
388 2011–2013. *Preventive Veterinary Medicine* 116, 391–403.
389 doi:http://dx.doi.org/10.1016/j.prevetmed.2014.02.012
- 390
- 391 Agerholm, J.S., Hewicker-Trautwein, M., Peperkamp, K., Windsor, P.A., 2015. Virus-induced
392 congenital malformations in cattle. *Acta Veterinaria Scandinavica* 57, 54. doi:10.1186/s13028-
393 015-0145-8
- 394
- 395 Alarcon, P., Häslér, B., Raboisson, D., Waret-Szkuta, A., Corbière, F., Rushton, J., 2014.
396 Application of integrated production and economic models to estimate the impact of
397 Schmallerberg virus for various sheep production types in the UK and France. *Veterinary*
398 *Record Open* 1, e000036. doi:10.1136/vetreco-2014-000036
- 399
- 400 Ayllón, T., Nijhof, A.M., Weiher, W., Bauer, B., Allène, X., Clausen, P.-H., 2014. Feeding
401 behaviour of *Culicoides* spp. (Diptera: Ceratopogonidae) on cattle and sheep in northeast
402 Germany. *Parasites & Vectors* 7, 1–9. doi:10.1186/1756-3305-7-34
- 403
- 404 Azkur, A.K., Albayrak, H., Risvanli, A., Pestil, Z., Ozan, E., Yılmaz, O., Tonbak, S., Cavunt, A.,
405 Kadi, H., Macun, H.C., Acar, D., Özenç, E., Alparslan, S., Bulut, H., 2013. Antibodies to
406 Schmallerberg virus in domestic livestock in Turkey. *Tropical Animal Health and Production*
407 45, 1825–1828. doi:10.1007/s11250-013-0415-2
- 408
- 409 Balenghien, T., Pagès, N., Goffredo, M., Carpenter, S., Augot, D., Jacquier, E., Talavera, S.,

410 Monaco, F., Depaquit, J., Grillet, C., Pujols, J., Satta, G., Kasbari, M., Setier-Rio, M.-L., Izzo,
 411 F., Alkan, C., Delécolle, J.-C., Quaglia, M., Charrel, R., Polci, A., Bréard, E., Federici, V.,
 412 Cêtre-Sossah, C., Garros, C., 2014. The emergence of Schmallenberg virus across *Culicoides*
 413 communities and ecosystems in Europe. Preventive Veterinary Medicine 116, 360–369.
 414 doi:10.1016/j.prevetmed.2014.03.007
 415

416 Balseiro, A., Royo, L.J., Gómez Antona, A., García Marín, J.F., 2015. First confirmation of
 417 Schmallenberg virus in cattle in Spain: tissue distribution and pathology. Transboundary and
 418 Emerging Diseases 62, e62–e65. doi:10.1111/tbed.12185
 419

420 Barrett, D., O'Neill, R., Sammin, D., Clegg, T.A., More, S.J., 2015. The impact of infection with
 421 Schmallenberg virus on weaning rate in Irish sheep flocks. Preventive Veterinary Medicine
 422 122, 332–338. doi:http://dx.doi.org/10.1016/j.prevetmed.2015.10.012
 423

424 Baylis, M., Parkin, H., Kreppel, K., Carpenter, S., Mellor, P.S., McIntyre, K.M., 2010. Evaluation
 425 of housing as a means to protect cattle from *Culicoides* biting midges, the vectors of
 426 bluetongue virus. Medical and Veterinary Entomology 24, 38–45. doi:10.1111/j.1365-
 427 2915.2009.00842.x
 428

429 Bayrou, C., Garigliany, M.-M., Sarlet, M., Sartelet, A., Cassart, D., Desmecht, D., 2014. Natural
 430 intrauterine infection with Schmallenberg virus in malformed newborn calves. Emerging
 431 Infectious Diseases 20, 1327–1330. doi:10.3201/eid2008.121890
 432

433 Bessell, P.R., Auty, H.K., Searle, K.R., Handel, I.G., Purse, B. V, de C. Bronsvoort, B.M., 2014.
 434 Impact of temperature, feeding preference and vaccination on Schmallenberg virus
 435 transmission in Scotland. Scientific Reports 4, 5746. doi:10.1038/srep05746
 436

437 Bilk, S., Schulze, C., Fischer, M., Beer, M., Hlinak, A., Hoffmann, B., 2012. Organ distribution of
 438 Schmallenberg virus RNA in malformed newborns. Veterinary Microbiology 159, 236–238.
 439 doi:http://dx.doi.org/10.1016/j.vetmic.2012.03.035
 440

441 Bishop, A.L., Barchia, I.M., Spohr, L.J., 2000. Models for the dispersal in Australia of the arbovirus
 442 vector, *Culicoides brevitarsis* Kieffer (Diptera: Ceratopogonidae). Preventive Veterinary
 443 Medicine 47, 243–254. doi:10.1016/S0167-5877(00)00175-6
 444

445 Bouwstra, R.J., Kooi, E.A., de Kluijver, E.P., Verstraten, E.R.A.M., Bongers, J.H., van Maanen, C.,
 446 Wellenberg, G.J., van der Spek, A.N., van der Poel, W.H.M., 2013. Schmallenberg virus
 447 outbreak in the Netherlands: Routine diagnostics and test results. Veterinary Microbiology
 448 165, 102–108. doi:10.1016/j.vetmic.2013.03.004
 449

450 Bréard, E., Lara, E., Comtet, L., Viarouge, C., Doceul, V., Desprat, A., Vitour, D., Pozzi, N., Ab,
 451 C., De Regge, N., Pourquier, P., Schirrmeier, H., Hoffmann, B., Beer, M., Sailleau, C.
 452 Stéphan, Z., 2013. Validation of a commercially available indirect ELISA using a nucleocapsid
 453 recombinant protein for detection of Schmallenberg virus antibodies. PloS One, 8(1), doi:
 454 10.1371/journal.pone.0053446. Epub 2013 Jan 15.
 455

456 Breard, E., Sailleau, C., Quenault, H., Lucas, P., Viarouge, C., Touzain, F., Fablet, A., Vitour, D.,
 457 Attoui, H., Zientara, S., Blanchard, Y., 2016. Complete genome sequence of Bluetongue virus
 458 serotype 8, which reemerged in France in august 2015. Genome Announcements 4, e00163-16.
 459 doi:10.1128/genomeA.00163-16
 460

461 Chaintoutis, S.C., Kiossis, E., Giadinis, N.D., Brozos, C.N., Sailleau, C., Viarouge, C., Bréard, E.,

- Papanastassopoulou, M., Zientara, S., Papadopoulos, O., Dovas, C.I., 2014. Evidence of Schmallenberg virus circulation in ruminants in Greece. *Tropical Animal Health and Production* 46, 251–255. doi:10.1007/s11250-013-0449-5
- Claine, F., Coupeau, D., Wiggers, L., Muylkens, B., Kirschvink, N., 2013a. Schmallenberg virus among female lambs, Belgium, 2012. *Emerging Infectious Diseases* 19, 1115–1117. doi:10.3201/eid1907.121768
- Claine, F., Coupeau, D., Wiggers, L., Raes, M., Muylkens, B., Kirschvink, N., 2013b. Evidence for reemergence of Schmallenberg virus during summer and autumn 2012 among naïve female lambs and immunized ewes, in: *Proceedings of 7th Epizone Meeting. CODA-CERVA*, Brussels, p. 34.
- Collins, A.B., Barrett, D., Doherty, M.L., Larska, M., Mee J.F., 2016a. Post-epidemic Schmallenberg virus circulation: parallel bovine serological and *Culicoides* virological surveillance studies in Ireland. *BMC Veterinary Research* 12, 234.
- Collins, A., Mee, J. F., 2016b. Monitoring for re-emergence of Schmallenberg virus. *Veterinary Record*, 179, 549-550. doi: 10.1136/vr.i6279
- Coupeau, D., Claine, F., Wiggers, L., Kirschvink, N., Muylkens, B., 2016. S segment variability during the two first years of the spread of Schmallenberg virus *Archives of Virology*, 161, 1353-1358. doi: 10.1007/s00705-016-2787-x
- Daly, J.M., King, B., Tarlinton, R.A., Gough, K.C., Maddison, B.C., Blowey, R., 2015. Comparison of Schmallenberg virus antibody levels detected in milk and serum from individual cows. *BMC Veterinary Research* 11, 56. doi:10.1186/s12917-015-0365-1
- Davies, P., Daly, J., 2013. SBV transmission. *The Veterinary record* 172, 509–10. doi:10.1136/vr.f2958
- De Regge, N., Deblauwe, I., De Deken, R., Vantieghem, P., Madder, M., Geysen, D., Smeets, F., Losson, B., van den Berg, T., Cay, A.B., 2012. Detection of Schmallenberg virus in different *Culicoides* spp. by real-time RT-PCR. *Transboundary and Emerging Diseases* 59, 471–475. doi:10.1111/tbed.12000
- De Regge, N., van den Berg, T., Georges, L., Cay, B., 2013. Diagnosis of Schmallenberg virus infection in malformed lambs and calves and first indications for virus clearance in the fetus. *Veterinary Microbiology* 162, 595–600. doi:10.1016/j.vetmic.2012.11.029
- Delooz, L., Saegerman, C., Quinet, C., Petitjean, T., De Regge, N., Cay, B., 2016. Resurgence of Schmallenberg virus in Belgium after 3 years of epidemiological silence. *Transboundary and Emerging Diseases*. doi:10.1111/tbed.12552
- Diaz, JM., Prieto, A., Lopez, C., Diaz, P., Perez, A., Panadero, R., Pajares, G., Diez-Baños, P., Morrondo, P., Fernandez, G., 2015. High spread of Schmallenberg virus among roe deer (*Capreolus capreolus*) in Spain. *Research in Veterinary Science*, 102, 231-233
- Dominguez, M., Gache, K., Touratier, A., Perrin, J.-B., Fediaevsky, A., Collin, E., Bréard, E., Sailleau, C., Viarouge, C., Zanella, G., Zientara, S., Hendrikx, P., Calavas, D., 2014. Spread and impact of the Schmallenberg virus epidemic in France in 2012-2013. *BMC veterinary research* 10, 248. doi:10.1186/s12917-014-0248-x

514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565

- Eagles, D., Melville, L., Weir, R., Davis, S., Bellis, G., Zalucki, M.P., Walker, P.J., Durr, P. a, 2014. Long-distance aerial dispersal modelling of *Culicoides* biting midges: case studies of incursions into Australia. BMC Veterinary Research 10, 135. doi:10.1186/1746-6148-10-135
- EFSA, 2014. Schmallenberg virus: State of Art. EFSA Journal 12, 3681.
- EFSA, 2012a. "Schmallenberg virus": likely epidemiological scenarios and data needs, supporting publications. European Food Safety Authority. <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2012.EN-241/pdf> (accessed 17 July 2016)
- EFSA, 2012b. "Schmallenberg virus": analysis of the epidemiological data, supporting publications. EFSA, Italy. <http://onlinelibrary.wiley.com/doi/10.2903/sp.efsa.2012.EN-360/pdf> (accessed 17 July 2016).
- Eifan, S., Schnettler, E., Dietrich, I., Kohl, A., Blomström, A.-L., 2013. Non-structural proteins of arthropod-borne bunyaviruses: roles and functions. Viruses 5, 2447–2468. doi:10.3390/v5102447
- Elbers, A.R.W., Stockhofe-Zurwieden, N., van der Poel, W.H.M., 2014. Schmallenberg virus antibody persistence in adult cattle after natural infection and decay of maternal antibodies in calves. BMC Veterinary Research 10, 103. doi:10.1186/1746-6148-10-103
- Forrester, Naomi L., Mathilde Guerbois, Robert L. Seymour, Heidi Spratt, and Scott C. Weaver. 2012. 'Vector-Borne transmission imposes a severe bottleneck on an RNA virus population', PLOS Pathogens, 8: e1002897.
- Gache, K., Touratier, A., Bournez, L., Zientara, S., Bronner, A., Dion, F., Garin, E., Calavas, D. 2017. Detection of Schmallenberg virus in France since 2012. Veterinary Record, 180, 24. doi: 10.1136/vr.j38
- Geoghegan, J.L., Walker, P.J., Duchemin, J.B., Jeanne, I., Holmes, E.C., 2014. Seasonal drivers of the epidemiology of arthropod-Borne viruses in Australia. PLoS Neglected Tropical Diseases 8, e3325. doi:10.1371/journal.pntd.0003325
- Goffredo, M., Monaco, F., Capelli, G., Quaglia, M., Federici, V., Catalani, M., Montarsi, F., Polci, A., Pinoni, C., Calistri, P., Savini, G., 2013. Schmallenberg virus in Italy: a retrospective survey in *Culicoides* stored during the bluetongue Italian surveillance program. Preventive Veterinary Medicine 111, 230–236. doi:10.1016/j.prevetmed.2013.05.014
- Gubbins, S., Richardson, J., Baylis, M., Wilson, A.J., Abrahantes, J.C., 2014a. Modelling the continental-scale spread of Schmallenberg virus in Europe: Approaches and challenges. Preventive Veterinary Medicine 116, 404–411. doi:http://dx.doi.org/10.1016/j.prevetmed.2014.02.004
- Gubbins, S., Turner, J., Baylis, M., van der Stede, Y., van Schaik, G., Abrahantes, J.C., Wilson, A.J., 2014b. Inferences about the transmission of Schmallenberg virus within and between farms. Preventive Veterinary Medicine 116, 380–90. doi:10.1016/j.prevetmed.2014.04.011
- Harrup, L.E., Gubbins, S., Barber, J., Denison, E., Mellor, P.S., Purse, B.V., Carpenter, S., 2014. Does covering of farm-associated *Culicoides* larval habitat reduce adult populations in the United Kingdom? Veterinary Parasitology 201, 137–145. doi:10.1016/j.vetpar.2013.11.028

566
567 Hart, T.J., Kohl, A., Elliott, R.M., 2009. Role of the NSs protein in the zoonotic capacity of
568 orthobunyaviruses. *Zoonoses and Public Health* 56, 285–296. doi:10.1111/j.1863-
569 2378.2008.01166.x
570
571 Hechinger, S., Wernike, K., Beer, M., 2014. Single immunization with an inactivated vaccine
572 protects sheep from Schmallerberg virus infection. *Veterinary research* 45, 79.
573 doi:10.1186/PREACCEPT-1922244281270218
574
575 Helmer, C., Eibach, R., Tegtmeyer, P.C., Humann-Ziehank, E., Ganter, M., 2013. Survey of
576 Schmallerberg virus (SBV) infection in German goat flocks. *Epidemiology and Infection* 141,
577 2335–2345. doi:10.1017/S0950268813000290
578
579 Hoffmann, B., Scheuch, M., Höper, D., Jungblut, R., Holsteg, M., Schirrmeier, H., Eschbaumer,
580 M., Goller, K. V., Wernike, K., Fischer, M., Breithaupt, A., Mettenleiter, T.C., Beer, M., 2012.
581 Novel orthobunyavirus in cattle, Europe, 2011. *Emerging Infectious Diseases* 18, 469–472.
582 doi:10.3201/eid1803.111905
583
584 Hoffmann, B., Schulz, C., Beer, M., 2013. First detection of Schmallerberg virus RNA in bovine
585 semen, Germany, 2012. *Veterinary Microbiology* 167, 289–295.
586 doi:10.1016/j.vetmic.2013.09.002
587
588 Hofmann, Martin A., Markus Mader, Franziska Flückiger, and Sandra Renzullo. 2015. 'Genetic
589 stability of Schmallerberg virus in vivo during an epidemic, and in vitro, when passaged in the
590 highly susceptible porcine SK-6 cell line', *Veterinary Microbiology*, 176: 97-108.
591
592 Izzo, Francesca, Gian Mario Cosseddu, Andrea Polci, Federica Iapaolo, Chiara Pinoni, Andrea
593 Capobianco Dondona, Fabrizia Valleriani, Federica Monaco, 2016. Genetic characterization of
594 Italian field strains of Schmallerberg virus Based on N and Nss genes. *Virus Genes* 52, 582-85
595
596 Kato, T., Shirafuji, H., Tanaka, S., Sato, M., Yamakawa, M., Tsuda, T., Yanase, T., 2015. Bovine
597 arboviruses in *Culicoides* biting midges and sentinel cattle in southern Japan from 2003 to
598 2013. *Transboundary and Emerging Diseases* 63, e160-e172. doi:10.1111/tbed.12324
599
600 Kim, Yeon-Hee, Chang-Hee Kweon, Dong-Seob Tark, Seong In Lim, Dong-Kun Yang, Bang-Hun
601 Hyun, Jae-Young Song, Won Hur, and Se Chang Park. 2011. Development of inactivated
602 trivalent vaccine for the teratogenic Aino, Akabane and Chuzan viruses, *Biologicals*, 39, 152-
603 57
604
605 King, B., O'Shea Brown, T., Tarlinton, R., Daly, J.M., 2015. Seroprevalence of Schmallerberg
606 virus in the United Kingdom and the Republic of Ireland: 2011–2013. *Veterinary*
607 *Microbiology* 180, 36–40. doi:http://dx.doi.org/10.1016/j.vetmic.2015.07.025
608
609 Kirkland, P.D., 2004. Bluetongue viruses, vectors and surveillance in Australia – the current
610 situation and unique features. *Veterinaria italiana* 40, 47-50.
611
612 Kirkland, P.D., Barry, R.D., Harper, P.A., Zelski, R.Z., 1988. The development of Akabane virus-
613 induced congenital abnormalities in cattle. *Veterinary Record* 122, 582–586.
614
615 Kono, R., Hirata, M., Kaji, M., Goto, Y., Ikeda, S., Yanase, T., Kato, T., Tanaka, S., Tsutsui, T.,
616 Imada, T., Yamakawa, M., 2008. Bovine epizootic encephalomyelitis caused by Akabane virus
617 in southern Japan. *BMC veterinary research* 4, 20. doi:10.1186/1746-6148-4-20

618
619 Kirkland, P.D. 2015. Akabane virus infection, Scientific and Technical Review of the Office
620 International des Epizooties (Paris), 34, 403-10.
621

622 Kraatz, F., Wernike, K., Hechinger, S., König, P., Granzow, H., Reimann, I., Beer, M., 2015.
623 Deletion mutants of Schmallerberg virus are avirulent and protect from virus challenge.
624 Journal of Virology 89, 1825–1837. doi:10.1128/JVI.02729-14
625

626 Krzysiak, M. K., Iwaniak, W., Kęsik-Maliszewska, J., Olech, W., Larska, M., 2016. Serological
627 study of exposure to selected arthropod-borne pathogens in European Bison (*Bison bonasus*) in
628 Poland. Transboundary and Emerging Diseases. doi:10.1111/tbed.12524
629

630 Kurogi, H., Inaba, Y., Takahashi, E., Sato, K., Satoda, K., 1977. Congenital abnormalities in
631 newborn calves after inoculation of pregnant cows with Akabane virus. Infection and
632 Immunity 17, 338–343.
633

634 Kurogi, H, Y Inaba, H Akashi, E Takahashi, K Sato, K Satoda, C Sugimoto, H Hatekeyama, and T
635 Omori. 1979. Immune response of various animals to Akabane disease live virus vaccine,
636 National Institute for Animal Health, 19, 23-31.
637

638 Laloy, E., Riou, M., Barc, C., Belbis, G., Bréard, E., Breton, S., Cordonnier, N., Crochet, D.,
639 Delaunay, R., Moreau, J., Pozzi, N., Raimbourg, M., Sarradin, P., Trapp, S., Viarouge, C.,
640 Zientara, S., Ponsart, C., 2015. Schmallerberg virus: experimental infection in goats and
641 bucks. BMC Veterinary Research 11, 221. doi:10.1186/s12917-015-0516-4
642

643 Larska, M., Polak, M.P., Grochowska, M., Lechowski, L., Związek, J.S., Żmudziński, J.F., 2013.
644 First report of Schmallerberg Virus Infection in Cattle and Midges in Poland. Transboundary
645 and Emerging Diseases 60, 97–101. doi:10.1111/tbed.12057
646

647 Lazutka, J., Spakova, A., Sereika, V., Lelesius, R., Sasnauskas, K., Petraityte-Burneikiene, R.,
648 2015. Saliva as an alternative specimen for detection of Schmallerberg virus-specific
649 antibodies in bovines. BMC Veterinary Research 11, 1–7. doi:10.1186/s12917-015-0552-0
650

651 Lievaart-Peterson, K., Luttikholt, S.J.M., Van den Brom, R., Vellema, P., 2012. Schmallerberg
652 virus infection in small ruminants: first review of the situation and prospects in northern
653 Europe. Small Ruminant Research 106, 71–76. doi:10.1016/j.smallrumres.2012.03.006
654

655 Loeffen, Quak, S., Boer-Luijze, E. de, Hulst, M., Poel, W. van der, Bouwstra, R., Maas, R., 2012.
656 Development of a virus neutralisation test to detect antibodies against Schmallerberg virus and
657 serological results in suspect and infected herds. Acta Veterinaria Scandinavica 54, 44.
658 doi:10.1186/1751-0147-54-44
659

660 Luttikholt, S., Veldhuis, A., Van Den Brom, R., Moll, L., Lievaart-Peterson, K., Peperkamp, K.,
661 Van Schaik, G., Vellema, P., 2014. Risk factors for malformations and impact on reproductive
662 performance and mortality rates of Schmallerberg virus in sheep flocks in the Netherlands.
663 PLoS ONE 9, e100135. doi:10.1371/journal.pone.0100135
664

665 Madouasse, A., Marceau, A., Lehébel, A., Brouwer-Middelesch, H., van Schaik, G., Van der Stede,
666 Y., Fourichon, C., 2014. Use of monthly collected milk yields for the detection of the
667 emergence of the 2007 French BTV epizootic. Preventive Veterinary Medicine 113, 484–491.
668 doi:10.1016/j.prevetmed.2013.12.010
669

670 Madouasse, A., Marceau, A., Lehébel, A., Brouwer-Middelesch, H., van Schaik, G., Van der Stede,
671 Y., Fourichon, C., 2013. Evaluation of a continuous indicator for syndromic surveillance
672 through simulation. application to vector borne disease emergence detection in cattle using
673 milk yield. PLoS ONE 8, e73726. doi:10.1371/journal.pone.0073726
674

675 Martinelle, L., Dal Pozzo, F., Gauthier, B., Kirschvink, N., Saegerman, C., 2014. Field veterinary
676 survey on clinical and economic impact of Schmallenberg virus in Belgium. Transboundary
677 and Emerging Diseases 61, 285–288. doi:10.1111/tbed.12030
678

679 Martinelle, L., Poskin, A., Dal Pozzo, F., De Regge, N., Cay, B., Saegerman, C., 2015.
680 Experimental infection of sheep at 45 and 60 days of gestation with
681 Schmallenberg virus readily led to placental colonization without causing congenital
682 malformations. PLoS ONE 10, e0139375. doi:10.1371/journal.pone.0139375
683

684 Mathew, C., Klevar, S., Elbers, A.R.W., van der Poel, W.H.M., Kirkland, P.D., Godfroid, J.,
685 Mdegela, R.H., Mwamengele, G., Stokstad, M., Coetzer, JAW, et al., 2015. Detection of serum
686 neutralizing antibodies to Simbu sero-group viruses in cattle in Tanzania. BMC Veterinary
687 Research 11, 208. doi:10.1186/s12917-015-0526-2
688

689 Mellor, P.S., Boorman, J., Baylis, M., 2000. Culicoides Biting Midges: Their Role as Arbovirus
690 Vectors. Annual Review of Entomology 45, 307–340. doi:10.1146/annurev.ento.45.1.307
691

692 Méroc, E., Poskin, A., Van Loo, H., Quinet, C., Van Driessche, E., Delooz, L., Behaeghel, I.,
693 Riocreux, F., Hooyberghs, J., De Regge, N., Caij, A.B., van den Berg, T., van der Stede, Y.,
694 2013. Large-scale cross-sectional serological survey of Schmallenberg virus in Belgian cattle
695 at the end of the first vector season. Transboundary and Emerging Diseases 60, 4–8.
696 doi:10.1111/tbed.12042
697

698 Méroc, E., Poskin, A., Van Loo, H., Van Driessche, E., Czaplicki, G., Quinet, C., Riocreux, F., De
699 Regge, N., Caij, B., van den Berg, T., Hooyberghs, J., Van der Stede, Y., 2015. Follow-up of
700 the Schmallenberg virus seroprevalence in Belgian cattle. Transboundary and Emerging
701 Diseases 62, e80–e84. doi:10.1111/tbed.12202
702

703 Met-Office, 2012. Supporting the institute for animal health on the Schmallenberg virus.
704 <http://www.metoffice.gov.uk/publicsector/animalhealth/schmallenberg> (accessed 20 July
705 2016).
706

707 Monaco, F., Goffredo, M., Federici, V., Carvelli, A., Dondona, A.C., Polci, A., Pinoni, C.,
708 Danzetta, M.L., Selli, L., Bonci, M., Quaglia, M., Calistri, P., 2013. First cases of
709 Schmallenberg virus in Italy: surveillance strategies. Veterinaria Italiana 49, 269–275.
710

711 Peperkamp, N.H., Luttikholt, S.J., Dijkman, R., Vos, J.H., Junker, K., Greijdanus, S., Roumen,
712 M.P., van Garderen, E., Meertens, N., van Maanen, C., Lievaart, K., van Wuyckhuise, L.,
713 Wouda, W., 2015. Ovine and Bovine congenital abnormalities associated with intrauterine
714 infection with Schmallenberg virus. Veterinary Pathology 52, 1057–1066.
715 doi:10.1177/0300985814560231
716

717 Ponsart, C., Pozzi, N., Bréard, E., Catinot, V., Viard, G., Sailleau, C., Viarouge, C., Gouzil, J., Beer,
718 M., Zientara, S., Vitour, D., 2014. Evidence of excretion of Schmallenberg virus in bull semen.
719 Veterinary Research 45, 37. doi:10.1186/1297-9716-45-37
720

721 Poskin, A., Martinelle, L., Mostin, L., Van Campe, W., Dal Pozzo, F., Saegerman, C., Cay, A.B.,

- De Regge, N., 2014. Dose-dependent effect of experimental Schmallerberg virus infection in sheep, *The Veterinary Journal* 201, 419-422 doi:10.1016/j.tvjl.2014.05.031
- Poskin, A., Théron, L., Hanon, J.-B., Saegerman, C., Vervaeke, M., Van der Stede, Y., Cay, B., De Regge, N., 2016. Reconstruction of the Schmallerberg virus epidemic in Belgium: Complementary use of disease surveillance approaches. *Veterinary Microbiology* 183, 50–61. doi:http://dx.doi.org/10.1016/j.vetmic.2015.11.036
- Poskin, A., Verite, S., Comtet, L., Van der Stede, Y., Cay, B., De Regge, N., 2015. Persistence of the protective immunity and kinetics of the isotype specific antibody response against the viral nucleocapsid protein after experimental Schmallerberg virus infection of sheep. *Veterinary Research* 46, 1–9. doi:10.1186/s13567-015-0260-6
- Promed Mail 2016, Schmallerberg Virus – Europe: Netherlands, Belgium, reemergence. Archive number 20161023.4578989
- Raboisson, D., Waret-Szkuta, A., Rushton, J., Häslér, B., Alarcon, P., 2014. Application of integrated production and economic models to estimate the impact of Schmallerberg virus for various beef suckler production systems in France and the United Kingdom. *BMC veterinary research* 10, 254. doi:10.1186/s12917-014-0254-z
- Regge, N. De, 2016. Schmallerberg virus: on its way out or due for a comeback? *The Veterinary record* 179, 432–434. doi:10.1136/vr.i5548
- Ruiz-Fons, F., Sánchez-Matamoros, A., Gortázar, C., Sánchez-Vizcaíno, J.M., 2014. The role of wildlife in bluetongue virus maintenance in Europe: lessons learned after the natural infection in Spain. *Virus Research* 182, 50–58. doi:10.1016/j.virusres.2013.12.031
- Saegerman, C., Martinelle, L., Dal Pozzo, F., Kirschvink, N., 2014. Preliminary survey on the impact of Schmallerberg virus on sheep flocks in south of Belgium. *Transboundary and Emerging Diseases* 61, 469–472. doi:10.1111/tbed.12047
- Sailleau, C., Bréard, E., Viarouge, C., Vitour, D., Romey, A., Garnier, A., Fablet, A., Lowenski, S., Gorna, K., Caignard, G., Pagneux, C., Zientara, S., 2015. Re-emergence of bluetongue virus serotype 8 in France, 2015. *Transboundary and Emerging Diseases*. Epub 2015 Nov 30. doi:10.1111/tbed.12453
- Schulz, C., Beer, M., Hoffmann, B., 2015. Schmallerberg virus infection in south American camelids: field and experimental investigations. *Veterinary Microbiology* 180, 171–179. doi:10.1016/j.vetmic.2015.08.024
- Schulz, C., Wernike, K., Beer, M., Hoffmann, B., 2014. Infectious Schmallerberg virus from bovine semen, Germany. *Emerging infectious diseases* 20, 338–40. doi:10.3201/eid2002.131436
- Sedda, L., Brown, H.E., Purse, B. V, Burgin, L., Gloster, J., Rogers, D.J., 2012. A new algorithm quantifies the roles of wind and midge flight activity in the bluetongue epizootic in northwest Europe. *Proceedings. Biological sciences / The Royal Society* 279, 2354–62. doi:10.1098/rspb.2011.2555
- Sedda, L., Rogers, D.J., 2013. The influence of the wind in the Schmallerberg virus outbreak in Europe. *Scientific Reports* 3, 3361. doi:10.1038/srep03361

774
775 Sprygin, A.V., Fiodorova, O.A., Babin, Y.Y., Elatkin, N.P., Mathieu, B., England, M.E., Kononov,
776 A.V., 2014. *Culicoides* biting midges (*Diptera*, *Ceratopogonidae*) in various climatic zones
777 of Russia and adjacent lands. Journal of Vector Ecology 39, 306–315. doi:10.1111/jvec.12105
778
779 Stokes, J.E., Baylis, M., Duncan, J.S., 2016. A freedom from disease study: Schmallenberg virus in
780 the south of England in 2015. The Veterinary record 179, 435. doi:10.1136/vr.103903
781
782 Tarlinton, R., Daly, J., 2013. Testing for Schmallenberg virus. The Veterinary Record 172, 190.
783 doi:10.1136/vr.f972
784
785 Tarlinton, R., Daly, J., Dunham, S., Kydd, J., 2012. The challenge of Schmallenberg virus
786 emergence in Europe. The Veterinary Journal 194, 10–18.
787 doi:http://dx.doi.org/10.1016/j.tvjl.2012.08.017
788
789 Tarlinton, R., Daly, J., Dunham, S., Kydd, J.H., 2013. Schmallenberg virus: Could wildlife
790 reservoirs threaten domestic livestock? The Veterinary Journal. doi:10.1016/j.tvjl.2013.10.003
791
792 Toson, M., Mughini-Gras, L., Capello, K., Gagliazzo, L., Bortolotti, L., Mazzucato, M., Marangon,
793 S., Bonfanti, L., 2015. Productive and reproductive performances of dairy cattle herds in
794 Treviso province, Italy (2009-2012): an assessment of the potential impact of Schmallenberg
795 virus epidemic. BMC veterinary research 11, 193. doi:10.1186/s12917-015-0527-1
796
797 Tsuda, T., Yoshida, K., Ohashi, S., Yanase, T., Sueyoshi, M., Kamimura, S., Misumi, K., Hamana,
798 K., Sakamoto, H., Yamakawa, M., 2004. Arthrogryposis, hydranencephaly and cerebellar
799 hypoplasia syndrome in neonatal calves resulting from intrauterine infection with Aino virus.
800 Veterinary Research 35, 531–538.
801
802 Unknown, 2016. APHA disease surveillance report: Disease surveillance in England and Wales,
803 November 2016. Veterinary Record 179, 565-568 doi:10.1136/vr.i6365
804
805 Van Der Poel, W.H.M., Parlevliet, J.M., Verstraten, E.R.A.M., Kooi, E.A., Hakze-Van Der Honing,
806 R., Stockhofe, N., 2014. Schmallenberg virus detection in bovine semen after experimental
807 infection of bulls. Epidemiology and infection 142, 1495–500.
808 doi:10.1017/S0950268813002574
809
810 Varela, M., Schnettler, E., Caporale, M., Murgia, C., Barry, G., McFarlane, M., McGregor, E.,
811 Piras, I.M., Shaw, A., Lamm, C., Janowicz, A., Beer, M., Glass, M., Herder, V., Hahn, K.,
812 Baumgärtner, W., Kohl, A., Palmarini, M., 2013. Schmallenberg virus pathogenesis, tropism
813 and interaction with the innate immune system of the host. PLoS Pathog 9, e1003133.
814 doi:10.1371/journal.ppat.1003133
815
816 Veldhuis, A., Brouwer-Middelesch, H., Marceau, A., Madouasse, A., Van der Stede, Y., Fourichon,
817 C., Welby, S., Wever, P., van Schaik, G., 2016. Application of syndromic surveillance on
818 routinely collected cattle reproduction and milk production data for the early detection of
819 outbreaks of Bluetongue and Schmallenberg viruses. Preventive Veterinary Medicine 124, 15–
820 24. doi:10.1016/j.prevetmed.2015.12.006
821
822 Veldhuis, A.M.B., Mars, M.H., Roos, C.A.J., van Wuyckhuise, L., van Schaik, G., 2015. Two years
823 after the Schmallenberg virus epidemic in the Netherlands: does the virus still circulate?
824 Transboundary and Emerging Diseases n/a-n/a. doi:10.1111/tbed.12349
825

826 Veldhuis, A.M.B., Santman-Berends, I.M.G.A., Gethmann, J.M., Mars, M.H., van Wuyckhuise, L.,
827 Vellema, P., Holsteg, M., Höreth-Böntgen, D., Conraths, F.J., van Schaik, G., 2014.
828 Schmallenberg virus epidemic: impact on milk production, reproductive performance and
829 mortality in dairy cattle in the Netherlands and Kleve district, Germany. Preventive Veterinary
830 Medicine 116, 412–422. doi:10.1016/j.prevetmed.2014.04.015
831

832 Veldhuis, A.M.B., van Schaik, G., Vellema, P., Elbers, A.R.W., Bouwstra, R., van der Heijden,
833 H.M.J.F., Mars, M.H., 2013. Schmallenberg virus epidemic in the Netherlands: spatiotemporal
834 introduction in 2011 and seroprevalence in ruminants. Preventive Veterinary Medicine 112,
835 35–47. doi:10.1016/j.prevetmed.2013.06.010
836

837 Veronesi, E., Antony, F., Gubbins, S., Golding, N., Blackwell, A., Mertens, P., Brownlie, J.,
838 Darpel, K., Mellor, P., Carpenter, S., 2013. Measurement of the infection and dissemination of
839 Bluetongue virus in *Culicoides* biting midges using a semi-quantitative RT-PCR assay and
840 isolation of infectious virus. PLoS ONE 8, e70800. doi:10.1371/journal.pone.0070800
841

842 Veronesi, E., Henstock, M., Gubbins, S., Batten, C., Manley, R., Barber, J., Hoffmann, B., Beer,
843 M., Attoui, H., Mertens, P.P.C., Carpenter, S., 2013. Implicating *Culicoides* biting midges as
844 vectors of Schmallenberg virus using semi-quantitative RT-PCR. PLoS ONE 8, e57747.
845 doi:10.1371/journal.pone.0057747
846

847 Weiher, W., Bauer, B., Mehlitz, D., Nijhof, A.M., Clausen, P.-H., 2014. Field trials assessing
848 deltamethrin (Butox®) treatments of sheep against *Culicoides* species. Parasitology Research
849 113, 2641–2645. doi:10.1007/s00436-014-3916-7
850

851 Wernike, K., Eschbaumer, M., Breithaupt, A., Hoffmann, B., Beer, M., 2012. Schmallenberg virus
852 challenge models in cattle: infectious serum or culture-grown virus? Veterinary Research 43,
853 84. doi:10.1186/1297-9716-43-84
854

855 Wernike, K., Eschbaumer, M., Schirrmeier, H., Blohm, U., Breithaupt, A., Hoffmann, B., Beer, M.,
856 2013a. Oral exposure, reinfection and cellular immunity to Schmallenberg virus in cattle.
857 Veterinary Microbiology 165, 155–159. doi:10.1016/j.vetmic.2013.01.040
858

859 Wernike, K., Hoffmann, B., Bréard, E., Bøtner, A., Ponsart, C., Zientara, S., Lohse, L., Pozzi, N.,
860 Viarouge, C., Sarradin, P., Leroux-Barc, C., Riou, M., Laloy, E., Breithaupt, A., Beer, M.,
861 2013b. Schmallenberg virus experimental infection of sheep. Veterinary Microbiology 166,
862 461–466. doi:10.1016/j.vetmic.2013.06.030
863

864 Wernike, K., Hoffmann, B., Conraths, F.J., Beer, M., 2015a. Schmallenberg Virus Recurrence,
865 Germany, 2014. Emerging Infectious Diseases 21, 1202–1204. doi:10.3201/eid2107.150180
866

867 Wernike, K., Holsteg, M., Saßerath, M., Beer, M., 2015b. Schmallenberg virus antibody
868 development and decline in a naturally infected dairy cattle herd in Germany, 2011–2014,
869 Veterinary Microbiology. doi:10.1016/j.vetmic.2015.10.014
870

871 Wernike, K., Holsteg, M., Schirrmeier, H., Hoffmann, B., Beer, M., 2014. Natural Infection of
872 pregnant cows with Schmallenberg virus – a follow-up study. PLoS ONE 9, e98223.
873 doi:10.1371/journal.pone.0098223
874

875 Wernike, K., Kohn, M., Conraths, F.J., Werner, D., Kameke, D., Hechinger, S., Kampen, H., Beer,
876 M., 2013c. Transmission of Schmallenberg virus during winter, Germany. Emerging Infectious
877 Disease Journal 19, 1701. doi:10.3201/eid1910.130622

878
879 Wernike, K., Nikolin, V.M., Hechinger, S., Hoffmann, B., Beer, M., 2013d. Inactivated
880 Schmallerberg virus prototype vaccines. *Vaccine* 31, 3558–3563.
881 doi:10.1016/j.vaccine.2013.05.062
882
883 Wisløff, H., Nordvik, B.S., Sviland, S., Tønnessen, R., 2014. First documented clinical case of
884 Schmallerberg virus in Norway: fetal malformations in a calf. *Veterinary Record* 174, 120.
885 doi:10.1136/vr.102149
886
887 Wüthrich, M., Lechner, I., Aebi, M., Vögtlin, A., Posthaus, H., Schüpbach-Regula, G., Meylan, M.,
888 2016. A case–control study to estimate the effects of acute clinical infection with the
889 Schmallerberg virus on milk yield, fertility and veterinary costs in Swiss dairy herds.
890 *Preventive Veterinary Medicine* 126, 54–65. doi:10.1016/j.prevetmed.2016.01.021
891
892 Yilmaz, H., Hoffmann, B., Turan, N., Cizmecigil, U.Y., Richt, J.A., Van der Poel, W.H.M., 2014.
893 Detection and partial sequencing of Schmallerberg virus in cattle and sheep in Turkey. *Vector-*
894 *Borne and Zoonotic Diseases* 14, 223–225. doi:10.1089/vbz.2013.1451
895

Table 1

Production System	Cost range of disease £/1000 head	Cost benefit of vaccination	Likelihood of use
Dairy cattle	8200 to 51400	-5720 to 37480	High risk only
Beef cattle	18000 to 30650	4080 to 16730	Yes
Lamb production	4750 to 20850	-9170 to 7000	High risk only
Dairy Sheep	10340 to 29,810	3580 to 15890	Yes

896 Cost of the disease per 1000 animal vs. cost benefit of vaccination (adapted from Raboisson et al.
897 (2014). Costs are shown for high risk and low risk cases and exclude labour costs. Vaccination cost
898 assumed at UK £13.92 per head (£13920 per herd) (Price as of Dec 2015 “farmacy” website ¹)
899 (£1UK= approximately US \$1.23, € 1.16 as of 18th Nov 2016)

¹ “Farmacy” website: <http://www.farmacy.co.uk/categories/575-schmallenberg> (accessed 22nd March 2017)