Development of a syndromic surveillance system to enhance early detection of emerging and re-emerging animal diseases

INAUGURALDISSERTATION

zur

Erlangung der Würde einer Doktorin der Philosophie

vorgelegt der

Philosophisch-Naturwissenschaftlichen Fakultät

der Universität Basel

von

Rahel Struchen

aus

Täuffelen (BE)

Bern, 2017

Genehmigt von der Philosophisch-Naturwissenschaftlichen Fakultät
auf Antrag von
Prof. Dr. Jürg Utzinger
Prof. Dr. Jakob Zinsstag
Dr. Petter Hopp

Basel, den 10. November 2015

Prof. Dr. Jörg Schibler
Dekan

In loving memory of René Staub

Summary

Animal health surveillance plays an important role in protecting animal health, production and welfare, public health and trade from the negative impacts of disease. To address the challenges posed by new, exotic or re-emerging diseases as well as the limitations of traditional surveillance, new approaches, including syndromic surveillance (SyS) and modern communication technologies have been developed to improve early disease detection. SyS is based on the continuous monitoring of unspecific pre-diagnostic health data in order to detect an unusual increase in counts which may indicate a health hazard in a timely manner. An increasing number of studies has been investigating different types of animal health data for a possible use in SyS. Although the potential of cattle mortality data routinely collected in the Swiss system for individual identification and registration of cattle (Tierverkehrsdatenbank TVD) for use in a SyS system was highlighted, the performance of aberration-detection algorithms applied to such data has not yet been investigated. Furthermore, knowledge about the impact of delayed reporting of these data on outbreak detection performance is limited. Clinical observations made by veterinary practitioners reported in real-time using web- and mobile-based communication tools may improve the timeliness of outbreak detection. The willingness of practitioners to report their observations is essential for the successful implementation of such systems. A lack of knowledge about factors that motivate or hinder practitioners to participate in surveillance was found.

The aim of this work was to contribute to the development of a national surveillance system for the early detection of emerging and re-emerging animal diseases in Switzerland, focusing on two Swiss data sources: cattle mortality data routinely reported by farmers to the TVD; clinical data voluntarily reported by veterinary practitioners to Equinella, an electronic reporting and information system for the early detection of infectious equine diseases in Switzerland.

Time series of on-farm and perinatal cattle deaths, extracted from the TVD, were analysed with regard to data quality and explainable temporal patterns, e.g. day-of-week effect or seasonality. A set of three temporal aberration detection algorithms (Shewhart, CuSum, EWMA) was retrospectively applied to these data to assess their performance in detecting varying simulated disease outbreak scenarios. The effect of reporting delay on outbreak

detection was investigated in a Bayesian framework. Participation of veterinary practitioners during the first 12 months of the new internet-based reporting platform of Equinella was assessed. Telephone interviews were conducted to gain insights into factors that motivate or hinder practitioners to participate in a voluntary surveillance system offering non-monetary incentives. Furthermore, the suitability of mobile devices such as smartphones for collecting health data was investigated.

The TVD provided timely cattle mortality data with comprehensive geographical information, making it a valuable data source for Sys. Mortality time series exhibited temporal patterns, associated with non-health related factors, that had to be considered before applying aberration detection algorithms. The three evaluated control chart algorithms adequately performed under specific outbreak conditions, but none of them was superior in detecting outbreak signals across multiple evaluation metrics. Combining algorithms outputs according to different rules did not satisfactorily increase the system's overall performance, further illustrating the difficulty in finding a balance between a high sensitivity and a manageable number of false alarms. The Bayesian approach performed similarly well in the scenario where delayed reporting was accounted for to the (ideal) scenario where it was absent.

Non-monetary incentives were attractive to sentinel practitioners and overall participation was experienced positive. Insufficient understanding of the reporting system and of its relevance, as well as concerns over the electronic dissemination of health data were identified as potential challenges to sustainable reporting. Mobile devices were sporadically used during the first year and an awareness of the advantages of mobile-based surveillance was yet lacking among practitioners, indicating that they may require some time to become accustomed to novel reporting methods.

This work highlighted the value of routinely collected cattle mortality data for use in SyS, but also the need to carefully optimise aberration detection algorithms for a particular data stream. Alternative methods to the binary alarm system may be chosen for a prospective use of cattle mortality data in a SyS system. The value of evidence framework may be suitable for surveillance systems with multiple syndromes and delayed reporting of data. Before integrating these data into a national surveillance system for the early detection of new, exotic or re-emerging diseases, health authorities need to define response protocols enabling investigation of the data that triggered a statistical alarm and to identify the underlying cause. Possibilities for improving sensitivity and specificity were identified that may be addressed when implementing a future SyS system. In addition, the potential of voluntary reporting surveillance system based on non-monetary incentives was shown. Many of the identified barriers to reporting can be addressed in the future, making the outcome of the pilot project favourable. Continued information feedback loops within voluntary sentinel networks will be important to ensure sustainable participation. Combining reporting of syndromic data and mobile devices in a One Health context has the potential to benefit animal and public health as well as to enhance interdisciplinary collaboration.

Acknowledgements

I wish to express my gratitude to all those who contributed to this thesis and accompanied me along the way.

First and foremost, I wish to thank both of my supervisors, Flavie Vial and Jakob Zinsstag, for their support and advice. Flavie, thank you for accepting to be my main supervisor; for always providing me with constructive and prompt feedback; and for your patience, understanding and excellent guidance. Merci pour tout! Jakob, thank you for your challenging questions, for allowing me great latitude in the conduction of this work, and for the inspiring insights into 'One Health'.

I wish to thank Fernanda Dórea, Petter Hopp, Martin Reist, Gerti Schüpbach and John Berezowski for being part of my PhD committee, and for all your valuable and highly appreciated advice and inputs.

I have been very privileged to be part of the Equinella project. A big thank you to the Equinella team: Daniela Hadorn, Franziska Wohlfender, Sandra Balmer, Sven Süptitz, Claudia Graubner and, in a wider sense, Patrick Presi, Ernest Peter and the people at 4eyes. It was a pleasure to work within such a great team.

I wish to thank the Equinella veterinarians who were willing to spend some of their time to answer my questions.

A warm thank you to Marie-Eve Cousin, for her advice regarding questionnaire conduction and phrasing of questions in such a way as to encourage people to talk.

I appreciated the possibility to work with Gunnar Andersson on the topic of reporting delay. Thank you, Gunnar, for your patient explanations; I learned a lot from your way of writing R codes.

I am grateful to Laura Falzon and Andrew Tedder for proofreading; to Esther Schelling and Samuel Fuhrimann for their input and advice regarding data on Rift Valley Fever outbreaks; and to Stefan Widgren for some last minute help with R coding shortly before his holidays.

I wish to thank Sara Schärrer for her support with data storage and queries; Dana Zingg for a briefing on how to get started with the Ubelix cluster; and Rebekka Nafzger Bigler for helping a biologist better understand veterinary conversations, and for answering my many questions.

A big thank you to all the members of the VPHI for being part of my PhD experience, and especially to Susanne Lerch for all the help provided.

I wish to thank Heinzpeter Schwermer, Martin Moser, Ruth Hauser and Silke Bruhn at the FSVO for answering my questions.

I am grateful to all those who supported me during the time spent at the Cantonal and Federal Veterinary Service, especially Dagmar Heim, Markus Seiler, Christoph Keller, Elena Di Labio, Lukas Perler, and Patrick Schaller. Thank you Dagi for encouraging me to do a PhD.

I wish to thank the FSVO for funding this work, as part of project 1.12.12.

A warm thank you also goes to the team at Clocktower Station in Thun, Switzerland, for providing me with the pleasure of biting into the best veggie burger in town after a hard day's work.

I am grateful to my friends for the numerous hours spent together, which allowed me to escape the stress for a while.

My deep gratitude goes to my family for all their love, support and understanding, especially to my parents for all the latitude they allowed me in finding my way.

And most importantly, I wish to thank Chrigu, my beloved partner and friend, for his unlimited patience and support, particularly during the final months of my PhD; for providing me with a reasonable diet; for being there during my lowest moments; and for making me laugh.

Table of contents

List of figures

List of tables

List of appendices

List of abbreviations

AIC	Akaike Information Criterion
ARMA	Autoregressive and moving average
BIC	Bayesian Information Criterion
BSE	Bovine spongiform encephalopathy
BTV8	Bluetongue virus serotype 8
CUD	Cases until detection
CuSum	Cumulative sum
EWMA	Exponentially weighted moving average
FMD	Foot-and-mouth disease
FPR	False positive rate
FSVO	Federal Food Safety and Veterinary Office
IBR	Infectious bovine rhinotracheitis
ICT	Information and communication technologies
MERS-CoV	Middle East respiratory syndrome coronavirus
NB	Negative binomial
OIE	World Organisation for Animal Health
PPV	Positive predictive value
PRRS	Porcine reproductive and respiratory syndrome
SARS	Severe acute respiratory syndrome
Swiss TPH	Swiss Tropical and Public Health Institute

SyS	Syndromic surveillance
TTD	Time to detection
TVD	Tierverkehrsdatenbank (animal movement database)
VPHI	Veterinary Public Health Institute
WHO	World Health Organisation
WNV	West Nile virus

CHAPTER 1

Introduction

1.1 Emerging and re-emerging infectious diseases

Emerging and re-emerging infectious diseases are of global concern in view of their significant impact on animal and public health, livestock production, international trade and biodiversity. While considered to be under control or even eradicated during the middle of the 20th century, infectious diseases have gained in importance again since the 1980s (Binder et al. 1999). In particular, emerging zoonoses (diseases transmitted between humans and animals) have increasingly posed a serious threat to global health (Jones et al. 2008). Between 60% and 75% of emerging diseases in humans are caused by zoonotic pathogen species, a majority being of wildlife origin (Taylor et al. 2001; Jones et al. 2008).

According to recent efforts in finding agreed-upon definitions for animal health surveillance, emerging diseases encompasses "new" and "exotic" diseases (Hoinville 2013). A disease is considered "new" when there is e.g. a change in the host range or an increase in pathogenicity of an existing pathogen due to evolution, leading to a previously undefined (unknown) disease or condition. A previously defined (known) disease is considered "exotic" when e.g. a pathogen occurs in a new geographic area where it is not recorded as present. A previously defined (known) disease can re-emerge (or significantly increase in prevalence) in the population in a defined geographic area where it is recorded as absent (or present at a low level).

Human population growth and globalisation are considered driving factors of this recent "resurgence of microbial threat" (Brown 2004; Heymann et al. 2001). As consequence, expansion of human population, intrusion into new ecological areas, intensification of livestock production as well as growing widespread trade and travel have resulted in increased contacts between humans, domestic and wild animals and created numerous new niches for microbes to exploit and adapt to. Additionally, climate change can further contribute to disease emergence by shifting or extending the geographic range of vectors such as mosquitoes or ticks (Daszak et al. 2000).

Another difficulty arises from the wide range of pathogen and host species involved in emerging and re-emerging diseases (Cleaveland et al. 2001). A consequence of this variety is a "huge diversity of life cycles, transmission routes, biochemistries, pathogenicites and epidemiologies" for which detailed or basic knowledge is often missing (Woolhouse 2002). Furthermore, addressing all of these species individually by implementing active surveillance or laboratory diagnostics is not feasible due to the limited resources of health authorities. Given these circumstances, the development of surveillance systems as well as diagnostics and therapeutics for effective prevention, detection and control of (re-)emerging infectious diseases pose a major challenge to veterinary and public health (Meslin et al. 2000; Woolhouse 2002).

1.2 Animal health surveillance

Animal health surveillance plays an important role in protecting animal health, production and welfare, public health and trade. For example, the foot-and-mouth disease (FMD) outbreak in Great Britain in 2001 affected more than 10 million cattle and sheep (a majority due to culling to control disease spread) and associated losses to agriculture and the food chain amounted to an estimated £3.1 billion (Thompson et al. 2002). Economic losses due to animal diseases can result from treatment or diagnostic costs, production losses due to mortality, weight loss, or reduced milk production or fertility, as well as costs of control measures, e.g. animal movement restrictions (Tago et al. 2014). For example, the financial consequences of the bluetongue virus serotype 8 (BTV8) epidemic in The Netherlands in 2007 were estimated at €164-175 million (Velthuis et al. 2010). The negative impacts of animal disease on animal welfare can include not only suffering due to morbidity, but also due to control measures, e.g. obligatory indoor housing of livestock in case of vector-transmitted diseases caused by bluetongue or Schmallenberg virus. Several recent examples of zoonotic diseases can be found that considerably affected human health. The Middle East respiratory syndrome coronavirus (MERS-CoV), typically causing influenza-like illness and often leading to pneumonia, was first detected in June 2012. Since then, 1,587 confirmed human cases occurred worldwide (as of 25th of September 2015, WHO), with a case fatality rate (i.e. the proportion of deaths among the total number of cases) of 35-50% (Banik et al. 2015). The transmission route is not yet fully understood, but camels and bats seem to be a likely animal host reservoir. Ebola virus disease is another example of a complex zoonosis that is highly virulent in humans. Epidemiological and genomic analyses suggested a single zoonotic transmission event in December 2013 in the Republic of Guinea as a source for the 2014 outbreak in West Africa (Gire et al. 2014). This event was followed by subsequent human-to-human transmission. As of 21 October 2015, 28,547 cases and 11,313 deaths had been reported worldwide (World Health Organisation Ebola Statistics[1])

The value of surveillance lies in enabling an "informed decision" (Stärk & Häsler 2015), i.e. generating information relevant for veterinary decision makers in planning, implementing and evaluating disease prevention and control measures, achieved through the "systematic (continuous or repeated) measurement, collection, collation, analysis, interpretation, and timely dissemination of animal-health and -welfare data from defined populations" (Hoinville et al. 2013). Major objectives of animal health surveillance are early detection of disease, demonstrating freedom from disease, and measuring the level of disease.

Traditional animal health surveillance activities include notifications of individual suspect or disease cases and diagnostic laboratory testing. With regard to data collection, surveillance can be categorised as "active" and "passive" surveillance (Doherr & Audigé 2001). Active surveillance refers to data collection driven and controlled by the health authorities (investigator-initiated), e.g. the national surveys routinely conducted every year among a random sample of the livestock population in Switzerland to demonstrate freedom from diseases such as infectious bovine rhinotracheitis (IBR), brucellosis, and porcine reproductive and respiratory syndrome (PRRS). (Enhanced) passive surveillance (Hoinville et al. 2013) is understood as observer-initiated data collection, e.g. mandatory or voluntary reporting of clinical suspect cases by farmers or veterinary practitioners. If and what data is provided from which animals is typically decided by the data providers. The health authorities can influence this process by actively encouraging data collection e.g. by enhancing disease awareness or through monetary incentives. Such methods are typically designed to target specific (and mostly rare) diseases and may therefore not be appropriate for detecting emerging diseases. Furthermore, traditional surveillance

[1] http://apps.who.int/gho/data/view.ebola-sitrep.ebola-summary-latest?lang=en

programs tend to be time- and resource-consuming and not achieve a high population coverage (Doherr & Audigé 2001).

1.3 Early detection

Early detection of disease outbreaks has become a major task for health authorities (Wagner et al. 2001) since it is fundamental to contain the spread of infectious diseases and keep morbidity, mortality and economic losses at a minimum (Binder et al. 1999). It is understood as the "surveillance of health indicators and diseases in defined populations to increase the likelihood of timely detection of undefined (new) or unexpected (exotic or re-emerging) threats" (Hoinville et al. 2013).

In the words of Lewis Carroll's Red Queen, "[…] it takes all the running you can do, to keep in the same place." To address the challenges posed by emerging and re-emerging diseases, the limitations of traditional surveillance, and to keep up with the ability of pathogens to rapidly evolve and adapt, new approaches and tools to early detect disease outbreaks are required for further strengthening human and animal health.

During the past 15 years, political and economic drivers of cost-effectiveness and new technologies have fostered new approaches to surveillance to assist in filling the gaps of conventional surveillance methods and focusing limited resources. One of these strategies is risk-based surveillance (Rodríguez-Prieto et al. 2014), which makes use of information about the probability of occurrence of a disease and its consequences to, for example, reduce the costs of surveillance by sampling a subpopulation that is more likely to be infected. New media technologies and advances in electronic data capture, transfer and storage have made the collection and storage of large amounts of meaningful health and health-related digital data possible (Rodríguez-Prieto et al. 2014), creating an opportunity for syndromic surveillance. Both surveillance methods have the potential to benefit early detection of disease outbreaks by improving the timeliness of a surveillance system, but this thesis will focus on the application of the latter.

1.4 Syndromic surveillance

Syndromic surveillance (SyS) can be defined as “the real-time (or near real-time) collection, analysis, interpretation and dissemination of health-related data to enable the early identification of the impact (or absence of impact) of potential human or veterinary public health threats which require effective public health action” (Triple-S definition, http://www.syndromicsurveillance.eu/). The underlying principle of SyS systems is the continuous monitoring of unspecific health indicators in (near) real-time to detect unexpected excess patterns in the data that may result from infectious disease outbreaks. These indicators can come from any data source that is sensitive to changes in disease level and available before a diagnosis is made. Such pre-diagnostic data are assumed to contain earlier, but weaker signatures of a disease outbreak (Yahav & Shmueli 2007) which can be detected by various statistical methods as reviewed by (Buckeridge et al. 2005) and (Unkel et al. 2012). Data most accessible for syndromic surveillance are stored electronically, collected and analysed in a timely fashion and having extensive geographic, demographic and temporal coverage (Mandl, Overhage, et al. 2004).

SyS does not aim to replace but to complement traditional surveillance. The use of pre-diagnostic data can make SyS systems timelier than laboratory-based surveillance. As syndromic data are unspecific, SyS systems may enable the detection of a broad range of diseases, including unknown or unexpected diseases. However, this also means that once a signal is detected, further epidemiological investigations are required in order to find the underlying cause.

While conceivable goals of for animal and public health SyS systems tend to fall into the “early outbreak detection” or the “situation awareness” category (Vial & Berezowski 2014), it is important to note that the "use of existing health data in real time will also provide immediate feedback to those charged with investigation and follow-up of potential outbreaks" (Henning 2004), greatly supporting the work of the epidemiologists in the response teams. The SyS framework, which is described in more details below also has the potential to enhance collaboration among public health agencies, health-care providers, and the industry.

1.4.1 SyS in public health

In public health, the development of SyS systems has been motivated by bioterrorist events such as the anthrax attacks in the U.S. in 2001 and outbreaks of emerging infectious diseases such as severe acute respiratory syndrome (SARS). Rapid advances in bioinformatics and data mining techniques during the past decade have further facilitated the storage and handling of huge amounts of data. In Europe, a total of 39 SyS systems in 17 countries have been identified (Conti et al. 2012), a majority (79%) being currently active systems or event-specific, meaning that they are active for an event with a predefined time period such as the Olympic Games. Syndromic data used in human SyS include over-the-counter medication sales (Edge et al. 2006), school absenteeism (Kom Mogto et al. 2012), data from search engines (Zhou et al. 2013) or social networks (Signorini et al. 2011).

1.4.2 SyS in veterinary health

In veterinary public health, SyS has increasingly gained attention during the past few years. A first systematic review of peer-reviewed and grey literature identified 13 SyS systems (Dórea et al. 2011). Using an active approach including a questionnaire, Dupuy et al. (2013) presented a European inventory of 27 SyS systems with more than half of them still being in an exploratory or pilot phase. These systems commonly use clinical data from veterinary practitioners (Del Rocio Amezcua et al. 2010; Vourc'h et al. 2006) and diagnostic laboratory data (Odoi et al. 2009; Dórea et al. 2014). Other data sources have increasingly been explored for the use of SyS: meat inspection data (e.g. whole or partial carcass condemnations) from slaughterhouses (Thomas-Bachli et al. 2014; Vial & Reist 2015); mortality data from rendering plants or national registers (Torres et al. 2015; Perrin et al. 2012); reproductive events (e.g. intervals between artificial insemination and calving, abortion rates) recorded by breeding organisations (Bronner et al. 2015; Marceau et al. 2014); milk production data (Madouasse et al. 2013); post-mortem examinations of wildlife (Warns-Petit et al. 2010).

The use of SyS in veterinary medicine for the early detection of health hazards needs yet to be clarified and available systems need to be evaluated (Rodríguez-Prieto et al. 2014). However, a few studies could prove the potential of different data to detect outbreaks one to four weeks earlier than traditional methods (Leblond et al. 2007; Odoi et al. 2009).

1.5 One Health

During the past two centuries, human and animal health developed into disciplines considerably separated from each other. However, the health of humans and animals as well as ecosystems is inextricably linked which has been acknowledged by the ‘One Health’ concept. ‘One Health’ is an integrative thinking approach that aims at providing solutions to contemporary health problems through closer collaboration between the animal and human health sectors (Zinsstag et al. 2011). The resulting added value (improved human and animal health, financial savings) could not be achieved with each sector acting separately. For example, in Kyrgyzstan, joint sample collection through veterinarians and physicians to estimate brucellosis seroprevalence in humans and animals enabled simultaneous assessment of the impact of this zoonosis on humans and livestock and assisted in identifying its source (Bonfoh et al. 2011). Benefits can also result from interventions in animals such as mass vaccination of livestock or of dogs to prevent human brucellosis or rabies, respectively (Roth et al. 2003a) (Zinsstag et al. 2009). West Nile virus (WNV) is one of the most serious public health threats that Europe and the Mediterranean countries are currently facing. As of 22 October 2015, 104 cases of West Nile fever in humans have been reported in the EU Member States and 134 cases in the neighbouring countries, since the beginning of the 2015 transmission season (European Center for Disease Control official statistics[2]). The screening of mosquitoes (vector), birds (endemic foci of infection) and horses (other hosts) for WNV can assist in identifying affected areas and in detecting virus circulation before the occurrence of human cases (Anon 2011).

Increasing efforts for developing and implementing integrated animal-human surveillance systems are ubiquitous: Vrbova and colleagues’ systematic review of surveillance systems for emerging zoonoses identified 36 systems for emerging zoonoses (Vrbova et al. 2010) while Wendt and colleagues, more recently, identified 20 systems that integrated information from humans and animals on zoonotic diseases (Wendt et al. 2015). Bisson and Marra strongly argue that public health surveillance systems integrating the reporting of animal morbidity and mortality could have detected recent outbreaks of emerging zoonoses in humans earlier (Bisson et al. 2015). They showed that out of the 143 recent emerging zoonotic pathogens which are known to cause morbidity

[2] http://ecdc.europa.eu/en/healthtopics/west_nile_fever/West-Nile-fever-maps/pages/index.aspx

or mortality in their animal host, only 9% were first detected from an animal morbidity or mortality event prior to or concurrent with signs of illness in humans. Van den Wijngaard and colleagues retrospectively investigated hospitalisation data, mandatory reports and data on the spatial-temporal distribution of goat and sheep farms positively tested for *C. burnetii* for indications of human Q-fever outbreaks in The Netherlands prior to the known outbreaks in 2007 (van den Wijngaard et al. 2011). They found substantial evidence that a prospective real-time syndromic surveillance system could have detected signals of human Q-fever outbreaks up to two years earlier. This example illustrates the importance of communication and information sharing between veterinary and public health professionals and the value of SyS in a One Health framework.

Holistic research, combining data from multiple sectors (intersectoral) and applying methods from different disciplines (interdisciplinary), is becoming more and more important to address the complex processes at the animal-human-ecosystem interface, including social, cultural, economic or political aspects. An exemplary, intersectoral and interdisciplinary study analysed animal, human, environmental and meteorological data in order to find the most likely source of a large human Q-fever outbreak in The Netherlands in 2009 (Ladbury et al. 2015). In Western Kenya, 1,500 households were enrolled in a study collecting data on animal and human syndromes as well as socio-economic household characteristics through regular interviews (Thumbi et al. 2015). Integrated data analysis aimed at better understanding the relationships between animal health, human health and nutrition, and social and economic status of households in livestock-dependent rural communities. While One Health surveillance initiatives have sprouted in the last few years they tend to remain limited in space, time or scope. They have largely been initiated in developing countries as an economically attractive way to share resources and costs linked to surveillance between animal and human health authorities. Animal health and human health are even more tightly linked in countries in which populations still rely heavily on subsistence agriculture, and human health can greatly benefit from interventions aimed at animal populations. A model of livestock vaccination against brucellosis in Mongolia concluded that if the costs of vaccination of livestock against brucellosis were allocated to all sectors in proportion to the benefits, the intervention might be profitable and cost effective for the agricultural and health sectors (Roth et al. 2003b). The future of One Health surveillance looks bright with cross-country initiatives such as the African One Health e-Surveillance Initiative (http://www.afenet.net/); a pilot project helping African countries to implement sustainable digital surveillance within the World Health Organization African Regional Office (WHO/AFRO) Integrated Disease Surveillance and Response framework.

1.6 Modern communication tools

Widespread access to the internet and mobile phones has promoted the use of modern communication technologies to collect human and animal health data (Madder et al. 2012; Chunara et al. 2012; Walker 2013). In the era of digital disease detection, "harnessing the web for public health surveillance" (Brownstein et al. 2009) is done on a daily basis by reporting systems such as ProMED-mail (www.promedmail.org) or HealthMap (www.healthmap.org). The development of sophisticated data mining tools has allowed transformed new media such as internet searches (Kang et al. 2013), social media platforms (Fung et al. 2015) and mobile phone applications (Freifeld et al. 2010) into information sources capable of complementing more traditional epidemiological databases and have the potential to improve the timeliness of outbreak detection. These technologies offer the advantages of increased speed and automation of data collection, provide accurate geo-location data, and allow for rapid communication of information.

In a few short years, the proliferation of mobile phone networks and internet access has transformed communications in sub-Saharan Africa and offers new possibilities for SyS (SyS is very tightly linked to digital surveillance frameworks (Rodríguez-Prieto et al. 2014)) surveillance in resource-poor countries where diagnostic capacities (used for active surveillance) may be limited. Information and communication technologies (ICT) could enhance surveillance sensitivity significantly and at low cost. While mobile-phone-based participatory systems for human public health have become widespread (Freifeld et al. 2010), their application to animal disease surveillance programs is more recent and less ubiquitous. Still, the feasibility of mobile phone based surveillance in collecting reliable, nearly real-time data in a cost-effective way was demonstrated in the frame of a demographic surveillance system for mobile pastoralists and their livestock herds (Jean-Richard et al. 2014). It is recently being recognised that mobile phone technologies could have an important role to play in obtaining animal health information in a timely fashion from field veterinarians, who in contrast to general practitioners or practice-based veterinarians visit their patients on their premises (Robertson et al. 2010).

1.7 Research gaps

National systems for the individual identification and registration of cattle may be useful for SyS by providing routinely collected historical data that are collected, transmitted and stored in an already existing infrastructure. In a retrospective analysis of cattle mortality data from the French National Cattle Register, Perrin and colleagues (Perrin et al. 2012) found a positive association between the spatiotemporal distribution of weekly excess mortality and notifications of infected herds during the BTV8 outbreak in France in 2007 and 2008. Despite this potential of cattle mortality data routinely reported by farmers to such systems for surveillance/early detection of disease outbreaks, the performance of aberration-detection algorithms applied to such data (on a daily basis) has not yet been investigated. Furthermore, the impact of reporting delay (time interval between the date the event occurred and the date it was reported) on outbreak detection performance is unknown.

SyS systems based on clinical observations made by veterinary practitioners and reported in real-time using web- and mobile-based communication tools may further improve the timeliness of outbreak detection. However, practitioner-based surveillance systems are often faced with problems concerning sustainability (Dórea et al. 2011). The willingness of veterinarians to report their observations as well as their continuous participation are essential for the successful implementation of such systems (Vourc'h et al. 2006). Therefore, it is important to better understand what strategies are successful in improving sustainability and what factors motivate or hinder practitioners to participate in surveillance. Knowledge about factors that motivate or constrain veterinary practitioners to submit clinical data and to participate in surveillance programmes is limited. Previous studies addressing a better understanding of such factors have focused on diagnostic laboratory-based surveillance systems (Robinson & Epperson 2013; Sawford et al. 2013; Sawford et al. 2012). To better understand the willingness of veterinary practitioners for participating in surveillance systems and to improve such systems, more studies investigating motivating and constraining factors are needed. In addition, a limited number of peer-reviewed publications, especially for veterinary diseases surveillance systems, hinders learning from the experiences made with existing systems using mobile technology for health data collection (Madder et al. 2012; Walker 2013).

1.8 Animal health and surveillance in Switzerland

In international comparison, Switzerland benefits from a high standard of animal health due to the control or eradication of classical animal diseases such as IBR and diseases with high zoonotic potential (e.g. brucellosis, tuberculosis, rabies). However, Switzerland is faced with the same risks as other countries due to emerging and re-emerging infectious animal diseases and zoonoses as illustrated by the following examples. With the import of semen from infected pigs in Germany, the PRRS was introduced to Switzerland in 2012. Consequently, extensive movement restrictions and diagnostic examinations of blood samples were undertaken to prevent further spread of the disease and to preserve the freedom from disease status according to OIE regulations. In 2013, several cantons of Switzerland were affected by the re-emergence of bovine tuberculosis, a disease that was successfully eradicated and from which the country has officially been free since 1960. The most recent risk for re-emergence of a previously eradicated disease occurred in 2015, when two cattle were imported from an IBR-positive farm in Austria. In Switzerland, 250 contact farms were affected by movement restrictions and further investigations. Owing to these measures, the spread of this disease in Switzerland could be prevented.

To maintain the good animal health situation in Switzerland, the Swiss Animal Health Strategy 2010+ was elaborated in close collaboration between the Swiss Federal Food Safety and Veterinary Office (FSVO) and the cantonal veterinary authorities. Prevention is one of the key aspects of this strategy, with the early detection of animal diseases as an important component. The development of a “system for early detection through syndromic surveillance” represents a concrete measure. Thus, the FSVO plans to establish a national early detection system for emerging and re-emerging disease by 2016, using information from various sources.

1.9 Study objectives

The overarching goal of this thesis was to contribute to the development of a national surveillance system for the early detection of emerging and re-emerging animal diseases (including zoonoses) in Switzerland. This work was part of a project funded by the FSVO (project 1.12.12) for the evaluation of different Swiss data sources regarding their potential use for syndromic surveillance and focused on:

I. The "Tierverkehrsdatenbank" (TVD), the system for the mandatory identification, registration and tracing of individual cattle in Switzerland, as a secondary source of health information.
II. Equinella, a voluntary reporting and information system for the monitoring and early detection of equine diseases in Switzerland, as primary health information source.

Specific objectives with regard to (I) were:

a. to describe available syndromic data and the underlying data management system in terms of data quality and population coverage
b. to define temporal patterns present in the data
c. to establish a baseline model describing the normal behaviour of the data (in the absence of disease outbreaks)
d. to evaluate the performance of temporal aberration detection algorithms in detecting disease outbreaks
e. to investigate the impact of delayed reporting on the detection of outbreaks in the data

Specific objectives with regard to (II) were:

f. to evaluate the suitability of mobile devices for reporting of surveillance data
g. to assess the participation of veterinarians in a voluntary reporting system
h. to identify motivating and constraining factors for participation of veterinarians in a voluntary reporting system

1.10 Thesis overview

This PhD thesis is divided into the following chapters:

Chapter 2 includes a retrospective analysis of three years of cattle mortality data reported by farmers to the TVD, with regard to the temporal patterns caused by non-disease related factors (study objectives a-c).

Chapter 3 provides an evaluation of the performance of three temporal aberration-detection algorithms in signalling disease outbreaks in routinely collected cattle mortality data using a simulation approach (study objective d).

Chapter 4 contains an investigation of the effect of reporting delay on outbreak detection in cattle mortality data by defining the value of evidence using a Bayesian approach (study objective e).

Chapter 5 describes the experiences made during the first operational year of Equinella in terms of motivations and barriers of veterinary practitioners to voluntarily report clinical data to health authorities as well as the suitability of mobile devices for real-time reporting (study objectives f-h).

1.11 Collaboration

This PhD project was conducted as collaboration between the Veterinary Public Health Institute (VPHI, University of Bern) and the Swiss Tropical and Public Health Institute (Swiss TPH, an associate institute of the University of Basel) and co-supervised by Dr. Flavie Vial (VPHI) and Prof. Dr. Jakob Zinsstag (Swiss TPH).

Part of this work to meet objectives f-h could be integrated into the Equinella project which aimed to re-launch the Equinella system based on a previous evaluation (see chapter 5). The project was conducted as collaboration between the Federal Food Safety and Veterinary Office, the Vetsuissy Faculty and the Swiss Association of Equine Practitioners.

1.12 Ethical considerations

This project did not include human health data or animal testing and did therefore not undergo formal ethical approval.

Related to chapter 5, short telephone interviews with veterinary practitioners were conducted. Before the start of an interview, each veterinarian was asked for permission to record the conversation. Audio files were stored on a password-protected computer after removal of personal identifiers to ensure anonymity of participants. Data collected during these interviews were published anonymously.

CHAPTER 2

Investigating the potential of reported cattle mortality data in Switzerland for syndromic surveillance

Rahel Struchen [a,*], Martin Reist [b], Jakob Zinsstag [c], Flavie Vial [a]

[a] Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Schwarzenburgstrasse 155, 3003 Bern, Switzerland

[b] Swiss Federal Food Safety and Veterinary Office, Schwarzenburgstrasse 155, 3003 Bern, Switzerland

[c] Swiss Tropical and Public Health Institute, University of Basel, Socinstrasse 57, 4051 Basel, Switzerland

* Corresponding author: rahel.struchen@vetsuisse.unibe.ch

Published in:

Preventive Veterinary Medicine 2015, 121(1-2): 1-7

2.1 Abstract

Systems for the identification and registration of cattle have gradually been receiving attention for use in syndromic surveillance, a relatively recent approach for the early detection of infectious disease outbreaks. Real or near real-time monitoring of deaths or stillbirths reported to these systems offer an opportunity to detect temporal or spatial clusters of increased mortality that could be caused by an infectious disease epidemic. In Switzerland, such data are recorded in the "Tierverkehrsdatenbank" (TVD). To investigate the potential of the Swiss TVD for syndromic surveillance, 3 years of data (2009-2011) were assessed in terms of data quality, including timeliness of reporting and completeness of geographic data. Two time-series consisting of reported on-farm deaths and stillbirths were retrospectively analysed to define and quantify the temporal patterns that result from non-health related factors.

Geographic data were almost always present in the TVD data; often at different spatial scales. On-farm deaths were reported to the database by farmers in a timely fashion; stillbirths were less timely. Timeliness and geographic coverage are two important features of disease surveillance systems, highlighting the suitability of the TVD for use in a syndromic surveillance system. Both time series exhibited different temporal patterns that were associated with non-health related factors. To avoid false positive signals, these patterns need to be removed from the data or accounted for in some way before applying aberration detection algorithms in real-time. Evaluating mortality data reported to systems for the identification and registration of cattle is of value for comparing national data systems and as a first step towards a European-wide early detection system for emerging and re-emerging cattle diseases.

Keywords: Syndromic surveillance; Cattle mortality; Early detection; Time-series analysis; Animal health surveillance

2.2 Introduction

Systems for the individual identification and registration of cattle were implemented in all European Union (EU) states in the aftermath of the bovine spongiform encephalopathy (BSE) crisis in 1996 (Council Regulation (EC) No 1760/2000 of 17 July 2000). These computerized, databased systems were designed to restore consumer faith in food safety, by enabling the tracing of cattle suspected of having BSE from the slaughterhouse back to their various holdings of origin. Since then, they have proven valuable for other types of epidemiological investigations, for example tracing the movements of animals potentially infected with other agents such as bovine viral diarrhoea virus (Presi et al. 2011), estimating population dynamics for modelling disease transmission (Green et al. 2006) and designing cost-effective disease control and monitoring programs (Blickenstorfer et al., 2011, Schärrer et al., 2014).

These identification systems have gradually been receiving attention for use in syndromic surveillance (Dupuy et al. 2013). Syndromic surveillance is a recent surveillance approach, based on the continuous monitoring of unspecific health related data in (near) real-time. Its primary purpose is the early detection of potential health threats, to inform timely and effective control measures (Triple-S Project 2011). Assessing the impact of identified events on population health (Elliot et al. 2010) is another reported benefit. Data most accessible for syndromic surveillance are those that are stored electronically, collected and analysed in a timely fashion and that have extensive geographic, demographic and temporal coverage (Mandl, Overhage, et al. 2004). In veterinary public health, syndromic data are typically clinical observations collected from veterinary practitioners (Vourc'h et al. 2006) or diagnostic laboratory test requests (Dórea, McEwen, McNab, Revie, et al. 2013). Such pre-diagnostic data are assumed to contain earlier, but weaker signatures of a disease outbreak (Yahav & Shmueli 2007). Various statistical algorithms exist (Unkel et al. 2012) for identifying unexpected patterns in these data that may result from infectious disease outbreaks.

Mortality (or fertility) data from cattle identification systems may be useful for syndromic surveillance. In a retrospective analysis of mortality data from the French National Cattle Register, Perrin et al. (2012) reported a positive association between the spatiotemporal distribution of weekly excess mortality and notifications of infected herds during the Bluetongue outbreak in 2007 and 2008. Such systems contain large amounts of data routinely collected on a daily basis over several years. Historical data are needed for constructing a baseline model defining expected normal behaviour in time series from these databases. Reporting is compulsory, ensuring reasonably good coverage of the population. Existing data collection, transmission and storage infrastructures can be used, making surveillance convenient and reducing surveillance costs. However, these data were originally collected for purposes other than surveillance, and for this reason may be of insufficient quality, have limited timeliness or may contain biases. The temporal patterns observed in the data, such as seasonality, day-of-week effects or global trends (Nöremark et al., 2009, Robinson and Christley, 2006), are to a large degree caused by factors which are not health-related. These patterns need to be removed from the data or accounted for before applying aberration detection algorithms in a prospective fashion (Shmueli & Burkom 2010).

Early detection of animal diseases is an important component of the '*Swiss Animal Health Strategy 2010+*'[3] that aims to maintain and improve the high standard of animal health in Switzerland. The Swiss Federal Food Safety and Veterinary Office (FSVO) plans to build a national early detection system by 2016, using information from various sources. Many syndromic surveillance systems rely on clinical data collected from veterinarians (Dórea et al. 2011). In Switzerland, there was no computerised system for recording clinical data in place yet by the time this study started and therefore, alternative data were being evaluated. For example, the (near) real-time monitoring of cattle deaths could be used to identify temporal or spatial clusters of increased mortality, which may be indicative of a disease outbreak. Outbreaks of emerging or re-emerging diseases such as Rift Valley fever or brucellosis, and changes in endemic diseases such as botulism or leptospirosis, may produce clusters of excess cases in reported mortality data. In Switzerland, cattle mortalities are reported by farmers to the system for the identification and registration of cattle, the "Tierverkehrsdatenbank" (TVD). The objectives of our study were to assess the quality of the TVD data, and to define the temporal patterns caused by non-health related factors in two non-slaughter mortality time-series. Understanding non-health related patterns is a prerequisite step before choosing appropriate prospective methods for detecting temporal aberrations in the data that might be linked to disease outbreaks.

[3] See http://www.blv.admin.ch/gesundheit_tiere/03007/index.html?lang=en

2.3 Materials and methods

Data source

In Switzerland, it has been compulsory, since 2000, for cattle farmers to report all births and deaths of animals on their holding and all movements to and from their holding to the TVD. Births are required to be reported within 30 days, whereas all movements (on- and off-farm) and non-slaughter deaths are required to be reported within 3 days (Animal Health Ordinance (AHO), SR 916.401). Reporting is either electronic via the internet or by paper forms. Detailed information is captured for animals (e.g. sex, breed) and farms (e.g. location, farm type). Monetary incentives to report do exist. For example, farmers receive a carcass disposal fee for each dead calf whose birth had been previously reported to the TVD, and slaughterhouses receive a similar fee for each slaughtered animal whose movement history is complete. Missing or incomplete reports are penalised by reducing the incentive. Two possible syndromic indicators were identified in the TVD: on-farm deaths and stillbirths. Both events are recorded as separate entries. On-farm deaths include deaths occurring either naturally or by euthanasia. Stillbirth reporting is not compulsory and therefore an explicit definition of stillbirths could not be made.

Data extraction

All reported on-farm deaths and stillbirths for the period from January 1st 2009 to December 31st 2011 were extracted from the TVD. Data prior to 2009 were available, but were excluded because analyses had shown that the quality of the data improved notably due to incentives that were implemented in 2009. The date that each event (on-farm death or stillbirth) was reported to have occurred and the date it was reported were extracted. Additional data about the animal affected (e.g. breed) and the farm that reported the event (e.g. geographical coordinates) were also extracted. Data were stored in a PostgreSQL database (The PostgreSQL Global Development Group) and data handling using SQL was performed with Squirrel (Bell et al.).

Data quality & descriptive statistics

Data quality was assessed by estimating the timeliness of report submission and the completeness of records. Timeliness was defined as the time between the reported occurrence of an event and its reporting to the system and is further referred to as reporting timeliness. Completeness was estimated by calculating the proportion of reports with missing geographic data. Geographic data were chosen because they are critically important for geo-locating disease and outbreak occurrences.

For the descriptive analyses, mortality data were stratified by sex and production type. Production type was subset into dairy, beef, mixed and other according to breed of cattle reported. On-farm deaths were also divided into five categories by the age at death: 1) up to 7 days old, 2) 8 to 120 days, 3) 121 days to 1 year, 4) 1 to 2 years, and 5) more than 2 years. Classification was based on livestock units used to calculate direct payments offered to farmers for their services for the common good. For the time series analyses, daily time series for the total numbers of on-farm deaths and stillbirths were generated. All statistical analyses were performed in R (R Core Team 2013) using the packages timeDate (Wuertz et al. 2013), TSA (Chan & Ripley 2012) and gcmr (Masarotto & Varin 2012).

Model building & comparison

Regression models were fitted to the data to determine the effects of trend, seasonality, day of the week and bank holidays. Poisson and negative-binomial regression models were applied to the daily counts of on-farm deaths or stillbirths. Alternative models tested included different variants for some of the predictors: trend was defined either as a continuous time variable or as categorical variables for the years. Seasonality was modelled using either categorical variables for each month or months grouped into two or four seasons, or a sinusoidal function using the term: $\sin(2*pi*t/365) + \cos(2*pi*t/365)$ where t is the day number from 1 to 1,095. Days of the week were included using categorical variables either for each day or grouped into Mondays, other weekdays and weekends. Bank holidays were included in the model using a variable for common Swiss holidays and a second variable for the day after a holiday. For stillbirths, the total number of births (also obtained from the TVD) was included into the models as an offset.

Likelihood ratio tests were used to test for the significance of each predictor at a statistical significance level of 5%. The models were compared using their Akaike Information Criterion (AIC) values. Regression diagnostics were based on plots of the deviance residuals (residuals against the fitted values; QQ plot of the standardized residuals and plots of the Cook statistics). Autocorrelation function plots were used to estimate whether there was any dependency structure in the residuals. When some autocorrelation remained, models were refitted using a Gaussian copula marginal regression (available from the gcmr package in R), allowing incorporation of a correlation structure by defining an autoregressive and moving average (ARMA) process of orders p and q, in order to obtain independent and identically distributed errors. Several subsets of ARMA models were tested and compared based on their Bayesian Information Criterion (BIC).

2.4 Results

Data quality & reporting timeliness

Geographic information about the farm reporting an event was present in the TVD as coordinates, postal code, location, community and canton (cantons are member states within the Swiss Federation). Coordinate data were missing for less than 1% of the reports. Postal code and location were missing for less than 5%, and there were no missing data for community and canton variables. The median difference between the date the event was reported to have occurred and the date the event was reported to the TVD was 1 day for on-farm deaths and 3 days for stillbirths (Figure 1). On-farm deaths were reported within 7 days 81.95% of the time and stillbirths 73.03% of the time.

Figure 1 Reporting timeliness for on-farm deaths and stillbirths. Timeliness was defined as the difference in days between the reported occurrence of a cattle mortality event and its reporting by farmers to the system for the individual identification and registration of cattle in Switzerland ("Tierverkehrsdatenbank", TVD). The dotted line represents the maximum reporting time for deaths allowed under Swiss law. Stillbirth reporting is currently not compulsory.

Descriptive statistics

Between 2009 and 2011, the Swiss cattle population was constant at approximately 1.6 million animals (Schärrer et al. 2014). During this period there were 201,428 cattle on-farm deaths and 68,911 stillbirths reported to the TVD. The proportion of stillbirths among the total number of cattle births was 3.1%. The median number of events per day was 180 for on-farm deaths (ranging from 62 to 413) and 64 for stillbirths (ranging from 25 to 112) (Table 1). Females accounted for 52.1% of reported on-farm deaths and 40.8% of reported stillbirths. Dairy cattle accounted for approximately 70% of reported on-farm deaths and stillbirths. Almost two third of cattle mortalities were in cattle four months of age or younger.

The time series of the daily number of reported events revealed a strong seasonal pattern in both on-farm deaths (Figure 2) and stillbirths (Figure 3). The highest number of on-farm deaths was observed during winter and the minimum during summer. A peak in stillbirths occurred during the autumn and a trough during the late spring corresponding to the seasonality observed in the cattle reproductive cycle in Switzerland.

Model comparison

For the on-farm deaths time series, a negative binomial model including trend (continuous time variable), seasonality (modelled as month), day of the week as well as national holiday and day after national holidays fitted the data best (Appendix A: Supplementary material). All predictors were significant at the 5% level. Residuals showed significant autocorrelation at lags 2, 3, 5 and 10 so the model was refitted with an AR process of order p=5 (leaving a marginal autocorrelation at lag 10). On-farm deaths were reported to occur more often on Mondays compared to other weekdays and were lower on Saturdays and Sundays (Figure 4). The number of reported on-farm deaths was significantly lower on bank holidays and significantly higher the day after a bank holiday compared to other days. A significant, negative trend was observed over the 3 years.

Table 1 Summary statistics of daily numbers of reported cattle mortalities in Switzerland between 2009 and 2011. On-farm deaths and stillbirths were reported by farmers to the "Tierverkehrsdatenbank" (TVD), the system for the individual identification and registration of cattle in Switzerland (overall, by sex, production type and age class).

	On-farm deaths						**Stillbirths**					
	Min	25%	Med	75%	Max	Total (%)	Min	25%	Med	75%	Max	Total (%)
Total	62	147	180	217	413	201'428	25	49	64	75	112	68'911
Sex												
Males	26	67	84	105	227	96'423 (47.9)	12	29	37	44.5	69	40'782 (59.2)
Females	32	76	95	113	198	105'005 (52.1)	5	20	25	31	50	28'129 (40.8)
Production type												
Dairy	41	101	127	151.5	294	140'034 (69.5)	13	34	45	54	88	48'718 (70.7)
Beef	3	12.5	17	23	117	19'867 (9.9)	0	3	5	6	19	5'358 (7.8)
Mixed	0	4	6	8	25	6'657 (3.3)	0	1	2	3	10	2'354 (3.4)
Other	9	24	30	38	76	34'870 (17.3)	1	8	11	14	32	12'481 (18.1)
Age class												
≤ 7 days	9	31	41	53	112	47'220 (23.4)						
8 - 120 days	17	53	70	95	213	83'340 (41.4)						
121 days to 1 year	2	17	22	27	59	24'718 (12.3)						
1 year to 2 years	0	4	7	9	28	7'654 (3.8)						
> 2 years	1	26	36	44	126	38'496 (19.1)						

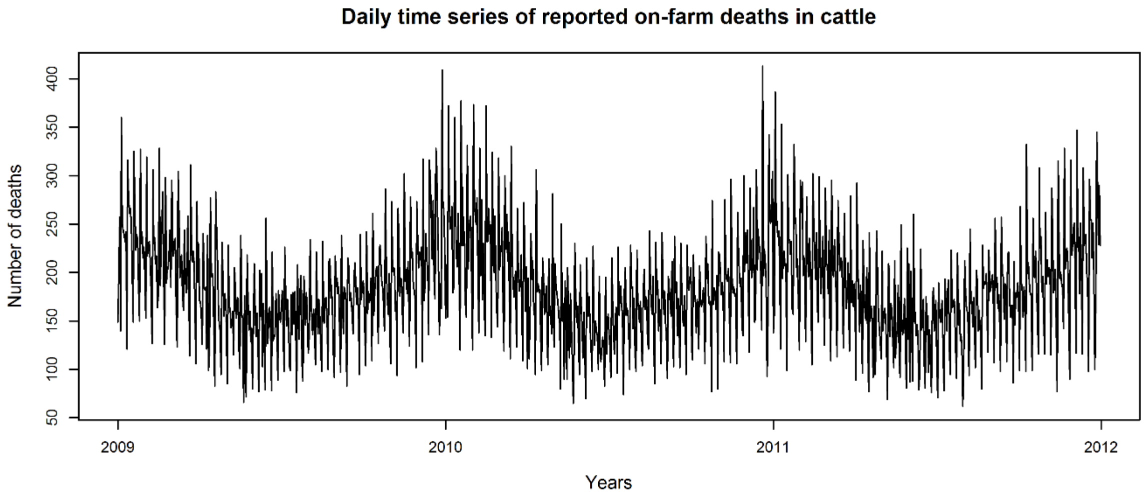


Figure 2 Time series of the daily numbers of on-farm deaths reported by farmers to the system for the identification and registration of cattle in Switzerland ("Tierverkehrsdatenbank", TVD) between 2009 and 2011.

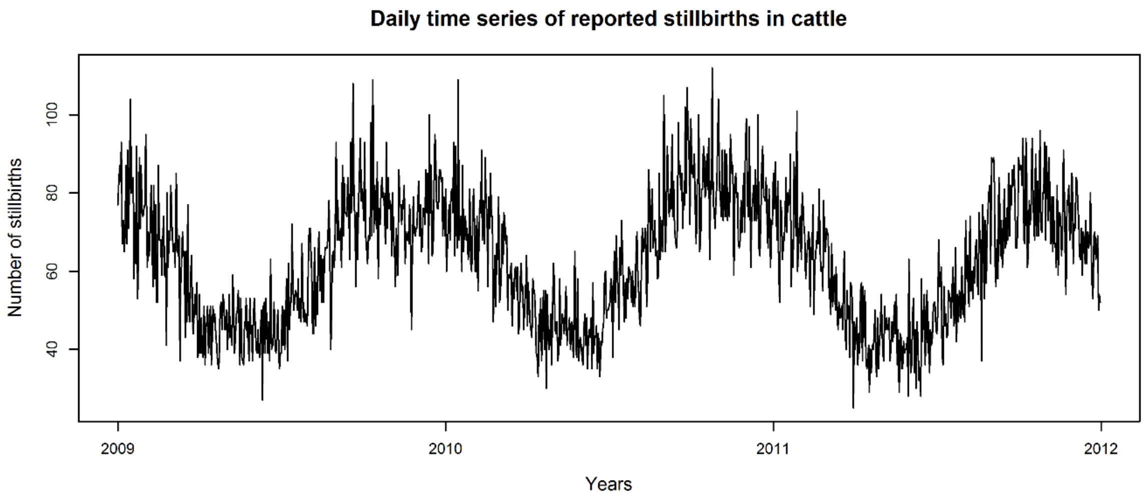


Figure 3 Time series of the daily numbers of stillbirths reported by farmers to the system for the identification and registration of cattle in Switzerland ("Tierverkehrsdatenbank", TVD) between 2009 and 2011.

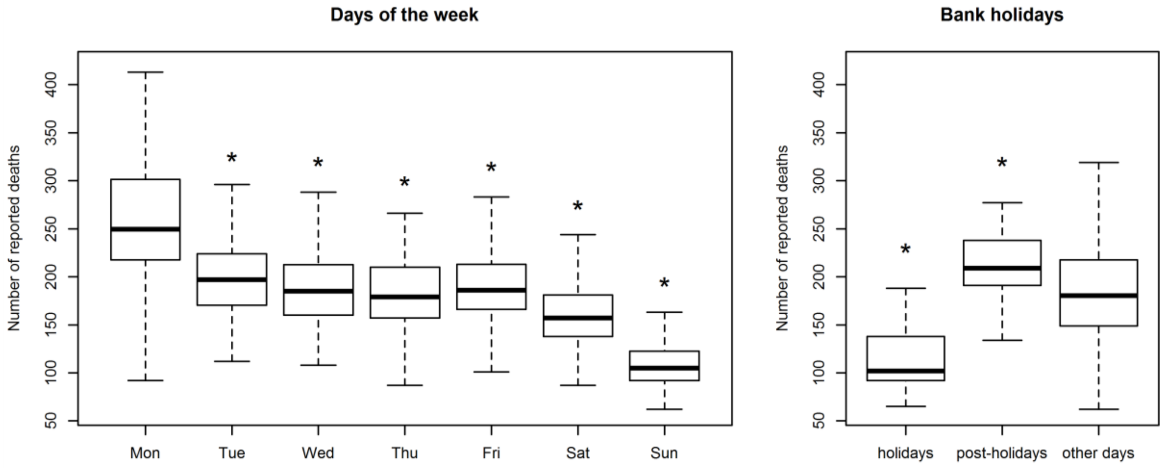


Figure 4 Days of the week and bank holidays in on-farm deaths reported by farmers to the system for the identification and registration of cattle in Switzerland ("Tierverkehrsdatenbank", TVD). Asterisks indicate those days that were significantly different from the reference (Mondays for days of the week or other days for bank holidays).

For the stillbirths time series, a negative binomial model including trend (categorical year variable), seasonality (modelled as month) and national holidays fitted the data best (Appendix A: Supplementary material). Day of the week and day after national holidays were not significant predictors in this model. No autocorrelation was left in the residuals. A significantly lower number of stillbirths was found on holidays compared to other days (Figure 5). The number of stillbirths was significantly higher in 2010 and lower in 2011 compared to the year 2009.

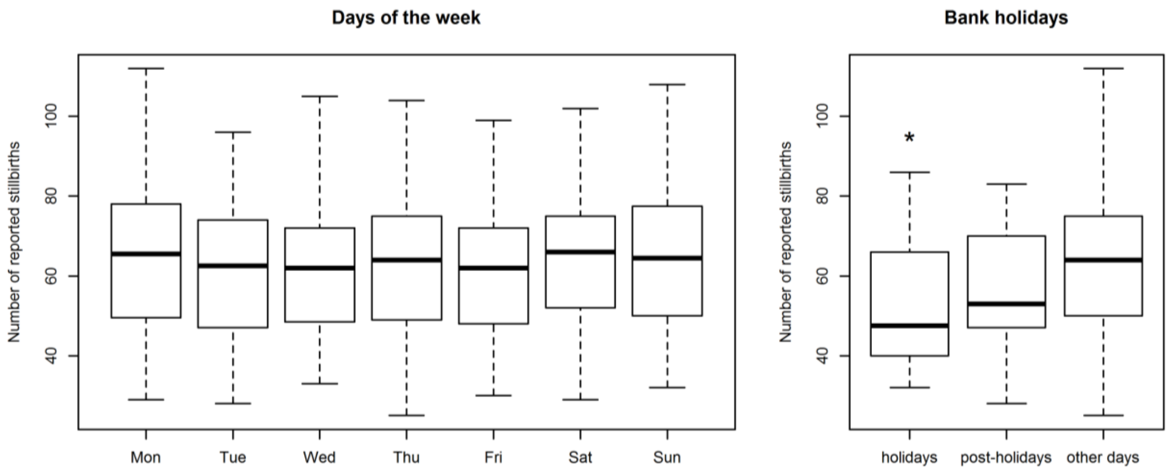


Figure 5 Days of the week and bank holidays in stillbirths reported by farmers to the system for the identification and registration of cattle in Switzerland ("Tierverkehrsdatenbank", TVD). Asterisks indicate those days that were significantly different from the reference (Mondays for days of the week or other days for bank holidays).

2.5 Discussion

The quality of the data in the TVD was relatively high. Geographic information was available at different scales and for more than 95% of the reported events, providing a high degree of certainty that statistical alarms produced by aberration detection algorithms could be traced back to the farms of origin. Having geographic data at different levels should allow investigation of the effect of geographic resolution (e.g. canton vs. community) on the ability to detect potential disease clusters in the data. Selecting the appropriate scale of analysis is important as outbreaks can be detected earlier when monitoring data at a lower geographic scale (Odoi et al. 2009).

On-farm deaths were reported to the TVD in a timelier fashion than stillbirths. At least half of all on-farm deaths were reported within 1 day after having occurred. Timeliness of on-farm death reporting probably benefitted from the fairly strict Swiss federal law which requires reporting of cattle deaths within 3 days. Half of the stillbirths were reported 3 three days even though this is not currently required under Swiss law. As stillbirths are likely to be monitored using birth as denominator, the timeliness of stillbirths might be limited by the reporting timeliness of births which was found to be lower with a median of 4 days (Appendix A: Supplementary material). The reporting timeliness is satisfactory for the use of these data for early detection. Quantifying the distribution of reporting delays for each mortality time series does have value. It could be used to more realistically simulate disease outbreaks for validating aberration detection algorithms for these time series.

Our estimates of reporting timeliness in this study should be interpreted with some caution. Some farmers may have reported the date of occurrence of an event as being the same date on which they reported the event to the TVD ("recall error"), rather than the date that the event actually occurred. This could result in an underestimation of the true reporting delay. However, it was not possible to estimate the magnitude of this effect.

An important attribute of surveillance systems is coverage of the population, i.e. the proportion of the population of interest that is included in the surveillance system (Drewe et al. 2013). Since registration of cattle is compulsory for farmers, the data should cover the whole Swiss cattle population. However, in 2011, less than 10% of Swiss cattle farms randomly selected for quality assurance had a TVD herd register that did not match the actual on-farm herd (Heim, personal communication), possibly as a result of delayed reporting of births, deaths or animal movements. It can be speculated that the proportion of cattle farms holding unregistered animals is considerably lower, because farmers failing to register an animal to the TVD would not benefit from subsidies (i.e. a carcass disposal fee). However, this could not be determined from this study.

It is possible that some farmers have reported stillbirths as the birth of a calf that was alive and died after a few days. This is due to the carcass disposal fee farmers receive for dead calves as long as their births have been reported to the TVD. An observation supporting this supposition was that the sex ratio of the subset of on-farm deaths within 7 days after birth (40% females, data not shown), differed greatly from the sex ratio of all on-farm deaths, but was similar to the sex ratio of stillbirths. However, an alternative explanation could be that mortality is generally higher in male than in female cattle or that male dairy calves are given less care than female calves. In order to more accurately monitor stillbirths and neonatal mortality using the TVD data, they should be combined into one time series that includes both reported stillbirths and on-farm deaths within the first 7 days after birth.

Even though the size of the Swiss cattle population was constant between 2009 and 2011, a decreasing linear trend was found in reported on-farm deaths. However, care should be taken when interpreting this trend as it was estimated only for a period of 3 years. The pronounced seasonal patterns observed in stillbirths were likely due to the management of reproduction in the Swiss cattle herd. Approximately one fourth of the Swiss cattle population is moved to alpine pastures during summer, and to avoid calving on these pastures, calving mainly occurs during autumn and winter, with corresponding peak in stillbirths observed during the autumn and winter. The peak in the number of cattle on-farm deaths was shifted approximately three to four months later than the peak in stillbirths. This corresponds to the time of the year when there is the largest population of young calves on Swiss farms and two thirds of all cattle mortalities were in young calves (less than 4 months of age).

The effects of days of the week and bank holidays found in cattle on-farm deaths may be related to higher veterinary consultation fees on weekends and bank holidays. These may cause farmers to wait until Mondays or the day after a bank holidays to call a veterinarian for euthanasia of an animal (Nöremark et al., 2009, Robinson and Christley, 2006). The lower number of reported on-farm deaths on weekends and bank holidays compensated by much higher numbers of reported events on Mondays and days after holidays could also be due to a less vigilant observation of cattle herds on weekends and holidays. For this reason dead animals simply may not be detected immediately (Robinson & Christley 2006). A similar pattern would also be expected for stillbirths then; however, they were more evenly distributed among the days of the week. Another explanation is that farmers may use the reporting date as the date for the occurrence of the event, when the date of the event may have been earlier.

The remaining autocorrelation in on-farm deaths at a lag of 10 days results from the choice of incorporating a dependency structure following an autoregressive process of order 5 (which was only the second best subset ARMA model). The best subset ARMA model (p=5, q=10) could not converge. An explanation for this serial correlation of every 10th day might be reporting bias due to digit preference. Preferential reporting of dates such as the first of a month or those ending in zero or five was found to be present in the bovine identification systems of Sweden (Nöremark et al. 2009) and the UK (Robinson & Christley 2006).

For both reported on-farm deaths and stillbirths, a negative binomial regression model was found to fit the data best. The explainable patterns found in the data were much more complex for on-farm deaths where all predictors were significant. Aggregating the daily number of on-farm deaths into a weekly data stream as done by Perrin et al. (2010) might be an alternative approach for removing day-of-week effects, but it may not overcome the difficulties with bank holidays and remaining autocorrelation. Furthermore, data aggregation may introduce a lag between the time of an event occurring and its detection in the time series.

2.6 Conclusions

The TVD system collects timely mortality data with complete geographic information. These are two important features of disease surveillance systems, highlighting the suitability of the TVD for use in a syndromic surveillance system. Strict laws and attractive subsidies are thought to be factors that have increased the data quality. The work presented in this paper is a prerequisite for using the TVD data prospectively in syndromic surveillance to detect potential disease outbreaks. The mortality time series exhibited temporal patterns that were associated with non-health related factors. These should be taken into consideration during the next step when different temporal and spatial algorithms will be fitted onto the data and validated using either historical or simulated disease outbreaks.

Cattle identification systems are ubiquitous across the whole EU. Much effort has been dedicated to the use of the animal movement data contained within those systems and their relevance to disease spread between herds. However, comparatively few studies have considered how the birth and mortality data in these systems may be used in epidemiological surveillance despite the fact that these data are easier to work with than complex movement data. There is value in describing all data coming from cattle identification systems and sharing summary output with other countries to promote the comparisons of national data systems. Only then, will it be possible to aggregate the output from national mortality surveillance systems in an early detection system for emerging and re-emerging cattle diseases at the European level (Dupuy et al. 2013).

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 this paper.

Acknowledgements

We wish to thank the Swiss Federal Food Safety and Veterinary Office (FSVO) for funding; Fernanda Dórea (National Veterinary Institute, Sweden), John Berezowski (VPHI), Dagmar Heim, Heinzpeter Schwermer and Martin Moser (FSVO) for valuable inputs and discussions; Sara Schärrer (FSVO) for support with data management; Cristiano Varin and Guido Masarotto for support with the gcmr package; and anonymous reviewers for their valuable comments.

2.7 Appendix A: Supplementary material

Table 2 Akaike Information Criterion (AIC) and likelihood ratio test ($\chi 2$, p-value) for Poisson and negative binomial regression model applied to raw data of reported on-farm deaths in cattle. The variable in bold illustrates the predictor that was tested for in the likelihood ratio test. The frame indicates the model that fitted the data best.

	Poisson			**Negative binomial**		
	AIC	χ^2	**p-value**	**AIC**	χ^2	**p-value**
count ~ 1	27118.09	-	-	11924.89	-	-
count ~ **weekday**[a]	16762.71	10367.00	< 0.001	11067.89	869.00	< 0.001
count ~ **weekday_gr**[b]	18382.21	8739.90	< 0.001	11289.99	638.90	< 0.001
count ~ **month**[c]	22072.72	5067.40	< 0.001	11625.76	321.13	< 0.001
count ~ **season2**[d]	23264.22	3855.90	< 0.001	11689.41	237.47	< 0.001
count ~ **season4**[e]	23086.83	4037.30	< 0.001	11686.65	244.24	< 0.001
count ~ **sin+cos**[f]	22216.10	4906.00	< 0.001	11620.59	308.30	< 0.001
count ~ **time**[g]	27077.98	42.11	< 0.001	11924.61	2.28	0.1314
count ~ **year**[h]	27111.67	10.42	0.0055	11928.31	0.57	0.7502
count ~ **holiday**[i]	26156.62	963.47	< 0.001	11863.59	63.30	< 0.001
count ~ **afterholiday**[j]	26995.40	124.68	< 0.001	11920.34	6.55	0.0105
count ~ weekday + **month**	11698.14	5086.60	< 0.001	10217.71	872.17	< 0.001
count ~ weekday + **season2**	12897.32	3867.40	< 0.001	10479.33	590.56	< 0.001
count ~ weekday + **season4**	12640.03	4128.70	< 0.001	10438.42	635.46	< 0.001
count ~ weekday + **sin+cos**	11851.95	4914.80	< 0.001	10250.92	820.97	< 0.001
count ~ weekday + month + **time**	11689.74	10.40	0.0013	10215.86	3.86	0.0496
count ~ weekday + month + **year**	11692.12	10.02	0.0067	10217.95	3.76	0.1524
count ~ weekday + month + time + **holiday**	10915.42	776.32	< 0.001	10001.49	216.37	< 0.001
count ~ weekday + month + time + **afterholiday**	11496.74	195.01	< 0.001	10158.75	59.11	< 0.001
count ~ weekday + month + time + holiday + **afterholiday**	10759.24	158.18	< 0.001	9943.36	60.13	< 0.001

[a] weekday: a categorical variable for each day of the week
[b] weekday_gr: a categorical variable for days of the week grouped into 1) Mondays, 2) other weekdays and 3) weekends
[c] month: a categorical variable for each month
[d] season2: a categorical variable for months grouped into two seasons
[e] season4: a categorical variable for months grouped into four seasons
[f] sin+cos: a variable for a sine and cosine function
[g] time: a continuos variable from 1 to 1095
[h] year: a categorical variable for each year
[i] holiday: a variable representing Swiss bank holidays
[j] afterholiday: a variable representing the day after a Swiss bank holidays

Table 3 Akaike Information Criterion (AIC) and likelihood ratio test (X2, p-value) for Poisson and negative binomial regression model applied to raw data of reported stillbirths in cattle. The variable in bold illustrates the predictor that was tested for in the likelihood ratio test. The frame indicates the model that fitted the data best.

	Poisson			**Negative binomial**		
	AIC	**χ^2**	**p-value**	**AIC**	**χ^2**	**p-value**
count ~ 1	11220.779	-	-	9221.797	-	-
count ~ **weekday**[a]	8073.796	3159.00	< 0.001	7999.288	1234.50	< 0.001
count ~ **month**[b]	7807.699	3435.10	< 0.001	7794.117	1449.70	< 0.001
count ~ **season2**[c]	8068.647	3154.10	< 0.001	7992.388	1231.40	< 0.001
count ~ **season4**[d]	7907.493	3319.30	< 0.001	7873.599	1354.20	< 0.001
count ~ **sin+cos**[e]	8012.892	3211.90	< 0.001	7950.811	1275.00	< 0.001
count ~ **time**[f]	8067.063	3155.70	< 0.001	7991.612	1232.20	< 0.001
count ~ **year**[g]	8017.242	3207.50	< 0.001	7957.326	1268.50	< 0.001
count ~ **holiday**[h]	8065.018	3157.80	< 0.001	7989.670	1234.10	< 0.001
count ~ **afterholiday**[i]	8067.883	3154.90	< 0.001	7992.159	1231.60	< 0.001
count ~ month + **weekday**	7814.048	5.65	0.4634	7801.335	4.78	0.5721
count ~ month + **time**	7803.217	6.48	0.0109	7790.567	5.55	0.0185
count ~ month + **year**	7756.783	54.92	< 0.001	7750.771	47.35	< 0.001
count ~ month + **holiday**	7805.116	4.58	0.0323	7792.173	3.94	0.0470
count ~ month + **afterholiday**	7808.010	1.69	0.1936	7794.591	1.53	0.2168
count ~ month + year + **weekday**	7763.112	5.67	0.4610	7757.731	5.04	0.5386
count ~ month + year + **holiday**	7754.179	4.60	0.0319	7748.645	4.13	0.0422
count ~ month + year + **afterholiday**	7757.145	1.64	0.2007	7751.253	1.52	0.2178
count ~ month + year + holiday + **afterholiday**	7754.808	1.37	0.2416	7749.367	1.28	0.2584

[a] weekday: a categorical variable for each day of the week
[b] month: a categorical variable for each month
[c] season2: a categorical variable for months grouped into two seasons
[d] season4: a categorical variable for months grouped into four seasons
[e] sin+cos: a variable for a sine and cosine function
[f] time: a continuos variable from 1 to 1095
[g] year: a categorical variable for each year
[h] holiday: a variable representing Swiss bank holidays
[i] afterholiday: a variable representing the day after a Swiss bank holidays

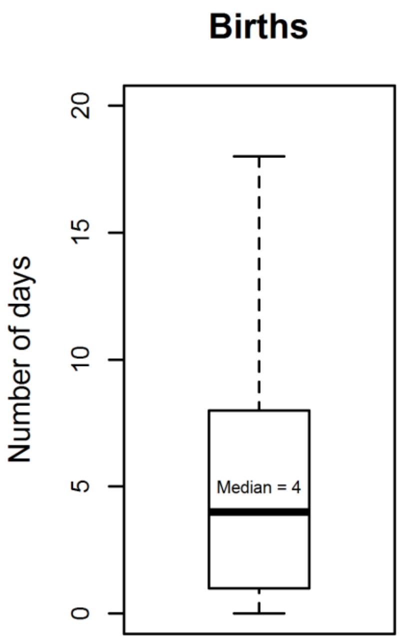


Figure 6 Reporting timeliness for cattle births. Timeliness was defined as the difference in days between the reported occurrence of a birth event and its reporting by farmers to the system for the individual identification and registration of cattle in Switzerland ("Tierverkehrs-datenbank", TVD).

CHAPTER 3

Syndromic surveillance of bovine perinatal mortality: algorithms combination and performance

Rahel Struchen[1*], Jakob Zinsstag[2], Flavie Vial[1]

[1] Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Bern, Switzerland

[2] Swiss Tropical and Public Health Institute, University of Basel, Basel, Switzerland

* Corresponding author: rahel.struchen@blv.admin.ch (RS)

To be submitted to:

Veterinary Medicine: Research and Reports

3.1 Abstract

Data routinely collected in national livestock identification systems may be used for the early detection of mortality clusters potentially indicative of a disease outbreak. We evaluated the performance of temporal outbreak detection algorithms retrospectively applied to daily perinatal mortality data extracted from the Swiss system for the individual identification and registration of cattle between 2009 and 2011. Simulated disease outbreaks of different sizes, durations and shapes were injected into baseline time-series of perinatal mortality. The performance of three control chart algorithms (Shewhart, cumulative sum and exponentially weighted moving average) were assessed based on several measures including sensitivity, false positive rate and positive predictive value. The algorithms were evaluated separately, using different detection limits, and by combining their binary outputs (generating an alarm or not) under two rules. In rule 1, a statistical alarm is raised if the number of cases observed is larger than the detection limit of two out of three algorithms. In rule 2, an alarm is raised only if the number of cases surpasses all three detection limits. Sensitivity and false positive rate generally decreased with increasing detection limit, but the strength of this effect was not the same for all three algorithms and depended on the characteristics of the outbreaks. The algorithms adequately performed under specific outbreak conditions, but none of them was superior in detecting outbreak signals across multiple evaluation metrics. While combination rule 1 obtained comparable results as the three algorithms separately, rule 2 leaded to a considerable reduction in the false positive rate, but at the cost of sensitivity. Our findings highlight the need to carefully optimise aberration detection algorithms for a particular data stream and indicate that alternative methods to the binary alarm system may be chosen for a prospective use of cattle perinatal mortality data in a national early detection system. Methods for improving overall sensitivity and specificity of the surveillance system are discussed.

3.2 Introduction

Bovine abortions and stillbirths can be of relevance for animal and public health surveillance as they may provide an early signal of disease outbreaks. These non-specific clinical signs can be caused by a range of animal and zoonotic diseases, including Schmallenberg virus infections (Doceul et al. 2013), Neosporosis (Dubey & Schares 2011), or Brucellosis (Bronner et al. 2014). Surveillance systems based on mandatory notification of abortions play an important role in early outbreak detection and are in place in many Northern countries. However, they depend on the preparedness of farmers and veterinarians to participate and under-reporting of abortions can be considerably high (Bronner et al. 2013), resulting in a low sensitivity of the system. Furthermore, precise definitions of abortions and stillbirths differ not only between countries (national regulations), but can also be perceived differently between health authorities on the one side and veterinarians and farmers on the other (Bronner et al. 2014).

Syndromic surveillance (SyS) provides an alternative to overcome some of these limitations by making use of data collected for other purposes than surveillance. Bronner et al. (2015) demonstrated the value of artificial insemination data for use as an indicator of mid-term abortions in cattle in order to complement the surveillance of abortive diseases. Another alternative would be the use of mortality data routinely reported by farmers to systems for the individual identification and registration of cattle, such as the Swiss “Tierverkehrsdatenbank” (TVD). In Switzerland, cattle holders are required to report movements as well as births and deaths of their animals to the TVD. The reporting of stillbirths is not mandatory. A previous study noted that a perinatal mortality indicator grouping reported stillbirths with reported early (within 7 days of birth) neonatal mortality may constitute a more sensitive syndromic indicator than stillbirths alone (Struchen et al. 2015).

A diverse set of animal health data has been evaluated for inclusion in SyS systems (Dupuy et al. 2013). However, assessing the performance of such systems can be difficult as a result of the limited availability of historical outbreak data (Mandl et al. 2004). Simulated outbreak data tend to be used instead (Dórea, McEwen, McNab, Revie, et al. 2013; Dupuy et al. 2015; Vial et al. 2015), allowing the performance to be evaluated across a range of outbreak scenarios (Dórea, McEwen, McNab, Revie, et al. 2013). This approach is appropriate for SyS systems which do not target specific diseases, but aim to detect a variety of diseases, including new or exotic ones, which may manifest themselves as unpredictable outbreak shapes.

Numerous methods exist for the detection of aberrations, potentially indicative of disease outbreaks, in temporal syndromic data (Unkel et al. 2012; Buckeridge et al. 2005). The so-called aberration detection algorithms can vary in their outbreak detection performance based on distinct evaluation criteria (Dupuy et al. 2015). They may complement each other by exhibiting a superior performance for different outbreak shapes (Dórea, McEwen, McNab, Revie, et al. 2013), highlighting the importance of evaluating and combining several algorithms. Combining the output of different algorithms according to a flexible scoring system has been described (Dórea, McEwen, McNab, Sanchez, et al. 2013). The score considered the outputs of several algorithms based on multiple detection limits (Figure 7) and enables customisation of the system for different syndromic time series. This approach was explored in the frame of a SyS system based on daily counts of diagnostic test requests for cattle diseases (Dórea, McEwen, McNab, Sanchez, et al. 2013). It has been proven useful in improving overall system's performance, resulting in increased sensitivity while keeping the false alarm rate still at a manageable level. Another method proposed the theoretical combination of the algorithms' binary outcome (Figure 7), i.e. whether it produces an alarm or not, according to different rules (Yahav & Shmueli 2007). For example, a final alert is generated only if a majority of algorithms signals an alarm for a given point in time (majority rule). Under the M+n rule, only those alarms produced by a subset M and at least n of the remaining algorithms are considered. While such rules may be appropriate to reduce the number of false alarms, sensitivity could benefit from examining alerts caused from at least one in a set of algorithms (Dupuy et al. 2015). The proof of concept for such combination rules has been illustrated using 2 year time-series of respiratory symptoms collected from military clinic visits (Yahav & Shmueli 2007) but, to our knowledge, they have not yet been applied in the field of SyS.

The objective of our study was to evaluate the performance of three temporal algorithms in detecting simulated disease outbreaks of different shapes in Swiss bovine perinatal mortality data (i.e. stillbirths and early neonatal deaths). Algorithms were applied separately with different parameter settings in order to find an optimal balance between sensitivity and false alarms. In addition, two simple combination rules were tested for their ability to potentially reduce the number of false alarms, without notably compromising sensitivity. Such evaluation can provide useful insights into the capability and limitations of a surveillance system and how it could complement existing surveillance activities. These information may be relevant to health authorities with regard to potential integration into a national surveillance system for the early detection of new, exotic or re-emerging diseases.

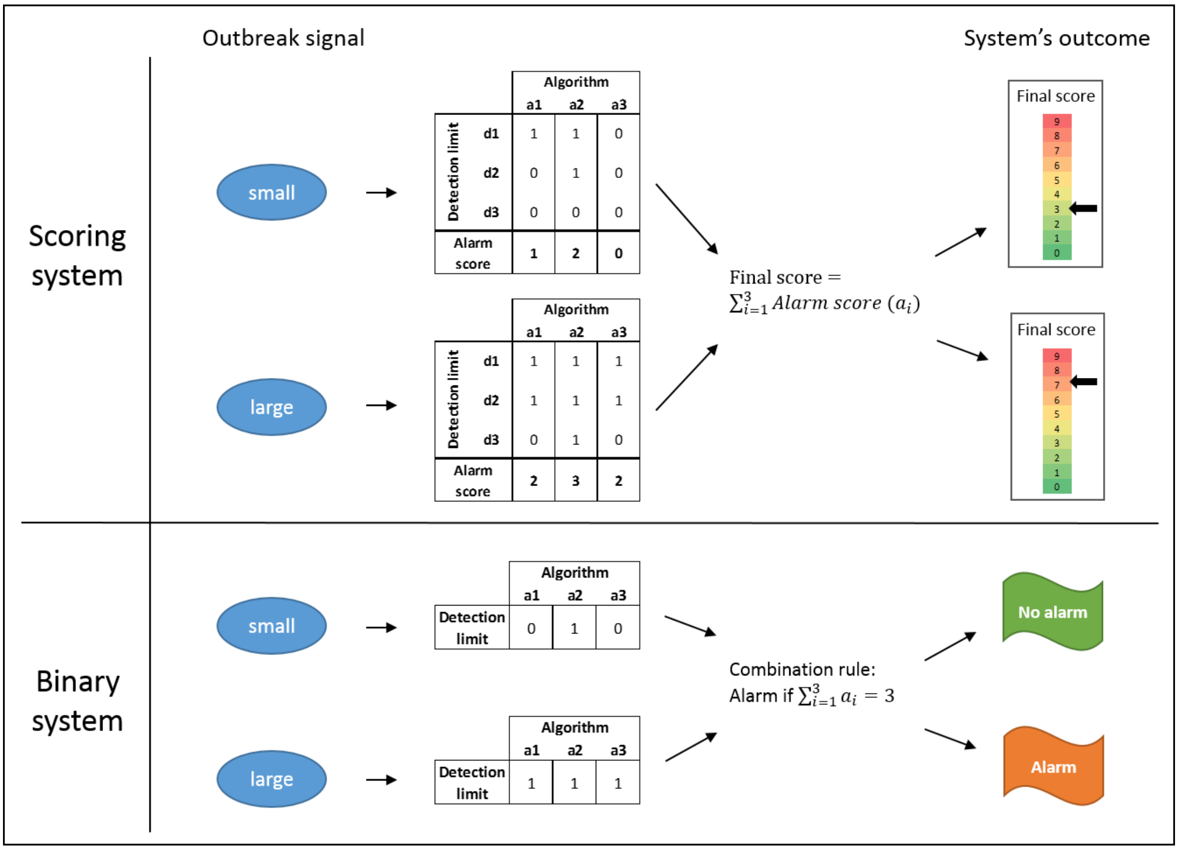


Figure 7 Schematic representation of a SyS system's outcome based on calculation of a final alarm score as proposed by Dórea et al. (2013)(upper panel) or on combination of binary outputs of algorithms following a defined rule (bottom panel). Generally, an algorithm ai generates an alarm (=1) if the observed value of the evaluated day exceeds a detection limit di. Otherwise, there is no alarm (=0). Here, the scoring system is illustrated using three algorithms and three detection limits. The binary system is illustrated using three algorithms with a specific detection limit and a combination rule that triggers an alarm only if generated by all three algorithms simultaneously.

3.3 Materials and Methods

Data

Perinatal mortality data reported by Swiss farmers to the TVD between 1st January 2009 and 31st December 2011 were used. Daily numbers of reported stillbirths and on-farm deaths occurring within 7 days of birth were aggregated into one time series consisting of 1,095 days (i.e. three years). In contrast to on-farm deaths, stillbirths reporting is not mandatory and no definition by national regulations existed until 2014.

To describe the behaviour of the perinatal time series under normal conditions (i.e. in the absence of an outbreak), a negative binomial regression model including a continuous time variable, categorical variables for month, day of the week, holidays and days after holidays as well as 4 autoregressive terms was used. The model was the result of a forward selection procedure, including different temporal covariates, similar as described in a previous study (Struchen et al. 2015) analysing on-farm deaths and stillbirths time series separately.

No major disease outbreaks in the Swiss cattle population were known for the years 2009 to 2011. To avoid contamination of the baseline time series by temporal aberrations (which might represent unnoticed outbreak signals, but also extreme events such as e.g. heat waves, or excessive random noise), it was cleaned using an iterative method of model fitting and aberration removal (Dupuy et al. 2015; Dórea et al. 2012): Temporal aberrations were identified in the observed data as those values exceeding the 95th percentile of the model that best fitted the perinatal time series. Such outlier values were then replaced by the value of this percentile. The procedure was repeated until outliers were no longer identified (more details can be found in the supplementary material.

Baseline and outbreak simulation

The resulting "outbreak-free" historical baseline was used to simulate a set of 1,000 baseline time series (Figure 8), each consisting of 1,095 days (three years). For each of these time series, the daily number of mortality events was randomly sampled from a negative binomial distribution with a mean defined by the predicted value for the corresponding day of the model that was previously re-fitted to the cleaned historical baseline.

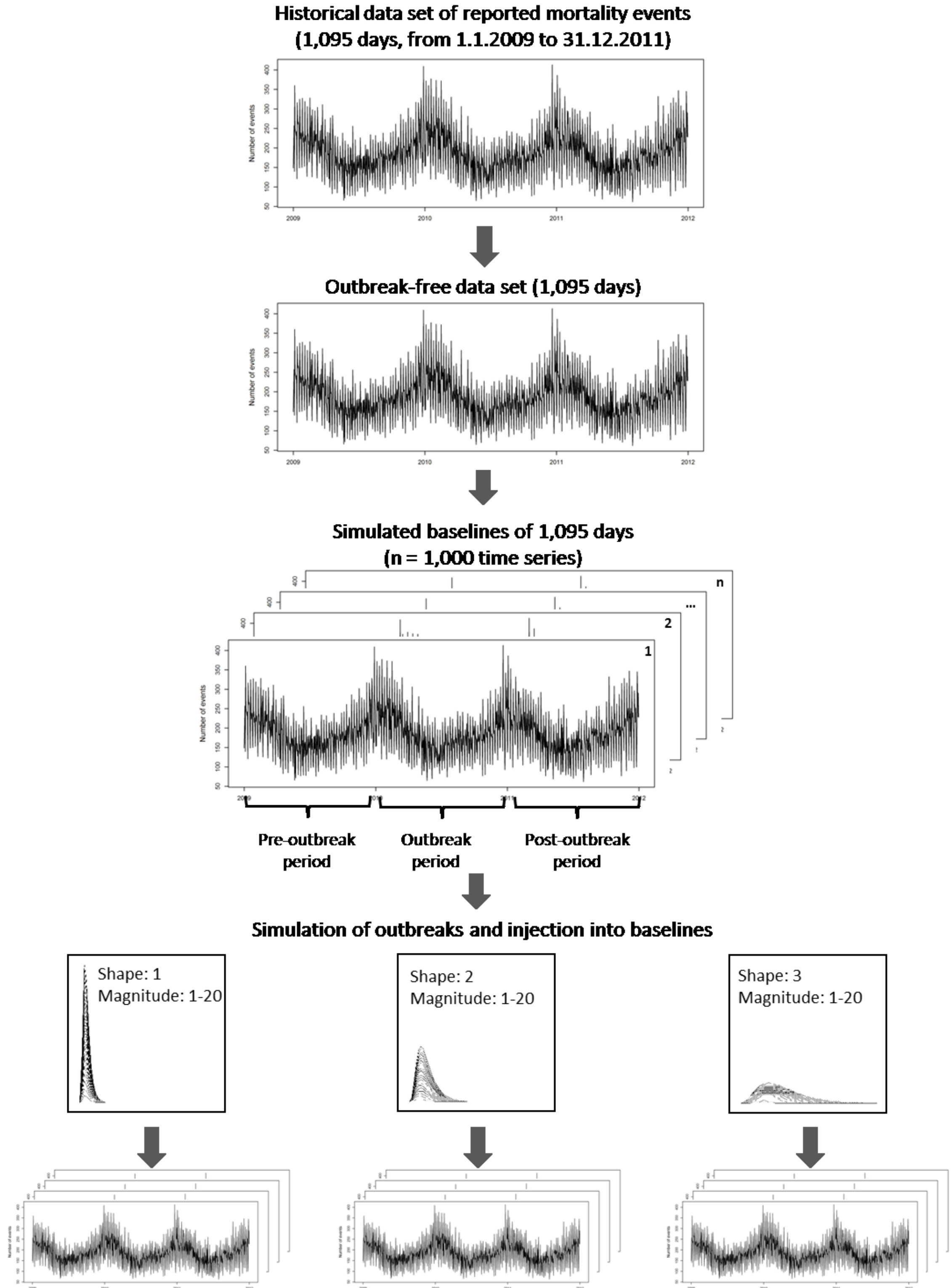


Figure 8 Overview of the different methodological steps: 1) Outliers removal from historical data set; 2) simulated baseline time series; and 3) injected outbreaks of different magnitudes and shapes.

Non-specific disease outbreaks of different magnitude, duration and shape were simulated as presented by Noufaily et al. (2013) and adopted by Vial et al. (2015) for meat inspection data (described in detail in Supplementary Material). Each baseline time series was divided into 1) a baseline period; 2) an outbreak period; and 3) a post-outbreak period (Figure 8). While the baseline period was used to train the algorithms, the post-outbreak period ensured that outbreaks starting at the end of the outbreak period could still be fully evaluated by the algorithms. Three different outbreak shapes (further referred to as shape 1-3) and 20 different outbreak sizes (further referred to as magnitude 1-20) were defined. Shape 1 theoretically illustrated spike-like outbreaks which tend to be short in duration but for which the number of cases increases rapidly (near exponential growth) at the beginning of the outbreak. Shape 3 represented flatter types of outbreaks for which the increase in the number of cases is slower and which tend to have a long tail. Shape 2 had intermediate characteristics. For each of the resulting 60 outbreak scenarios, a set of 1,000 outbreaks was simulated and inserted into a new copy of the 1,000 simulated baseline time series (i.e. one outbreak per outbreak period in one time series). Thus, a total number of 60,000 outbreak time series were evaluated per algorithm. Start, end, duration and size were recorded for each outbreak. Resulting characteristics of the 60 outbreak scenarios are summarised in Figure 9. The median total outbreak size over 1,000 simulated outbreaks ranged from 11 to 227 outbreak cases for magnitudes from 1 to 20. The median outbreak duration was 6-11 days for shape 1, 14-28 days for shape 2, and 35-75 days for shape 3, (Figure 9).

Outbreak detection algorithms

Three aberration detection algorithms were investigated for their ability to detect simulated outbreak signals: Shewhart (Shewhart 1931), cumulative sum (CuSum) (PAGE 1954) and exponentially weighted moving average (EWMA) control charts (Roberts 2012). These statistical process control methods are commonly used in public health (Woodall 2006) and have increasingly been evaluated for veterinary health data (Dórea, McEwen, McNab, Revie, et al. 2013; Dupuy et al. 2015; Shaffer 2007).

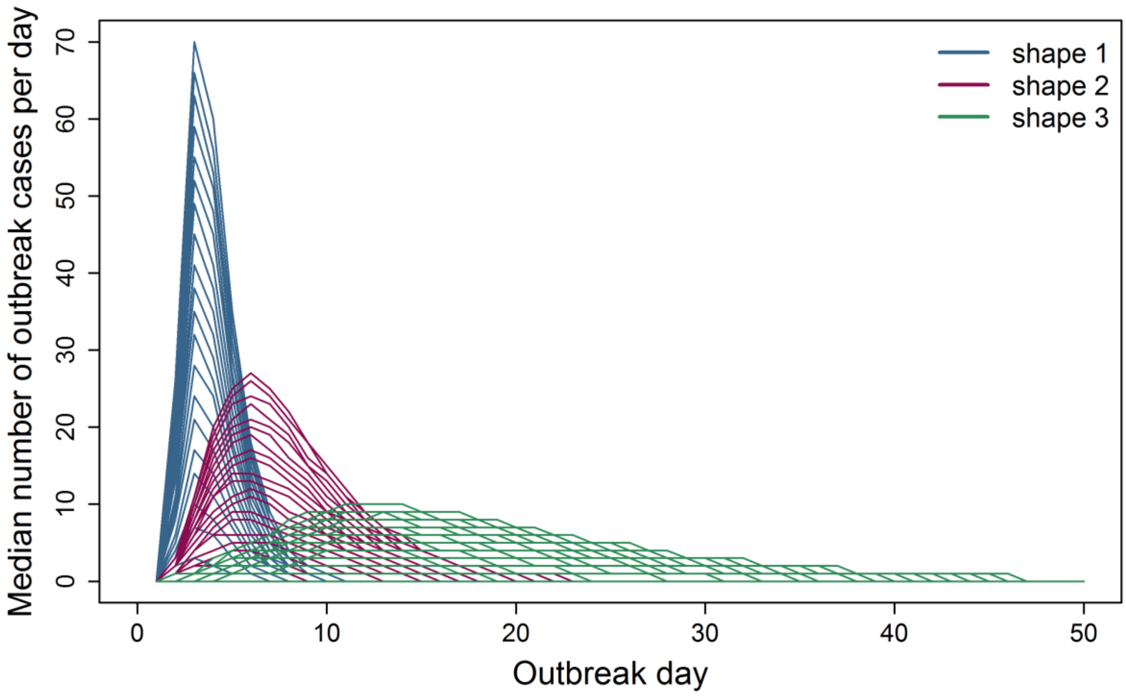


Figure 9 Median number of outbreak cases per day (summarised over 1,000 outbreaks) for each of the 60 different simulated outbreak scenarios (shape 1-3 and magnitude 1-20).

With the Shewhart control chart, an alarm is raised when the standardized difference between an observed value and a mean exceed an upper detection limit. Detection limits are based on a number of standard deviations above an expected value. While the Shewhart algorithm takes into account only one observation, CuSum and EWMA evaluate observed values within a pre-defined window. With CuSum, an alarm is raised when the cumulative sum of deviations of the observations from a mean exceeds an upper detection limit. The EWMA algorithm allocates weights to the observed values that are exponentially decreasing with time, i.e. recent observations are more relevant than past observations. A parameter λ defines the assignment of these weights, i.e. an increase of λ increases the relevance of past values. All three algorithms were applied using the R (R Core Team 2013) package vetsyn (Dórea et al. 2015).

Since control charts are based on the assumption that data are independent and identically distributed, pre-processing of the time series was required (Lotze et al. 2008). Therefore, the algorithms were applied to residuals time series after removal of explainable temporal effects such as day-of-week effect or seasonality using the previously selected regression model. Pre-processing was directly implemented within the vetsyn package.

Evaluation measures and performance assessment

The performance of the algorithms was evaluated based on the following measures:

- Sensitivity was defined at overall outbreak level as the proportion of detected outbreaks among the total number of simulated outbreaks. An outbreak was determined as detected if an alarm was generated on at least one outbreak day.
- False positive rate (FPR) was defined as the number of false alarms divided by the total number of outbreak-free days.
- Time to detection (TTD) was computed as the difference between the day of outbreak detection and the day of the first outbreak cases.
- The proportion of cases until detection (CUD) was defined as the proportion of outbreak cases occurring until (and including) the day of detection.
- Positive predictive value (PPV), i.e. the probability that an alarm truly represents an outbreak, was computed as the number of true alarms divided by the total number of alarms.

Algorithms were tested with varying values for two parameters: upper detection limit and λ. An upper detection limit of i) 2.0, 2.5 and 3.0, ii) 2.5, 3.0 and 3.5, and iii) 1.5, 2.0 and 2.5 standard deviations was used for Shewhart, CuSum and EWMA, respectively. Values of 0.1, 0.2 and 0.4 for λ were used for EWMA. The choice of these parameter values was based on a preliminary assessment of the algorithms' performance with regard to the number of false alarms generated in the absence of outbreak signals (FPR) when applied separately to each of the simulated baseline time series. In addition, a baseline window of one year (i.e. 365 days) and a guard band of seven days were used.

First, all three algorithms were separately applied to each of the 60,000 simulated outbreak time series for each set of parameters (3 sets for Shewhart and CuSum, 9 sets for EWMA). Evaluation measures were summarized over the 1,000 time series per outbreak scenario. The set of parameters that optimized algorithm performance in terms of sensitivity, TTD and CUD was determined. Second, the outputs of the three algorithms when using the optimum set of parameters were combined according to the following rules: an alarm was considered only if generated by two algorithms, irrespective which ones (rule 1), or by all three algorithms simultaneously (rule 2).

3.4 Results

With decreasing detection limit (and increasing λ for EWMA) sensitivity and FPR generally increased while CUD decreased (Table 4). TTD and PPV were either only marginally influenced by decreasing detection limit (and increasing λ for EWMA) or decreased for some outbreak scenarios. Accordingly, the set of parameters that optimised sensitivity, TTD and CUD included the lowest detection limit for each algorithm (2.0, 2.5 and 1.5 standard deviations for Shewhart, CuSum and EWMA, respectively) and the highest λ for EWMA (a value of 0.4).

Based on the optimum parameter setting, sensitivity increased with increasing outbreak magnitude for each algorithm (Figure 10). The strength of this effect differed between outbreak shapes, being most pronounced for shape 1. Outbreaks of shape 1 were more often detected than shapes 2 and 3, but only for larger magnitudes (magnitudes >8, >5, >7 for Shewhart, CuSum, and EWMA, respectively). PPV increased with increasing outbreak magnitude for each algorithm (Figure 10). The strength of this effect was more pronounced for outbreak shapes 1 and 2 and for CuSum. CUD decreased with increasing outbreak magnitude for each algorithm (Figure 10). Best values of CUD, i.e. a smaller proportion of outbreak cases occurred until outbreak detection, were obtained for outbreak shape 3. In addition, TTD decreased with increasing outbreak magnitude for each algorithm, with smallest values for outbreak shape 1 and largest for outbreak shape 3.

For each outbreak shape, EWMA showed the highest sensitivity and smallest CUD (Figure 10). Differences between algorithms regarding TTD were small, with EWMA obtaining the smallest values. The largest values of PPV were obtained with the CuSum algorithm (Figure 10). Shewhart had the best performance in terms of FPR (median=0.032, range=0.011-0.050), followed by CuSum (median=0.036, range=0.011-0.075) and EWMA (median=0.073, range=0.045-0.105), corresponding to 11.7, 13.1, and 26.6 false alarms per year, respectively.

Table 4 Evaluation measures (summarised over 1,000 simulated time series per outbreak scenario) for the three outbreak detection algorithms, by different detection limits and values of λ. Results are shown for four selected outbreak scenarios (shape 1, magnitudes 5, 10, 15 and 20.

		Sensitivity				TTD[a]				CUD[b]				PPV[c]			
Magnitude		5	10	15	20	5	10	15	20	5	10	15	20	5	10	15	20
Shewhart																	
sd[d] = 2.0		0,59	0,92	1,00	1,00	1	1	1	0	0,51	0,41	0,35	0,16	0,03	0,08	0,11	0,13
sd = 2.5		0,34	0,80	0,99	1,00	1	1	1	1	0,56	0,45	0,39	0,34	0,04	0,12	0,20	0,25
sd = 3.0		0,17	0,63	0,94	0,99	1	1	1	1	0,60	0,48	0,42	0,38	0,05	0,21	0,37	0,44
CuSum																	
sd = 2.5		0,57	0,93	1,00	1,00	2	1	1	1	0,61	0,45	0,39	0,33	0,06	0,17	0,24	0,28
sd = 3.0		0,43	0,89	1,00	1,00	2	1	1	1	0,67	0,50	0,42	0,37	0,08	0,24	0,35	0,39
sd = 3.5		0,32	0,81	0,99	1,00	2	1	1	1	0,72	0,54	0,43	0,40	0,09	0,32	0,47	0,51
EWMA																	
sd = 1.5	λ = 0.1	0,36	0,77	0,96	1,00	2	1	1	1	0,67	0,51	0,43	0,39	0,06	0,18	0,30	0,35
	λ = 0.2	0,64	0,95	1,00	1,00	2	1	1	1	0,60	0,44	0,38	0,32	0,05	0,11	0,15	0,18
	λ = 0.4	0,82	0,98	1,00	1,00	1	1	1	0	0,51	0,39	0,29	0,15	0,04	0,07	0,09	0,10
sd = 2.0	λ = 0.1	0,13	0,51	0,86	0,98	2	1	1	1	0,81	0,59	0,48	0,43	0,09	0,37	0,60	0,68
	λ = 0.2	0,39	0,83	0,99	1,00	2	1	1	1	0,68	0,50	0,43	0,38	0,07	0,21	0,32	0,37
	λ = 0.4	0,60	0,94	1,00	1,00	2	1	1	1	0,60	0,44	0,38	0,32	0,05	0,13	0,18	0,21
sd = 2.5	λ = 0.1	0,04	0,30	0,69	0,91	2	2	1	1	0,82	0,70	0,53	0,47	0,14	0,63	0,84	0,90
	λ = 0.2	0,19	0,66	0,95	1,00	2	1	1	1	0,75	0,56	0,46	0,42	0,10	0,38	0,58	0,65
	λ = 0.4	0,38	0,84	0,99	1,00	2	1	1	1	0,67	0,49	0,42	0,38	0,07	0,23	0,35	0,40

[a]Time to detection
[b]Proportion of cases until detection
[c]Positive predictive value
[d]Standard deviation

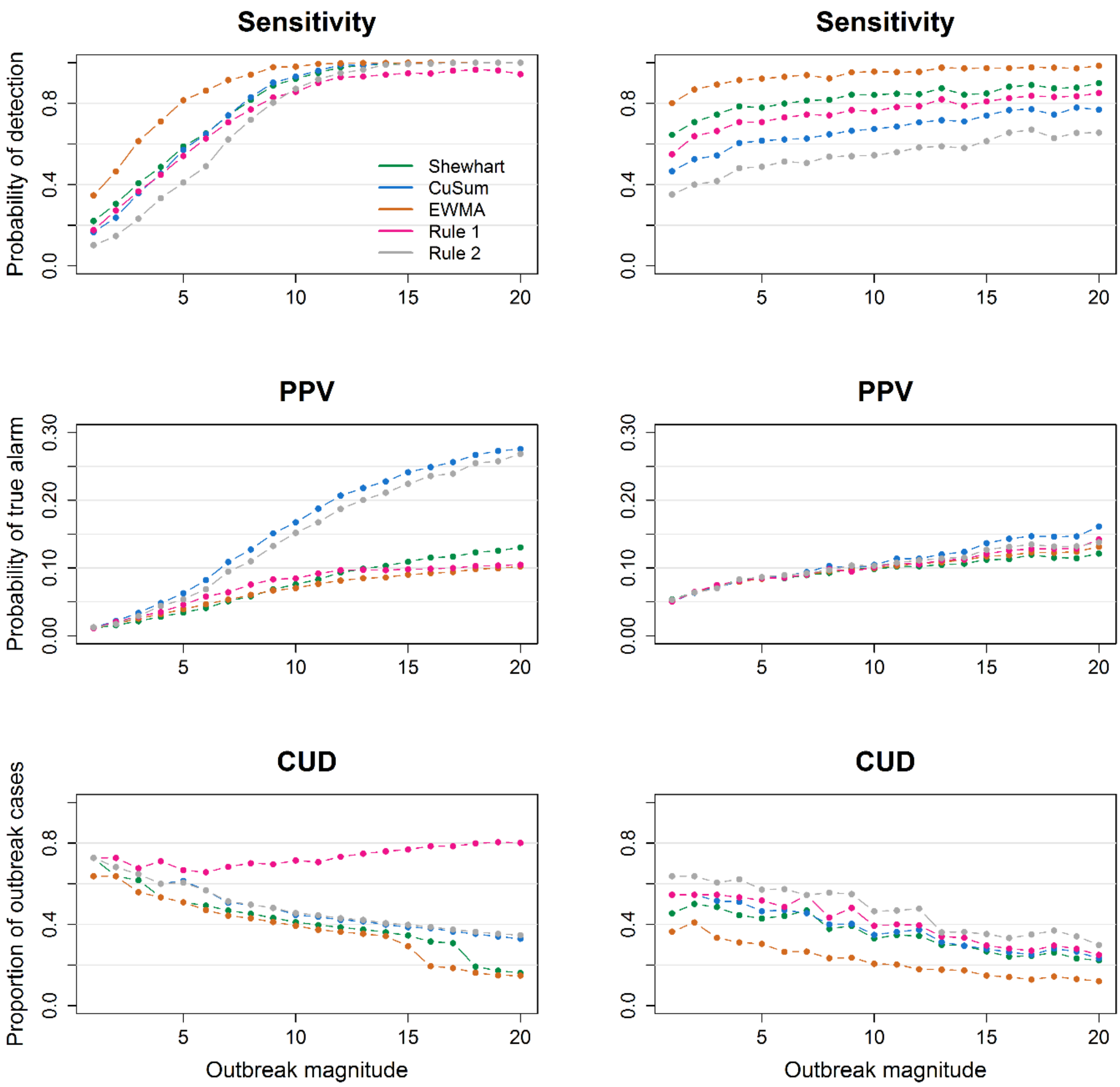


Figure 10 Sensitivity and median values of positive predictive value (PPV) and proportion of outbreak cases occurred until detection (CUD) summarised over 1,000 time series per outbreak scenario. Results are shown for outbreak scenarios based on shape 1 (left column) and shape 3 (right column).

When applying the combination rules, the median FPR for rule 1 was at a comparable level as for Shewhart with a value of 0.031 (range=0.013-0.056), while for rule 2 it decreased to 0.014 (range=0.004-0.026), resulting in 11.3 and 5.1 false alarms per year. For outbreak shape 1, a higher sensitivity was obtained for rule 2 in case of larger outbreaks (magnitude>9, Figure 10). For all other outbreak scenarios, including shape 2 and 3, outbreaks were more often detected with rule 1. Sensitivity with combination rules was for all outbreak scenarios smaller than with EWMA and Shewhart. Values of PPV did not differ much between the two combination rules, except for larger outbreaks of shape 1 (magnitude>10) where rule 2 resulted in higher values, and were always smaller than those of CuSum. CUD for rule 2 was smaller for outbreak shape 1, while it did not differ much between combination rules (outbreak shape 2) or was smaller for rule 1 (outbreak shape 3). In case of outbreak shape 1, CUD for rule 1 increased with increasing outbreak size (Figure 10). CUD obtained with EWMA and Shewhart was always smaller than with combination rules.

3.5 Discussion

In this study, we investigated the performance of three temporal algorithms in detecting simulated outbreak signals in routinely collected perinatal cattle mortality data.

Before simulation of baseline time series and outbreaks, temporal outliers were removed from the historical data set in order to ensure absence of possible undetected outbreak signals. As an effect of this data pre-processing, extreme variation inherent of the data may artificially be reduced, resulting in more false alarms generated by the algorithms. However, the number of false alarms on days where outlier removal occurred was not considerably different from other days, based on visual inspection (results not shown).

The impact of varying parameters for algorithms on outbreak detection performance is congruent with that found in other studies (Dórea, McEwen, McNab, Revie, et al. 2013; Dupuy et al. 2015). With a lower detection limit, alarms are signalled at lower daily counts improving the detection of smaller outbreaks but simultaneously increasing the number of false alarms. Higher value of λ reduce the influence of individual (extreme) counts as more historical data are included in the forecasting.

Sensitivity was generally higher for spike-like (shape 1) than for flatter outbreaks (shape 3), in contrast to findings from other studies (Dórea, McEwen, McNab, Revie, et al. 2013; Dupuy et al. 2015). It is possible that this can be attributed to the characteristics of the data monitored due to the small number of outbreak cases per day resulting from the longer outbreak duration, even if the total outbreak magnitude for shape 3 was as large as for shape 1. Therefore, many of these outbreaks may have been detected by chance. The median TTD for shape 3 outbreaks ranged between 6 and 14 days. The frequency of false alarms and our finding of a relatively high sensitivity (at least 60%) even for the smallest outbreak magnitude further support this proposition. For outbreak shape 3, simulation of larger outbreaks should thus be considered.

Our results showed that none of the three algorithms experienced a superior performance in detecting outbreak signals with regard to several evaluation measures. The EWMA could detect outbreaks of various shapes and magnitudes with a relatively high sensitivity. However, using this algorithm resulted, on average, in a false alarm every 2 weeks. Shewhart would be the choice with regard to obtaining a minimum number of false alarms. But also CuSum should be considered due to its higher probability in representing a true alarm (PPV), at least for some outbreak scenarios.

Combining algorithm outputs did not satisfactorily increase the system's performance due to the trade-off between sensitivity and FPR. While the more restrictive rule led to a considerable reduction in the number of false alarms per year, this was at the cost of sensitivity. As proposed by Dórea et al. (2013), the use of a scoring approach, as opposed to a binary alarm, to motivate epidemiological response to abnormal health events may further improve system's specificity and assist the work of decision-makers. Magnitude scores (Figure 7) may assist data analysts in deciding whether a true health issue has emerged in light of the external factors that are known to influence animal data submissions (for example changing market prices), and in customising the response protocol to the apparent strength of the statistical signal (e.g. from requesting additional testing of animals to initiating a full outbreak investigation). Such approach may be considered in future work, alongside the testing of whether different sets of rules (e.g. rule 3: an alarm is considered only if one algorithm signals on 2 consecutive days, rule 4: only if all 3 algorithms signals within 5 days of each other …) reduce the number of false alarms.

As a next step, other aberration detection algorithms may be evaluated. For example, Dupuy et al. (2015) found that a negative binomial regression algorithm obtained good performance in detecting simulated outbreak signals in weekly proportions of whole carcass condemnations. Another strategy to increase sensitivity could be to stratify the data according to production type or sex. Definitions of categories may however not always be explicit. In case of the TVD, e.g. production type may be categorised according to breed or based on the production type of the farm on which an animal stayed (Schärrer et al. 2014). In addition, knowledge about the reasons for cattle deaths on farm, including perinatal mortality, might be valuable. Currently, such data are not recorded in the TVD.

Collecting this information in an additional data field using a pre-defined check list would not increase the reporting workload for farmers.

A SyS system based on Swiss bovine perinatal mortality data would aim to assist the veterinary authorities in the early detection of emerging and re-emerging diseases. As such, its performance in terms of sensitivity and timeliness of outbreak detection should be prioritised. However, the false alarm rate was at a level that would be difficult to manage in practice. As perinatal mortality can be caused by many different reasons (Mee et al. 2008),including welfare or management issues, further investigations will be necessary, not only to confirm the statistical signal, but also to find its underlying cause (Vial & Berezowski 2014). The number of reported events per day for perinatal mortality ranged between 49 and 202. Consequently, a relatively high number of animals and farms can be involved in triggering an alarm and translating the statistical signal into an epidemiological alarm could be challenging for veterinary authorities. Further investigations, e.g. finding geographic or demographic similarities between these animals, consulting veterinarians or farmers, or taking samples for diagnostic analyses, may be resource intensive. Information from additional data sources could be accessed and examined for further indications whether an alarm could be due to a disease outbreak or not, including e.g. diagnostic laboratory analyses of bovine abortion material, stored in a national database of the Federal Food Safety and Veterinary Office, for which no diagnosis had been reached. Temperature data from meteorological institutes could indicate mortality clusters caused by heat waves (Morignat et al. 2014). Such processes could be implemented in an automated manner, generating reports to be analysed and interpreted by designated analysts / epidemiologists at veterinary authorities.

Using the date of event occurrence rather than the date of event reporting may benefit the prospective SyS system. Although the median reporting timeliness of on-farm deaths and stillbirths was estimated at 1 and 3 days (Struchen et al. 2015), respectively, there is still a certain amount of cases that are reported only after several days or even weeks. This reporting delay is expected to considerably reduce the sensitivity and timeliness of the system as daily counts may stay below the detection levels even in the middle of an outbreak. Evaluating methods that allow accounting for delayed reporting of perinatal mortality will therefore be an important next step. Finally, methods that move away from a binary alarm system may constitute an interesting alternative to the approach developed above. In contrast to traditional (frequentist) outbreak detection algorithms, Bayesian approaches, such as the value of evidence approach (Andersson et al. 2014), does not have a built-in decision threshold but may instead use the probability densities for the observed signal given an outbreak (or no outbreak) and let the threshold be defined by an obtained posterior probability or expected utility of action (e.g. cost of missing an outbreak vs. cost of investigating a false alarm). We illustrate such an alternative in chapter 4.

3.6 Conclusions

This study demonstrated the value of bovine perinatal mortality data routinely collected in the TVD for integration into a SyS system. Despite the adequate performance of the algorithms under specific outbreak conditions, our mitigated results illustrate the difficulty in finding a balance between a high sensitivity and a manageable number of false alarms. Further work may seek to improve the system's sensitivity by stratification of the surveillance data (e.g. by production type) and its specificity by including additional data sources linked to perinatal mortality (e.g. artificial insemination data).

While it is essential to carefully optimize aberration detection algorithms for a particular data stream (as presented in this paper) before their integration into an early detection surveillance system, our work raises the question of whether binary alarms constitute the best way to present circumstantial evidence of a disease outbreak from SyS.

Acknowledgements

We wish to thank Fernanda Dórea for advice and support with the R vetsyn package; Stefan Widgrén for help with R coding; and the Federal Food Safety and Veterinary Office for funding this work (project 1.12.12). Calculations were performed on UBELIX (http://www.id.unibe.ch/hpc), the HPC cluster at the University of Bern.

3.7 Supplementary Material

Removed temporal aberrations from baseline data

During the process to generate a historical outbreak-free baseline time series by removing temporal aberrations, observations were replaced by the value of the 95th percentile at 62 time points (out of 1,095), removing 398 (0.34%) reported neonatal mortality events. Four iterations were necessary until no temporal outliers were identified.

Simulation of non-specific disease outbreak signals

The start of the outbreak at day t was randomly sampled among the outbreak period which was set to 365 days. This ensured outbreaks starting on different weekdays and occurring in different months during the year (i.e. different background noise). While the baseline period was used to train the algorithms, the post-outbreak period ensured that outbreaks starting at the end of the outbreak period could still be fully evaluated by the algorithms. The outbreak size was randomly generated from a Poisson distribution with mean equal to a constant k times the standard deviation of the predicted baseline count at day t. The resulting total number of outbreak cases was then randomly distributed in time according to a lognormal distribution with mean μ and standard deviation σ and the daily outbreak cases were added to the baseline counts starting at day t. With increasing μ, the same number of outbreak cases for a given k was distributed over a wider time window.

Subsequent to a visual inspection of the resulting shape and duration of outbreaks when using different values for constant k (which mainly influences the total outbreak size) as well as the parameters μ and σ (which influence the temporal progression of the outbreak), values in the range $\mu = \{1,2,3\}$, $\sigma = 0.5$ and $k = \{1,2,\ldots,20\}$ were selected. For each of the resulting 60 outbreak scenarios (three values for μ times 20 values for k), a set of 1,000 outbreaks were simulated and inserted into a new copy of the 1,000 simulated baseline time series (i.e. one outbreak in one time series). Thus, a total number of 60,000 outbreak time series were evaluated per algorithm. Start, end, duration and size were recorded for each outbreak.

CHAPTER 4

Value of evidence from syndromic surveillance with cumulative evidence from multiple data streams with delayed reporting

Rahel Struchen [a], Flavie Vial [a], Mats Gunnar Andersson [b]

[a] Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Schwarzenburgstrasse 155, 3003 Bern, Switzerland

[b] Department of Chemistry, Environment and Feed Hygiene, National Veterinary Institute (SVA), SE- 751 89 Uppsala, Sweden

Working Paper

4.1 Introduction

Timeliness is a key measure of any public health surveillance system, on which system users and decision makers depend to take appropriate action based on the urgency and the type of responses required by the situation. As such, it should be assessed regularly (Jajosky & Groseclose 2004).

Most classical surveillance algorithms (including Salmon et al., 2015; Farrington et al., 1996; Noufaily et al., 2013) look for peaks with unusually high number of reported syndromic cases within a particular time period, for example a week, and generate an alarm if the counts exceed the threshold. Albeit simple, the approach has limitations that may hamper sensitivity and timeliness. Delays in the reporting of syndromic cases may result in counts remaining below a defined threshold until a majority of cases are reported, resulting in a delay or even failure of outbreak detection.

Delays in surveillance data may originate from an intrinsic biological process (e.g. incubation period) or from external processes (e.g. transport delay of the sample to the laboratory (Jones et al. 2014)). While delays originating from the former cannot be reduced, analyses may be hindered by delays in case reporting decreasing the overall timeliness and usefulness of the early-warning surveillance systems (Jefferson et al. 2008). Reporting delays depend, among other things, on statutory reporting regulations; on whether an electronic reporting system is in place; on the disease(s) under surveillance (whose identification process may be more or less complex); and on reporting units (e.g. different laboratories) (Freeman et al. 2013). Time lags between disease onset and notification can be estimated in terms of weeks (mostly as a result of lag between onset and diagnosis) even for notifiable disease reports (e.g. in Korea (Yoo et al. 2009), in the UK (Noufaily et al. 2015)). Reporting delays may be monitored to detect trends, for example following an intervention aimed at improving reporting timeliness (Silin et al. 2010) or following a change in case definition (Tabnak et al. 2000). They may also be modelled in order to better understand the factors leading to increasing time between disease onset and notification to the health systems (Midthune et al. 2005; Jones et al. 2014).

The statistical interest in modelling delays in surveillance data is not new, but has so far mainly focused on the development of methods to obtain valid estimates of recent disease incidence (Lawless 1994). Indeed, large reporting delays (e.g. as may be seen in cancer registries) may produce downwardly biased incidence trends, especially in the most recent years, when case ascertainment or reporting is subject to delays (Clegg 2002). In the context of outbreak detection, delays occurring in a short time-window (on a scale of days or a few weeks) are more relevant than data with longer delays as they cannot be acted on promptly (Noufaily et al. 2015). Accounting for reporting delays in outbreak detection algorithms (e.g. in syndromic surveillance SyS) is not trivial. This is, partly, the reason why most surveillance systems use the date of the reception of data, rather than the (often unknown) date of the health event itself. The main drawback of this common approach is the resulting reduction in sensitivity and specificity of the system (Farrington & Andrews 2004). In the relatively few systems for which all dates are known, a correction factor can be imputed based on mathematical models adjusting for the under-reporting bias owing to the time lag of the reporting process (Lui & Rudy 1989).

Another difficulty may arise when faced with slowly increasing outbreaks. The number of cases in each time unit (e.g. each week or each day) may be too small to trigger an alarm. If the baseline is recalculated iteratively as in Noufaily et al. (2013), this may also result in outbreak-related cases being incorporated into the baseline. Guard bands leaving a short time lag between the current value under evaluation and the baseline have been used in order to reduce this risk of baseline contamination (Burkom et al. 2004; Dórea, McEwen, McNab, Revie, et al. 2013; Buckeridge et al. 2008).

Finally, many diseases cause more than one syndrome and combining data streams (Sonesson & Frisén 2005) may result in increased sensitivity (Dubrawski 2011). It is also desirable to combine the result from surveillance with other information. However, there is no straightforward approach when the algorithm is based on an alarm threshold (Vial et al. 2016). Combining syndromic data from multiple data streams with other knowledge may be done within a Bayesian framework where the result is presented in the form of a posterior probability for a disease, or, when the hypotheses in the model are not exhaustive, as the odds for outbreak versus baseline. In Andersson et al. (2014) we proposed a framework where the result from SyS is expressed as the value of evidence in favour of an outbreak, i.e. the likelihood ratio for the evidence under outbreak versus baseline conditions. This approach was evaluated using three syndromic indicators (nervous syndromes in horses, mortality in both horses and wild birds) for early detection of West Nile virus in France, achieving better performance in a multivariate than univariate system (Faverjon et al. 2016). The most important difference between the value of evidence approach and classical SyS is that the former explicitly incorporates the assumptions about the disease of interest and also refers to these assumptions when the results are presented. By including in the model assumptions distribution of syndromes under outbreaks and baseline conditions, it is possible to apply change point analysis to estimate the probability that the system is in outbreak or baseline conditions, and the most likely point of transition.

In this study, we show how the empirical Bayes (Lawson 2005) likelihood ratio framework can be applied to perform change point analysis for multiple data streams and estimate the evidence accounting for delayed reporting of syndromes, using routinely collected cattle mortality data as an example.

4.2 Methods

The reporting system & reporting delay

Since 2000, it is compulsory for Swiss cattle farmers to report all births and deaths of animals on their holding to the Tierverkehrsdatenbank or TVD. Deaths on farm need to be reported within 3 days but the reporting of stillbirths is not compulsory (Animal Health Ordinance (AHO), SR 916.401). It is likely that some farmers report stillbirths as the birth of a calf that was alive and died after a few days (Struchen et al. 2015). For this reason, we termed perinatal mortality the sum of reported stillbirths and on-farm deaths within the first seven days after birth. We extracted all deaths on farm and perinatal deaths reported to the TVD between 01/01/2009 and 31/12/2011.

The time interval between the date the event occurred and the date it was reported to the TVD is termed reporting delay. It includes the time needed for the farmer to observe the event but may also include data entry errors. Reporting delay in the TVD has been previously assessed (Struchen et al. 2015) with a median of one day for deaths (range: 0-968) and two days for perinatal deaths (range: 0-907). Over 80% of deaths on farm and over 70% of perinatal deaths were reported within seven days of occurrence (Figure 11). The focus of this study was on reports with relatively short reporting delays (≤ 14 days); since the minority of reports with longer delays (9% and 12% of on-farm death and perinatal death reports respectively) are less relevant for timely, "early" outbreak detection. Based on the cumulative probability distribution of the estimated reporting delays (Figure 11), we used a binomial distribution to calculate for each day the number of cases occurring on day *t* that were reported on the same day (delay s=0), 1 day later (s=1), 2 days later (s=2), etc. until all cases of day *t* were reported 14 days later (s=14):

$$R_{ts} \sim Bin(n_{ts}, p_{ts})$$

where n_{ts} is the number of deaths occurring on day *t* if s=0 or the number of deaths occurring on day *t* minus R_{ts-1} if s>0, and p_{ts} is defined from the cumulative probability distribution of the reporting delays as the proportion of deaths c_{ts} occurring on day *t* that were reported on day s if s=0 or as $(c_{ts}-c_{ts-1})/(1-c_{ts-1})$ if s>0.

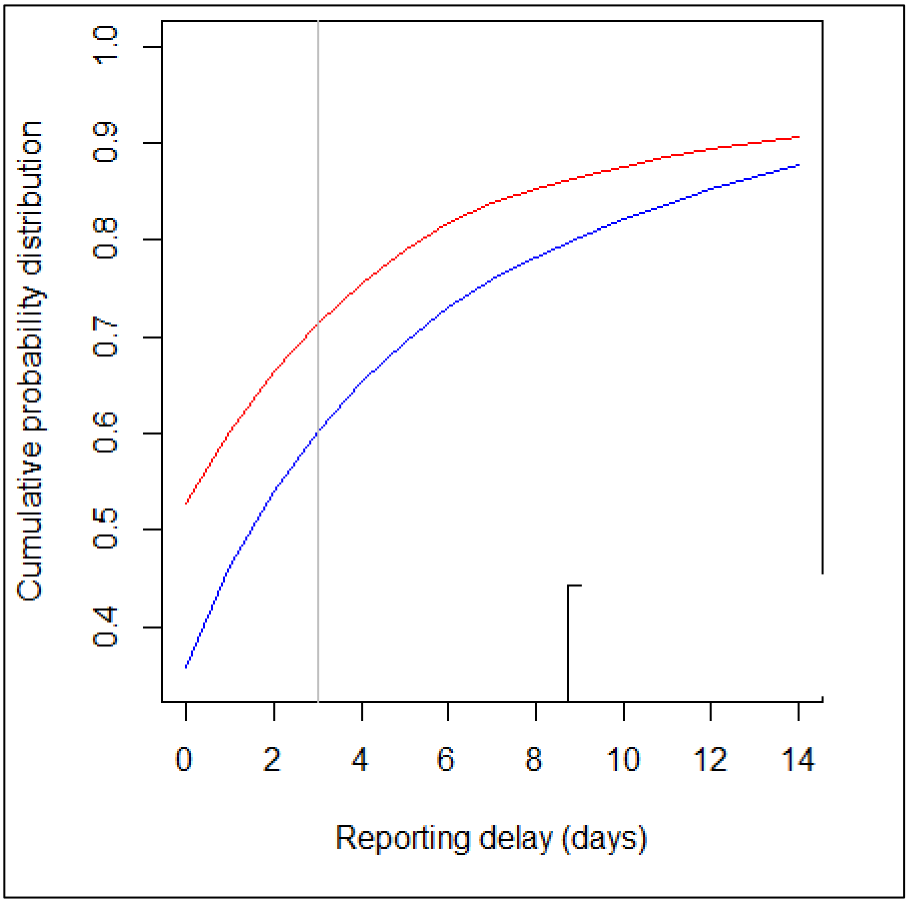


Figure 11 Cumulative probability distribution of the reporting delays for on-farm deaths (red) and perinatal deaths (blue) in the TVD. The Swiss legislation states that deaths on farm need to be reported within 3 days (grey line). We focused on reports with relatively short reporting delays (≤ 14 days) which are the most relevant for timely outbreak detection.

The value of evidence from syndromic surveillance

We have previously proposed a tool for evaluating and presenting circumstantial ‘‘evidence’’ of a disease outbreak from SyS in which prior information and evidence (E) from the data are explicitly separated (Andersson et al. 2014). Applying Bayes’ theorem, the a-posteriori odds (O_{post}) define our posterior belief about the disease state of the system given our prior belief and the syndromic evidence:

$$O_{post} = \frac{P(H_1|E)}{P(H_0|E)} = \frac{P(E|H_1)}{P(E|H_0)} * \frac{P(H_1)}{P(H_0)} \qquad \text{Eq. 1}$$

Where H_1 is our hypothesis of interest (system is experiencing an outbreak of a specific disease of a group of diseases producing similar syndromes); H_0 is the “null hypothesis” (the system is operating under baseline, non-outbreak, conditions); and E is the evidence represented by a set of vectors with reported cases of (a) syndrome(s) (cattle deaths on-farm and perinatal deaths in our case).

In reality, the probability of observing a given number of syndrome(s) is not constant throughout an outbreak and the appearance of different syndromes may not be simultaneous. If, for example, syndrome A usually appears before syndrome B, the absence of syndrome A will speak against an outbreak when a peak in syndrome B is observed. However when a peak of syndrome A is observed, the absence of B does not speak against an outbreak at an early stage.

Our previous model evaluated evidence from only one day or week at a time (Andersson et al. 2014). In this study, we extend the framework to accumulate evidence over *n* points in time (30 days in this case).

In order to estimate the evidence in favour of an outbreak, we consider H_1 being composed of *n* sub-hypotheses H_{11}... H_{1n}, representing an outbreak being in its first 1 to *n* days. The system may be represented as an *n*+1 state Hidden Markov Model (Figure 12), where state S_0 corresponds to hypothesis H_0, no outbreak, and states S_1 to S_n correspond to the sub-hypotheses H_{11}… H_{1n}. The probability of an outbreak starting, that is a transition from state S_0 to S_1, is non-constant (i.e. seasonal). We set it so that outbreaks were more likely to occur in late winter/early spring. Therefore, the prior probabilities $P(S_i)$ of the system being in each state S_i (i=0:n) also vary.

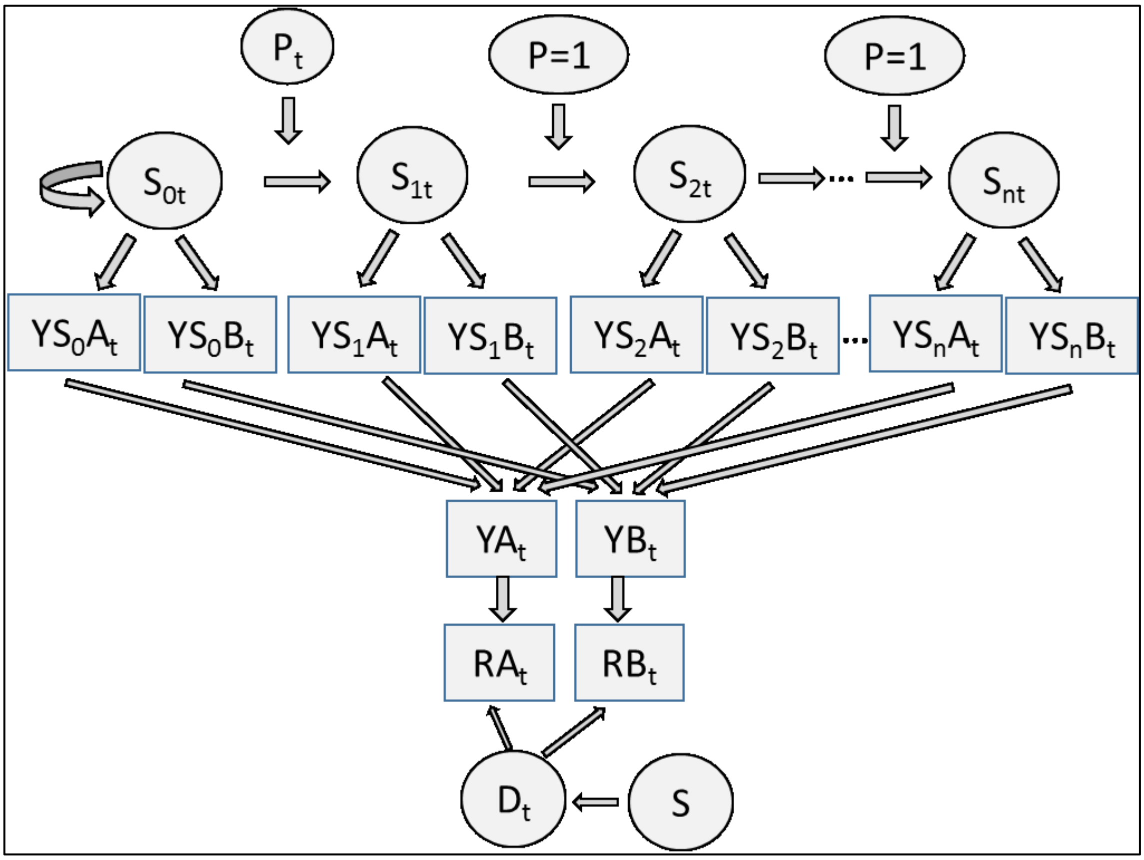


Figure 12 Representation of the system as an n+1 Hidden Markov Model. P_t is the probability of transition from state S_0 to S_1 at time t. S_{it} is the probability of the model being in state i at time t. YS_iA_t/B_t is the number of observed cases of syndrome A and B emitted by state i at time t. D_t is the probability that a syndrome observed at time t was reported at the time of observation (s). Finally RA_t/B_t is the number of observed syndromes that was reported from time t as seen on day s.

The probability distributions for the number of reported syndrome cases in a non-outbreak situation and for an outbreak in state *n*, in combination with the prior probability for each state, were used to derive $P(E|H_1)$ and $P(E|H_0)$. H_0 is the hypothesis that no outbreak is ongoing (S=0) and H_1 is the hypothesis that an outbreak is ongoing (S=1:*n*).

The posterior probability of each hypothesis and the cumulative probability of an ongoing outbreak were obtained by numerically calculating the marginal probability of evidence P(E), given the vector of prior probability of introduction. Marginal probability of evidence P(E) at a given time is defined as:

$$P(E) = \sum_{i=0}^{30} P(S_i)P(E|S_i) \qquad \text{Eq. 2}$$

where $P(S_i)$ is the prior probability of state S_i at time t. Posterior probability of state S_i (post(S_i)) can subsequently be calculated using the formula

$$post(S_i) = P\ \frac{P(S)P(E|S_i\,)}{P(E)} \qquad \text{Eq. 3}$$

The value of evidence (V) in favour of an ongoing outbreak at each time t is defined as the Bayes' factor, i.e. the ratio between the posterior and prior odds for H_1 versus H_0:

$$V = B = \frac{\sum_{i=1}^{30} P(S_i|E)/P(S_{i=0}|E)}{\sum_{i=1}^{30} P(S_i)/P(S_{i=0})} \qquad \text{Eq. 4}$$

Modelling the data

In our previous work (Andersson et al. 2014), the distribution of baseline and outbreak-related syndrome cases was modelled using a negative binomial (NB) distribution obtained from the regression (a similar method is also used by Salmon et al. (2015)). The total outbreak distribution, i.e. the probability of observing n cases from the sum of baseline distribution and outbreak-related distribution, was calculated by numerical integration. However, the time to compute the distribution is proportional to the square of the maximum number of counts that result in very long computational time as the maximum number of counts increases. In this work, the number of counts at outbreak and baseline conditions is a magnitude higher calling for a faster, approximate solution.

To speed up calculations, the NB distributions were approximated with a (truncated) normal distribution with a standard deviation proportional to the mean. However, this approximation results in erroneous probabilities at very low counts, since it implicitly assumes the possibility of negative number of outbreak related syndromic cases. This will lead to artificially high values of evidence in favour of an outbreak on days when an extremely small number of counts are reported. This primarily happens when a reporting delay is present but not accounted for. To handle this, we introduced a heuristic 2-stepts filtering algorithm:

- For each day, the algorithm finds the number of reported cases ($nmin_{ts}$) that returns the minimum value of V (i.e. provides the strongest support against an ongoing outbreak);
- If number of observed and reported cases ($nobs_{ts}$) is smaller than $nmin_{ts}$, it substitutes obs_{ts} with $nmin_{ts}$.

This approximation effectively means that cumulative probability for the left tail of the distribution of outbreak related cases corresponding to negative counts is added to the probability of zero outbreak-related cases. The substitutions taking place were logged to estimate how frequent substitutions were and to confirm that it does not significantly impact the performance.

We compared the evolution of V for H_0 and H_1 in both syndromic time-series before, during and after a simulated outbreak under three reporting scenarios:

- "Delay non-aware" scenario: the number of deaths occurring on day *t* is equal to the number of deaths reported on day *t* (i.e. regardless of when they truly occurred)
- "Delay aware" scenario: the number of deaths occurring on day *t* is estimated based on the number of deaths reported on day *t* and the probability distribution of the reporting delay.
- "No delay" scenario: all deaths are reported on the same day they occur and the number of deaths occurring on day *t* is equal to the number of deaths reported on day *t*.

Evaluation of the framework

The performance of the system with regard to outbreak detection was compared among the three reporting scenarios in two ways. First, the value of evidence, Log(V) of both syndromes for a particular day was compared to all potential thresholds between 0 (evidence neither in favour of or against outbreak) and 15 (evidence extremely strong in favour of outbreak), with ΔLog(V) = 0.125. An alarm was recorded if Log(V) exceeded these thresholds. Second, the probability of observed counts given the baseline condition $P(E|H_0)$ was used. To incorporate changes due to cases reported with delay, the values of the last *d* days were considered, where *d* corresponds to the maximum reporting delay. For each day of observation, an alarm was recorded if the smallest of these values fell below a set of thresholds defined between 0 and -15 in steps of 0.125.

For each of the three reporting scenarios, timeliness and false alarm rate were calculated based on both types of alarms. Timeliness, measured as time to detection, was estimated for the outbreak period (i.e. days 300 to 330 in this case) and defined as the first day of outbreak detection (i.e. when an alarm was raised). False alarm rate was estimated for the non-outbreak period (i.e. days 31 to 299 in this case) and calculated as the number of days with an alarm divided by the total number of days.

4.3 Results

The evolution of V based on the information available on the 2nd, 8th and 15th day after the onset of an outbreak for each of the three reporting scenarios was visualised in Figure 13. As a result of delayed reporting, daily counts of observed perinatal and on-farm deaths (syndromes A and B, respectively) are lower for the most recent days in the two scenarios with reporting delay (middle and bottom row) compared to the scenario without reporting delay (top row). While V estimated for day 302 (left column) speaks against an outbreak for all scenarios, estimates for days 308 (middle column) show evidence in favour of an outbreak for both syndromes combined as well as for the on-farm deaths (syndrome B) alone for the scenarios "Delay aware" and "No delay". The development of V for the perinatal deaths (syndrome A) alone highlights the importance of considering multiple syndromic data streams for outbreak detection, as it speaks in favour of an outbreak at a later stage (right column, day 315) than on-farm deaths alone or both syndromes combined. The change in corresponding posterior probabilities of each state S_i for different days of observation is illustrated in Figures 14-16 for all scenarios.

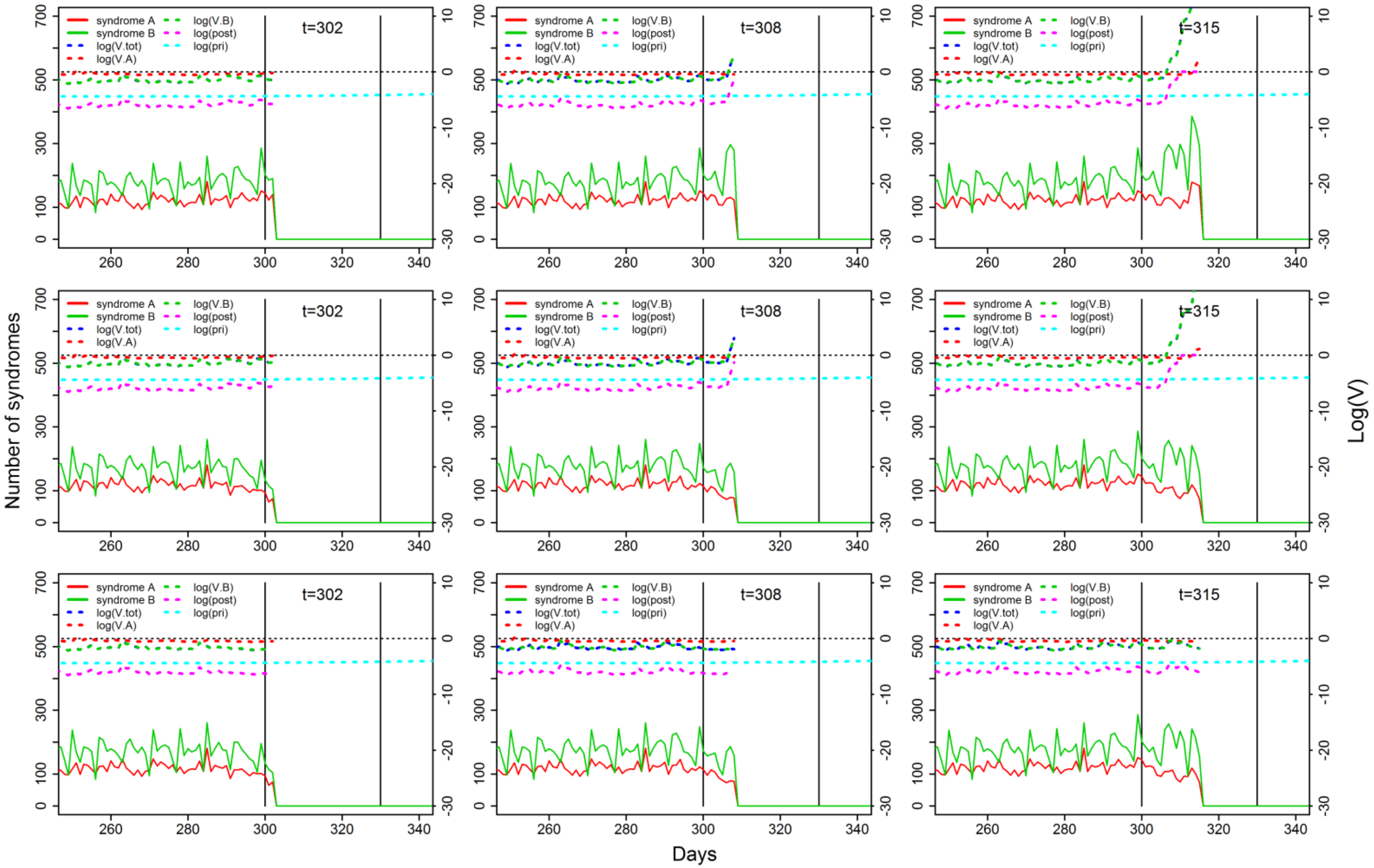


Figure 13 Comparison of results at two days of observation (t) for the three reporting scenarios no delay (top row), delay aware (middle row), and delay non-aware (bottom row): number of observed perinatal (syndrome A) and on-farm deaths (syndrome B), value of evidence for both syndromes (V.tot) and separately (V.A, V.B), prior probability that an outbreak is ongoing (log(pri)) and posterior probability that an outbreak is ongoing given the evidence (log(post)). Vertical black lines show the outbreak interval from days 300 to 330 while the horizontal dotted line represents a value of evidence equal to 1, i.e. log10(V)=0.

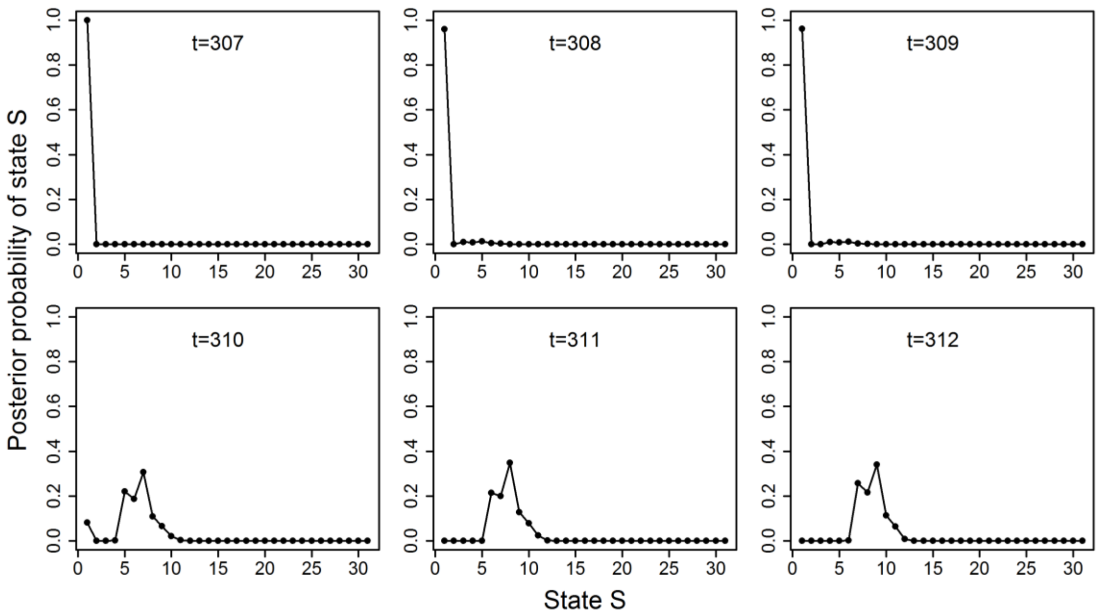


Figure 14 Posterior probability of being in state S (0-30) at a given day of observation (t) for the scenario without reporting delay. Six days of observation were chosen to illustrate the transition of the system from baseline to outbreak condition.

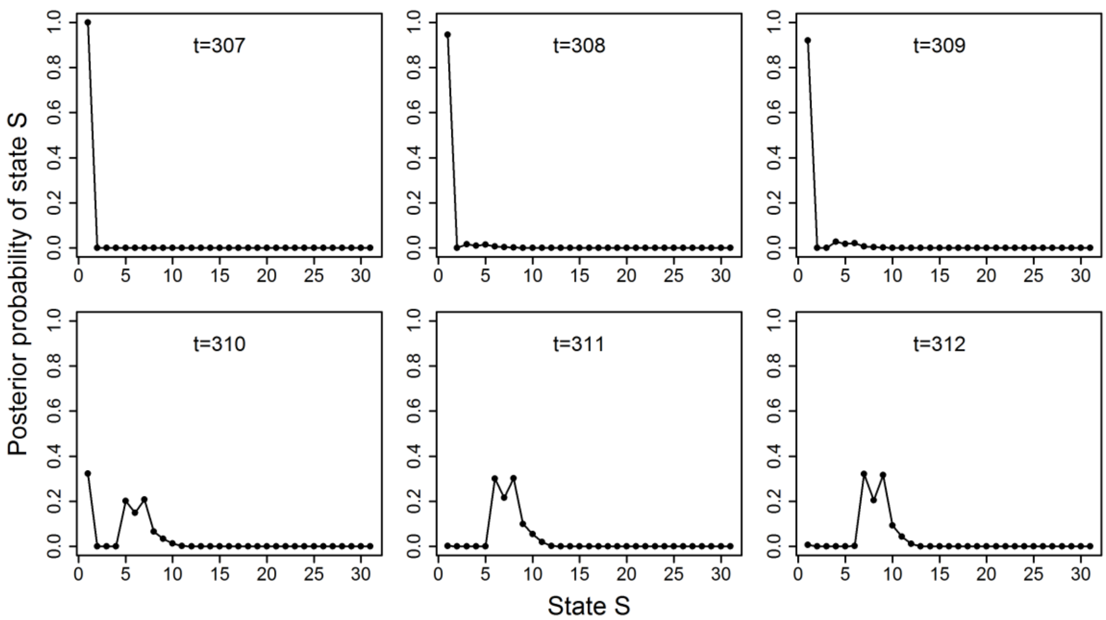


Figure 15 Posterior probability of being in state S (0-30) at a given day of observation (t) for the scenario with reporting delay and awareness. Six days of observation were chosen to illustrate the transition of the system from baseline to outbreak condition.

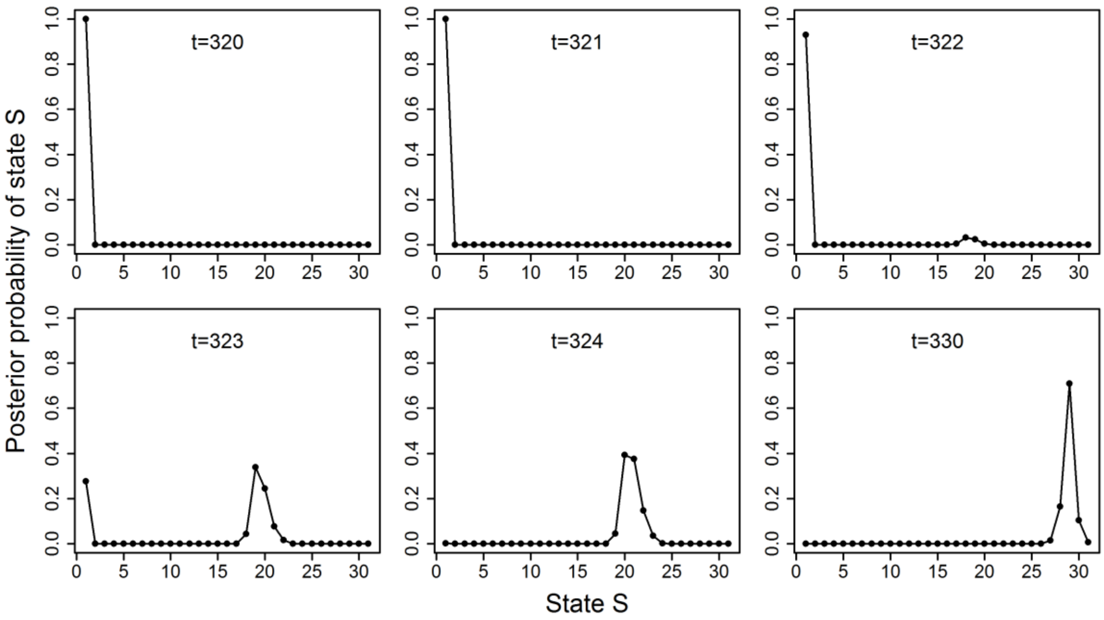


Figure 16 Posterior probability of being in state S (0-30) at a given day of observation (t) for the scenario with reporting delay, but no awareness. Six days of observation were chosen to illustrate the transition of the system from baseline to outbreak condition.

With a more restrictive alarm threshold (i.e. when only large values of V and small probabilities of observed counts given the baseline condition raised an alarm) time to detection generally impaired (i.e. increased), whereas the false alarm rate improved (i.e. decreased).

illustrates this trade-off between time to outbreak detection and false alarm rate at different alarm thresholds.

Under the two scenarios "no delay" and "delay aware", evidence in favour of an outbreak starts accumulating (i.e. V > 1) on day 8 of the outbreak in contrast to day 22 under the "delay non-aware" scenario. The V-based alarm threshold that minimised the false alarm rate while holding time to detection at a constant level of 8 days was 0.625 and 1.25 (at the $\log_{10}$ level) for the "delay aware" and the "no delay" scenario, respectively (Table 5). Given these thresholds, the false alarm rate was lower for the "delay aware" scenario. Based on $P(E|H_0)$, the alarm threshold minimising the false alarm rate while keeping time to detection at 8 days was -5.5 and -6.125 (at the $\log_{10}$ level) for the "delay aware" and the "no delay" scenario, respectively. Here, the false alarm rate was lower for the "no delay" scenario, given the thresholds.

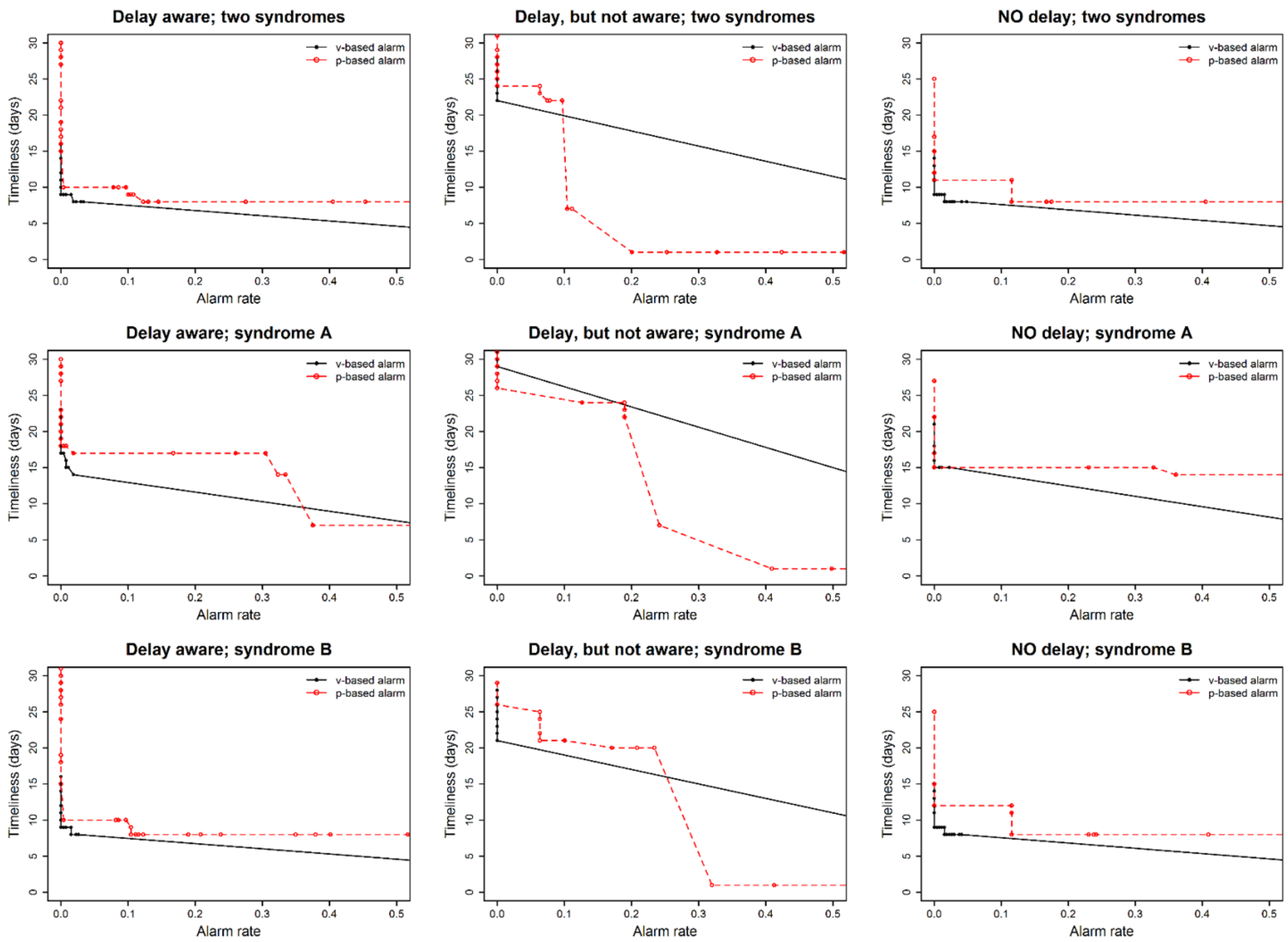


Figure 17 Timeliness (based on outbreak period) against false alarm rate (based on outbreak-free period) for a range of alarm thresholds based on the value of evidence (black) or the probability of observed counts given that H_0 is true (red).

Table 5 Performance measures for some selected alarm thresholds.

	timeliness	false alarm rate	timeliness	false alarm rate
V	threshold = 0.625		threshold = 1.250	
delay aware	8	0,0186	9	0,0074
delay non-aware	23	0,0000	23	0,0000
no delay	8	0,0260	8	0,0149
$P(E\|H_0)$	threshold = -5.5		threshold = -6.125	
delay aware	8	0,1227	10	0,0967
delay non-aware	1	0,2007	22	0,0743
no delay	8	0,1673	8	0,1152

Table 6 Alarm thresholds resulting in no false alarms when based on the value of evidence (V) or the probability of observed counts given H0 (i.e. no outbreak, P(E|H0)) and corresponding timeliness.

	threshold	timeliness
V		
delay aware	1.625	9
no delay	2.750	9
$P(E\|H_0)$		
delay aware	-6.750	15
no delay	-6.625	11

The thresholds at which no false alarms were obtained were less restrictive for the "delay aware" scenario with regard to V, but more restrictive with regard to $P(E|H_0)$, as summarised in Table 6. In the latter case, time to detection was more impaired.

4.4 Discussion

Our results indicate that disease outbreaks can be detected much earlier and with only a marginal loss of specificity when incorporating delayed reporting compared to a system where reporting delay is present but not considered. Furthermore, the performance is on a comparable level as in an ideal system where no reporting delay is present, i.e. where all cases are reported on the day they occur.

Moreover, the results indicate that the accumulation of evidence from several days resulted in a significantly better outbreak detection timeliness, at a given specificity; or a similar timeliness, but higher specificity, compared to an algorithm that, analogous to Salmon et al. (2015), only looks for days with unusual high number of counts. We expect that this pattern will be even more pronounced for outbreaks that initially produce a moderate number of outbreak-related counts. If, for example, we expect a rather flat (i.e. slowly propagating) outbreak, the threshold based on $P(E|H_0)$ may need to be set at a low level, resulting in many false alarms. On the other hand, a higher threshold could only be used for spike-like (i.e. rapidly propagating) outbreaks. The method based on the value of evidence might be more appropriate for timely detection of flat outbreaks since it is computed by considering the evidence of the past *d* days.

In this preliminary study, we used one time series (for each of two syndromes) as a baseline and simulated one outbreak of 30 days occurring in winter for proof of concept. However, the performance of the framework needs to be further validated. First of all, it will be applied to a set of simulated baseline time series with and without outbreaks. Outbreak types of different magnitude and shape will be simulated. Sensitivity, timeliness and false alarm rate will then be calculated and summarised for each outbreak type.

In addition, a more sophisticated measure for specificity / false alarm rate needs to be computed. In the case of thresholds based on $P(E|H_0)$ or V, a false alarm on a given day may continuously be raised during the subsequent days as this method considers the last *d* days. Thus, it seems reasonable to assume that a series of false alarms over *d* days represents a single false alarm. However, such subsequent false alarms may obscure a second false alarm caused by a different signal, resulting in an underestimation of the false alarm rate. A better measure of specificity may be the “in-control average run length”, ARL, or median run length, MRL (Schiöler & Frisén 2012).

The effect of delayed reporting in SyS was assessed in a Bayesian framework by Salmon et al. (2015) using a similar approach as in our study. However, while the authors used a full Bayes approach (Sonesson & Frisén 2005) to model the baseline distribution and impact on delayed reporting, the SyS model is basically a Shewhart plot for which, in each time step, the count is compared with a threshold based on quantiles of the baseline distribution. In comparison, our work is an empirical Bayes approach (Lawson 2005) where parameters for baseline and outbreak distributions and delayed reporting are estimated separately using classical methods. This information is then combined to estimate the posterior probability for an ongoing outbreak or the odds between outbreak and baseline. As proposed in Andersson et al. (2014), we separate the prior probability and the strength of the signal from SyS by estimating the value of evidence, i.e. the odds ratio between prior and posterior odds which is a proxy for the likelihood ratio for the observed evidence under the competing hypothesis (H_1 ongoing outbreak and H_0 baseline conditions).

Whereas neither approach can be claimed to be generally superior, they fulfil different niches. The approach of Salmon and colleagues is intended for automatic analysis of a large number of data streams with little human intervention, in which case it may be impractical to formulate assumptions for each possible disease. The disadvantage is an output that may not always be very informative. On the contrary, our approach is designed to provide comprehensive decision support when SyS is implemented for surveillance of a moderate number of specific diseases or classes thereof. By building in empirical knowledge from previous outbreaks in the form of probability distributions, we can present the user with a clearer picture of the possible significance of a peak. In veterinary SyS, the number of data streams is generally small, compared to human SyS. In this situation, it may no longer be optimal to focus on algorithms that can be easily automatized. Rather, we argue, that one should incorporate as much knowledge as possible in the system to make maximum use of the data that is available.

In this study, one way of measuring outbreak detection performance included setting a threshold for $P(E|H_0)$, the probability of observing exactly n cases given baseline condition. As a next step, the cumulative probability of observing 1 to n cases given that H_0 is true will be computed. The alarm threshold can then be defined as a quantile (e.g. 0.95 or 0.99) from the resulting distribution, similar as applied by Salmon and colleagues.

At first glance, incorporating a prior distribution for the expected number of outbreak related counts may be deemed more subjective than a method that solely relies on how unusual the peek is. However, even is such cases the definition of the alarm threshold and estimation of the sensitivity is typically performed by simulating outbreaks. Thus, the Shewhart method also makes use of implicit assumption about the size and shape of the outbreak distribution. In practice, the decision whether the detection of an unusual peak should be considered sufficient to trigger an alarm depends also on what we expect to see in case of an outbreak. We argue that explicitly defining the outbreak distribution makes the reasoning of the system more transparent.

CHAPTER 5

Experiences with a voluntary surveillance system for early detection of equine diseases in Switzerland

Rahel Struchen[1*], Daniela Hadorn[2], Franziska Wohlfender[1,3], Sandra Balmer[2], Sven Süptitz[2], Jakob Zinsstag[4], Flavie Vial[1]

[1] Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Switzerland

[2] Swiss Federal Food Safety and Veterinary Office, Bern, Switzerland

[3] Institut suisse de médecine équine, Vetsuisse Faculty, University of Bern, Switzerland

[4] Swiss Tropical and Public Health Institute, University of Basel, Switzerland

* Author for correspondence: Ms. R. Struchen, Veterinary Public Health Institute, Schwarzenburgstrasse 155, 3003 Bern, Switzerland.
(Email: rahel.struchen@vetsuisse.unibe.ch)

Published in:

Epidemiology and Infection 2016; 144(9): 1830-6

5.1 Summary

Clinical observations made by practitioners and reported using web- and mobile-based technologies may benefit disease surveillance by improving the timeliness of outbreak detection. Equinella is a voluntary electronic reporting and information system established for the early detection of infectious equine diseases in Switzerland. Sentinel veterinary practitioners have been able to report cases of non-notifiable diseases and clinical symptoms to an internet-based platform since November 2013. Telephone interviews were carried out during the first year to understand the motivating and constraining factors affecting voluntary reporting and the use of mobile devices in a sentinel network. We found that non-monetary incentives attract sentinel practitioners; however, insufficient understanding of the reporting system and of its relevance, as well as concerns over the electronic dissemination of health data were identified as potential challenges to sustainable reporting. Many practitioners are not yet aware of the advantages of mobile-based surveillance and may require some time to become accustomed to novel reporting methods. Finally, our study highlights the need for continued information feedback loops within voluntary sentinel networks.

Running head: Voluntary participation & mobile reporting for surveillance

Keywords: Voluntary reporting; Mobile devices; Veterinary practitioners; Sentinel networks; Infectious diseases

5.2 Introduction

Widespread access to the internet and mobile phones over the past decade has promoted the use of modern communication technologies to collect human and animal health data (Chunara et al. 2012; Madder et al. 2012; Walker 2013); while new approaches to outbreak detection, such as syndromic surveillance, have simultaneously emerged to further strengthen human and animal health surveillance (Rodríguez-Prieto et al. 2014).

Mobile phone applications can benefit disease surveillance by increasing speed and automation of data collection, providing accurate geo-location data, and allowing for rapid two-way transfer of information between data collectors and data users/analysts (Halliday et al. 2012). While the development of mobile-phone-based participatory systems for human public health has really taken off (Freifeld et al. 2010), they are yet to be extensively exploited for animal disease surveillance. Mobile phone technologies can be particularly beneficial to large-animal veterinarians who, in contrast to general practitioners or companion-animal veterinarians, visit their patients on their premises.

Reliable surveillance systems are needed to reduce the impacts of emerging, and potentially zoonotic, diseases on animal and human health and the primary sector. Consequently, the willingness of veterinarians to continuously report their observations is essential for the successful implementation of practitioner-based surveillance systems (Vourc'h et al. 2006). However, little is known about previous experiences in implementing mobile technologies for veterinary diseases surveillance systems (Walker 2013; Robertson et al. 2010; Madder et al. 2012); or about the factors that motivate or constrain veterinary practitioners to submit clinical data to surveillance programmes, although a few studies looked into these factors in the context of laboratory-based surveillance systems (Robinson & Epperson 2013; Sawford et al. 2012; Sawford et al. 2013).

In Switzerland, a new electronic reporting and information system for the monitoring of equine health, Equinella, has been operational since November 2013. We present here results from its first year during which we aimed to better understand the motivations and barriers to voluntary participation in practitioner-based surveillance systems; and evaluated the suitability of mobile devices to collect animal health data in a timely fashion for surveillance.

5.3 Equinella system

Equinella was first established in 1990 and primarily focused on the paper-based reporting of non-notifiable[4] equine diseases by a network of sentinel (Hoinville et al. 2013) veterinary practitioners. In 2012, an evaluation of the system showed that it was no longer representative of the Swiss horse population (Wohlfender et al. 2012) (with only six reports received in 2012); and a survey performed among veterinarians revealed that most veterinarians would prefer to report cases electronically; and that many were willing to additionally report syndromes in addition to disease cases (Wohlfender et al. 2013).

The new Equinella was re-launched in 2013 as a collaborative surveillance system run by the Federal Food Safety and Veterinary Office (FSVO), the Vetsuisse Faculty (Bern) and the Swiss Association of Equine Practitioners. It relies on the reporting of cases of non-notifiable diseases as well as clinical symptoms through any device with an internet connection and a web browser installed such as desktop computers or mobile devices like smartphones or tablets.

To guarantee data protection and facilitate data management, sentinel practitioners must register. Sentinel veterinarians were recruited in September 2013 from both mixed-animal and purely equine practices through mailing lists and an article published in the journal of the Society of Swiss Veterinarians (Anonymous 2013). Participating practitioners do not receive monetary compensation but benefit from various non-monetary incentives. These include password-secured access to an interactive overview of all incoming, anonymized reports; a monthly electronic newsletter relaying national and international equine health news; and a mobile phone text message service to alert them in case of an outbreak. They can contact and draw from the expertise of the Equinella support team (veterinarians with equine infectious disease specialization) and attend one free professional development course per year. Additionally, smartphones specialized for outdoor use (ESP, Supplementary material) were provided to those indicating an interest in using such a device for reporting directly from the field.

To facilitate and standardize data collection without substantially increasing workload, veterinarians can choose clinical symptoms or diseases (Supplementary material) from

[4] Notifiable diseases according to the Swiss Animal Health Ordinance (AHO, SR 916.401) must be reported to the cantonal veterinary office by telephone.

pre-defined check lists. Data on the equid and the holding visited are collected (to preserve anonymity, no unique identifiers are required). The ID of the reporting veterinarian and the date of the report are automatically recorded by the system. Additional information can be entered in a free text box and pictures can be uploaded. A reminder email is automatically sent to all sentinel veterinarians once a month. Recipients can then either confirm that they had no clinical observations of relevance to Equinella in their practice in the previous month or they can report their observations retrospectively.

5.4 Participation

The number of sentinel veterinarians increased from 39 in December 2013 to 67 in November 2014 (Figure 18), with only one practitioner dropping out. Two continuing professional development courses were organised in October and November 2014. The possibility for registered practitioners to attend one of them for free together with the increased publicity around Equinella at that time probably explain the increased number of registrations during these two months.

A relatively high participation was found throughout the first year [median 73%, interquartile range (IQR) 70-76, Figure 18] computed as the monthly proportion of sentinel veterinarians that either submitted a report or confirmed not having observed any relevant cases. The drop (27%) in January 2014 was caused by a technical problem with the reminder e-mails, resulting in many sentinel veterinarians not being able to confirm that they did not have observations to report. A comparable participation was found at the practitioner-level (proportion of months a sentinel veterinarian participated: median = 75%, IQR = 54-91%).

Between December 2013 and November 2014, a total of 78 reports were submitted to Equinella by 24 sentinel veterinarians: 35 reports (44.9%) included only clinical symptoms, six (7.7%) only diseases and 37 (47.4%) had both. The median number of reports received per month was six (IQR=3.8-9). These numbers constitute a real improvement from the reporting frequency observed in the last years of the paper-based surveillance system. Mobile devices were infrequently used for reporting with only ten reports (12.8%) submitted using mobile devices (none of which were ESP) by five different sentinel veterinarians. A minor, but non-significant improvement (Wilcoxon rank sum test = 422.5, p-value = 0.215) in reporting timeliness (difference in days between the diagnosis date and the reporting date) was found when using mobile devices (median = 5.5 days, IQR = 0-8.5) over desktop computers (median = 6.5 days, IQR = 0-16.3). Although no precise data on reporting timeliness are available for the old paper-based Equinella, prior to 2013, participants were encouraged to mail forms to the Federal Veterinary Office (now FSVO) every two weeks (Hauser & Meier 2000). The timeliness of the new electronic system is therefore most likely a significant improvement on its predecessor. Still, our findings were surprising as 45% of the veterinarians surveyed in 2012 said they would be willing to report on a daily basis when cases were observed (Wohlfender et al. 2013). While, in an ideal surveillance system, cases would be reported to the authorities on the day they were observed, a reporting timeliness of less than a week remains acceptable for the early detection purpose of the system and is comparable to the reporting delay observed in other animal health data sources (Perrin et al. 2012; Struchen et al. 2015).

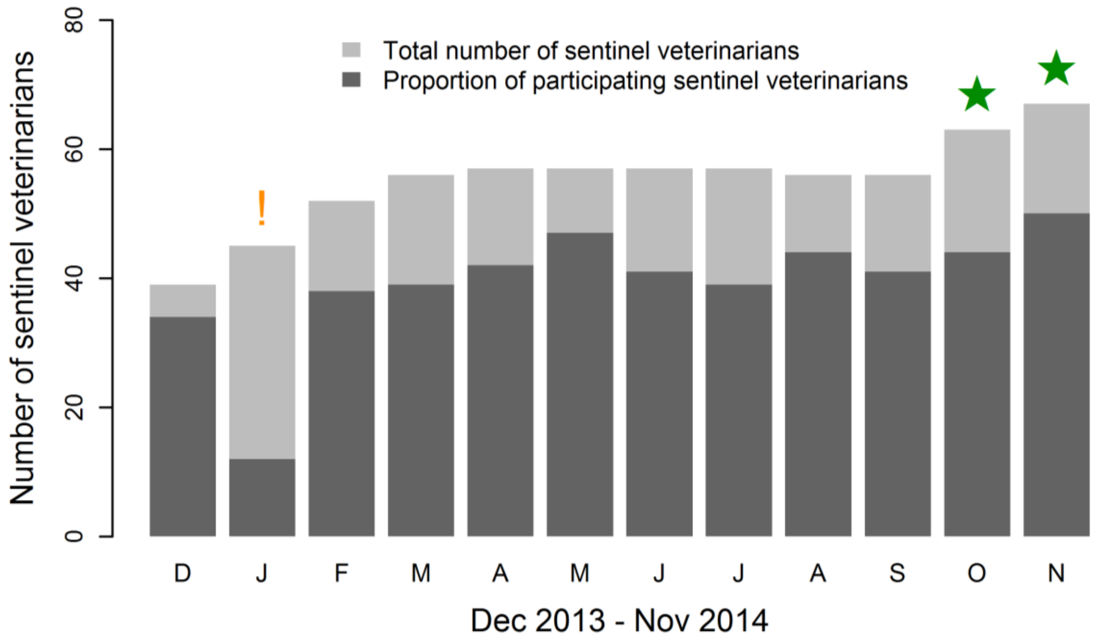


Figure 18 Participation of the sentinel veterinarians to the new Equinella system within its first operational year. Light grey bars represent the monthly number of registered sentinel veterinarians. Dark grey bars represent the monthly number of participating sentinel veterinarians (i.e. that either submitted a report or confirmed not having observed any relevant cases in their practice area during the preceding month). The orange exclamation mark (!) indicates a technical problem which prevented many sentinel veterinarians from confirming that they did not have observations to report. The green stars indicate the months when continuing professional development courses were organised.

5.5 Interviews

Telephone interviews were conducted in May-June 2014 (n=6), investigating the reasons for the initial low reporting frequency, and November 2014 (n=5), focusing on the use of mobile devices. Interviews were based on a series of primarily open questions and protocols were generated for all interviews (Supplementary material). For both sets of interviews, a convenience sample of registered veterinarians was used, with the second drawn only from those having an ESP.

Motivation

Receiving up-to-date information on the health status of the population under surveillance was stated as a strong incentive for participation in Equinella. This was especially important for small practices without close contacts to the university referral clinics or the larger clinics. The interviews highlighted the value of practitioners knowing that certain diseases still occur in Switzerland or that there are clinical manifestations present which are not observed in their own practice. Some interviewees mentioned that receiving such information made them feel better prepared to alleviate their customers' concerns or answer their questions. Further benefits included 1) an improved flow of information between veterinarians; 2) knowing what to expect in potentially risky situations (e.g. in auctions); and 3) reaching a correct diagnosis based on the knowledge of the current health situation. Being aware of the relevance of international animal movements for disease spread, one practitioner mentioned expanding the Equinella system to neighbouring countries. Another suggested that the treatments administered and their outcomes could be reported in the future.

However, many practitioners did not make full use of the Equinella information platform, often only accessing a single information source (such as the list of incoming reports, the interactive map or the latest newsletter). This may be the result of the time constraints of busy practitioners as well as their unfamiliarity with the electronic dissemination and display of health information.

Reasons for low reporting frequency

Approximately half of the interviewees believe that the low reporting frequency reflects the good health situation of the equine population in Switzerland, although some admitted to not consistently reporting new cases. The choice of an electronic reporting method was not unanimous amongst interviewees, one preferring a paper-based system and another expressing concerns over the dissemination of (potential erroneous or sensitive) information over new media, such as the internet.

The trade-off between user-friendliness and security needs was considered when designing the Equinella electronic system. Before a disease report is published online, an Equinella expert verifies each report and contacts the reporting sentinel veterinarian if anything is unclear. Despite all reports being anonymized before publication, communication between the Equinella team, the practitioners and their clients, regarding data privacy, must be improved. A practitioner explained that some animal holders fear being considered as a risk to others, and therefore do not wish disease cases occurring on their holdings to be reported.

Interviewees who had not reported to Equinella stated that they had made no appropriate observations in their practice area - with a single exception in which the participant considered the reporting procedure as too complicated. However, the interviews delivered insight into how reports submitted to Equinella by sentinel veterinarians might be biased. The perceived low relevance of the system by some participants and an insufficient knowledge about the diseases and clinical symptoms that can be reported became apparent during the interviews. Two interviewees admitted never having read the list of diseases and clinical symptoms that had been actively communicated; while one interviewee had not yet submitted a report to Equinella because they had not dealt with cases they considered relevant. This sentiment was echoed in the words of another participant: “For us practitioners, such a system is only relevant for infectious disease outbreaks and that mainly concerns equine herpes virus and maybe strangles. Regarding everything else, it is actually not in our interest to know what is happening in the neighbourhood.” Another interviewee said that they would only report a disease once confirmed by a laboratory test since a report of suspected disease without laboratory confirmation may easily be misinterpreted.

For a new surveillance system to be successfully implemented, it is essential that the sentinel practitioners fully understand the purpose and functionality of the system. Sustained communication between the data providers and the system users should facilitate a better understanding. In our case, improving and continuing our communication efforts, particularly on the topic of the clinical symptoms of interest for syndromic surveillance, may help to reduce some of the shortcomings identified in this pilot study.

Reporting and use of mobile devices

The uptake of mobile devices for reporting was low. Our suspicion that many practitioners were not fully aware of the advantages of mobile reporting was confirmed during the interviews. One practitioner felt mobile reporting to be unnecessary while another explained that they preferred reporting from the comfort of their home (irrespective of the device) seeing no benefit in doing so from the field. We found that the large-scale distribution of ESP, as an additional incentive to mobile reporting, to be challenging due to individual preferences regarding operating systems or mobile devices. Despite some sentinel veterinarians reporting having had positive experiences with the ESP in the field (due to its robustness), other ESP owners did not use the phones at all.

Several practitioners expressed a basic aversion to the use of mobile devices. It is therefore important, when designing new surveillance systems, to take into account the fact that the uptake of novel reporting methods may be slow as practitioners may require time and extra incentives to overcome possible technological aversions.

5.6 Conclusions

Our findings indicate that a voluntary surveillance system based on non-monetary incentives has the potential to attract sentinel practitioners. For example, offering regular relevant professional development courses may help recruit additional sentinel veterinarians in the future. Different types and formats of equine health information useful to practitioners were identified during the interviews. This will help the Equinella team to improve information feedbacks to data providers. Whether these incentives will be enough to keep motivation at a high level and ensure sustainable participation over the long-term still remains questionable, and participation needs to be monitored in the coming years. Understanding the barriers to participation might be further improved by interviewing veterinarians who have not yet registered.

Within the FSVO framework of establishing a national early detection system for emerging and re-emerging diseases, Equinella represents a pilot system to evaluate how a network of sentinel veterinarians can contribute to the early detection of animal disease outbreaks. For example, reporting of non-notifiable diseases such as equine influenza or strangles is of relevance due to their considerable economic impacts on the horse industry sector (Smyth et al. 2011; Waller 2013). Spatio-temporal clusters of reported clinical symptoms such as fever of unknown origin, neurological or respiratory symptoms, or abortions might provide an early signal of the presence of a tropical or emerging disease such as West Nile virus (Leblond et al. 2007) or equine herpes virus. The role of surveillance is to provide information for effective veterinary public health action (Figure 19). All incoming reports are evaluated by an Equinella expert and interpreted in light of the national and international equine health situation and other available scientific data. If a potential problem is identified during this risk assessment phase, the early detection team at the FSVO is contacted to discuss potential measures. In the first 12 months of Equinella, treatment schemes were jointly set up with veterinarians, sampling plans for further diagnostic analysis were proposed, and advice on hygiene or isolation measures to prevent further spread of the disease was given. A descriptive analysis of the reports is prepared and published via a newsletter and on the Equinella website to increase disease awareness and preparedness among practitioners.

We encountered some hurdles with the sporadic use of mobile devices and the lack of awareness of the advantages of mobile reporting during the first year. Our experiences in terms of overall participation were positive and many of the barriers to reporting we identified can be addressed in the future, making the outcome of the pilot project favourable. The use of a web-based application enabling individuals to report from their preferred device may increase the overall acceptability of the system and its sustainability. The Swiss veterinary authorities are now holding discussions to extend the concept to other animal species (e.g. cattle or pigs) which would also cover a broader spectrum of zoonoses of relevance to public health.

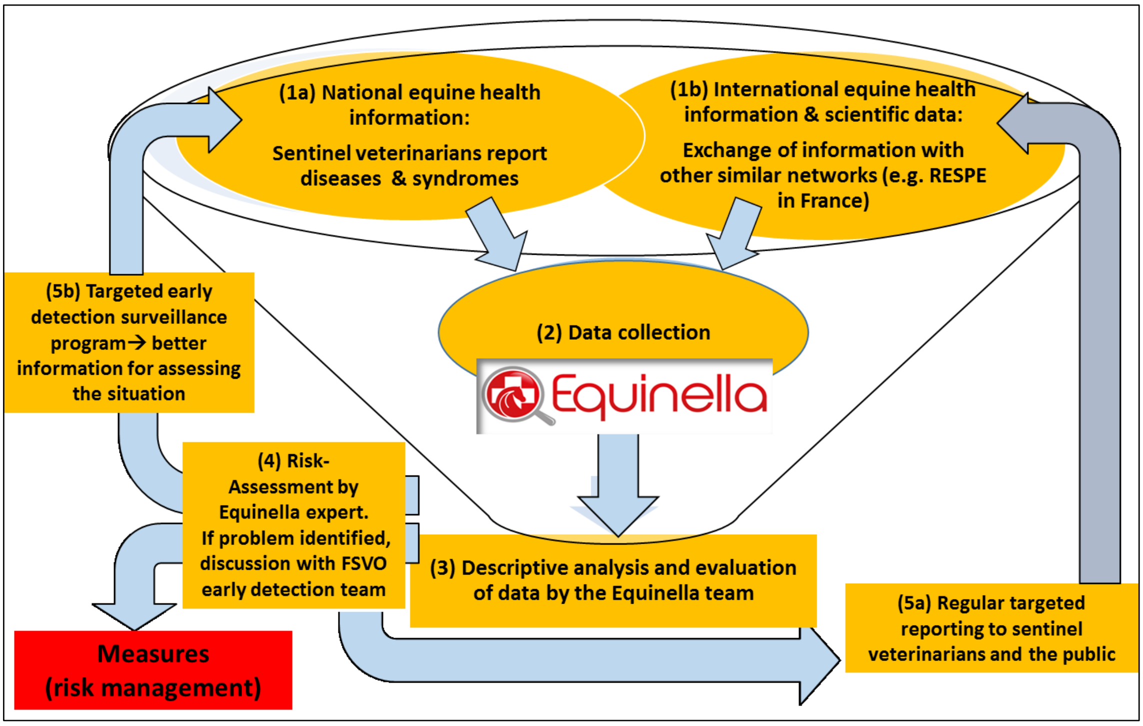


Figure 19 Role of Equinella in providing information for effective veterinary public health action.

5.7 Supplementary material

Methods: Interviews

Sentinel veterinarians were contacted by telephone and asked for their willingness to participate in an interview of approximately fifteen minutes duration. A script including primarily open question was prepared (Supplementary Table S1). Depending on the individual responses, specific wording as well as choice and order of questions varied between interviews.

Each veterinarian was asked for permission to record the conversation at the beginning of the interview. The software Audacity was used for recording. Audio files were stored on a password-protected computer after removal of personal identifiers to ensure anonymity of participants. Verbatim protocols were generated for all but two interviews. In one case, we refrained to record the conversation due to time constraints whereas in the other case, the participant refused to give permission for recording. Notes were taken during both interviews and protocols were instantaneously written after the phone call to document as much information as possible.

Figure 20 The Equinella smartphone (ToughShield R500+, picture adapted from http://www.tough-shield.com/device/r500-2/) with snapshots of the Equinella welcome page. The list of reportable diseases and clinical symptoms is shown in the password-protected area of the website. The use of a responsive design allows the adjustment of the website presentation onto small displays.

Table 7 List of clinical symptoms and diseases that can be reported to Equinella.

Symptoms	Diseases
Abortion	*Viral diseases*
Anaemia of unknown origin	Borna disease
CNS symptoms	EHV-1
Death of unknown origin	EHV-2
Diarrhoea	EHV-3
Fever of unknown origin	EHV-4
Pruritus	EHV-5
Respiratory tract symptoms	Equine influenza
Weight loss of unknown origin	Rotavirus infection
Other *[free text]*	Other *[free text]*
	Bacterial diseases
	Borreliosis
	Clostridia
	Strangles
	Lawsonia intracellularis infection
	Rhodococcus infection
	Other *[free text]*
	Parasitic diseases
	Ehrlichiosis
	Mites
	Piroplasmosis
	Other *[free text]*
	Other diseases
	Atypical myopathy
	Botulism
	Grass sickness
	Tetanus
	Other *[free text]*

Table 8 Questions asked during telephone interviews.

Please tell me of your experiences made with Equinella so far.

Have you already made a report?

> ***If no:***
>
> Can you give any reasons why you have not yet made any reports?
>
> How familiar are you with the list of diseases and symptoms that can be reported?
>
> ***If yes:***
>
> Did you have any difficulties during reporting? ***If yes:*** What kind of difficulties?
>
> How much time did it take?

Did you already have a chance to access the information available for sentinel veterinarians in the secured area of the Equinella platform?

Generally, we have observed a relatively low reporting frequency so far. What might be a reason from your point of view?

What was your motivation to register as a sentinel veterinarian with Equinella?

What is your personal benefit in taking part in Equinella?

Did you already report anything using the Equinella smartphone or any other mobile device, e.g. tablet or laptop?

> ***If no:*** Can you give any reasons why not?
>
> ***If yes:*** What were your experiences?

Do you consider the possibility to submit reports immediately "on the road" useful?

Why have you been interested in getting an Equinella smartphone?

What were your experiences with the Equinella smartphone?

How do you think about the possibility to submit reports using a mobile device? Do you consider it as being practical?

Table 9 Overview of 11 interview participants.

Set	1	1	1	1	1	1	2	2	2	2	2
Canton	ZH	BE	AG	BE	TG	SO	LU	ZH	SO	AG	BE
Sex	F	M	F	F	M	M	M	F	F	F	M
Equine specialisation	No	No	No	Yes	Yes	No	No	Yes	No	No	Unknown
% of equids in practice	40	25	100	70	60	20	50	50	25	100	Unknown
Participation at practitioner-level	100%	60%	80%	50%	80%	67%	90%	100%	100%	87%	89%
No of reports submitted prior to the interview	1	0	0	0	0	0	1	4	8	2	0
Equinella smartphone	No	No	No	No	No	No	Yes	Yes	Yes	Yes	Yes
Device used for reporting	Desktop computer	NA	NA	NA	NA	NA	ESP	Desktop computer	Desktop computer	Desktop computer	NA

Set refers to the time when the interview took place (set 1: May-June 2014, set 2: Nov 2014). F, female; M, male. ESP, Equinella smartphone.

Acknowledgements

The authors thank the 11 sentinel veterinarians who took part in the telephone interviews; all sentinel veterinarians for their valuable contribution to Equinella; the team at 4eyes for developing and implementing the electronic system; Ernest Peter for his contribution as technical project leader; Claudia Graubner for professional inputs and support; Patrick Presi for organising the Equinella smartphones; Martin Reist and Andrew Tedder for helpful inputs; Marie-Eve Cousin for valuable support regarding the interviews; and the FSVO for funding this work.

Declaration of interest

None.

CHAPTER 6

Discussion & conclusion

6.1 Summary and significance of findings

Routinely collected cattle mortality data (TVD)

This work demonstrated the value of routinely collected cattle mortality data for integration into a SyS system. The TVD provides a level of data quality (objective a) which is considered sufficiently high for the purpose of early outbreak detection. Geographic information about the farm reporting an event was available for a majority of reports at different scales. This is relevant for further investigation of the data that triggered a statistical alarm produced by aberration detection algorithms. Mortality events were generally reported in a timely manner with a median reporting timeliness of 1 day for on-farm deaths, 3 days for stillbirths, and 2 days for perinatal deaths. This was attributed to the strict law requiring farmers to report non-slaughter deaths of cattle to the TVD within 3 days. Nonetheless, there was still a certain amount of events that were reported with a delay of several days or weeks which might impair sensitivity and timeliness of a prospective system.

Population coverage (objective a) was assumed to be at a high level due to mandatory reporting as well as monetary incentives. Based on available information from randomly selected Swiss cattle farms for annual quality assurance it was not possible to estimate the proportion of farms holding unregistered animals. Data on the type of mismatch between TVD herd registers and actual on-farm herds were not recorded systematically.

Because it is likely that to some extent stillborn calves are reported to the TVD as born alive but dying shortly after birth due to monetary incentives for each properly reported birth, stillbirths and early (within 7 days of birth) neonatal mortality were grouped into one indicator (perinatal mortality) and used for further analyses.

Different temporal patterns including seasonality, day of the week, and national bank holidays were identified in the data streams (objective b). Possible explanations encompassed management of reproduction of Swiss cattle herd, varying intensity of observing the animals, economically driven decisions, and reporting behaviour. For each of the syndromic time series, a baseline model describing the normal behaviour of the data (in the absence of disease outbreaks) was established (objective c) by fitting regression models to the data and removing temporal outliers.

Three commonly used temporal control charts were applied to on-farm deaths and the perinatal mortality time series to assess their performance in detecting simulated disease outbreaks of varying size and shape (objective d). Each of the three algorithms was of value with regard to at least one of the evaluation metrics. EWMA showed the highest probabilities of outbreak detection (sensitivity) and the shortest time to detection, resulting in the lowest proportion of outbreak cases until detection. However, it also obtained the highest number of false alarms, in contrast to Shewhart or combination rule 2 which showed best results for this measure. CuSum showed the highest probability of an alarm truly representing an outbreak. Finding an optimum balance between sensitivity and manageable number of false alarms was difficult, even when combining binary outputs of algorithms according to defined rules. This highlights the need to carefully optimise aberration detection algorithms for a particular syndromic time series.

Quantification of the reporting timeliness allowed testing the possibility to incorporate the information of delayed reporting into a Bayesian framework in order to investigate its effect on the detection of outbreaks in the data (objective e). Proof of concept showed that disease outbreaks could be detected much earlier and with only a marginal loss of specificity when incorporating delayed reporting compared to a system where reporting delay is present but not taken into account. Furthermore, performance was at a comparable level as in an ideal system where no reporting delay is present and could even be enhanced. In addition, this approach offers an alternative way to present evidence from a disease outbreak compared to the binary output presentation of algorithms. Furthermore, it provides a way of combining multiple data streams.

Before integrating cattle mortality data into a national surveillance system for the early detection of new, exotic or re-emerging diseases, several possibilities for improving sensitivity and specificity may be addressed (see section 6.3).

Voluntary participation and mobile reporting (Equinella)

Valuable experiences were made during the first operational year of the new Equinella surveillance and information system, based on voluntary reporting of clinical observations of veterinary practitioners. As a novelty of the system, veterinarians can report not only (suspect) cases of disease but also clinical symptoms. In addition, reporting can be done using mobile devices such as smartphones.

We experienced some barriers with the sporadic use of mobile devices and the lack of awareness of the advantages of mobile reporting, indicating that practitioners may require some time to become accustomed to mobile reporting methods (objective f). Reporting timeliness using mobile devices showed a minor, non-significant improvement over desktop computers. Overall, it is likely that the timeliness of the new electronic reporting system improved compared to the old paper-based system.

The relatively high participation throughout the first year (objective g) and the insights into factors motivating for participation (objective h) gained during telephone interviews indicated that a voluntary surveillance system based on non-monetary incentives, including providing relevant information feedback and offering regular professional development courses, has the potential to attract sentinel practitioners. Different types and formats of equine health information useful to practitioners were identified which may help the Equinella team to improve information feedbacks to data providers.

Barriers to sustainable reporting by sentinel practitioners identified during interviews (objective h) included insufficient understanding of the reporting system, concerns regarding the electronic dissemination of (false) information, and a perceived low relevance of the system. Many of these can be addressed in the future. The study findings highlighted the importance of continued information feedback loops and communication efforts with sentinel networks to promote better understanding of the system.

6.2 Potential of findings for international health with regard to surveillance and response system

Clinical observations made by (veterinary) practitioners and reported using web- and mobile-based communication tools may benefit disease surveillance by improving the timeliness of outbreak detection. The reporting of clinical symptoms by medical doctors or patients to a centralised database using mobile phones may have enabled earlier detection of e.g. the Ebola outbreak and effective response programs could have been put in place in a timelier manner. In animals, for example, real-time reporting due to a SyS system based on mobile reporting e.g. using smartphones, may benefit surveillance of abortive diseases in developing countries by enabling the timely collection of fresh materials for further diagnostic analyses. Implementing SyS systems collecting livestock health data in real-time using mobile devices in disease "hot spots" areas may prevent further disease spread and enable eliminating new diseases where they originated.

6.3 Agenda of future research towards a real-time, high-sensitivity SyS and response system

Possibilities for future work and improvements of a SyS system, based on the data analysed in the frame of this work, with regard to surveillance and response were identified and are summarised in the following sections.

Surveillance system

- Alternative combination rules may be tested to reduce the number of false alarms by taking into account the time dimension. A rule could consider an alarm only if one algorithm signals on 2 consecutive days. Another rule could consider an alarm if all 3 algorithms signal within 5 days.

- Alternative temporal algorithms may be applied to cattle mortality data, e.g. a negative binomial regression algorithm could be useful with regard to obtaining more historical data.

- Spatio-temporal algorithms may be applied to the data in order to make use of the availability of comprehensive geographic information. Different resolutions may be investigated to assess the spatial scale that obtains best sensitivity performance.

- Sensitivity may be improved by stratifying the data e.g. by production type or age (for on-farm deaths only). Definitions of categories may depend on the goals / purpose of the surveillance system.

- Capturing the reasons for cattle deaths on farm may be valuable to further improve sensitivity.

- During the past years, an increasing amount of equine mortality data have been captured in the TVD because registration of individual equids is mandatory since 2011. Investigation of these data in a similar way as done in this thesis for the cattle mortality data may be interesting. Furthermore, the potential of linking such data to those captured in the frame of Equinella could be assessed.

- The possibility for interfaces between the Equinella reporting system and veterinary practice software may be investigated.

- Assessing the potential to involve animal owners into the Equinella reporting system may be valid as this could increase the reporting frequency, resulting in improved sensitivity.

Response system

- Given the unspecific nature of cattle mortality as well as symptoms reported to Equinella, health authorities will need to set up appropriate response protocols in order to further investigate a statistical alarm and to determine whether the signal may be due to a disease outbreak or not.

- Additional data sources may be accessed for further investigation of an alarm. Cattle mortality data, for example, may be linked with meteorological data in order to identify the impacts of heat waves.

- Continuous efforts for communication between data providers and animal holders will be needed.

6.4 Conclusions

This work demonstrated the value of routinely collected cattle mortality data for use in a SyS system. Before integration of these data into a national surveillance system, health authorities need to define response protocols enabling investigating the data that triggered a statistical alarm and to identify the underlying cause. In addition, the potential of voluntary reporting surveillance system based on non-monetary incentives was shown. Combining reporting of syndromic data and mobile devices in a One Health context has the potential to benefit animal and public health as well as to enhance interdisciplinary collaboration.

Appendices

Appendix 1 Poster: Annual Conference of the Society for Veterinary Epidemiology and Preventive Medicine (SVEPM), March 2014, Dublin, Ireland.

VETERINARY • PUBLIC • HEALTH • INSTITUTE

UNIVERSITÄT BERN

Feasibility and motivation of veterinarians to collect equine epi-data using smartphones

R Struchen[1,*], F Wohlfender[1,2], F Vial[1], J Zinsstag[3], M Reist[4], D Hadorn[4]

[1] Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Switzerland, [2] Institut suisse de médecine équine, Bern, Switzerland,
[3] Swiss Tropical and Public Health Institute, University of Basel, Switzerland, [4] Federal Food Safety and Veterinary Office, Bern, Switzerland

* Corresponding author: rahel.struchen@vetsuisse.unibe.ch

1. Background

Observations made by veterinarians in the field can contribute to the timely detection of first disease outbreak cases, as they often are the first point of contact when animals have health issues[1].

In animal health surveillance, the use of modern communication technologies such as SMS, web-based forms or smartphone (Web-) Apps has increased in recent years, offering a fast, user-friendly and cheap way to collect large quantities of epidemiological data[2]. By using smartphones, practitioners can submit data in (near) real-time directly from the field, and thereby improving the timeliness of an early detection surveillance system.

2. Reporting system

To re-establish "Equinella" (= a network of sentinel equine practitioners) for the early detection of infectious equine diseases, a new electronic reporting system was developed in 2013, in a collaboration between stakeholders from research (Vetsuisse Faculty, Bern), the Swiss Association of Equine Practitioners (SVPM) and the Federal Food Safety and Veterinary Office (FSVO). The system is based on an online platform and a Web-App (Fig. 1), allowing registered veterinarians to report symptoms as well as cases of non-notifiable diseases* using either computers or smartphones (Fig. 2). Submitted data are stored in a centralised database and automatically synchronised between devices.

Fig. 1 Equinella Web-App icon

Fig. 2 The Equinella smartphone ToughShield R500+ (www.tough-shield.com)

* Notifiable diseases must be reported to the Cantonal Veterinary Officer.

References:

1. Sawford, K et al. (2012). A Focused Ethnographic Study of Sri Lankan Government Field Veterinarians' Decision Making about Diagnostic Laboratory Submissions and Perceptions of Surveillance. PLOS One 7 (10)
2. Walker, JG (2013). New media methods for syndromic surveillance and disease modelling. CAB Reviews 8 (031)
3. Vourc'h, G et al. (2006). Detecting Emerging Diseases in Farm Animals through Clinical Observations. Emerging Infectious Diseases 12 (2)

3. Challenges

The success of practitioner-based surveillance systems depends on the willingness of veterinarians to submit data[3].

To facilitate data collection without increasing the workload, the system was designed to be self-explanatory, and only a limited but essential set of information is collected. Check lists of individual and grouped symptoms as well as non-notifiable diseases are provided (Fig. 3), allowing for standardised data collection while simplifying the handling on smartphone displays.

To maintain participation of veterinarians:

- information relevant for their practice is provided through a regular newsletter which summarises trends / maps on reported symptoms and cases
- a regular reminder is sent by e-mail
- a free continued professional training is offered yearly
- a certain number of a robust smartphone specialised for the use in the field was distributed (Fig. 2)

Fig. 3 Screenshots of the Equinella reporting platform on the smartphone display.

4. Pilot study

Towards the end of the first year of data collection, veterinarians will be interviewed to discuss their experiences of using Equinella. Furthermore, the motivation and non-technological constraints of practitioners to centrally submit clinical data in (near) real time will be evaluated.

5. Outlook

This study assesses the potential for a successful wider deployment of this epi-data collecting tool in the field by veterinarians (equine and non-equine). This finding is meaningful for the Swiss FSVO for the further building-up of a national early detection system over the next few years.

In the long run, the continuous real-time analyses of the Equinella data using temporal and spatial algorithms to detect anomalies that might be related to disease outbreaks will benefit the early detection of emerging infectious diseases, thereby allowing for the implementation of timely control measures.

Universität Bern
Veterinary Public Health Institute
Schwarzenburgstrasse 155
CH - 3097 Liebefeld
Tel +41 (0)31 631 5738
Fax +41 (0)31 631 5749

www.equinella.ch
info@equinella.ch

Appendix 2 Poster: DACh-Epidemiologietagung, September 2014, Zürich, Switzerland.

VETERINARY • PUBLIC • HEALTH • INSTITUTE

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Lebensmittelsicherheit und Veterinärwesen BLV

ISME
Institut suisse de médecine équine
Schweiz. Institut für Pferdemedizin
Instituto svizzero di medicina equina
Swiss Institute of Equine Medicine

Equinella – Melde- und Informationsplattform für die Früherkennung von Pferdekrankheiten in der Schweiz

R Struchen[1], F Wohlfender[1,2], S Balmer[3], S Süptitz[3], D Hadorn[3]

[1] Veterinary Public Health Institute, Vetsuisse-Fakultät, Universität Bern, Schweiz, [2] Institut suisse de médecine équine, Bern, Schweiz,
[3] Bundesamt für Lebensmittelsicherheit und Veterinärwesen, Bern, Schweiz

Hintergrund

Pferdehaltung ist in der Schweiz ein wichtiger Wirtschaftszweig. Intensive Kontakte zum Ausland durch Pferdesportveranstaltungen oder den Zukauf von Tieren, Samen oder Embryonen bergen das Risiko einer Einschleppung von Pferdekrankheiten in die Schweiz.

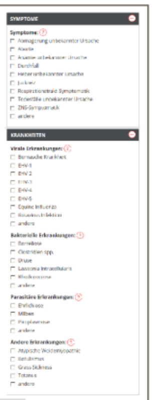
Damit Seuchen und Krankheiten in der nationalen Pferdepopulation* frühzeitig entdeckt und rechtzeitig geeignete Massnahmen ergriffen werden können, braucht es ein effizientes Früherkennungs- und Überwachungssystem. Deshalb wurde eine elektronische Melde- und Informationsplattform für Pferdekrankheiten aufgebaut und im November 2013 in Betrieb genommen: www.equinella.ch

Equinella ist ein wichtiger Pfeiler im Aufbau eines nationalen Früherkennungssystems in der Schweiz. Am Beispiel der Pferdepopulation werden Praktikabilität und Nutzen eines solchen Sentinel-Systems evaluiert.

* Mit Pferden sind sämtliche Equiden bzw. «Pferdeartige» gemeint.

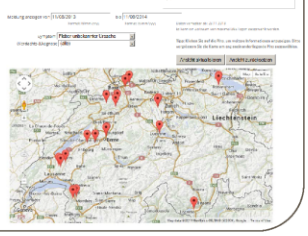
Plattform

Registrierte TierärztInnen, sog. Sentinel-TierärztInnen, können nicht-meldepflichtige Krankheitsfälle* und bestimmte Symptome bei Equiden online via Computer oder mobilem Gerät melden.



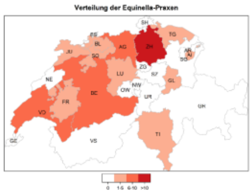
Nutzen für Sentinel-TierärztInnen

- Anonymisierte Übersicht über alle eingegangenen Meldungen (tabellarisch sowie interaktive Kartendarstellung)
- Monatlicher Newsletter mit aktuellen Informationen zur Pferdegesundheit
- Fachliche Beratung
- SMS-Alarm im Falle eines grösseren Krankheitsausbruchs
- Jährliche Gratis-Weiterbildung
- Nutzung eines Outdoor-Smartphones (auf Wunsch)



* Meldepflichtige Infektionskrankheiten müssen gemäss Tierseuchenverordnung nach wie vor direkt dem kantonalen Veterinärdienst gemeldet werden.

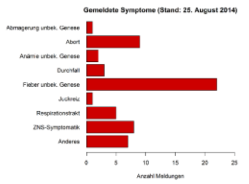
Repräsentativität

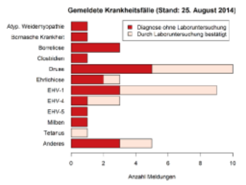


Seit November 2013 haben sich insgesamt 58 Sentinel-TierärztInnen aus 56 Praxen bei Equinella registriert. Basierend auf den Angaben der Praxen bei der Registrierung wird damit bereits eine geschätzte Abdeckung der Schweizer Pferdepopulation von fast 50% erreicht.

Meldungen

In den ersten 9 Monaten wurden 56 Meldungen an Equinella übermittelt. Die am häufigsten gemeldeten Symptome waren Aborte und Fieber unbekannter Genese. Bei den Krankheitsfällen wurden Infektionen mit Equinem Herpesvirus (EHV-1) und Druse am häufigsten diagnostiziert.





Ausbruchsuntersuchungen

Das Equinella-Team half auf Anfrage bereits zweimal bei Ausbruchsuntersuchungen mit. Im ersten Fall handelte es sich um einen Ausbruch von EHV-1 mit seuchenhaftem Abortieren, im zweiten Fall um ein Druse-Bestandesproblem. Zu beiden Abklärungen erhielt die Sentinel-Tierärzteschaft ausführliche Fallberichte zu Weiterbildungszwecken.

Ausblick

Die Herausforderung eines freiwilligen Meldesystems wie Equinella liegt darin, die fortlaufende Teilnahme der Sentinel-TierärztInnen zu gewährleisten. Eine erste telefonische Umfrage im kleinen Rahmen hat bestätigt, dass es ihnen wichtig ist, über das Auftreten von Krankheitsfällen informiert zu sein. Eine regelmässige Rückmeldung an die Meldenden, die laufende Optimierung der Benutzerfreundlichkeit sowie stetige Bemühungen zur Rekrutierung neuer Sentinel-TierärztInnen sind unerlässlich für den Erfolg von Equinella.

www.equinella.ch
info@equinella.ch
Equinella

Rahel Struchen
PhD student
rahel.struchen@vetsuisse.unibe.ch
Tel +41 (0)31 631 5741
Fax +41(0)31 631 5749

Appendix 3 Poster: Annual Conference of the Society for Veterinary Epidemiology and Preventive Medicine (SVEPM), March 2015, Ghent, Belgium.

VETERINARY • PUBLIC • HEALTH • INSTITUTE

Schweizerische Eidgenossenschaft
Confédération suisse
Confederazione Svizzera
Confederaziun svizra

Eidgenössisches Departement des Innern EDI
Bundesamt für Lebensmittelsicherheit und Veterinärwesen BLV

ISME
Institut suisse de médecine équine
Schweiz. Institut für Pferdemedizin
Instituto svizzero di medicina equina
Swiss Institute of Equine Medicine

Voluntary participation & mobile reporting for surveillance – a one-year experience

R Struchen[1], D Hadorn[2], F Wohlfender[1,3], S Balmer[2], S Süptitz[2], J Zinsstag[4], F Vial[1]
[1] Veterinary Public Health Institute, University of Bern, Switzerland, [2] Federal Food Safety and Veterinary Office, Bern, Switzerland,
[3] Institut suisse de médecine équine, University of Bern, Switzerland, [4] Swiss Tropical and Public Health Institute, University of Basel, Switzerland

Background

Clinical observations made by veterinary practitioners and reported in real time using web- and mobile-based communication tools may benefit disease surveillance by improving the timeliness of outbreak detection.

We discuss our experiences with the practitioner-based Swiss surveillance system Equinella during its first operational year. Telephone interviews were carried out with 11 sentinel veterinarians to

1) better understand motivations and constraints to sustainable participation in a voluntary system
2) judge the suitability of mobile devices (e.g. smart-phones or tablets) to collect animal health data for surveillance

Equinella

Equinella is a voluntary reporting and information system established for the early detection of infectious equine diseases. Swiss sentinel practitioners can report cases of non-notifiable diseases as well as clinical symptoms to an internet-based platform using computers or mobile devices in real time.

Non-monetary incentives to participate are offered such as regular information feedback, a free continuing professional development course per year or the use of a smartphone (Fig. 1).

Figure 1 Smartphone of robust condition suitable for outdoor use (ToughShield R500+, www.tough-shield.com)

Voluntary participation

A relatively high participation of sentinel veterinarians was found during the first year (median = 73%, Fig.2).

Continuing professional development courses provide a useful incentive to gain new sentinel veterinarians.

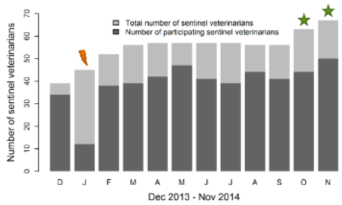


Figure 2 Participation is measured as the proportion of registered sentinel veterinarians that either submitted a report or confirmed not having observed any relevant cases in their practice area.

Receiving up-to-date information on the health status of the equine population was clearly stated to be motivating.

Barriers identified included an insufficient knowledge about what can be reported, concerns such as the uncontrollable dissemination of (false) information, or the perception of low relevance of the system.

Main interview outcomes

Mobile reporting

Mobile devices were sporadically used for reporting during the first year (12.8% of reports).

Some veterinarians were not aware of the advantages of mobile reporting.

No common underlying problem or reason explaining the infrequent use of mobile devices was found.

Distributing a robust mobile device as incentive and promoting mobile reporting was challenging due to individual preferences on the type of mobile device or operating system.

Conclusions

- **Non-monetary** participation **incentives** can help attract and retain sentinel veterinarians.
- Veterinarians may require some time to become accustomed to **novel reporting methods.**
- **Continued information feedback loops** and sustained communication efforts with sentinel networks to promote better understanding of the system are needed.

www.equinella.ch
info@equinella.ch

Equinella

Rahel Struchen
PhD candidate
rahel.struchen@vetsuisse.unibe.ch
Tel +41 (0)31 631 5741
Fax +41(0)31 631 5749

Appendix 4 Poster: European Congress on Tropical Medicine and International Health (ECTMIH), September 2015, Basel, Switzerland.

VETERINARY • PUBLIC • HEALTH • INSTITUTE

Swiss TPH
Swiss Tropical and Public Health Institute
Schweizerisches Tropen- und Public Health-Institut
Institut Tropical et de Santé Publique Suisse
Associated Institute of the University of Basel

Detecting simulated disease outbreaks in routinely collected cattle mortality data

Rahel Struchen[a,*], Jakob Zinsstag[b], Flavie Vial[a]
[a] Veterinary Public Health Institute, Vetsuisse Faculty, University of Bern, Switzerland; [b] Swiss Tropical and Public Health Institute, University of Basel, Switzerland

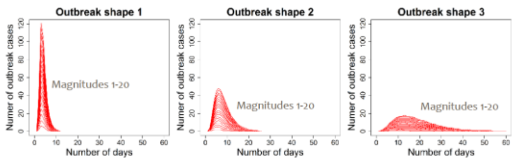
Background

Cattle on-farm mortality data are routinely collected in identification and registration systems such as the "Tierverkehrsdatenbank" (TVD) in Switzerland. Such data may be used as health indicators for syndromic surveillance (SyS): an un-expected increase in the number of deaths could provide an early signal of a disease outbreak [1].

We evaluated the performance of three temporal algorithms in detecting simulated outbreaks in cattle mortality data based on evaluation measures including sensitivity (ability to detect an outbreak), false positive rate (FPR, an alarm is generated when there is no outbreak) and positive predictive value (PPV, probability that an alarm truly represents an outbreak).

Methods

A historical outbreak-free data set of on-farm deaths reported daily by farmers to the TVD between 2009 and 2011 was used to simulate 1,000 baseline time series. Outbreaks of different magnitude (1-20) and shape (1-3) were simulated and added to these baselines.



Explainable temporal patterns such as seasonality or day-of-week effect were removed [2]. Three algorithms were retrospectively applied to the data: the Shewhart, cumulative sum (CuSum) and exponentially weighted moving average (EWMA) control charts. The performance of these algorithms was assessed:

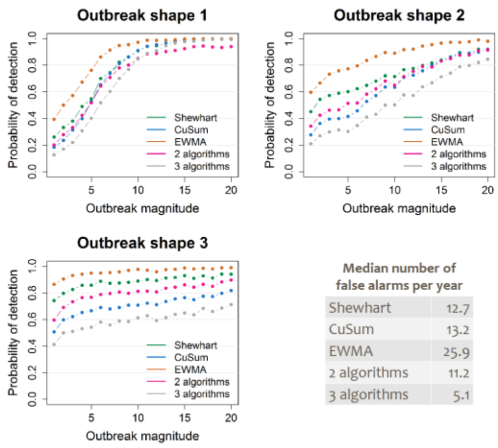
- separately using different detection thresholds (defined as *n* standard deviations above expected value)
- by combining their outputs: an alarm was considered only if generated by either 2 or all 3 algorithms (rules "2 algorithms" or "3 algorithms", respectively)

Results: separate evaluation

- Overall, sensitivity and FPR decreased with increasing detection threshold
- **Evaluation measures differed between algorithms**: the highest sensitivity was obtained by EWMA whereas Shewhart had the lowest FPR and CuSum the highest PPV

Results: combined evaluation

Median sensitivity



Median number of false alarms per year

Shewhart	12.7
CuSum	13.2
EWMA	25.9
2 algorithms	11.2
3 algorithms	5.1

Applying **combination rules reduced** the number of **false alarms** marginally (2 algorithms) or considerably (3 algorithms), but **at the cost of sensitivity and PPV**.

Conclusions

None of the algorithms showed an overall superior performance in detecting outbreak signals. Combining algorithm outputs did not satisfactorily increase the system's performance due to the trade-off between sensitivity and FPR. As it is difficult for decision makers to estimate the costs of missing an outbreak vs. the costs of investigating a false alarm, all 3 algorithms should be separately applied to the cattle mortality data and individual output interpreted in view of the current health context.

Universität Bern
Veterinary Public Health Institute
Schwarzenburgstrasse 155
CH - 3097 Liebefeld
Phone +41 31 631 5738
Fax +41 31 631 5749
* rahel.struchen@vetsuisse.unibe.ch

References

[1] Perrin et al. (2012) Prev. Vet. Med. 105: 244-252
[2] Struchen et al. (2015) Prev. Vet. Med. 121: 1-7

Universität Basel
Swiss Tropical and Public Health Institute
Socinstrasse 57
CH - 4002 Basel
Phone +41 61 284 81 11
Fax +41 61 284 81 01

Appendix 5 Abstract: Conference of the International Society for Veterinary Epidemiology and Economics (ISVEE), November 2015, Mérida, Mexico.

Evaluating the ability of aberration-detection temporal algorithms to detect simulated disease outbreaks in routinely collected cattle mortality data

Rahel Struchen [1], Flavie Vial [1], Jakob Zinsstag [2]

[1] *Veterinary Public Health Institute, Schwarzenburgstrasse 155, 3003 Bern, Switzerland*

[2] *Swiss Tropical and Public Health Institute, Socinstrasse 57, 4002 Basel, Switzerland*

Purpose: Mortality data are routinely collected in national livestock identification systems (“Tierverkehrsdatenbank” or TVD in Switzerland). Such data may be used for the real-time detection of mortality clusters potentially indicative of a disease outbreak. We evaluated the performance of temporal outbreak detection algorithms retrospectively applied to Swiss cattle mortality data.

Methods: We extracted the daily number of on-farm cattle deaths from the TVD between 2009 and 2011. Negative binomial regression models were used on the historical data to simulate baseline time-series, into which we injected simulated disease outbreaks of different size, duration and shape (n=60,000). The performance of Shewhart, cumulative sum (CuSum) and exponentially weighted moving average (EWMA) control charts were assessed based on several measures including sensitivity, false positive rate (FPR) and time to detection (TTD). Control charts were evaluated separately, under different combination rules, and using different detection limits.

Results: Sensitivity and FPR generally decreased with increasing detection limit, but the strength of this effect was not the same for all three algorithms and depended on the size and shape of the outbreaks. EWMA exhibited overall the highest sensitivity. The Shewhart algorithm was the best performer in terms of FPR, but required a longer TTD compared to EWMA. CuSum was between Shewhart and EWMA for most performance

measures. The combination rules (two or three out of three algorithms, respectively) only marginally lowered FPR without improving the system's overall performance.

Conclusions: None of the algorithms showed a superior performance in detecting outbreak signals. For the prospective use of cattle mortality data in Switzerland, output from both EWMA and Shewhart should be concomitantly used by decision-makers when interpreting statistical alarms.

Relevance: Surveillance systems have intrinsic statistical trade-offs, as illustrated by the trade-off between sensitivity, FPR and TTD that we observed. Algorithms need to be carefully optimised for a particular data stream before their integration into a national early detection system.

References

Andersson, M.G. et al., 2014. Using bayes' rule to define the value of evidence from syndromic surveillance. *PloS one*, 9(11), p.e111335.

Anon, 2011. Early Warning System for West Nile Virus Risk Areas, California, USA. *Emerging Infectious Disease journal - CDC*, 17(8).

Anonymous, 2013. Neulancierung von Equinella: Sentinel-Tierärztinnen und -Tierärzte gesucht! *Schweizer Archiv für Tierheilkunde*, 155(10), pp.594–595.

Banik, G.R., Khandaker, G. & Rashid, H., 2015. Middle East Respiratory Syndrome Coronavirus "MERS-CoV": Current Knowledge Gaps. *Paediatric respiratory reviews*, 16(3), pp.197–202.

Bell, C. et al., SQuirreL SQL Client.

Binder, S. et al., 1999. Emerging Infectious Diseases: Public Health Issues for the 21st Century. *Science*, 284, pp.1311–1314.

Bisson, I.-A., Ssebide, B.J. & Marra, P.P., 2015. Early Detection of Emerging Zoonotic Diseases with Animal Morbidity and Mortality Monitoring. *EcoHealth*, 12(1), pp.98–103.

Blickenstorfer, S. et al., 2011. Using scenario tree modelling for targeted herd sampling to substantiate freedom from disease. *BMC veterinary research*, 7(49).

Bonfoh, B. et al., 2011. Representative Seroprevalences of Brucellosis in Humans and Livestock in Kyrgyzstan. *EcoHealth*, 9(2), pp.132–138.

Bronner, A. et al., 2013. Assessing the mandatory bovine abortion notification system in France using unilist capture-recapture approach. *PloS one*, 8(5), p.e63246.

Bronner, A. et al., 2015. Devising an indicator to detect mid-term abortions in dairy cattle: a first step towards syndromic surveillance of abortive diseases. *PloS one*, 10(3), p.e0119012.

Bronner, A. et al., 2014. Why do farmers and veterinarians not report all bovine abortions, as requested by the clinical brucellosis surveillance system in France? *BMC veterinary research*, 10(1), p.93.

Brown, C., 2004. Emerging zoonoses and pathogens of public health significance – an overview. *Revue scientifique et technique (International Office of Epizootics)*, 23(2), pp.435–442.

Brownstein, J.S., Freifeld, C.C. & Madoff, L.C., 2009. Digital disease detection--harnessing the Web for public health surveillance. *The New England journal of medicine*, 360(21), pp.2153–5, 2157.

Buckeridge, D.L. et al., 2005. Algorithms for rapid outbreak detection: a research synthesis. *Journal of biomedical informatics*, 38(2), pp.99–113.

Buckeridge, D.L. et al., 2008. Predicting outbreak detection in public health surveillance: quantitative analysis to enable evidence-based method selection. *AMIA ... Annual Symposium proceedings / AMIA Symposium. AMIA Symposium*, pp.76–80.

Burkom, H.S. et al., 2004. Role of data aggregation in biosurveillance detection strategies with applications from ESSENCE. *MMWR. Morbidity and mortality* *weekly report*, 53 Suppl, pp.67–73.

Chan, K.-S. & Ripley, B., 2012. TSA: Time Series Analysis.

Chunara, R., Freifeld, C.C. & Brownstein, J.S., 2012. New technologies for reporting real-time emergent infections. *Parasitology*, pp.1–9.

Cleaveland, S., Laurenson, M.K. & Taylor, L.H., 2001. Diseases of humans and their domestic mammals: pathogen characteristics, host range and the risk of emergence. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 356(1411), pp.991–9.

Clegg, L.X., 2002. Impact of Reporting Delay and Reporting Error on Cancer Incidence Rates and Trends. *CancerSpectrum Knowledge Environment*, 94(20), pp.1537–1545.

Conti, S., Kanieff, M. & Rago, G., 2012. *Inventory of syndromic surveillance systems in Europe*,

Daszak, P., Cunningham, A.A. & Hyatt, A.D., 2000. Emerging infectious diseases of wildlife - threats to biodiversity and human health. *Science*, 287, pp.443–449.

Doceul, V. et al., 2013. Epidemiology, molecular virology and diagnostics of Schmallenberg virus, an emerging orthobunyavirus in Europe. *Veterinary research*, 44, p.31.

Doherr, M.G. & Audigé, L., 2001. Monitoring and surveillance for rare health-related events: a review from the veterinary perspective. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 356(1411), pp.1097–106.

Dórea, F.C. et al., 2012. Retrospective time series analysis of veterinary laboratory data: Preparing a historical baseline for cluster detection in syndromic surveillance. *Preventive veterinary medicine*, 109(3-4), pp.219–227.

Dórea, F.C. et al., 2014. Syndromic surveillance using laboratory test requests: a practical guide informed by experience with two systems. *Preventive veterinary medicine*, 116(3), pp.313–24.

Dórea, F.C., McEwen, B.J., McNab, W.B., Sanchez, J., et al., 2013. Syndromic surveillance using veterinary laboratory data: algorithm combination and customization of alerts. *PloS one*, 8(12), p.e82183.

Dórea, F.C., McEwen, B.J., McNab, W.B., Revie, C.W., et al., 2013. Syndromic surveillance using veterinary laboratory data: data pre-processing and algorithm performance evaluation. *Journal of the Royal Society, Interface / the Royal Society*, 10(83), p.20130114.

Dórea, F.C., Sanchez, J. & Revie, C.W., 2011. Veterinary syndromic surveillance: Current initiatives and potential for development. *Preventive veterinary medicine*, 101(1-2), pp.1–17.

Dórea, F.C., Widgren, S. & Lindberg, A., 2015. Vetsyn: An R package for veterinary syndromic surveillance. *Preventive veterinary medicine*.

Drewe, J. a et al., 2013. SERVAL: A New Framework for the Evaluation of Animal Health Surveillance. *Transboundary and emerging diseases*, pp.1–13.

Dubey, J.P. & Schares, G., 2011. Neosporosis in animals - the last five years. *Veterinary parasitology*, 180(1-2), pp.90–108.

Dubrawski, A., 2011. Detection of Events In Multiple Streams of Surveillance Data. In C. Castillo-Chavez et al., eds. *Infectious Disease Informatics and Biosurveillance*. Integrated Series in Information Systems. Boston, MA: Springer US, pp. 145–171.

Dupuy, C. et al., 2013. Inventory of veterinary syndromic surveillance initiatives in Europe (Triple-S project): Current situation and perspectives. *Preventive Veterinary Medicine*, 111(3), pp.220–229.

Dupuy, C. et al., 2015. Pilot simulation study using meat inspection data for syndromic surveillance: use of whole carcass condemnation of adult cattle to assess the performance of several algorithms for outbreak detection. *Epidemiology and infection*, pp.1–11.

Edge, V.L. et al., 2006. Syndromic Surveillance of Norovirus using Over-the-counter Sales of Medications Related to Gastrointestinal Illness. *The Canadian journal of infectious diseases & medical microbiology = Journal canadien des maladies infectieuses et de la microbiologie médicale / AMMI Canada*, 17(4), pp.235–41.

Elliot, A.J. et al., 2010. Syndromic surveillance to assess the potential public health impact of the Icelandic volcanic ash plume across the United Kingdom, April 2010. *Euro surveillance : bulletin Européen sur les maladies transmissibles = European communicable disease bulletin*, 15(23), pp.10–13.

Farrington, C.P. et al., 1996. A Statistical Algorithm for the Early Detection of Outbreaks of Infectious Disease. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 159(3), pp.547–563.

Farrington, C.P. & Andrews, N.J., 2004. Outbreak detection: application to infectious disease surveillance. In R. Brookmeyer & D. E. Stroup, eds. *Monitoring the Health of Populations*. Oxford: Oxford University Press.

Faverjon, C. et al., 2016. Evaluation of a Multivariate Syndromic Surveillance System for West Nile Virus. *Vector borne and zoonotic diseases*, 16(6), pp.382–390.

Freeman, R. et al., 2013. Evaluation of a national microbiological surveillance system to inform automated outbreak detection. *The Journal of infection*, 67(5), pp.378–84.

Freifeld, C.C. et al., 2010. Participatory epidemiology: use of mobile phones for community-based health reporting. *PLoS medicine*, 7(12), p.e1000376.

Fung, I.C.-H., Tse, Z.T.H. & Fu, K.-W., 2015. The use of social media in public health surveillance. *Western Pacific Surveillance and Response*, 6(2).

Gire, S.K. et al., 2014. Genomic surveillance elucidates Ebola virus origin and transmission during the 2014 outbreak. *Science*, 345(6202), pp.1369–72.

Green, D.M., Kiss, I.Z. & Kao, R.R., 2006. Modelling the initial spread of foot-and-mouth disease through animal movements. *Proceedings. Biological sciences / The Royal Society*, 273(1602), pp.2729–35.

Halliday, J. et al., 2012. Bringing together emerging and endemic zoonoses surveillance: shared challenges and a common solution. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 367(1604), pp.2872–80.

Hauser, R. & Meier, H.P., 2000. Equinella - The Monitoring of Infectious Equine Diseases in Switzerland. In *Proceedings of the 9th International Symposium on Veterinary Epidemiology and Economics*.

Henning, K.J., 2004. Overview of Syndromic Surveillance What is Syndromic Surveillance? Available at: http://www.cdc.gov/mmwR/preview/mmwrhtml/su5301a3.htm [Accessed June 7, 2012].

Heymann, D.L., Rodier, G.R. & WHO, O.S.T. to the G.O.A. and R.N., 2001. Hot spots in a wired world: WHO surveillance of emerging and re-emerging infectious diseases. *The Lancet Infectious Diseases*, 1, pp.345–353.

Hoinville, L., 2013. *Animal Health Surveillance Terminology Final Report from Pre-ICAHS Workshop*,

Hoinville, L.J. et al., 2013. Proposed terms and concepts for describing and evaluating animal-health surveillance systems. *Preventive veterinary medicine*, 112(null).

Jajosky, R.A. & Groseclose, S.L., 2004. Evaluation of reporting timeliness of public health surveillance systems for infectious diseases. *BMC public health*, 4, p.29.

Jean-Richard, V. et al., 2014. The use of mobile phones for demographic surveillance of mobile pastoralists and their animals in Chad: proof of principle. *Global health action*, 7, p.23209.

Jefferson, H. et al., 2008. Evaluation of a syndromic surveillance for the early detection of outbreaks among military personnel in a tropical country. *Journal of public health (Oxford, England)*, 30(4), pp.375–83.

Jones, G. et al., 2014. The French human salmonella surveillance system: Evaluation of timeliness of laboratory reporting and factors associated with delays, 2007 to 2011. *Eurosurveillance*, 19, pp.1–10.

Jones, K.E. et al., 2008. Global trends in emerging infectious diseases. *Nature*, 451, pp.990–993.

Kang, M. et al., 2013. Using Google Trends for influenza surveillance in South China. *PloS one*, 8(1), p.e55205.

Kom Mogto, C.A. et al., 2012. School absenteeism as an adjunct surveillance indicator: experience during the second wave of the 2009 H1N1 pandemic in Quebec, Canada. *PloS one*, 7(3), p.e34084.

Ladbury, G.A.F. et al., 2015. Integrating interdisciplinary methodologies for One Health: goat farm re-implicated as the probable source of an urban Q fever outbreak, the Netherlands, 2009. *BMC infectious diseases*, 15(1), p.372.

Lawless, J.F., 1994. Adjustments for reporting delays and the prediction of occurred but not reported events. *Canadian Journal of Statistics*, 22(1), pp.15–31.

Lawson, A.B., 2005. Spatial and Spatio-Temporal Disease Analysis. In A. B. Lawson & K. Kleinman, eds. *Spatial and Syndromic Surveillance for Public Health*. Chichester, UK: John Wiley & Sons, Ltd, pp. 53–76.

Leblond, A., Hendrikx, P. & Sabatier, P., 2007. West Nile Virus outbreak detection using syndromic monitoring in horses. *Vector-Borne and Zoonotic Diseases*, 7(3), pp.403–10.

Lotze, T., Murphy, S. & Shmueli, G., 2008. Implementation and Comparison of Preprocessing Methods for Biosurveillance Data. *Advances in Disease Surveillance*, 6(1), pp.1–20.

Lui, K.J. & Rudy, R.K., 1989. An application of a mathematical model to adjust for time lag in case reporting. *Statistics in medicine*, 8(3), pp.259–62; discussion 279–81.

Madder, M. et al., 2012. e-Surveillance in animal health: use and evaluation of mobile tools. *Parasitology*, 139(14), pp.1831–42.

Madouasse, A. et al., 2013. Evaluation of a Continuous Indicator for Syndromic Surveillance through Simulation. Application to Vector Borne Disease Emergence Detection in Cattle Using Milk Yield. *PloS one*, 8(9), p.e73726.

Mandl, K.D., Overhage, J.M., et al., 2004. Implementing Syndromic Surveillance: A Practical Guide Informed by the Early Experience. *Journal of the American Medical Informatics Association*, 11(2), pp.141–150.

Mandl, K.D., Reis, B. & Cassa, C., 2004. Measuring Outbreak-Detection Performance By Using Controlled Feature Set Simulations. *Morbidity and Mortality Weekly Report*, 53(Cdc), pp.130–136.

Marceau, A. et al., 2014. Can routinely recorded reproductive events be used as indicators of disease emergence in dairy cattle? An evaluation of 5 indicators during the emergence of bluetongue virus in France in 2007 and 2008. *Journal of dairy science*.

Masarotto, G. & Varin, C., 2012. Gaussian Copula Marginal Regression. *Electronic Journal of Statistics*, 6, pp.1517–1549.

Mee, J.F., Berry, D.P. & Cromie, A.R., 2008. Prevalence of, and risk factors associated with, perinatal calf mortality in pasture-based Holstein-Friesian cows. *Animal : an international journal of animal bioscience*, 2(4), pp.613–20.

Meslin, F., Stöhr, K. & Heymann, D., 2000. Public health implications of emerging zoonoses. *Revue scientifique et technique (International Office of Epizootics)*, 19(1), pp.310–317.

Midthune, D.N. et al., 2005. Modeling Reporting Delays and Reporting Corrections in Cancer Registry Data. *Journal of the American Statistical Association*, 100(469), pp.61–70.

Morignat, E. et al., 2014. Assessment of the impact of the 2003 and 2006 heat waves on cattle mortality in France. *PloS one*, 9(3), p.e93176.

Nöremark, M. et al., 2009. Spatial and temporal investigations of reported movements, births and deaths of cattle and pigs in Sweden. *Acta veterinaria Scandinavica*, 51, p.37.

Noufaily, A. et al., 2013. An improved algorithm for outbreak detection in multiple surveillance systems. *Statistics in medicine*, 32(7), pp.1206–22.

Noufaily, A. et al., 2015. Modelling reporting delays for outbreak detection in infectious disease data. *J. R. Statist. Soc. A*, 178(1), pp.205–222.

Odoi, A. et al., 2009. Application of an automated surveillance-data-analysis system in a laboratory-based early-warning system for detection of an abortion outbreak in mares. *American Journal Of Veterinary Research*, 70(2), pp.247–256.

PAGE, E.S., 1954. Continuous inspection schemes. *Biometrika*, 41(1-2), pp.100–115.

Perrin, J.-B. et al., 2012. Assessment of the utility of routinely collected cattle census and disposal data for syndromic surveillance. *Preventive veterinary medicine*, 105, pp.244–252.

Perrin, J.-B. et al., 2010. Using the National Cattle Register to estimate the excess mortality during an epidemic: application to an outbreak of Bluetongue serotype 8. *Epidemics*, 2(4), pp.207–14.

Presi, P. et al., 2011. Bovine viral diarrhea (BVD) eradication in Switzerland - Experiences of the first two years. *Preventive veterinary medicine*, 99(2-4), pp.112–121.

R Core Team, 2013. R: A Language and Environment for Statistical Computing.

Roberts, S.W., 2012. Control Chart Tests Based on Geometric Moving Averages. *Technometrics*.

Robertson, C. et al., 2010. Mobile phone-based infectious disease surveillance system, Sri Lanka. *Emerging infectious diseases*, 16(10), pp.1524–31.

Robinson, P.A. & Epperson, W.B., 2013. Farm animal practitioners' views on their use and expectations of veterinary diagnostic laboratories. *The Veterinary record*, 172(19), p.503.

Robinson, S.E. & Christley, R.M., 2006. Identifying temporal variation in reported births, deaths and movements of cattle in Britain. *BMC veterinary research*, 2(1), p.11.

Del Rocio Amezcua, M. et al., 2010. Evaluation of a veterinary-based syndromic surveillance system implemented for swine. *The Canadian Journal of Veterinary Research*, 74, pp.241–251.

Rodríguez-Prieto, V. et al., 2014. Systematic review of surveillance systems and methods for early detection of exotic, new and re-emerging diseases in animal populations. *Epidemiology and Infection*, pp.1–25.

Roth, F. et al., 2003a. Human health benefits from livestock vaccination for brucellosis: case study. *Bulletin of the World Health Organization*, 81(12), pp.867–76.

Roth, F. et al., 2003b. Human health benefits from livestock vaccination for brucellosis: case study. *Bulletin of the World Health Organization*, 81(12), pp.867–76.

Salmon, M. et al., 2015. Bayesian outbreak detection in the presence of reporting delays. *Biometrical journal. Biometrische Zeitschrift*.

Sawford, K., Vollman, A.R. & Stephen, C., 2013. A focused ethnographic study of Alberta cattle veterinarians' decision making about diagnostic laboratory submissions and perceptions of surveillance programs. *PloS one*, 8(5), p.e64811.

Sawford, K., Vollman, A.R. & Stephen, C., 2012. A focused ethnographic study of Sri Lankan government field veterinarians' decision making about diagnostic laboratory submissions and perceptions of surveillance O. A. Dellagostin, ed. *PLoS ONE*, 7(10), p.e48035.

Schärrer, S. et al., 2014. Demographic model of the Swiss cattle population for the years 2009-2011 stratified by gender, age and production type. *PloS one*, 9(10), p.e109329.

Schiöler, L. & Frisén, M., 2012. Multivariate outbreak detection. *Journal of Applied Statistics*, 39(2), pp.223–242.

Shaffer, L.E., 2007. *Using pre-diagnostic data from veterinary laboratories to detect disease outbreaks in companion animals*. The Ohio State University.

Shewhart, W.A., 1931. *Economic control of quality of manufactured product*, Princeton: VanNostrandReinhold.

Shmueli, G. & Burkom, H., 2010. Statistical Challenges Facing Early Outbreak Detection in Biosurveillance. *Technometrics*, 52(1), pp.39–51.

Signorini, A., Segre, A.M. & Polgreen, P.M., 2011. The use of Twitter to track levels of disease activity and public concern in the U.S. during the influenza A H1N1 pandemic. *PloS one*, 6(5), p.e19467.

Silin, M. et al., 2010. The Impact of Monitoring Tuberculosis Reporting Delays in New York City. *JOURNAL OF PUBLIC HEALTH MANAGEMENT AND PRACTICE*, 16(5), pp.E9–E17.

Smyth, G.B., Dagley, K. & Tainsh, J., 2011. Insights into the economic consequences of the 2007 equine influenza outbreak in Australia. *Australian veterinary journal*, 89 Suppl 1, pp.151–8.

Sonesson, C. & Frisén, M., 2005. Multivariate Surveillance. In A. B. Lawson & K. Kleinman, eds. *Spatial and Syndromic Surveillance for Public Health*. Chichester, UK: John Wiley & Sons, Ltd, pp. 153–166.

Stärk, K.D.C. & Häsler, B., 2015. The value of information: Current challenges in surveillance implementation. *Preventive veterinary medicine*.

Struchen, R. et al., 2015. Investigating the potential of reported cattle mortality data in Switzerland for syndromic surveillance. *Preventive Veterinary Medicine*, 121, pp.1–7.

Tabnak, F. et al., 2000. A change-point model for reporting delays under change of AIDS case definition. *EUROPEAN JOURNAL OF EPIDEMIOLOGY*, 16(12), pp.1135–1141.

Tago, D. et al., 2014. Cost assessment of the movement restriction policy in France during the 2006 bluetongue virus episode (BTV-8). *Preventive Veterinary Medicine*, 117(3-4), pp.577–589.

Taylor, L.H., Latham, S.M. & Woolhouse, M.E.J., 2001. Risk factors for human disease emergence. *Philosophical transactions of the Royal Society of London. Series B, Biological sciences*, 356, pp.983–989.

The PostgreSQL Global Development Group, 2013. PostgreSQL.

Thomas-Bachli, A.L. et al., 2014. Exploring relationships between whole carcass condemnation abattoir data, non-disease factors and disease outbreaks in swine herds in Ontario (2001-2007). *BMC research notes*, 7(1), p.185.

Thompson, D. et al., 2002. Economic costs of the foot and mouth disease outbreak in the United Kingdom in 2001. *Revue scientifique et technique (International Office of Epizootics)*, 21(3), pp.675–87.

Thumbi, S.M. et al., 2015. Linking human health and livestock health: a “one-health” platform for integrated analysis of human health, livestock health, and economic welfare in livestock dependent communities. *PloS one*, 10(3), p.e0120761.

Torres, G. et al., 2015. Syndromic surveillance system based on near real-time cattle mortality monitoring. *Preventive Veterinary Medicine*.

Triple-S Project, 2011. Assessment of syndromic surveillance in Europe. *Lancet*, 378, pp.1833–4.

Unkel, S. et al., 2012. Statistical methods for the prospective detection of infectious disease outbreaks: a review. *Journal of the Royal Statistical Society: Series A (Statistics in Society)*, 175(1), pp.49–82.

Velthuis, A.G.J. et al., 2010. Financial consequences of the Dutch bluetongue serotype 8 epidemics of 2006 and 2007. *Preventive Veterinary Medicine*, 93(4), pp.294–304.

Vial, F. & Berezowski, J., 2014. A practical approach to designing syndromic surveillance systems for livestock and poultry. *Preventive veterinary medicine*.

Vial, F. & Reist, M., 2015. Comparison of whole carcass condemnation and partial carcass condemnation data for integration in a national syndromic surveillance system: The Swiss experience. *Meat science*, 101C, pp.48–55.

Vial, F., Thommen, S. & Held, L., 2015. A simulation study on the statistical monitoring of condemnation rates from slaughterhouses for syndromic surveillance: an evaluation based on Swiss data. *Epidemiology and Infection*, pp.1–11.

Vial, F., Wei, W. & Held, L., 2016. Methodological challenges to multivariate syndromic surveillance: a case study using Swiss animal health data. *BMC veterinary research*, 12(1), p.288.

Vourc'h, G. et al., 2006. Detecting emerging diseases in farm animals through clinical observations. *Emerging infectious diseases*, 12(2), pp.204–10.

Vrbova, L. et al., 2010. Systematic review of surveillance systems for emerging zoonoses. *Transboundary and emerging diseases*, 57, pp.154–161.

Wagner, M.M. et al., 2001. The emerging science of very early detection of disease outbreaks. *Journal of public health management and practice*, 7(6), pp.51–59.

Walker, J., 2013. New media methods for syndromic surveillance and disease modelling. *CAB Reviews: Perspectives in Agriculture, Veterinary Science, Nutrition and Natural Resources*, 8(031).

Waller, A.S., 2013. Strangles: Taking steps towards eradication. *Veterinary Microbiology*, 167(1-2), pp.50–60.

Warns-Petit, E. et al., 2010. Unsupervised clustering of wildlife necropsy data for syndromic surveillance. *BMC veterinary research*, 6(1), p.56.

Wendt, A., Kreienbrock, L. & Campe, A., 2015. Zoonotic disease surveillance - inventory of systems integrating human and animal disease information. *Zoonoses and public health*, 62, pp.61–74.

van den Wijngaard, C.C. et al., 2011. In search of hidden Q-fever outbreaks: linking syndromic hospital clusters to infected goat farms. *Epidemiology and infection*, 139(1), pp.19–26.

Wohlfender, F. et al., 2013. Überwachung von Pferdeinfektionskrankheiten in der Schweiz: Vergangenheit, Gegenwart und Zukunft. In *ALP Science*. pp. 22–23.

Wohlfender, F.D. et al., 2012. A review of twenty years of equine infectious disease monitoring in Switzerland: past, present and future. *Journal of Equine Veterinary Science*, 32(10), p.S92.

Woodall, W.H., 2006. The use of control charts in health-care and public-health surveillance. *Journal of Quality Technology*, 38, pp.89–104.

Woolhouse, M.E.J., 2002. Population biology of emerging and re-emerging pathogens. *Trends in Microbiology*, 10(10), pp.s3–s7.

Wuertz, D. et al., 2013. timeDate: Rmetrics - Chronological and Calendar Objects.

Yahav, I. & Shmueli, G., 2007. Algorithm Combination for Improved Performance in Biosurveillance Systems. In D. Zeng et al., eds. *Intelligence and Security Informatics: Biosurveillance*. Springer Berlin Heidelberg, pp. 91–102.

Yoo, H.-S. et al., 2009. Timeliness of national notifiable diseases surveillance system in Korea: a cross-sectional study. *BMC public health*, 9(1), p.93.

Zhou, X. et al., 2013. Monitoring Epidemic Alert Levels by Analyzing Internet Search Volume. *IEEE transactions on bio-medical engineering*, 60(2), pp.446–452.

Zinsstag, J. et al., 2011. From "one medicine" to "one health" and systemic approaches to health and well-being. *Preventive veterinary medicine*, 101(3-4), pp.148–56.

Zinsstag, J. et al., 2009. Transmission dynamics and economics of rabies control in dogs and humans in an African city. *Proceedings of the National Academy of Sciences of the United States of America*, 106(35), pp.14996–5001.

Curriculum Vitae

Personal information

Last name	Struchen
First name	Rahel
Mobile phone	+41 79 751 54 68
E-mail	rahel.struchen@bluewin.ch
Date of birth	12.12.1983
Place of origin	Täuffelen (BE)
Nationality	Switzerland

Education

2012-2015	PhD in Epidemiology Swiss Tropical and Public Health Institute, University of Basel, Switzerland Supervisors: Dr. Flavie Vial & Prof. Dr. Jakob Zinsstag
2007-2009	Master of Science (MSc) in Ecology and Evolution with special qualification in Evolution University of Bern, Switzerland
2004-2007	Bachelor of Science (BSc) in Biology with Major in Zoology University of Bern, Switzerland
2002-2004	Introductory studies in economy, sociology and political science University of Bern, Switzerland
1999-2002	Grammar school with focus on biology and chemistry Gymnasium und Handelsmittelschule Thun-Schadau, Switzerland

Professional experience

03/2011 - 09/2012	Federal Veterinary Office, Bern, Switzerland BVD coordination, Association of the Swiss Cantonal Veterinarians (VSKT)
01/2011 - 03/2011	Cantonal Veterinary Service, Bern, Switzerland Scientific assistant
03/2010 - 12/2010	Cantonal Veterinary Service, St. Gallen, Switzerland Scientific assistant
03/2009 - 02/2010	Federal Veterinary Office, Bern, Switzerland Internship at the Animal Health division

Conference contributions

Annual Conference of ILS, EPI and VPHI. December 2015, Bern, Switzerland. Oral presentation: *Detecting simulated disease outbreaks in routinely collected cattle mortality data.*

Conference of the International Society for Veterinary Epidemiology and Economics (ISVEE). November 2015, Mérida, Mexico. Oral presentation: *Evaluating the ability of temporal aberration-detection algorithms to detect simulated disease outbreaks in routinely collected cattle mortality data.*

European Congress on Tropical Medicine and International Health (ECTMIH). September 2015, Basel, Switzerland. Poster: *Detecting simulated disease outbreaks in routinely collected cattle mortality data.*

Swiss Statistics Meeting. August 2015, Bern, Switzerland. Oral presentation: *Evaluating the ability of temporal aberration-detection algorithms to detect simulated disease outbreaks in routinely collected cattle mortality data.*

Annual Meeting of the Society for Veterinary Epidemiology and Preventive Medicine (SVEPM). March 2015, Ghent, Belgium. Poster: *Voluntary participation & mobile reporting for surveillance – a one-year experience.*

DACh-Epidemiologietagung. September 2014, Zürich, Switzerland. Poster: *Equinella – Melde- und Informationsplattform für die Früherkennung von Pferdekrankheiten in der Schweiz.*

International Conference on Animal Health Surveillance (ICAHS). May 2014, Havana, Cuba. Poster: *Feasibility and motivation of veterinarians to collect equine epi-data using smartphones.*

Annual Meeting of the Society for Veterinary Epidemiology and Preventive Medicine (SVEPM). March 2014, Dublin, Ireland. Poster: *Feasibility and motivation of veterinarians to collect equine epi-data using smartphones.*

Scientific publications

Struchen R, Vial F, Andersson MG (2017) Value of evidence from syndromic surveillance with cumulative evidence from multiple data streams with delayed reporting. Scientific Reports 7: 1191. doi: 10.1038/s41598-017-01259-5.

Struchen R, Hadorn D, Wohlfender F, Balmer S, Süptitz S, Zinsstag J, Vial F (2016) Experiences with a voluntary surveillance system for early detection of equine diseases in Switzerland. Epidemiology and Infection 144: 1830-6. doi: 10.1017/S0950268816000091.

Struchen R, Reist M, Zinsstag J, Vial F (2015) Investigating the potential of reported cattle mortality data in Switzerland for syndromic surveillance. Preventive Veterinary Medicine 121: 1-7. doi:10.1016/j.prevetmed.2015.04.012.

Martínkoná N, Barnett R, Cucchi T, **Struchen R**, Pascal M, Fischer MC, Higham T, Brace S, Ho SY, Quéré JP, O'Higgins P, Excoffier L, Heckel G, Hoelzel AR, Dobney KM, Searle JB (2013) Divergent evolutionary processes associated with colonization of offshore islands. Molecular Ecology 22 (20): 5205-20. doi: 10.1111/mec.12462.

Presi P, **Struchen R**, Knight-Jones T, Scholl S, Heim D (2011) Bovine viral diarrhea (BVD) eradication in Switzerland – Experiences of the first two years. Preventive Veterinary Medicine 99: 112-121. doi:10.1016/j.prevetmed.2011.01.012.