Review

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

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Abstract

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

Keywords: Schmallenberg virus; Monitoring; Re-emergence, Surveillance

Introduction

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

First detection and initial spread of SBV

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

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

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

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

Virus transmission

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

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

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

Clinical disease

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

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

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

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

Diagnosis

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

apparent reason) can lead to suspicion of viral infection.

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

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

(Lazutka et al., 2015).

Control

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

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

Anecdotal reports and the author's observations have indicated that uptake of the 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

Economic impact of SBV

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

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

One of the main economic impacts of the initial SBV outbreak was the loss of export markets for bovine genetics (semen, embryos and breeding stock) due to the introduction of trade barriers from countries free of SBV (60% of countries trading with Europe imposed restrictions). A decline of 10-20% in trade was observed in addition to the value of pure-bred breeding animal 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).

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.

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.

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-

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

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

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

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

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

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

Conclusions

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

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

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.

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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

Cost of the disease per 1000 animal vs. cost benefit of vaccination (adapted from Raboisson et al. (2014). Costs are shown for high risk and low risk cases and exclude labour costs. Vaccination cost assumed at UK £13.92 per head (£13920 per herd) (Price as of Dec 2015 "farmacy" website [1]) (£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)