Changing surveillance objectives during the different phases of an emerging disease outbreak: the Schmallenberg virus example

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Abstract
In the late summer of 2011, a new virus emerged in ruminants in north-western Europe causing fever, drop in milk production and diarrhoea. A sudden rise in incidence of these non-specific clinical signs was observed in dairy cows in the eastern region of the Netherlands and in north-western Germany. In November 2011, a novel orthobunyavirus was identified by metagenomic analyses in samples from acutely diseased cows on a farm near the German city of Schmallenberg, and was thereafter named Schmallenberg virus (SBV). Due to the novelty of the virus, there was an immediate need for knowledge regarding the epidemiological characteristics of SBV to inform surveillance and control strategies. A rapid assessment of the spread and impact of an emerging disease supports decision-makers on allocation of surveillance resources. This paper aims at reviewing the surveillance activities during and after the SBV epidemic in the Netherlands. The spread of the epidemic, its impact on cattle productivity parameters and herd-level risk factors for infection are described and discussed. Also, the added value for syndromic surveillance for early detection purposes was assessed.

Keywords: *surveillance, emerging diseases, cattle, vector-borne*

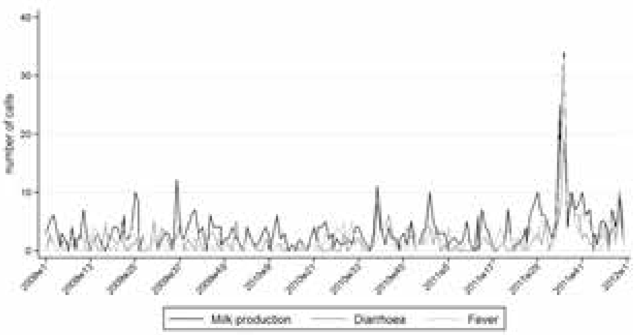
Introduction
Animal disease surveillance systems targeted at emerging diseases often comprise a combination of active and passive components. Finding the optimal surveillance strategy remains challenging as it is a dynamic process with changing objectives depending on the epidemiological phase of the infection. For example, in the first phase – when the target population is still free – surveillance is targeted at early detection of outbreaks. In the second phase, when prevalence of infection is rising, the objective changes to estimating the extent of infection in the population and identifying potentially useful control strategies. When the emerging disease is the result of an unknown or novel pathogen, resources need to be allocated to the identification of the pathogen, its transmission mechanisms and its zoonotic potential. Also, its impact in terms of clinical disease in affected animals and their offspring and impact in terms of loss of productivity needs to be estimated. The latter provides insight in the amount of effort that is needed for surveillance and control of the disease, for example through the development of a vaccine. In addition, risk factors for infection need to be identified to facilitate preventive measures, and potentially, contribute to a risk-based surveillance strategy. After the prevalence of infection reaches its peak it will most likely drop to an endemic equilibrium or to zero. At this stage, the objective of surveillance shifts to monitoring changes in prevalence of infection, monitoring the impact of control measures, or eventually, demonstrating freedom from infection.

In the last decade, the cattle industry in north-western Europe has been confronted with two emerging vector-borne viruses that caused economically damaging disease outbreaks: bluetongue virus (BTV) in 2006 and 2007 and Schmallenberg virus (SBV) in 2011. BTV and SBV are both transmitted by the vector *Culicoides* biting midges. Contrary to the well known BTV, when SBV was identified, very little was known about this emerging virus. Most assumptions were deduced from scientific information available on other viruses of the Simbu serogroup. The Netherlands was part of the primary outbreak area that was affected by SBV in the late summer of 2011. Due to the novelty of the virus, there was an immediate need for knowledge regarding the epidemiological characteristics of SBV to inform surveillance and control strategies.

Emergence and spread of SBV
In the Netherlands, the national animal health surveillance system is carried out by GD Animal Health (GD) and comprises a number of complementary components. One component is a telephone helpline, which is used by animal owners and veterinarians to consult experts at GD regarding atypical animal health problems. Calls regarding bovines are handled by a regular group of cattle health specialists. When deemed necessary for surveillance purposes, affected farms are visited – free of charge - by these specialists and pilot studies are performed. The surveillance purpose of the helpline service ('GD Veekijker') is to detect exotic, new or (re-)emerging diseases. In the late summer of 2011, the helpline service was contacted by numerous veterinarians within several days, all reporting sudden drop in milk production, diarrhoea and fever in dairy cattle. Although these symptoms can be considered non-specific and related to several (endemic) diseases or disorders in cattle, the frequency of calls regarding these symptoms was abnormal (Figure 1). Extensive bacteriological, virological and parasitological testing of the faeces of clinically affected cows did not reveal

an infectious cause of the clinical problems (1). In early September it appeared that cattle in Germany experienced similar clinical disease as observed in the Netherlands at the time. Analyses in samples from acutely diseased cows excluded several classical endemic and emerging viruses as causative agent (2). No causal agent was found until November 18th 2011, when a novel orthobunyavirus, provisionally named Schmallenberg virus (SBV), was identified by metagenomic analyses. From early December 2011 onward, SBV-induced congenital malformations, designated as arthrogryposis-hydranencephaly syndrome, were observed in newborn lambs and calves in the Netherlands. To date, the origin and way of introduction of SBV is unknown.

Figure 1. Number of calls to consultancy service “GD Veekijker” by week from 1 January 2009 to 1 January 2012, stratified by calls regarding milk production (black), diarrhoea (grey) and fever (light-grey) in dairy cattle. Source: GD Animal Health, courtesy of H. Brouwer-Middelesch.



A large-scale serosurvey performed in 2012 provided evidence that the introduction of SBV in the Netherlands had rapidly led to high seroprevalences in cattle, sheep and goats (3). This finding had two important implications. First, due to the small proportion of (remaining) naïve animals after one vector-active season, it was likely that the incidence of new cases following potential overwintering of SBV was going to be low. A lower seroprevalence might have been a justification for a vaccination campaign or other protective measures. Secondly, apparently this novel virus was transmitted throughout the ruminant population very efficiently, affecting 95.5% of the dairy cattle herds, 99.3% of the non-dairy cattle herds, 97.1% of the sheep flocks and 81.1% of the goat herds in the Netherlands within several months (3). No gradient spatial pattern in final seroprevalence could be detected and therefore no suggestions about the site of introduction and spread of SBV in the Netherlands in 2011 could be made. To identify the spatiotemporal introduction of SBV in the Netherlands, 11,493 archived sheep serum samples from April to November 2011 have been tested for presence of SBV-specific antibodies (3). To confirm a positive serostatus, all positive samples from June, July and August have been retested with a more specific virus neutralisation test (VNT). This resulted in a negative outcome for all samples from June and July. Seropositive samples from mid-August 2011 onwards were confirmed positive by VNT testing, indicating first seroconversions following SBV introduction in the Netherlands.

Impact estimation and risk factors

The likelihood and impact of an emerging disease outbreak determines the amount of effort that is needed for surveillance of the disease, as well as its control (e.g. the development of a vaccine). When a disease emerges for which the impact is unclear, for example when the disease is the result of an unknown or novel pathogen such as SBV, resources need to be allocated in the short term to quantify the impact of disease. The family Bunyaviridae contains several relevant zoonotic viruses. Therefore, the emergence of SBV triggered a joint veterinary and public health response in the Netherlands to address the possible consequences to human health. A public health risk assessment of the emergence of SBV in ruminants in the Netherlands was conducted by a consortium of experts from public and veterinary health institutes. The study comprised the monitoring of self-reported health problems in humans and a serological survey among persons living and/or working on SBV-affected farms (4). It was concluded that the public health risk for SBV was absent or extremely low, given the high seroprevalence of SBV in affected herds in the Netherlands (indicative for the level of exposure in humans) and the lack of evidence for zoonotic transmission from either the syndromic monitoring or the serological survey in humans.

During the epidemic, the level of morbidity at herd level was diverse, varying from subclinical infection to acute clinical disease in cattle and malformations in new-born calves. As little was known about the factors that determine the level of morbidity at herd level, a case-control study was performed to investigate potential risk factors for clinical disease in either adult cattle or new-born calves in dairy herds (5). Case herds were selected based on (i) presence of clinical signs in adult cattle that were likely due to SBV infection in the late summer of 2011, or (ii) the notification of malformations in new-born calves between December 2011 and March 2012. Control herds were selected based on a request to the veterinary practitioner of case farms to select a control herd located in the same geographical area as the case herd. The results of the study showed that malformations in new-born calves were more likely to occur in herds in which clinical signs were observed in combination with a high seroprevalence. Also, grazing was identified as risk factor for high seroprevalence as well as the occurrence of malformations in new-born calves.

It appeared that the number of affected herds with malformed new-borns was relatively low (6). Nevertheless, little was known with regard to the overall within-herd impact of SBV infection. Therefore, the impact of the SBV epidemic on the productivity of dairy cattle was quantified, by applying several statistical models on eight productivity parameters (regarding milk production, reproductive performance and mortality) (7). All fertility parameters analysed were slightly but significantly affected between August 1st and November 1st 2011 compared to the reference period in 2009-2010. Between 15 August and 19 September 2011, the average loss in milk production per cow was -0.26kg (95% CI: -0.30; -0.22) per day in dairy herds, compared to the reference period ($p<0.001$). SBV had no or limited impact on mortality rates, which was as expected given the relatively mild expression of SBV in adult cows and the low incidence of notified malformations in new-born calves. These results indicate that SBV had a limited impact on productivity of dairy cattle, which has contributed to the optimisation of the surveillance and control strategy of SBV in the Netherlands; the absence of a public health risk and the moderate direct impact of the disease provided confidence that control measures such as the application of a vaccine were unnecessary.

Monitoring seroprevalence

After the primary phase of an emerging disease outbreak, the objective of surveillance changes from early-detection to monitoring changes in prevalence of infection, monitoring the impact of control measures or eventually, demonstrating freedom from infection. Presence of SBV-specific antibodies in naive cattle was investigated in the Netherlands in winter 2013-2014, aiming to determine if SBV was still circulating two years after the primary outbreak, and if so, to what extent (8). First, 394 randomly selected dairy farms were sampled between October and December 2013 by collecting five serum samples per herd from youngstock (8-12 months of age). Antibodies were detected in 1.1% (95% confidence interval (CI): 0.7-1.7) of the animals. As all seropositive animals were single-reactors per herd, a more in-depth investigation was initiated to provide more insight: an additional sample of 20 youngstock within the same age category was collected from herds that tested positive in the first stage, to rule out potential false-positive test results. Also, seropositive samples were tested by VNT for confirmation. The combined results of this survey revealed a low level of SBV-seroconversions in the sampled youngstock, although the results were somewhat surprising as all but one of the seropositive calves were single-reactors in the 394 study herds. This suggested that these positive test results were unlikely the result of natural infection in 2013, as SBV circulation in a herd is known to result in high within-herd seroprevalences (5). Therefore, assuming the single-reactors to be false-positive, this survey showed that in 2013 SBV circulated in less than 1% of the dairy cattle herds the Netherlands.

In 2015, the serosurvey was repeated by sampling youngstock from 193 randomly selected dairy herds and 149 randomly selected beef suckling herds between 1 October and 31 December 2015. A low level of circulation of SBV was found, based on SBV-specific antibodies in youngstock born in 2015 and at least eight months old at time of sampling (unpublished data, GD). The overall true animal-level seroprevalence in dairy herds was significantly higher in 2015 (6.5% (95% confidence interval: 5.0-8.3)) compared to 2013 (0% (95% confidence interval: 0.0-0.2)) (8). This suggests that the virus is again circulating in the Netherlands, yet still at a low level. In 2015 (nor early 2016), no calves with the arthrogryposis-hydranencephaly syndrome or other malformations typical for SBV infection were submitted to GD for post-mortem examination. In one malformed lamb, submitted to GD for post-mortem examination in February 2015, SBV was detected in brain tissue and SBV-specific antibodies were found in the blood (GD, 2015). However, the number of phone calls to GD Veekijker regarding SBV was in 2015 not different from 2014 or 2013 (2% per year; unpublished data). This suggests that SBV did not cause significant health problems in cattle in 2015.

The added value of syndromic surveillance

When an emerging pathogen affects milk yield or reproductive performance, there is a potential to use such data for early detection purposes in the form of syndromic surveillance. Like SBV, BTV also had a negative impact on cattle productivity in the Netherlands. Therefore, the added value of a syndromic surveillance system based on routinely collected milk production or cattle reproductive performance data for the early detection of BTV and SBV was examined (9). Results showed that gestation-based reproductive indicators, such as the rate of short gestations (i.e. calving a few days earlier that what is expected based on AI date that led to gestation) have the potential to add value to existing passive surveillance strategies to detect emerging diseases in cattle similar to SBV, but not BTV. A first alert indicating the outbreak was obtained four days after the first clinical suspicion of SBV picked up by passive surveillance. A significant drop in milk production was also found at the start of the SBV outbreak, in particular in the weeks that farmers reported a severe drop in milk production in dairy cattle. Thus, a syndromic surveillance system based on milk production or reproductive performance data could have an added value, yet complementary to passive cattle health surveillance systems. In the investigated cases, syndromic surveillance would not have led to an increased sensitivity or timeliness but rather an increased sense of urgency.

Concluding remarks

SBV was not the first disease that emerged unexpectedly in Europe, and it will not be the last. With regard to vector-borne diseases, it is well-known that increasing travel and trade, including legal and illegal movement of animals and animal products, contribute to the introduction and establishment of vector-borne diseases in new geographic areas. In addition, climate change facilitates vector-borne diseases to move more regularly out of the tropics, spreading into temperate latitudes. The spread of viruses like SBV is not limited by territorial borders and incursion into previously-free areas is therefore difficult to prevent. The SBV epidemic underlined the need for a tailored surveillance strategy for emerging diseases, with changing objectives during the different epidemiological phases of an emerging disease outbreak.

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