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Review of surveillance approaches for early detection

WP2 - Detection of exotic, new, or re-emerging disease

Report

Systematic literature review of surveillance systems and methods for early detection of exotic, new and re-emerging diseases

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SUMMARY

Containing the spread of infectious diseases in this highly interconnected world requires effective surveillance strategies for rapidly detecting and minimising their impact on human and animal populations. Early detection is aimed at increasing the likelihood of timely detection of new, exotic or re-emerging threats. Enhancements to conventional surveillance strategies, specifically aimed at early warning, have been developed and implemented during the last decade worldwide. Considerable interest has been posed on approaches to detect health events instead of specific diseases, trying to establish a more generic, cost-effective and timely surveillance. These novel methods, which are mainly risk-based, include the development of technologies to better characterise the patterns of disease presence and spread, as well as the populations and areas at higher risk, in order to prioritise surveillance and optimise resources. Thus, the aim of this review consisted of determining whether and how novel methods for detection of emerging diseases can replace conventional strategies, while increasing the likelihood of early detection and still fulfilling all legal requirements.

Peer-reviewed articles focused on animal health surveillance written in English and published in 1993-2012 were considered. The search of the articles was carried out in CabAbstract and Scopus by a Boolean query to identify the topics of the review. Thereby, 3,507 articles were identified. Three screening rounds were performed to rule out articles according to several exclusion criteria, resulting in the inclusion of 128 articles in this systematic review. Information was extracted according to a list of 44 variables.

Most of the papers considered were published in 2011-2012 (n=62) and focused on Europe (n=57) and North America (n=33). Several diseases were highlighted in the review, as they have been the target of preventive and control measures in previous years, namely West Nile (n=21), bluetongue (n=16), or avian influenza (n=15). Many articles dealt with several wild and/or domestic species (n=25), and cattle was the most commonly targeted host species (n=31), followed by wild birds (n=15).

As for the methodologies described, three categories were mentioned: (i) **active surveillance strategies** (n=54); (ii) **passive surveillance strategies** (n=33); and (iii) **epidemiological methods applied in surveillance systems** (n=69). However, combinations between these three were also frequent (n=25). **Risk-based** approaches were used very commonly (n=61), especially in papers describing methods (n=45). Half of the papers (n=64) had a **scope for multiple diseases**.

The two most relevant active surveillance activities found in the review were ***vector surveillance*** (n=17) and ***sentinels*** (n=16). The former mostly involved the characterization of populations of midges (*Culicoides* spp.) (n=8) and mosquitoes (especially *Culex* spp.) (n=7), which are major vectors for emerging pathogens. Sentinel surveillance was applied for providing early information regarding susceptible animal species (n=5), periods (n=3) and/or areas (n=9) at higher risk of outbreak occurrence. When both strategies are combined (n=8), they seem to be an effective tool for early warning. As an alternative, especially for developing countries, ***participatory surveillance*** was also represented in the review (n=8). Although this method has several constraints, it is useful for providing a quick overview of the epidemiological situation of an area and establishing collaboration and communication between different institutions associated with animal and/or public health.

Regarding the passive surveillance strategies, ***syndromic surveillance*** is the most frequently mentioned approach (n=18). It is a novel and multi-purpose method, which was shown to provide a cost-effective reduction in the detection time, when compared with conventional methods for surveillance. Lack of harmonized criteria to define “syndromes” and exclusion of “false alarms” were found to be the most relevant disadvantages. However, once these limitations can be addressed, syndromic surveillance will be a useful component for integration into surveillance programmes.

In relation to the epidemiological methods, the most commonly used category were ***spatial epidemiology and GIS-based approaches*** (n=22), most of them risk-based (n=14). Risk mapping (n=6), and in combination with active surveillance activities (n=7), digital surveillance frameworks (n=5) and conventional epidemiological approaches (n=6) were the most frequent applications. A wide variety of ***statistical models*** (n=14) was also utilised, some of these based on innovative applications to surveillance. ***Digital surveillance*** (n=12) was presented as a recent framework with many advantages, though it is still in an adaptation phase. Other approaches found in the review included ***simulation modelling*** (n=8), ***risk assessments*** (n=7), ***scenario tree models*** (n=6) and ***cluster analyses*** (n=5). All of them offer potential to improve surveillance strategies, but several constraints were also identified.

This was the first systematic review of the scientific literature that has considered all approaches and methodologies targeting early detection. This information will be used to inform the development of tools to facilitate the design of cost-effective surveillance strategies in the framework of the RISKSUR project.

INTRODUCTION

Why is 'early detection' important?

In this globalized world, spread of diseases has become one of the most important threats to animal production. Recent disease examples such as the spread of West Nile disease across naïve populations in the United States, the devastating avian influenza pandemic and the appearance of emerging threats such as Schmallenberg virus or bioterrorism agents have highlighted the continuous change in disease patterns, as a consequence of the increase in global population, the intensification of livestock productions and the massive trade. Containing the spread of such diseases in an interconnected world requires new surveillance strategies for signs of an outbreak, rapid recognition of its presence, and diagnosis of its causative agent, together with strategies and resources for an appropriate and efficient response (NCR, 2007). Thus, early detection of these threats is essential not only for animal health and the trade of animals worldwide, but also for the benefit of global public health, in the context of a 'One Health' approach. Early detection (or early-warning surveillance) can be defined as "surveillance of health indicators and diseases in defined populations in order to increase the likelihood of timely detection of undefined (new) or unexpected (exotic or re-emerging) threats" (Hoinville *et al*., 2013). Early detection of diseases has been the focus of many surveillance programmes in Europe, as detecting the threat rapidly minimises the potential consequences of the disease spread. When there is a failure in early detection of an emerging disease, the consequences may be devastating. As an example, amongst the consequences of the foot-and-mouth outbreak in United Kingdom in 2001 were, apart from the disease in affected animals, the slaughter of more than 10 million livestock in UK and the spread of the infection to France, The Netherlands and Ireland. It resulted in a major economic loss of at least $12 billion due to the cost of farmer compensation and trade restrictions, as well as various other impacts such as reduced tourism to the UK (Kitching *et al*., 2006). Clearly, early detection of infectious diseases is the key requirement for being able to respond in a rapid and cost-effective manner to any disease incursions.

Shortcoming of conventional methods

In response to the realisation of the need of early detection of infectious diseases in animals, methods for early warning have been developed and implemented for several diseases. Depending on the methodology used to collect the data, surveillance is generally classified into active or passive approaches.

Passive surveillance

Passive surveillance is defined as "the observer-initiated provision of animal health related data (*e.g.* voluntary notification of suspect disease) or the use of existing data for surveillance" (ICAHS, 2012). Decisions about whether information is provided, and what information is provided from which animals is made by the data provider. In general, it is characterized by the report of clinical symptoms or disease suspicion to the veterinary authorities. Passive surveillance usually also involves laboratory confirmation of specific disease agents and disease reports by veterinarians. The main limitation of this type of surveillance is that it will involve a varying degree of under-reporting, a potentially long time lag between disease introduction and diagnosis and a misdiagnosis due to the use of laboratory test targeted for other specific pathogens (Dórea *et al*., 2011). The low sensitivity of traditional surveillance is related to its focus on specific and previously described diseases, which reduces the likelihood of early diagnosis of emerging threats. Moreover, the usually poor awareness of the symptoms of exotic or unknown diseases amongst farmers, technicians and veterinarians further reduces the sensitivity of passive surveillance. However, an important strength of this type of surveillance is that it provides coverage of the whole population at risk. For that reason, many authors recommend the inclusion of a passive component in early detection surveillance systems in order to complement other active methods of surveillance (Doherr and Audigé, 2001).

Active surveillance

Active surveillance is defined as “the investigator-initiated collection of animal health related data through actions scheduled in advance using a defined protocol” (ICAHS, 2012). Decisions about whether information is collected, and what information should be collected from which animals is made by the investigator. In general, it is characterized by targeted and purposive collection of data. The collected information can be both epidemiological (*e.g.* monitoring of susceptible populations) and demographic (*e.g.* collection of data on trade movements).

The probability of detecting the hazard depends on two characteristics: the sampling design (*i.e.* sampling method, spatial and temporal coverage and sample size) and the accuracy of the diagnostic method used to detect the agent in the samples obtained (Thurmond, 2003). Thus, these two characteristics are critical limitations of the surveillance component. In fact, the attributes of the active surveillance, such as precision, repeatability, reproducibility, timeliness, multiple utility and value, directly depend on it.

Another criterion used by the OIE to characterise different surveillance systems is on the basis of the sampling strategy. Regarding this, the following sampling strategies can be considered (ICAHS, 2012): (i) census; (ii) random; (iii) systematic (*e.g.* selected on certain days); (iv) convenient; (v) haphazard; (vi) purposive; (vii) volunteer; (viii) event-related (*e.g.* pre- or post-movement); and (ix) participant recommendation. Another classification could be based on the use of probabilistic or non-probabilistic sampling methods, which can be even more crucial to infer conclusions.

Apart from these, several other active strategies can be implemented, such as sentinels or vector surveillance. Sentinel surveillance is defined as “the repeated collection of information from the same selected sites or groups of animals (*e.g.* veterinary practices, laboratories, herds or animals) to identify changes in the health status of a specified population over time” (Hoinville et al., 2012). These sentinels should represent a larger population of interest and they may be selected on a risk basis, randomly, or on the basis of convenience or compliance. Vector surveillance consists of the continuous monitoring of vector populations, mainly mosquitoes and ticks, responsible for the transmission of infectious diseases. Vector surveillance, when supported by robust eco-climatic baseline data, may offer capability for early detection of pathogens in a specific area.

Historically, animal disease surveillance activities have focused on measuring the effects of endemic diseases or early detection of exotic disease introduction. However, these unifocal surveillance efforts, aimed at specific threats, are not particularly effective at detecting new diseases (Tataryn *et al*., 2007). Most of the current surveillance systems are poorly sensitive and therefore result in delayed detection of emerging infectious diseases, which by definition are unexpected and may be caused by unusual and previously unknown pathogens. Timeliness, referred to as “the difference between the onset of an outbreak and the discovery of the outbreak” (Wagner *et al*., 2001) is also often an issue, especially for highly contagious diseases, such as SARS or pandemic influenza (Morse, 2012). Other issues include the high costs and low sensitivity of random active surveillance and the frequent need to combine passive surveillance with an active surveillance component to improve the ability to detect hazards early. For these reasons, the scientific community is focusing on developing more cost-effective systems to improve surveillance.

In recent years, approaches have been developed to solve the limitations of traditional surveillance. This emerging need for efficient and cost-effective surveillance systems has led to the risk-based selection of hazards and screening of populations at increased risk (Stärk *et al.*, 2006). This concept of 'risk-based surveillance' offers a more efficient approach for early detection and management of diseases in order to prioritise efforts and optimise resources (Stärk *et al*., 2006). Other developments include new technologies and tools that allow better characterisation of the spatial and temporal patterns of the disease presence and spread, as well as the design of new strategies to improve the current surveillance systems.

Brief summary of recent developments of new methods and how they approach these challenges

Considerable interest in recent years has focused on the detection of health events, rather than specific diseases, as a pathway to more generic and timely surveillance (Morse, 2012). This strategy is especially aimed at improving sensitivity and timeliness, with the goal of near real-time detection. In the past years, several developments have helped to move this goal closer to reality (Morse, 2012). These include 'syndromic surveillance', the evolution of 'digital surveillance', the development of new enabling technologies in communication and diagnostics and the enhancement of 'participatory surveillance'.

Syndromic surveillance

Syndromic surveillance systems use pre-diagnostic information, often available in electronic health databases from different sources, with the premise that such pre-diagnostic information may provide earlier indications of a disease outbreak rather than waiting for a confirmed diagnosis (Babin, 2010). While syndromic surveillance shows great promise and may provide valuable information that would be missed by conventional systems, there is still a need for evaluation of these systems to understand how they can best contribute to achieving surveillance aims, which data are better for which situations, how to interpret these data and how these sources can be combined to provide a more accurate or complete picture and context (Morse, 2012).

Syndromic surveillance can be designed to minimize the main limitations of passive surveillance methods based on laboratory confirmation and disease reports by clinicians (Dórea *et al*., 2011). The advantages of this surveillance system are comprehensive coverage of many diseases within a single monitoring system, detection of potential emerging diseases, maximizing the value of existing data sources, integration of public health with veterinary data, development of new analytical methods, technological innovation, flexibility in the type of data available and desired system outcome, encouraging stakeholder participation and an increase in negative reporting (Dórea *et al*., 2011).

Participatory surveillance

Participatory surveillance is understood as an approach in which stakeholders are involved to identify and solve their problems. Using participatory methods in animal health surveillance systems gives owners an important role in describing, analysing and planning animal health tasks. This surveillance methodology presents several advantages, such as (i) direct involvement of people who can rapidly detect the hazards in the livestock due to their technical knowledge; (ii) it includes social aspects of the diseases; (iii) it allows the integration of different sources of information; (iv) it is relatively easy to implement; (v) it is risk-based in the sense that it uses a risk-based sampling approach that prioritises high-risk sites, especially for early detection purposes; (vi) it is a flexible qualitative approach that allows for the discovery of new un-expected threats (Mariner *et al*., 2011); and (vii) it helps reducing public costs as it is performed by private actors mostly on a voluntary basis. For these reasons, participatory surveillance is an emerging approach being implemented particularly for infectious diseases mainly in some developing countries, where it is essential to cost-effectively prioritise resources. Participatory approaches can therefore be used to improve and complement the quality of data obtained through active surveillance. Thus, prioritisation of diseases and sampling locations can increase the sensitivity of methods and improve timeliness, which are key factors in early detection of hazards.

Digital surveillance

Although there is no precise definition of the term, it broadly includes the use of the internet and computer technologies for collecting and processing health information, including outbreak reports and surveillance data (Morse, 2012). Digital surveillance systems have the advantage of fulfilling numerous basic criteria for early detection of infectious diseases: usefulness, simplicity of the operational phase, flexibility, data quality dependent on source databases, acceptability and timeliness. Digital systems can integrate a great amount of real-time information of various nature and origins, providing outputs that allow assessment of the risk of occurrence of a specific threat.

Introduction of the project aims and aim of the review

In recent years new epidemiological methodologies have been developed to overcome some of the difficulties mentioned above. However, these novel methods are not sufficiently recognised to become a standard component of current internationally recognized surveillance systems. Thus, the RISKSUR project was initiated in order “to find efficient and practical solutions taking advantage of the novel scientific methodologies” and “to define frameworks and integrated tools that allow the design and implementation of epidemiological and economically optimized animal health surveillance systems”. The project aims “to develop decision support tools for the design of cost-effective risk-based surveillance systems that integrate the most recent advances in epidemiological methodologies” for three different surveillance objectives: 1) early detection of animal disease, 2) demonstration of freedom from animal disease, and 3) determination of disease frequency and detection of cases of endemic animal disease.

This systematic review is a first step towards addressing the surveillance objective for ‘early detection of animal diseases’. The aim of this review is to “determine whether and where conventional strategies can be replaced by novel methods that overcome the limiting aspects of conventional methods, by improving the likelihood of early detection of emerging diseases and still fulfilling the legal requirements to the same extent as the established conventional methods”. Where appropriate, gaps in methodological concepts shall be identified that can be targeted by new developments.

MATERIAL AND METHODS

Literature sources and search strategy

The systematic review was aimed at scientific articles on current surveillance methods, systems and approaches. The RISKSUR partners developed an approach based on systematic search of public databases using keywords of general interest for surveillance data analysis and specific keywords for each work package (WP): early detection of new, exotic and re-emergent diseases (WP2), demonstration of freedom from disease (WP3) and prevalence estimation for endemic diseases (WP4).

The search for peer-reviewed articles was performed in CabAbstract and Scopus. It was restricted to articles written in English and published during the last 20 years (*i.e.* 1993-2013) in SCI (Scientific Citation Information, available at http://www.sci-thomsonreuters.org/) journals.

A list of keywords was combined into a Boolean query to identify the topics of this review, namely: (i) *general theme (surveillance)*, (ii) *exotic and emerging diseases*, (iii) *early detection*, and (iv) *novel methodologies* (Table 1). These terms were searched for in the title and abstract.

Table 1. List of terms used for the database search for WP2.

Topic	Search terms
General theme (surveillance)	surveillance OR monitor* AND animal* OR livestock OR veterinar* OR fish* OR wildlife OR "food system*" OR herd* OR farm* OR cattle OR cow* OR bovine OR ruminant* OR pig* OR porcine OR swine OR sheep OR goat* OR poultry OR bird* OR avian OR horse OR equine OR equid* OR cat* OR dog* AND disease* OR health OR infection* OR outbreak
	AND
Exotic and emerging diseases	exotic OR emerg*
	AND
Early detection	"early warning" OR "early detection"
	AND
Novel methodologies	syndromic OR participatory OR sentinel OR scanning

Definitions

Definitions are extracted from the report 'Animal health surveillance terminology- summary of key definitions from final report - November 2012', a workshop held to discuss the terminology used in animal health surveillance with the aim of standardizing the information between research groups, stakeholders and decision-makers (ICAHS, 2012).

- **Threat**: the hazard or infectious disease which can potentially affect a susceptible population and spread between individuals and herds. Depending on the spread of the hazard along populations, the health and economic consequences are variable.

- **Pattern of disease occurrence**:
  - ✓ ***Endemic***: a disease that is known to be present in the population of interest.
  - ✓ ***Sporadic***: a known disease which occurs intermittently in an irregular or haphazard pattern.
  - ✓ ***Exotic***: a previously defined (known) disease that crosses political boundaries to occur in a country or region in which it is not currently recorded as present.
  - ✓ ***Re-emerging***: a previously defined (known) disease that is currently either absent or present at a low level, in the population in a defined geographical area that re-appears or significantly increases in prevalence.
  - ✓ ***New (emerging)***: a previously undefined (unknown) disease or condition, which may result from the evolution or change in an existing pathogen or parasite causing a change of strain, host range, vector, or an increase in pathogenicity; or may be the occurrence of any other previously undefined condition.

- **Surveillance**: the systematic, continuous or repeated, measurement, collection, collation, analysis, interpretation and timely dissemination of animal health and welfare related data from defined populations, essential for describing health hazard occurrence and to contribute to the planning, implementation, and evaluation of risk mitigation measures.

- **Risk-based surveillance**: use of information about the probability of occurrence and the magnitude of the biological and/or economic consequence of health hazards to plan, design or interpret the results obtained from surveillance systems. Risk-based surveillance can include one or several of the following four approaches:

  - ✓ ***Risk-based prioritisation***: determining which hazards should be selected for surveillance based on information about the probability of their occurrence and the extent of biologic and/or economic consequence of their occurrence.
  - ✓ ***Risk-based requirement***: use of prior or additional information about the probability of hazard occurrence to revise the surveillance intensity required to achieve the stated surveillance purpose.
  - ✓ ***Risk-based sampling***: designing a sampling strategy to reduce the cost or enhance the accuracy of surveillance by preferentially sampling strata (*e.g.* age groups or geographical areas) within the target population that are more likely to be exposed, affected, detected, become affected, transmit infection or cause other consequences (*e.g*. large economic losses or trade restrictions).
  - ✓ ***Risk-based analysis***: use of prior or additional information about the probability of hazard occurrence, including contextual information and prior likelihood of disease, in the analysis of surveillance data to revise conclusions about disease status.

- **Sentinel surveillance**: the repeated collection of information from the same selected sites or groups of animals (*e.g.* veterinary practices, laboratories, herds or animals) to identify changes in the health status of a specified population over time. These sentinels should act as a proxy for the larger population of interest; they may be selected on the basis of risk but can also be selected randomly or on the basis of convenience or compliance.
- **Participatory surveillance/expert opinion**: participatory surveillance explores traditional information networks by using participatory rural appraisal methods such as ranking, scoring and visualising techniques to conduct risk-based, hazard-specific surveillance. The approach uses semi-structured interviews with key informants to enable communities to provide their knowledge regarding health events, risks, impacts and control opportunities by gathering qualitative health data from defined populations. The analysis of participatory data emphasises the comparison of information obtained from multiple informants using a variety of techniques to obtain the most likely interpretation of events. The objective is to enhance sensitivity by identifying cases based on a clinical case definition; these may then be evaluated and confirmed using rapid tests in the field or laboratory diagnostics. Conventional epidemiological investigation techniques can be used to evaluate and confirm outbreaks detected by participatory surveillance as part of trace-back and forwards.

- **Syndromic surveillance**: surveillance that uses health-related information (clinical signs or other data) that may precede or substitute for formal diagnosis; this information may be used to indicate a sufficient probability of a change in the health of the population to deserve further investigation or to enable a timely assessment of the impact of health threats which may require action. This type of surveillance is not usually focused on a particular threat and can be used to detect a variety of diseases or pathogens including new (emerging) diseases, so it is particularly applicable for early warning surveillance.

Study selection and data extraction

After a first screening for exclusion of articles not published in peer-reviewed journals, two more screenings were performed to apply primary and secondary exclusion criteria, in order to select articles relevant for the purposes of this review. These two later screenings were called 'primary' and 'secondary' and are described below as such.

Primary screening

The first screening was based on title and abstract, and consisted of the exclusion of papers that fulfilled at least one of the following criteria:

- **General criteria:**
  - ✓ The paper does not focus on animal health.
  - ✓ The paper does not focus on surveillance as defined for this project.
  - ✓ The paper focuses more on control measures than on surveillance.
  - ✓ The paper is only descriptive (historical trend of the disease, pathogenicity…).
  - ✓ The paper is a general review of a particular disease.
  - ✓ The paper focuses on experimental infections.
  - ✓ The paper is a case report.
  - ✓ The paper focuses on molecular characterizations of a pathogen.
  - ✓ The paper focuses on diagnostic test evaluations.
  - ✓ The paper focuses on the evaluation of vaccine efficacy.

- **Criteria for WP2**:
  - ✓ The paper does not focus on early detection.
  - ✓ The disease is endemic in the study area.
  - ✓ The paper focuses on early detection of new species rather than of new diseases.
  - ✓ The paper focuses on the early detection of antimicrobial resistance.

Secondary screening

The remaining selected papers were assessed for eligibility by five reviewers, who reviewed different sets of articles independently, but following common criteria and reaching an agreement that was exercised and improved. Thus, these reviewers selected the eligible articles by reading the full text and applying the following secondary exclusion criteria:

- Insufficient information provided to allow the evaluation of described methods;
- No surveillance design/methods described;
- The paper is a general review of a group of diseases (arboviroses, diseases of wildlife…);
- The paper is a general review of method(s) for surveillance (*e.g.* reviewing the use of participatory surveillance in a generalist way);
- Any of the primary exclusion criteria that was not apparent from reading the titles and abstracts only.

Variable extraction

A framework for data collection, based on harmonized data extraction protocols, was constructed in collaboration with members of WP 3 and 4. A list of the 44 selected variables was defined (Annex II).

Certain variables deserve further clarification:

- Disease/threat: we attempted to group threats or diseases in order to facilitate their analysis (*e.g.* certain papers dealt with avian influenza A; in the variable “General” we indicated avian influenza, while in the variable “Specific” we defined avian influenza A).

- Disease status in the study area: we used the categories defined above (see “Material and methods – Definitions – Patterns of disease occurrence”) with some modifications. We grouped the categories “Emerging” and “Re-emerging” together, since their nature in terms of disease surveillance is comparable. The category “New” was redefined as “Exotic” or “Emerging” depending on its absence or presence in the study area, respectively. However, we included the category “Suspected” (*i.e.* probably present but not detected nor confirmed yet).

- Type of approach – specific: we defined categories for each of the three main groups of methodologies found in the papers:
    - “Methods”:
        - “Statistical model”: including regression analyses, Bayesian modelling…
        - “Simulation model”: mathematical models to simulate disease epidemics (and their potential consequences) (*e.g.* SIR models, Monte Carlo models, agent-based models).
        - “Risk assessment”: models characterizing the likelihood of exposure and/or release of threats given certain risk pathways.
        - “Scenario tree model”: definition of a structure of nodes and branches representing all possible risk pathways and scenarios for the evaluation of surveillance systems.
            - Note: risk assessments and scenario tree models may have the same conceptual structure (*i.e.* tree-like, use of distribution for probabilities), but they have different aims.
        - “Cluster analysis”: study of the spatial and/or temporal pattern of disease transmission, based on different methods.
        - “Environmental model”: models predicting climatic and environmental factors affecting diseases. These factors may be related to the diseases or pathogens directly (*e.g.* effect on the incubation period or the resistance of the pathogen in the environment) or indirectly (*e.g.* effect on the vector population dynamics or movements).
        - “Spatial epidemiology (GIS)”: spatial epidemiological approaches, especially those that are GIS-based.
        - “Digital surveillance” (see definition above).
        - “Literature review”: search for and subsequent variable extraction from a subset of scientific documents (*e.g.* SCI journal articles, proceedings, reports, technical documents…) dealing with a specific topic.
        - “Others”: any other approaches not included in the categories mentioned above.

    - “Active”:
        - “Serosurvey”: search for antibodies against a specific pathogen.
        - “Pathogen determination”: search for a specific pathogen (or its antigens or nucleic acids).
        - “Sentinels” (see definition above).
        - “Vector surveillance”: search for vectors implied in transmission of diseases.
        - “Participatory” (see definition above).
        - “Others”: any other approaches not included in the categories mentioned above.

    - Passive:
        - “Clinical investigation”: monitoring of clinical signs compatible with disease(s).

- "Death investigation": monitoring of an unexpected or increased mortality rate.
- "Syndromic" (see definition above).
- "Parameter monitoring": screening of biological indicators (*e.g.* animal temperature, animal activity…).
- "Others": approaches not included in the categories mentioned above.

- Risk-based category: one of the four risk-based categories (or a combination of several) was chosen, namely "risk-based prioritisation", "risk-based requirement", "risk-based sampling", and "risk-based analysis".

- Surveillance nature: this variable was related to the target of surveillance, in terms of a "single" hazard or several. If the latter was the case, two options had to be considered:
  - "General": when the surveillance system was targeted towards a specific purpose, but not to any specific hazard.
  - "Multi-objective": when the mentioned system was focused towards more than one specified hazard.

- Data source: we considered "Primary" when the data were obtained in the same study, and "Secondary" when the authors used data from other studies or sources. Sometimes data used for the study included "Both" categories.

The relevant information was extracted from the articles and stored in an Excel database. Once all articles had been read, a cross-checking was performed in order to ensure harmonization of criteria.

Data analysis

Descriptive analyses of the data collected were performed. Variables were analysed separately and where appropriate in combination, in order to obtain maximum amount of information from the articles.

RESULTS

Selection process

The search in the scientific databases returned 3,507 articles, but 324 of those were not considered since they were not published in SCI journals. Thus, 3,183 papers remained after the first screening. Applying the primary criteria, 308 papers were selected (*i.e.* there was an approximate inclusion rate = 1/10). The process resulted in **271 articles** obtained in electronic format (Adobe PDF) either through download from the World Wide Web or through e-mail request from the corresponding authors. Upon review of these articles, other 73 papers were excluded due to the primary exclusion criteria, which were not obvious from title and abstract.

The two most frequently used exclusion criteria after this screening were "The paper is a general review of method(s) for surveillance" (n=27) and "The paper is a general review of a group of diseases" (*e.g.* arboviroses, diseases of wildlife…) (n=22). Other papers were excluded because there was "Insufficient information to allow evaluation of method(s) described" (n=12) or "No surveillance design/methods described" (n=9). In total, 70 papers were excluded based on the secondary criteria, meaning that the information provided was not appropriate for the purpose of this review. The frequency of the exclusion criteria used for the whole process is listed below (Table 2).

Table 2. Frequency and proportion of use of each exclusion criteria.

Exclusion criteria	Count	Percentage
The paper is a general review of method(s) for surveillance	27	18.88%
The paper is a general review of a group of diseases	22	15.38%
The paper does not focus on animal health	14	9.79%
Insufficient information to allow evaluation of method described	12	8.39%
No surveillance design/methods described	9	6.29%
The paper does not focus on surveillance as defined for this project	8	5.59%
The disease is endemic in the study area	7	4.90%
The paper focuses more on control measures than on surveillance	7	4.90%
The paper focuses on molecular characterizations of a pathogen	7	4.90%
The paper is only descriptive (historical trend of the disease, pathogenicity…)	7	4.90%
The paper is a general review of a particular disease	6	4.20%
Any of the primary exclusion criteria that were not apparent from reading the title and abstracts only	6	4.20%
The year of publication is before 1992	3	2.10%
The paper focuses on experimental infections	3	2.10%
The paper focuses more on control measures than on surveillance.	2	1.40%
The paper focuses on diagnostic test evaluations	2	1.40%
The papers focuses on the early detection of antimicrobial resistance	1	0.70%

Finally, 143 articles out of the 271 were excluded, which means **variables from 128 articles were collected**. (Annex I) (Figure 1).

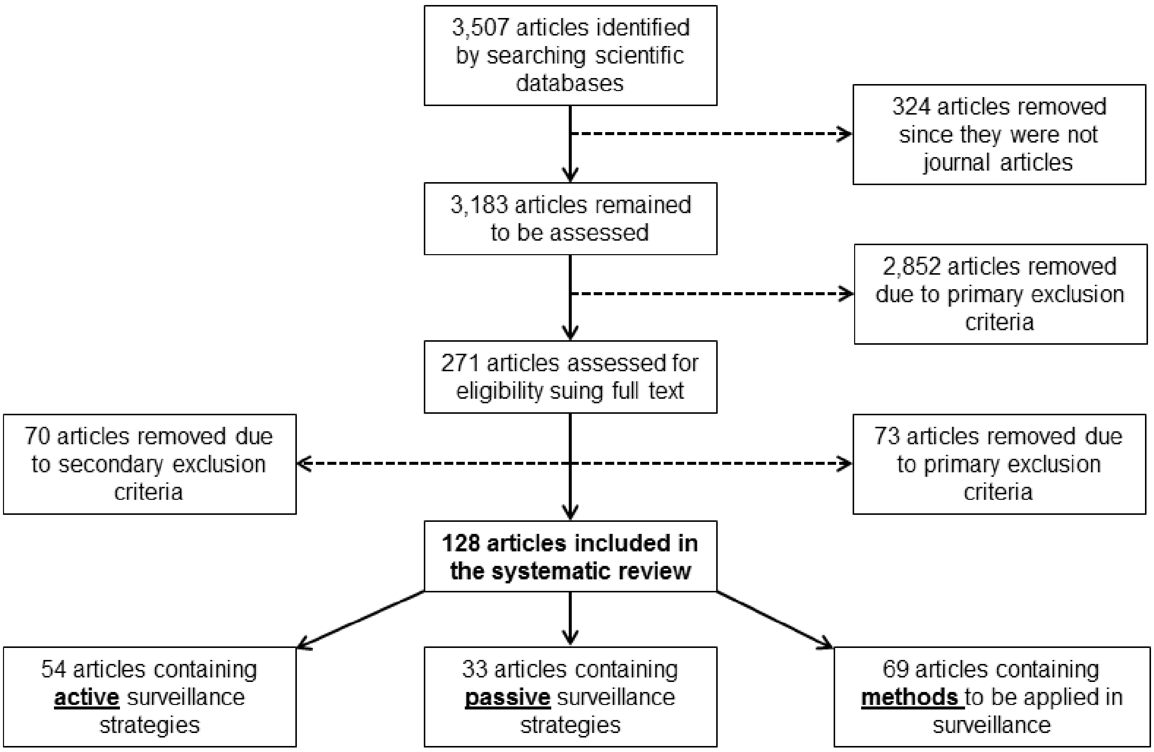

Figure 1. Flowchart summarising the article selection process.

Descriptive results

Most of papers included in the review were research articles (n=102), although we also included poster proceedings (n=13), reviews (n=6), reports (n=4) and oral communication proceedings (n=4). The majority of the articles were published after 2005, particularly in 2011 (n=35) and 2012 (n=27) (Figure 2). It is important to note that 16 of the 35 papers considered in 2011 (*i.e*. all the 13 posters and 3 out of the 4 oral communications) belong to the proceedings of the ICAHS 2011, namely *Epidémiologie et Santé Animal* volume 59-60.

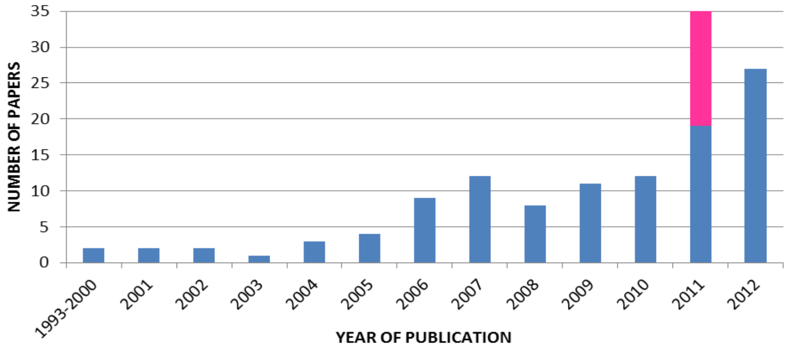

Figure 2. Distribution of the number of papers included in the review by year of publication. The bar in pink represents the papers reviewed in 2011 published in *Epidémiologie et Santé Animal* volume 59-60.

General aspects of the papers

There were four diseases or categories of threats that might be highlighted: West Nile (n=21), bluetongue (n=16), avian influenza (n=15), other emerging and/or re-emerging diseases (not specified) (n=7). In addition, 40 articles dealt with several diseases (*i.e.* not included in any category) (Table 3).

Table 3. Diseases studied in the articles, grouped per general category of disease.

Diseases	Count	Zoonotic	Considered disease status in the study areas
West Nile fever	21	Yes	Emg, Ex
Bluetongue	16	No	Emg, Ex
Avian influenza	15	Yes	Emg, Ex
Rift Valley Fever	5	Yes	End, Emg, Ex, Sus
Foot-and-mouth disease	3	No	Ex
Abortions	2	Yes/No	NA
Arboviral diseases	2	Yes	End, Emg, Ex
Classical swine fever	2	No	Ex
Lyme disease	2	Yes	Emg
Salmonellosis	2	Yes	Emg, Ex
African swine fever	1	No	Ex
Bovine spongiform encephalopathy	1	Yes	ND
Bovine tuberculosis	1	Yes	Emg
Eosinophilic meningitis (angiostrongyliasis)	1	Yes	Emg
Epizootic hemorrhagic disease	1	No	Ex

End: endemic; Emg: emerging; Ex: exotic; Sus: suspected; NA: not applicable; ND: no defined

Diseases	Count	Zoonotic	Considered disease status in the study areas
Erysipelosis	1	Yes	ND
Japanese encephalitis	1	Yes	Emg
Pigeon paramyxovirus	1	No	Emg
Rabies	1	Yes	Emg
St. Louis encephalitis	1	Yes	Emg
Usutu virus	1	Yes	Emg
Other emerging and/or re-emerging diseases	7	Yes/No	
Several diseases	40	Yes/No	
Total	128		

End: endemic; Emg: emerging; Ex: exotic; Sus: suspected; NA: not applicable; ND: no defined

As for the location of the studies, the main findings are summarized below (Table 4).

Table 4. Frequency of studies by target diseases in different regions of the world.

Continent	Count	Most relevant disease(s) or category(ies) of threat
Africa	9	Rift Valley fever (n=3), several diseases (n=5)
North America	33	West Nile (n=9), several diseases (n=12)
Central America	1	West Nile (n=1)
South America	3	Avian influenza (n=2)
Asia	9	Avian influenza (n=2), several diseases (n=3)
Europe	57	Bluetongue (n=15), West Nile (n=11), avian influenza (n=9), several diseases (n=12)
Oceania	5	Foot-and-mouth disease (n=2)
World	5	Emerging and/or re-emerging diseases (n=2)
(Not applicable)	1	
(No data)	5	

As displayed in the table, most of the studies were conducted in North America (n=33) and Europe (n=57), mainly in Italy (n=9), United Kingdom (n=9), Spain (n=7), France (n=6), and Germany (n=6). The diseases highlighted as the most studied in each continent are not surprising, since they are important infectious exotic or emerging diseases that have been the target of preventive and control measures over the last years in each region of the world. In fact, exotic (n=30) and the emerging (n=57) diseases are the most representative in this review.

In addition, the majority of the studies were related to zoonosis (n=69), which normally increases the relevance of the disease and the allocation of resources.

The review covered a wide range of target host species, both domestic and wild (Figure 3). The most common species were the bovines (n=44). Interestingly, 37 studies (*i.e.* 26.56%) from 2001 focused on methods involving wildlife, especially related to emerging diseases (n=27, 21.09%).

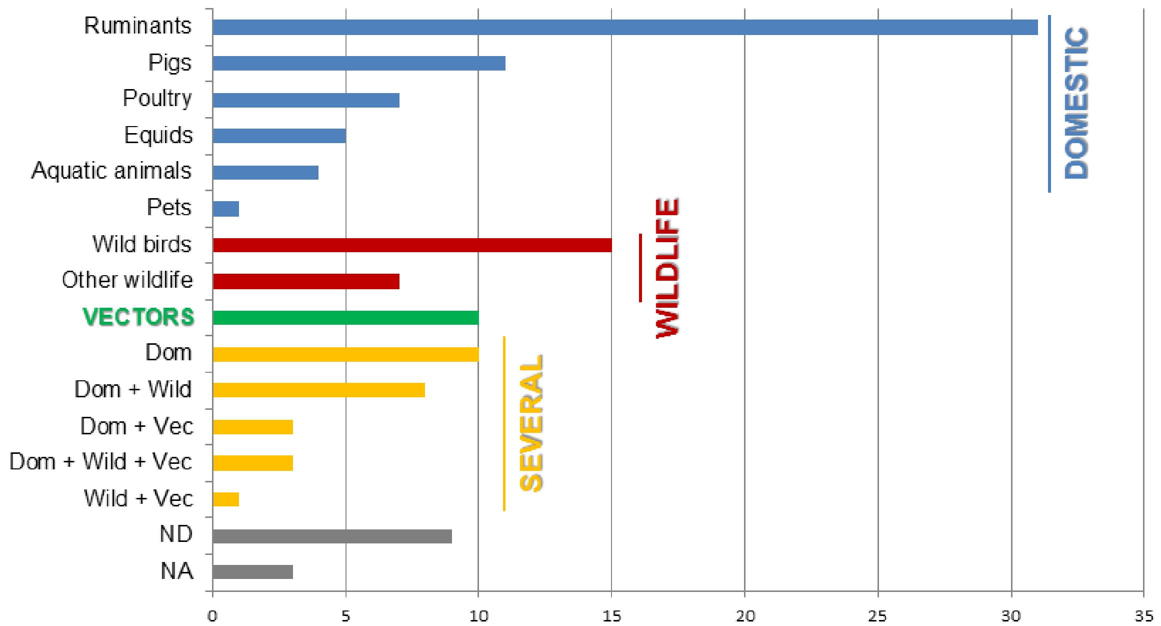

Figure 3. Distribution of the number of papers by target host species. The main host species include domestic animals (Dom, in blue), wildlife (Wild, in red), vectors (Vec, in green), and combination of several of those (in yellow). Papers in which the target host was not specifically defined (ND) or those in which the species was not applicable (NA) are also indicated.

Methodologies

The articles were classified into three categories (Figure 4):

- Papers including active surveillance strategies (n=54).
- Papers including passive surveillance strategies (n=33).
- Papers including methods to be applied in surveillance systems (n=69).

Some of the articles contained more than one of the above cited categories, as shown by the stripes in the second pie-chart of Figure 4 (*e.g.* active surveillance to collect the data, followed by implementation of a model).

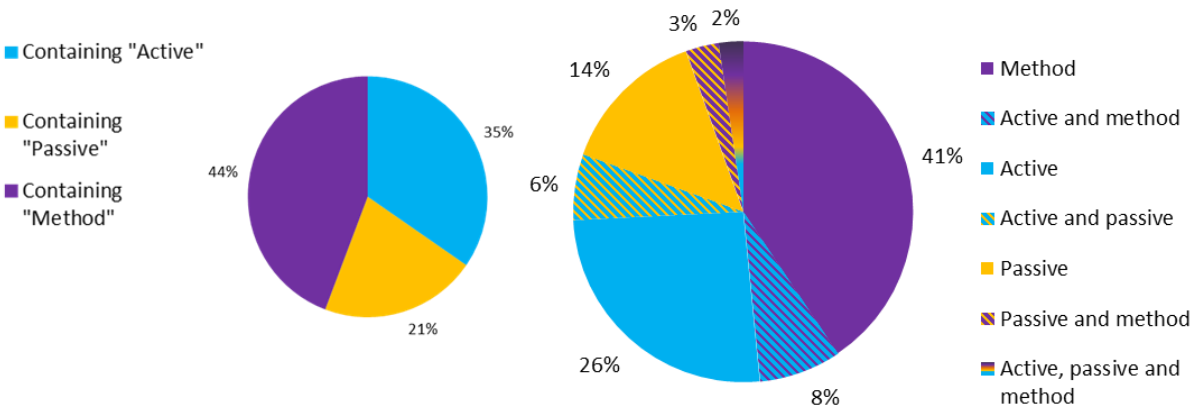

Figure 4. Distribution of the papers by type of approach. The pie chart on the left indicates the three main aggregated categories (see above), while the pie chart on the right shows the specific categories (*i.e.* including the combinations).

We identified papers which data source was primary (n=56), secondary (n=54), or both (n=18). As for the use of data, most of the papers were based on real data (n=66), while 41 are based on simulations and 25 on both. Interestingly, papers where real data were used were mostly classified as primary data, (Figure 5) indicating that real data is provided and analyzed by the authors, mainly from samplings and collection of epidemiological data. Another interesting observation is that papers which include simulations frequently use secondary data, mainly from databases external to the authors.

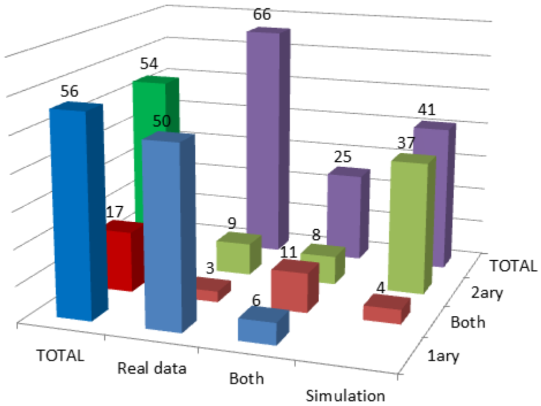

Figure 5. Distribution of the papers by data source (*i.e.* primary, secondary, or both) **and data management method** (*i.e.* real data, simulation, or both).

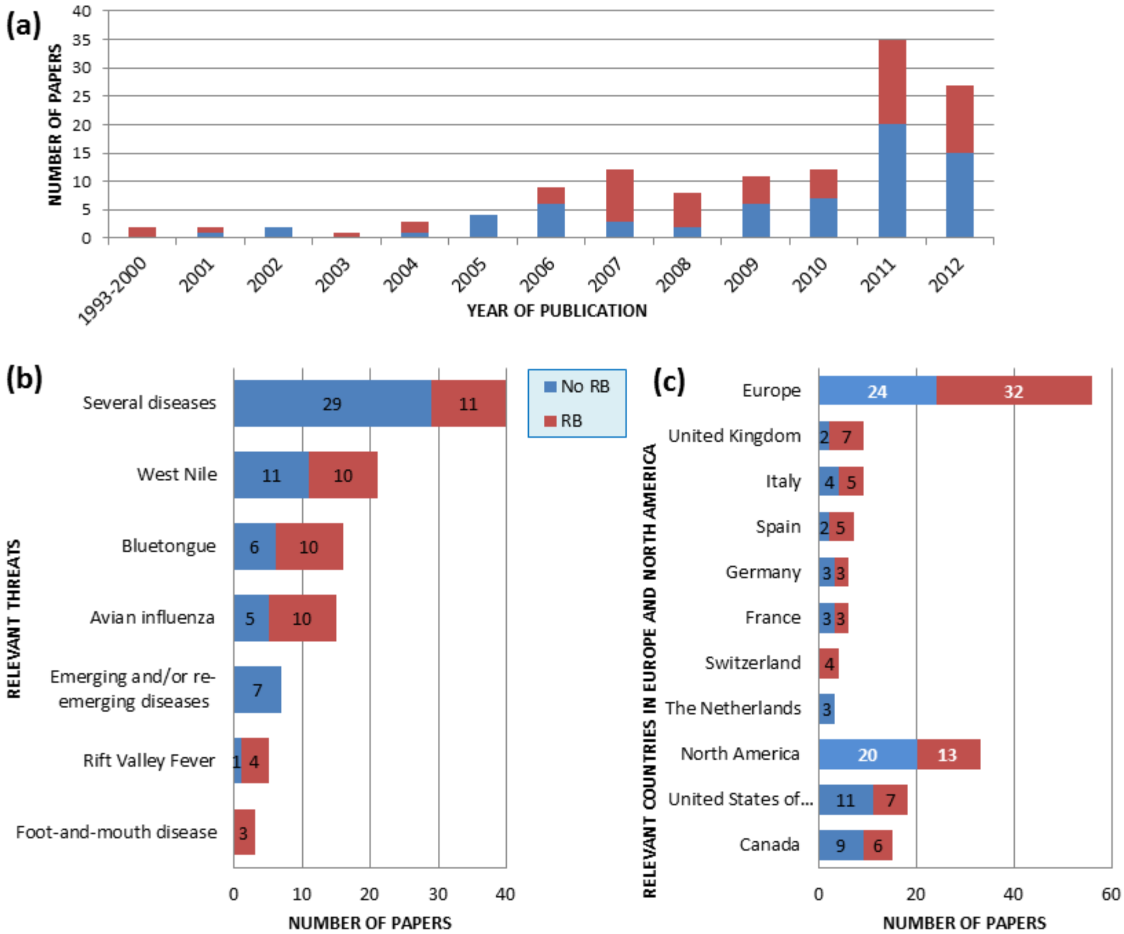

Figure 6. Distribution of the papers by risk-based (RB, in red) or not risk-based (No RB, in blue) approach. (a) Considering the year of publication. (b) Considering the most relevant threats. (c) Considering the most representative countries of Europe and North America.

Sixty-one papers included risk-based approaches, especially those describing methods (*i.e.* 45 out of 61). This 'risk-based' concept even appeared in 1993. An increase in the absolute number (but not the proportion) is observed after 2007 (Figure 6a). Risk-based approaches were especially applied to three diseases: bluetongue (n=7 out of 10), avian influenza (n=10 out of 15), and West Nile (n=6 out of 14) (Figure 6b). As for the countries, European risk-based studies had a higher proportion (n=32 out of 56) than North American ones (n= 13 out of 33) (Figure 6c).

When analysing the risk-based categories, **risk-based sampling** (n=20) and **risk-based requirement** (n=39) seemed to be the most frequently used ones. Both types were aiming to increase the chance of early detection of hazards, either by selecting the target population to be sampled or by identifying the critical points of surveillance programmes in order to intensify and improve their performance. The first category was mainly used when considering sentinel surveillance for exotic diseases. Conversely, a risk-based requirement was applied to many kinds of diseases (both emerging and exotic) and approaches. Amongst these types of diseases, **risk-based analyses** (n=7) were not highly represented, since the goal of these studies was not related to obtaining conclusions about disease status. **Risk-based prioritisation** (n=6) was a minor category, and applied to methodologies dealing with exotic diseases.

Half (n=64) of the papers covered multiple diseases, either based on **general** methods (n=41) or using a **multi-objective** approach (n=23). Most of the general papers were related to syndromic surveillance, which has a generalist nature *per* se. The multi-objective scope was typical for papers describing methods, passive surveillance strategies and the combination of both. These papers mainly dealt with (i) methods focused on several specific diseases of certain host species, (ii) a single disease but entailing some others, or (iii) vector surveillance.

Specific methodologies found

Each approach was assigned to a specific category, depending on the methodologies applied and described in the paper (Table 5).

Table 5. Frequency of different methodologies found in the review, identifying also the use of risk-based methods, and the number of papers addressing multiple threats.

General category	Specific category	Count	Risk-based	Percentage	Multiple nature	Percentage
EPIDEM. METHODS	**Spatial epidemiology (GIS)**	**22**	14	63.64%	7	31.82%
	Statistical model	**14**	10	71.43%	10	71.43%
	Digital surveillance	**12**	3	27.27%	9	75.00%
	Simulation model	**8**	6	75.00%	2	25.00%
	Risk assessment	7	7	100.00%	1	14.29%
	Scenario tree model	6	5	83.33%	0	0.00%
	Cluster analysis	5	4	80.00%	2	40.00%
	Environmental model	4	4	100.00%	2	50.00%
	Literature review	4	0	0.00%	4	100.00%
	Others	6	5	83.33%	4	66.67%
ACTIVE	**Vector surveillance**	**17**	2	11.76%	6	35.29%
	Sentinels	**16**	10	62.50%	1	6.25%
	Serosurvey	13	5	38.46%	1	7.69%
	Pathogen determination	12	2	16.67%	3	25.00%
	Participatory	8	1	12.50%	5	62.50%
	Others	3	1	33.33%	1	33.33%
PASSIVE	**Syndromic**	**18**	0	0.00%	18	100.00%
	Clinical investigation	10			0	0.00%
	Mortality investigation	5			0	0.00%
	Parameter monitoring	2			1	50.00%
	Others	3			2	66.67%

Papers focusing on epidemiological methods

The category that was mostly represented in the methodological papers was **spatial epidemiology and GIS-based approaches** (n=22). Fourteen of these were risk-based methods, while seven addressed multiple threats. The main purely spatial approach found was **risk mapping** (n=6), which consists of obtaining risk maps for the "probability of environmental suitability for the vector or disease in question" by spatial overlaying of relevant risk factors using statistical or other algorithms (Pfeiffer *et al*., 2008). These approaches were particularly applied to multi-factorial and/or vector-borne diseases, because they allow the inclusion of multiple factors, and result in easily interpretable outputs, with direct application to cost-effective allocation of surveillance and control resources. However, major constraints are the lack of adequate quality data, and the risk of missing important information in the spatial model, both resulting in potentially biased model outputs. This is the reason why almost all the studies included a validation step of their approaches (n=12 out of 16 studies for which validation is applicable).

In addition, other applications of the spatial approaches to early detection were:

- Supporting **active surveillance** activities (n=7), being useful for designing sampling sites or presenting surveillance results.
- Combining with **conventional epidemiological approaches** (n=6), such as regression models, risk assessments or simulation modelling, mainly as a tool for representation and interpretation of their results, since the raw output from these models is usually not easy to comprehend.
- Being part of **digital surveillance** frameworks (n=5), in order to support the visualization of the results or implement certain spatial transformations of the data.

A very common finding in the review was the use of **statistical models** (n=14). Most of them were risk-based (n=10) and for multiple diseases (n=10). We found a wide range of methodologies, from the simplest linear regression models to more advanced Bayesian approaches, such as Poisson Hidden Markov models. While there were papers describing methodologies that were not particularly novel or innovative, they were included in this review since their application for early detection was considered original and potentially useful. For instance, regression models were used to illustrate the potential identification of a novel swine disease (*i.e.* porcine circovirus associated disease) using test requests for PRRS (O'Sullivan *et al*., 2012). Typically, the utility of the outputs generated by these approaches was affected by restrictive or inappropriate model assumptions and/or problems with data acquisition and management. If data are not appropriate in terms of quality and quantity, the usefulness of the output is usually compromised. However, the potential utility of these methods for development of enhanced, risk-based surveillance systems has been documented in numerous articles of the past decades.

Another category highlighted in the review is **digital surveillance** (n=12). These papers comprise several tools for data collection, management and processing, which normally involve several diseases (n=9). They have a direct link with governments and institutions, and are beneficial for inter-institutional relationships and decision-making. Another advantage is their real-time nature, which allows constant update of the situation and earlier detection and intervention in case of animal health threats. As additional benefits, these platforms are considered to be useful, simple, flexible, acceptable, and timely. The main limitations are that they are still under development (*i.e.* pilot phases), which implies the need for future adjustments and calibrations, and a current lack of a standardised way to submit information safely, easily and providing data of good quality.

Simulation modelling was considerably represented in the review (n=8). These approaches aim to predict disease dynamics in a population in time and sometimes in space under specific circumstances. Once the epidemics are established, they are also useful for assessment of the capabilities for their diagnosis and mitigation. A novel inclusion in this model is the estimation of economic impact. In this case, sensitivity analyses showed to be the most useful way to evaluate the approaches, since there is usually some degree of subjectivity when assigning the model parameter values.

Three other methods represented in the review were **risk assessments** (n=7), **scenario tree models** (n=6), and **cluster analyses** (n=5). The first is a purely risk-based method (n=7), which generates risk estimates for use in designing and evaluating risk-based surveillance systems, although they focus on release and/or exposure of pathogens (not on surveillance itself). Risk assessments can also provide information about evaluation of the variations in risk, based on a standardised model framework which can be adjusted and updated, thereby allowing to improve the effectiveness of surveillance if the disease epidemiology and therefore risk changes over time. Similar to other methods, quantity and quality of the data used to parameterize the models determine the usefulness of the outputs. Scenario tree models reviewed were used for validation of surveillance systems, and demonstration of how the likelihood of early detection of diseases can be improved by combining the most appropriate passive and/or active strategies in the surveillance programmes for emerging and exotic diseases. As with risk assessments, data quality and model assumptions will greatly influence the usefulness of the outputs, and therefore sensitivity analyses should be performed (n=3) in order to understand this effect better. Lastly, cluster analysis is useful for early warning, especially if combined with syndromic surveillance data (n=2). However, detected clusters might not represent real outbreaks, so further epidemiological investigation would be required to determine the cause of any spatial, temporal or space-time clustering. For this reason, all the papers validated their models using field data.

In the review, **other types of methods** were also used, such as **environmental predictive models** (n=4), or **literature reviews** (n=4). Although these papers can provide some relevant information that can be directly used for surveillance design or for modelling purposes, they were too heterogeneous to allow a proper analysis under the remit of this systematic review.

Other approaches identified in the current review, but only used rarely, are a framework to integrate veterinary health reporting with public health systems (n=1), evaluation of methods to assess coverage and data availability of early-warning surveillance systems (n=1), network analysis contributing to the assessment of potential spread patterns through animal movements (n=1), a neural-network-based approach to identify significant risk factors for West Nile virus infection (n=1), validation of early-warning methods in abattoir monitoring systems (n=1), and studies to select the best sample for diagnosis of classical swine fever (n=1).

Active surveillance approaches

The two most relevant active surveillance activities found in the review were **vector surveillance** (n=17) and **sentinels** (n=16).

Vector surveillance focused on three main groups of vectors of interest: ***Culicoides* spp.** (n=8), **mosquitoes** (n=7) (especially *Culex* spp.) and ticks (n=2). *Culicoides* midges are represented relatively frequently due to the wide-spread surveillance efforts focused on bluetongue. Mosquito monitoring has been a component of surveillance for several diseases, such as Rift Valley fever, West Nile, Usutu virus, or St. Louis encephalitis, all of them important emerging diseases in recent years. This kind of surveillance does not seem very sensitive for the detection of the presence of the disease.

However, the main benefit of these approaches is the characterization of the distribution of the vectors, not only for the target disease, but also for other similar diseases, so that their potential spread can be predicted. Another issue, when deciding to place the traps for collection in areas at high risk for disease occurrence, is that density could be overestimated. Therefore, most of the studies recommend that the sampling area should be increased. This strategy, when combined with sentinels (n=8), seems to be effective for early warning and establishment of control measures.

The incorporation of **sentinels** in surveillance systems increases the probability of detection of first incursion of a particular disease at the earliest time possible, since they are in place to provide early information on the species (n=5), time periods (n=3) and/or areas (n=9) at higher risk. Therefore, it is a more effective system than traditional **serosurveys** (n=15) or **pathogen identification** (n=12). However, these methods were used:

- As a permanent component of surveillance systems, as occasional complementary activity (n=11), or
- As a data source for the parameterisation of a statistical or simulation model (n=4), or
- As a preliminary screening for exotic or emerging pathogens (namely West Nile, avian influenza, emerging salmonellosis, pigeon paramyxovirus, simian African viruses or eosinophillic meningitis) in order to obtain a preliminary overview of the sanitary situation before applying specific measures.

A novel approach for active surveillance (*i.e.* first appearance in the review in 2005) is the use of **participatory surveillance** (n=8). This emerging method provides an approach to enhance collaboration and communication between different sectors and institutions, understand the causes of the success or failure (*i.e.* strengths or weaknesses) of current surveillance programmes in order to help policy reforms, or obtain a quick overview of the epidemiological situation in an area. Most of them were conducted in developing countries (n=5). The main limitation is the non-response rate, mainly due to resistance to answer or lack of trust this methodology. This lack of participation may impede the conduction of further analyses in most situations. In addition, to be efficient this approach relies on reporting by observers (*e.g.* animal owners, veterinarians) when in fact there often are disincentives for outbreak reporting, due to the potential adverse economic impact on the livestock holding or sector. Other issues could be a poor representativeness of the interviewees or an inadequate design of the questionnaire, which could require a second round in order to be solved.

Passive surveillance approaches

Syndromic surveillance is the most commonly represented passive surveillance approach (n=18). The review shows that it is a novel method (*i.e.* first articles in 2006) and that it is characterized by its general surveillance nature (n=16). Although pure syndromic methods are mainly described in the articles, they can also be integrated into digital surveillance frameworks (n=2). In general, these articles propose a method for early detection of changes in the population health (*e.g.* clinical cases, abnormal mortality rates, post-mortem findings) that are defined as syndromes. Most of the papers described methods for grouping these syndromes, in order to allow the early identification of potential outbreak signals. In fact, the shortening of the detection time is highlighted in the majority of the studies as the main advantage (*i.e.* even several weeks prior to the laboratory testing). Other benefits are their potential cost-effectiveness, the integration and optimization of data from different sources, or the simplicity of having a simple system covering multiple threats. However, these methods appear always as retrospective approaches in the reviewed articles, in the sense that they are designed with information of previous outbreaks of disease and thus, they have not been proved for upcoming threats. The retrospective nature of these approaches means that a future validation is necessary to determine their full applicability and benefit.

Harmonization of criteria is also an important requirement when defining the syndromes, since the data may be obtained from several sources. In addition, a continuous update of the syndrome definition is necessary in order to include new diseases. Additionally, these approaches should consider an effective mechanism for the prevention of 'false alarms' (*i.e.* syndromes identified, but later not found to be associated with any true hazard). Several authors highlight that this method cannot replace the traditional surveillance methods, but it is useful for early warning and supporting planning and policy development.

Other passive surveillance methods (*i.e.* **clinical and mortality investigation**) identified as part of the current review consisted of traditional methods used as a data source for input into epidemiological models (n=4) or as a component of a surveillance system for exotic or emerging diseases (n=7).

DISCUSSION

The present report aims at reviewing current approaches and methodologies that have been developed over the last 20 years for the early detection of exotic, new and re-emerging diseases. In contrast to other previous reviews, which usually focused on general or specific aspects of one type of surveillance (*i.e.* syndromic surveillance or participatory surveillance), this systematic review of the scientific literature is the first that has considered all approaches and methodologies targeting early detection. Special focus has been given to the review of methodologies, evaluating both the benefits and the current limitations of each model. This information will be used to inform the development of tools to facilitate the design of cost-effective surveillance strategies in the RISKSUR project.

The selection process used was a systematic review based on combining general search terms for surveillance with specific ones for early detection. The selected articles were evaluated according to primary exclusion criteria reflecting the general theme, primary exclusion criteria for WP2 (early detection of exotic, new and re-emerging diseases) and secondary exclusion criteria. Based on this selection process, a total of 128 articles were carefully reviewed to extract the information about the variables of interest.

One limitation of our approach is that the search terms used to perform the systematic selection of the articles did not include the keywords of each article, since it has been assumed that the keywords would be included in the title and/or the abstract of the article. The use of this protocol may have resulted in a small number of relevant articles which were not included in this review. Moreover, the current review did not include the search of grey literature (*i.e.* documents found by internet search or in conference proceedings not included in SCI) nor included other articles cited in the selected articles that might also have been relevant. However, the impact of these limitations on the final result is not expected to have been substantial because it is plausible that most articles will have the search terms in the title or the abstract, and grey literature may contain scientific information of doubtful quality, since these publications are not peer-reviewed.

Passive components have historically formed the core of the surveillance approaches used for the detection of emerging and re-emerging threats (Doherr and Audigé, 2001). These 'traditional' surveillance activities are likely to provide an essential component of early warning surveillance in the future, but may need to be supplemented with new approaches. The evaluation of traditional surveillance systems for their accuracy (sensitivity or specificity), precision (repeatability), timeliness, multiple utility, value and cost-effectiveness (Thurmond, 2003) has highlighted the need for improvement, especially after the 2001 outbreak of foot-and-mouth disease in UK. In recent years, many new approaches to surveillance have been developed.

One of these developments is the use of risk-based surveillance methods, which is likely to be more efficient and cost-effective than traditional methods (Stärk *et al*., 2006). The 'risk-based' concept is not completely new, as such surveillance systems have already been implemented as 'targeted surveillance' since the 2000's as part of the surveillance of bovine spongiform encephalopathy (BSE) (Stärk *et al*., 2006). For example, vector-borne diseases such as bluetongue include sentinel surveillance, which must be performed in areas at high risk informed by a risk assessment considering entomological and ecological evaluations [Commission Regulation (EC) No 1266/2007]. However, its incorporation into existing surveillance systems is scarce. As an illustration, this review has identified 69 papers dealing with new risk-based methods proposed and, conversely, we found only 10 papers that actually reported risk-based methods already implemented into countries' surveillance systems. Nonetheless, current traditional systems can always be improved by the substitution or inclusion of new risk-based components, in order to enhance surveillance in a cost-effective manner.

A fact to highlight in the current review is that risk-based methods have been applied particularly for vector-borne diseases such as bluetongue, West Nile fever and Rift Valley fever. The main reason for this fact is the environmental influence on presence or density of mosquitoes, and consequentially on disease occurrence. Risk mapping, environmental models and simulations of vector spread are the risk-based approaches that have been used to identify the areas and time periods in which surveillance is more likely to successfully detect these diseases early. Other diseases in which risk-based methods have been applied are avian influenza and foot-and-mouth disease. In the case of avian influenza, the risk-based approaches are mainly focused on early detection of the disease entry by wild birds, taking into consideration the environmental factors such as presence of wetland areas. Regarding foot-and-mouth disease, the articles described risk-based models mainly for identifying optimal procedures for early detection of the disease in case of an outbreak, and the spread of the virus. In summary, risk-based methods have been mainly developed for diseases for which (i) there are biotic factors (such as vectors or wild birds) whose presence directly depends on abiotic environmental factors and which are essential for the presence and spread of the disease; or (ii) different scenarios pose several levels of risk of introduction and spread of the disease. In addition, the application of risk-based approaches was also related to the nature of the surveillance. While most of the studies which focused on a specific disease are risk-based (68.25%), it seems that those approaches dealing with multiple diseases (*i.e.* general or multi-objective) are mainly not risk-based (72.31%). Thus, the potential development of risk-based methods for simultaneous application on multiple diseases could be a field for further research. However, identification of risk factors suitable for prediction of the occurrence of multiple diseases represents a considerable challenge and may explain why risk-based approaches for general surveillance systems have not been developed yet.

The review has shown that a significant amount of work has been carried out in relation to the development of risk-based approaches for identifying populations at high risk for certain infections, especially by using risk mapping. Although risk maps provide very useful information for allocation of preventive measures and provide relatively easy to interpret, there is still some work to be done to integrate the results of these analyses into the design of risk-based sampling strategies. The same limitation is also encountered with the other approaches identified in the current review. Methods such as statistical or simulation models, risk assessments, and cluster analysis can be used to inform risk-based surveillance and provide useful output in relation to disease patterns, relevant risk factors and estimates, or efficiency of surveillance activities. However, their use in operational surveillance systems has been rare. This is mainly due to the complexity of the underlying epidemiological concepts, algorithms, and/or software used, as well as the lack of confidence of decision makers into outputs obtained and/or decision-makers inability or unwillingness to work constructively with the uncertainty estimates associated with these model outputs. Therefore, outputs generated by these quantitative methods need to be communicated more effectively to decision-makers and better evidence of the value of risk-based surveillance strategies is required. Other limitations found in the review (*e.g.* limited sample size, spatial or time clustering, lack of risk estimates, bias in selection of risk factors, imperfect test characteristics, public awareness of the emerging threat, inclusion of past surveillance results, multiple data sources, or low quality of data) could be overcome by appropriate selection of the method to use in relation to the threat of interest. In addition, those studies including validation of the particular methods investigated with real disease data have demonstrated the benefits of their inclusion in surveillance programmes. The adoption of risk-based methods and other new approaches can be facilitated by providing evidence of their cost-effectiveness. This will be essential since it is typically being argued that risk-based designs involve additional cost due to their increased complexity compared to random sampling approaches.

It can be concluded that another recent development in surveillance methods that has clear application to early detection systems is the use of syndromic data. However, the potential role of syndromic surveillance as part of early detection needs further investigation. It has been applied for early detection of seasonal increases in incidence of known human hazards, such as influenza or heat-related mortality (*e.g.* Josseran *et al*., 2009; Perry *et al*., 2011; Schrell *et al.*, 2013), or for assessing the impact of environmental disasters on the health of populations (*e.g.* CDC, 2006; Elliot *et al.*, 2010). There is much interest in the collection and analysis methods used for these data in the animal health field, but it is unclear whether these methods are sensitive enough to be useful for early detection of all type of health events. Analysis of syndromic data following the raising of an alert about an emerging disease or in the face of an increased risk of exotic disease incursion may also be useful to speed up the investigation of potential outbreaks to avoid disease spread. Collection of syndromic data may be useful but its role in the detection of different disease types requires further clarification, and systems currently developed need further validation as more data becomes available. However, its combination with rapid systems for data collection or good inter-institutional communication which would provide data of different nature potentially could be very advantageous. If incorporated into digital surveillance systems, which are still in very early stages of development, this could result in a real-time health monitoring system. Nevertheless, it is important to recognize that these systems will still rely on the availability of effective laboratory testing in order to diagnose the underlying infectious causes of any emerging trends and alarms (Koopmans, 2013).

There have also been developments in the active surveillance activities applied for early detection. Sentinel surveillance, as shown in this review, can be a very useful surveillance system component when dealing with exotic or emerging diseases, as it increases the probability and timeliness of detecting 'recently infected or new diseased' animals. In addition, it is useful for monitoring of vectors, especially since most of the emerging diseases occurring in recent years are vector-borne (Racloz *et al*., 2007; Pfeffer and Dobler, 2010). Thus, the combination of sentinel and vector surveillance could be particularly relevant for monitoring of vector-borne diseases with easily distinguishable clinical symptoms and a rapid onset. In fact, the usefulness of vector surveillance as a common monitoring activity is more and more proved in the recent years. For instance, it is believed that the outbreaks of bluetongue in Europe could have been better detected and controlled if more information about the vector distribution had been available (Giovannini, 2006). As a result of control efforts for this infection in Europe, *Culicoides* spp. distribution is now well documented, and this information will also benefit the design of surveillance and control programmes for other *Culicoides*-borne diseases, such as the recent Schmallenberg disease (Goffredo *et al*., 2013).

Another developing area of surveillance that is relevant to early detection is surveillance of wildlife populations. The consideration of wildlife health surveillance activities is not a novel concept (Mörner *et al*., 2002). In the current review 37 studies (*i.e.* 26.56%) from 2001 dealt with methods involving wild animal species, especially relating to emerging diseases (n=27, 21.09%). This increasing interest is explained by the recent appearance of infectious emerging or re-emerging threats involving wildlife (*e.g.* chytrid fungi in amphibians, morbillivirus infections in marine mammals or European brown hare syndrome), or those having an impact on human (*e.g.* severe acute respiratory syndrome, influenza, West Nile, Lyme disease, or *Hantavirus* infections) or livestock health (*e.g.* Newcastle disease, brucellosis, or tuberculosis) (Mörner *et al*., 2002; Kuiken *et al*., 2011). However, the meeting organised in 2009 by the European Wildlife Disease Association (EWDA) highlighted the fact that only 14 out of the 25 European countries represented performed some kind of surveillance activity in wild animal populations (Kuiken *et al.*, 2011). The implementation of surveillance activities in wildlife species may not be widespread for several reasons, such as: (i) limited access to wild animal populations because of the extent of their habitat; (ii) the protected status of certain emblematic or endangered species; (iii) lack of diagnostic assays adapted to wildlife; or (iv) environmental, habitat and behavioural factors having an influence in animal density and, thus, disease impact in populations (Giovannini, 2006). The migratory nature of some wild species makes surveillance more difficult, not only due to the rapid and long distance dispersal of pathogens across of political borders, but also hampering surveillance efforts. This situation is reflected in the current review, since 25 out of the 37 (*i.e.* 65.57%) studies relating to wildlife involve wild bird species.

Some surveillance strategies focused on wildlife consist of: (i) investigating morbidity and mortality events, (ii) identifying new pathogens, and (iii) monitoring the status of known diseases within wild animal populations (Mörner *et al.*, 2002). These activities may provide an insight into infectious disease pathologies and agents, as well as new host ranges. The more relevant data related to the incident are collected, the more realistic and useful this information will be for the total population at risk. All the conclusions gathered by these activities should be quickly shared around the world, to prevent the transboundary spread of pathogens. Fortunately, the 2011 EWDA meeting established the basis to create an international network for wildlife health surveillance (Kuiken *et al*., 2011). This network may be useful for setting up appropriate surveillance schemes focused on wildlife, as well as for fostering cooperation between public health and animal health professionals, in order to be able to deal with the emerging threats from a more global perspective. Since the interactions of the interface between humans, livestock and wildlife have intensified in the last 20-30 years (mainly as a result of anthropogenic factors), these have become an important driver of disease emergence (Siembieda *et al*., 2011). Therefore, further studies need to be conducted to establish methods of data collection and diagnosis of emerging pathogens adapted to this interface.

The expansion of the EU and the increase of population over the past 20 years have arisen important socio-economic and also health consequences for the partner countries. This expansion has promoted the concept of 'open trade', which means lowering commercial barriers to encourage trade between countries and to promote competitiveness, both within and outside the EU. As a consequence, the risk of introducing new or exotic diseases into the Member States rises with the number of movements between countries, as trade of live animals is one of the main introduction routes for infectious diseases. For that reason, severe legal and health requirements have been imposed by the DG Health and Consumers at European level, supervised by the OIE at a global level, to minimise the opportunity for high risk contacts. The implementation of surveillance programs for infectious diseases also needs to provide protection against the entrance of exotic, new and re-emerging diseases through trade as well as other entry routes (*e.g*. contacts with wildlife). However, recent health crises such as foot-and-mouth disease and avian influenza have highlighted the need for further improvement of this type of surveillance, which can fail in detecting new pathogens which have not been previously identified or fail in detecting early exotic or re-emerging diseases.

This current systematic review of the literature has shown that several novel methodologies can be incorporated into surveillance programs to improve their ability for early detection of exotic, new and re-emerging diseases. Approaches identified in this review to take into consideration in the future are risk-based methods, the monitoring of health events combined with specific disease outbreaks, the enhancing of participatory surveillance and the integration of information into digital databases that allow a rapid and cost-effective identification of threats also improving timeliness. The next steps to improve surveillance systems in the European Union are (i) the development of evaluation frameworks to study the application of these novel methodologies integrated with or replacing currently used methods whilst maintaining or improving upon the sensitivity and specificity of the current standards and (ii) the definition of the parameters that should be considered and recorded in each country and which level of detail this information should have (*i.e.* minimum requirements) to allow the implementation of novel methodologies and risk-based methods. Thus, the present literature review has provided key information about advantages, disadvantages, limitations and potential application of novel methodologies for early detection of exotic, new and re-emerging diseases.

CONCLUSIONS

Emerging diseases are at the top of the current priorities of the health institutions worldwide. The current review supports the impression that there is significant global interest to improve the ability of surveillance systems for early detection in order to be able to minimise the impact of such threats. To achieve this purpose, a series of new tools has been developed, and many of the traditional approaches have been adapted to be able to more effectively deal with the new threats. There is a clear trend towards utilising ‘risk-based’ methodologies aimed at optimising the surveillance efforts in the most efficient and cost-effective way. In addition, the complexity and dynamism of the underlying eco-social system within which these pathogens emerge has emphasized the need for interdisciplinary collaboration in order to improve early warning surveillance systems, comprising producers, field veterinarians, pathologists, animal health consultants, diagnostic laboratories, ecologists, wildlife experts, economists, social scientists and national and international institutions. Establishment of these ‘One Health / Ecohealth’ networks well become a key requirement for effective protection of public health, trade, and animal health and welfare.

The next step could be a single and global approach, which would merge the benefits of all these methodologies with a practical application. In the framework of the RISKSUR project, a decision-support framework will be developed which will allow linking the components and tools of a surveillance system aimed at early detection of diseases taking into account knowledge generated by risk assessment and financial and staff resources as well as variation in data quality and quantity in different Member States under different disease scenarios. Therefore, the current review sets up the basis for the selection of methodologies, based on the benefits and limitations of each approach identified, as well as suggestions for their combination. In addition, this review informs the assessment of the extent to which strategies are most appropriate for the design of surveillance for new, exotic and re-emerging diseases and the relative importance of passive and active risk-based sampling for early detection.

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ANNEXES

ANNEX I. List of the 128 scientific articles included in the review of the surveillance systems for early detection of new, exotic and re-emerging diseases.

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ANNEX II. List of variables for the literature review of surveillance approaches for early detection

Table	Name of the variable	Data type	Description	Comment
ID	ID	AutoID	Unique identifier for the paper	
ARTICLE GENERAL INFORMATION	Reviewer	Character	Name of the person that made the article review	
	Title	Character	Title of the article	
	Author(s)	Character	Author(s) of the article	
	Type of paper	Character	Describe the category of the article	Choose between "SCI article", "SCI review", "Oral communication", "Poster" or "Report"
	Year of publication	Numeric	Year of publication of the article	
REVIEW OF METHODS CURRENTLY APPLIED	Disease/threat - general	Character	Name of the disease(s) category in which the article focuses on	Indicate "several diseases" when the article focuses on several diseases
	Disease/threat - specific	Character	Name of the specific disease(s) in which the article focuses on	Specify diseases
	Disease status in the study area	Character	Describe the disease status in the study area	Choose between "Endemic", "Emerging", "Exotic", "Suspected", "Not applicable (NA)" or "No data(ND)"
	Target species	Character	Describe the animal species in which the article focuses on	
	Human involved (zoonosis)	Yes/No	Describe if the target disease is zoonotic	
	Continent	Character	Name of the continent(s) where the study area is located	
	Country/ies	Character	Name of the country(ies) where the study area is located	
	Region/s	Character	Name of the region(s) where the study area is located	
	Time frame	Date	Specify the period of time when the study took place	Provide date in YYYY/MM/DD-YYYY/MM/DD format
	Spatial/Temporal evolution	Character	Specify whether there has been changes mentioned in the article in spatial and temporal components in the method(s)/approach(es) described	For example: Arbovirus surveillance has evoluted in California: (1) monthly testing of sera from 2 flocks of sentinel chickens and sporadic virus isolation attempts from *Culex* mosquitoes collected from riparian and park habitants; (2) surveillance activities were expanded to include additional park sites and representative residential areas; and (3) n Orange County surveillance was also supplemented by monitoring to SLE virus in wild bird community

Table	Name of the variable	Data type	Description	Comment
REVIEW OF METHODS CURRENTLY APPLIED	Risk-based method	Yes/No	Specify whether the method(s)/approach(es) is (are) described in the article risk-based?	
	Risk-based category	Character (list)		Choose between “RB prioritisation”, “RB requirement”, “RB sampling”, “RB analysis”, or combination of these
	Risk factors	Character	Described the risk factors considered in the article	For example: Risk of entrance of EHDV by three possible entry pathways
	Type of approach - general	Character	Specify the general type of surveillance	Choose between "Active", "Passive", "Method” or combination
	Type of approach - specific	Character	Specify the specific type of surveillance	Choose between one of the specific categories (see “Material and methods – Study selection and data extraction – Variable extraction”, pages 12-13)
	Type of approach - detailed	Character	Describe the type of surveillance	Briefly described the type of approach(es) used
	Data source	Character	Describe the type of data	Choose between "Primary" (data obtained in the study), "Secondary" (external data used in the study) or "Primary and secondary"
	Surveillance nature	Character	Specify the nature of surveillance in terms of target hazard	Choose between “General”, “Multi-objective” or “Single”
	Aim(s) of the study	Character	Describe the aim(s) of the article	
	Aim defined?	Yes/No	Is the objective clearly defined?	
	New technologies affecting SS	Character	Describe the new technologies affecting surveillance systems used in the article	
	Data management	Character	Does the article describe real data obtained or does it perform simulation of data?	Choose between "Real data", "Simulation" or "Real data and simulation"
	Sample size	Character	Indicate sample size	
	Sample unit - general	Character	Indicate sample unit	Choose between "Individuals", "Herds" , "Holdings", "Several" (when the article focuses on several units) and "Other" (if the unit is not contained in any of the former categories)
	Sample unit - specific	Character	Specify sample unit for "Several" and "Other" categories	
	Pooled samples	Yes/No	Are the samples pooled?	
	Sampling method	Character	Describe the sampling method or the way of data collection	

Table	Name of the variable	Data type	Description	Comment
REVIEW OF METHODS CURRENTLY APPLIED	Sampling scheme	Character	Describe the sampling scheme	If applicable
	Tests used	Character	Describe the diagnostic test used	If applicable
	Surveillance results	Character	Describe the main results of the article	
	Method for analysis	Character	Describe the statistical methods to analyse the data obtained in the article	
	Standard legislation	Character	Indicate the legislation mentioned in the article	If applicable
	Benefits	Character	Describe the benefits mentioned in the article regarding the method(s)/approach(es) described	
COST-EFFECTIVENESS OF CURRENT SURVEILLANCE METHODS FOR EARLY DETECTION	Time to detection	Character	Describe the time necessary to detect the disease/threat using the method(s)/approach(es) described in the article	
	Personal / material / economic resources	Character	Describe the personal/material/economic resources necessary to detect the disease/threat using the method(s)/approach(es) described in the article	
	Total costs	Character	Describe the total costs necessary to detect the disease/threat using the method(s)/approach(es) described in the article	
CURRENT LIMITATIONS	Current limitations	Character	Describe the current limitations mentioned in the article regarding the method(s)/approach(es) described	
FUTURE PROSPECTS	Future prospects	Character	Describe the future prospects mentioned in the article regarding the method(s)/approach(es) described	
VALIDATION / EVALUATION	Validation / Evaluation	Character	Describe the method(s) used in the article to validate and/or evaluate the models developed	
EXCLUDE	Exclusion	Yes/No	Should this article be excluded from the analysis?	
	Reason	Character (predefined)	Provide reason(s) for the exclusion of the article	If applicable (see list on “Material and methods – Study selection and data extraction – Variable extraction”, pages 11-12)
WP ADDITIONAL	WP	Character	Indicate which WP(s) are more suitable for the analysis of the article	If applicable
COMMENTS	Comments	Character	Provide further comments	If applicable