

**Microbiological zoonotic emerging risks, transmitted between livestock animals and humans (2007-2015)**

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## **SUMMARY**

As part of the Emerging Risk Identification (ERI) activities of the European Food Safety Authority (EFSA), a literature search was conducted to identify the microbiological agents transmitted between livestock animals and humans that have been suggested as having emerged between 2007 and 2015 in peer-reviewed scientific literature published during the same period (2007-2015). According to the criteria set, the search identified seven such zoonotic agents, namely West Nile Fever virus, Rift Valley Fever virus, Crimean-Congo Haemorrhagic Fever virus, Influenza A H1N1 virus, *Coxiella burnetii*, *Streptococcus suis* and livestock associated methicillin-resistant *Staphylococcus aureus* clonal complex 398. An explanation of the agents' consideration as emerging risks is provided. The experience gained from these emergences has shown that, detection of and response to such risks can be achieved faster and more successfully within a multidisciplinary, collaborative context at the field, local, national and international levels.

## **KEY WORDS**

Emerging; Risk; Microbiological; Zoonosis; Literature review; Vector.

## **INTRODUCTION**

The landscape of infectious diseases is in flux. New microbiological agents emerge and known agents may acquire new characteristics and arise in unexpected environments or food vehicles. A significant number of the agents causing human infectious diseases are zoonotic, meaning that can be transmitted between vertebrate animals and man under natural conditions (EFSA/ECDC, 2013). These agents pose a potential risk to public health.

The successful identification of risks at their early inception is a core aspect of public health protection. For this purpose, in 2007, the EFSA established the Emerging Risks (EMRISK)

unit, which plays a key role in the coordination of EFSA's activities to develop a capacity for Emerging Risk Identification (ERI). The unit (merged with the Scientific Committee (SC) unit in May 2013, forming the Scientific Committee and Emerging Risks Unit (SCER)) is responsible for supporting the development, establishment and operation of structures for the collection and evaluation of information, and knowledge networks for the sharing information, with respect to identifying emerging risks in the fields of food and feed safety, and animal and plant health (EFSA 2012A, 2012B, 2014). According to the current EFSA definition, an emerging risk must fulfil the following criteria: (i) be a newly identified hazard (i.e. previously non-existing or not known) for which a significant exposure may occur; or (ii) be a re-emerging hazard (i.e. already known) to which an unexpected or increased exposure and/or (iii) increased susceptibility may occur (EFSA, 2007A, 2015).

Despite the unpredictable nature of disease emergence, there are lessons to be learnt from the diseases that have already emerged during the past few years. The study and understanding of these diseases could pave the way for the further development of strategies and activities on Emerging Risk Identification (ERI). Within the framework of the ERI procedure at EFSA (EFSA, 2015), this review aims to identify the microbiological agents that have been suggested as having emerged during the period 2007-2015, in peer-reviewed scientific literature published during the same period (2007-2015) and to explain why the above agents have been considered as "emerging risks". The scope of the review includes zoonotic agents transmitted between livestock and humans via various routes. These agents fall under the mandate of EFSA on biological hazards, which covers animal health (EFSA, 2008), food borne (EFSA, 2011A) and non-food borne zoonotic diseases (EFSA, 2011B).

## **MATERIALS AND METHODS**

This review took into consideration any virus, bacterium, alga, fungus, parasite, and their products (e.g. toxins, biological amines) according to four sets of criteria (Table 1). With a view to identifying emerging risks according to the criteria set, a literature search was performed between 01/2013 and 04/2013 as well as 11/2015 and 01/2016, and included peer-reviewed, scientific articles published in English from 01/2007 to 01/2016 (i.e. during 9 years). These articles were retrieved from eight journals, seven of which were selected based on their high impact factor according to ISI Web of Knowledge<sup>SM</sup> (Journal Citation Reports®) in the areas of interest (i.e. food microbiology, infectious diseases, veterinary sciences) and their inclusion in the list of sources of information that have been systematically screened by the SCER unit and based on this experience have been evaluated as appropriate and useful for information collection on the same areas (EFSA, 2010A). PLoS ONE was an additional journal selected after using the search string to screen PubMed in title. The PubMed screening was performed before the screening of the selected journals in title and abstract. The reason it was performed was to confirm our initial selection of search string and journals. The eight selected journals were: International Journal of Food Microbiology, Food Microbiology, Eurosurveillance, Emerging Infectious Diseases, Clinical Infectious Diseases, Journal of Infectious Diseases, PLOS ONE, Transboundary and Emerging Diseases. The following search string was used: (emerging OR new OR unknown) AND (zoonosis OR microbiological) AND (cattle OR goat OR horse OR pig OR poultry OR sheep). The search string was applied to the search function of the journals. Due to issues related to its search engine, the journal “Emerging Infectious Diseases” was screened issue by issue.

The articles retrieved were submitted to a “first screening” for their relevance on title and abstract. Those considered relevant were subject to “second screening” eligibility on the full text. When additional information on a particular issue was needed, the references of primary articles were also reviewed and taken into consideration, if relevant, as well as research

reports from international organizations. A database was created in Microsoft Excel, in order to gather information for the analysis (i.e. on the type of pathogens, hosts, transmission mechanisms, implications in human health, novelty and scale of specific incidents).

## **RESULTS**

The search strategy produced for seven of the journals a total of 1,241 scientific articles, from which 319 articles were subject to a second screening eligibility on the full text (Table 2).

The journal “Emerging Infectious Diseases” was screened issue by issue without using the search strings, due to issues related to its search engine. From its first screening in title and abstract, 80 articles were selected for second screening. The process resulted in the identification of seven biological agents suggested as emerging risks, transmitted between livestock animals and humans. The information collected in the Excel database justifying their selection is shown in Table 3.

### ***Biological Agents suggested as Emerging Risks***

#### **West Nile Virus (WNV)**

West Nile fever is a notifiable, mosquito-borne zoonotic disease caused by West Nile Virus (WNV). The infection is maintained in a bird-mosquito enzootic cycle, and birds (especially Passeriformes) are the primary reservoir hosts. Horses and humans are considered as accidental dead-end hosts, and considered not to transmit the virus to other mosquitoes (EFSA, 2011C; WHO, 2015). WNV is widely distributed throughout the world. In Europe, though, the disease situation has been evolving in recent years (DEFRA, 2012). In 2008, a large outbreak occurred in Italy affecting humans and horses (Angelini et al., 2010). In 2010, the first clinical cases in horses and humans were detected in Spain and Greece (García-Bocanegra 2011A, 2011B). In the same year, clinical cases in horses and humans were

reported again in Italy, while clinical cases in wild birds were reported in Hungary and Austria.

During 2010-2011, disease in humans and horses was reported from many EU (Greece, Italy, Spain, Bulgaria, Hungary, Romania) and neighbouring countries (Albania, FYROM, Israel, Morocco, Russia, Tunisia, Turkey, Ukraine) (DEFRA, 2012; EFSA, 2012C). Furthermore, the number of probable and confirmed human cases in the EU and in neighbouring countries increased considerably during the transmission season (June-November) in 2011 (128 cases detected in the EU and 212 in neighbouring countries) and 2012 (242 cases detected in the EU and 693 in neighbouring countries) (ECDC 2011, 2012). This situation raised concern regarding the public and animal health and required surveillance and control activities to be put in place (DEFRA, 2012; Angelini et al., 2010; EFSA 2012C). The WNV, and particularly lineage 2, is now considered endemic in parts of South Europe and risk-based surveillance is implemented (DEFRA, 2012).

### **Rift Valley Fever Virus (RVFV)**

Rift Valley Fever (RVF) is an infectious zoonotic disease mainly affecting livestock ruminants, and occasionally humans. It is listed as a notifiable disease according to the World Organization for Animal Health (OIE) (WHO, 2015). The virus is widespread in Africa and continues spreading into new areas. In 2000, the first outbreak of RVF outside the African continent occurred in Saudi Arabia and Yemen. The disease re-emerged in Kenya, Tanzania and Somalia by the end of 2006, Sudan in 2007 and South Africa in 2011. The RVF was introduced onto the French island of Mayotte, in the Indian Ocean, with several clinical human cases, in May 2007 (Chevalier et al., 2010; EFSA, 2005). The public health impact of RVF epidemics has been significant. Indicatively, the case fatality rate reached 14% during

the epidemic in Saudi Arabia in 2000, while in 2007-2008, 738 human cases were officially reported in Sudan, including 230 deaths (Chevalier et al., 2010).

RVF epidemics appeared for the first time in the Middle East in 2000 and became more frequent in Africa from 2006 to 2008, probably in association with the intensification of animal trade (Shoemaker et al., 2002) and climate change (Chevalier et al., 2010). Higher temperatures combined with increased precipitation may further affect distributions of potential competent vectors that already occur in EU (e.g. *Culex pipiens*) (EFSA, 2013) in the future, lead to a higher vector competence and, thus, a higher disease transmission rate. The risk of a potential disease spread into the EU, although generally considered as low, it has been suggested to be more relevant for EU countries of the Mediterranean basin, based on the abundance of the vector *Culex pipiens*, the livestock densities and the higher temperature in the region (Chevalier et al., 2010; EFSA, 2013; Vittecoq et al., 2012).

### **Crimean-Congo Haemorrhagic Fever Virus (CCHFV)**

Crimean-Congo haemorrhagic fever (CCHF) is an acute, highly-contagious, tick-borne viral zoonosis, listed as notifiable by OIE (WHO, 2015). A range of domestic (e.g. cattle, sheep and goats) and wild animals may serve as hosts of the virus. CCHF is an endemic disease in more than 30 countries of Africa, Asia, the Middle East and Eastern Europe. In the EU, the disease is currently endemic only in Bulgaria. However, since 2000, CCHF endemicity has also been established in other neighbouring Balkan countries and Turkey (EFSA, 2012C; Maltezou et al., 2009, 2010). In June 2008, the first non-imported fatal case was recorded in northern Greece (Papa et al., 2008). The emergence and/or re-emergence of CCHF in the aforementioned areas has been attributed to climate and ecologic changes and mainly to various anthropogenic factors that can affect the hosts or the distribution, abundance and competence of the tick vectors (Maltezou et al., 2009).

The first time reporting in an EU country (Greece, 2008) and the onset of community outbreaks involving an increased number of documented human cases in EU (i.e. Bulgaria) and EU neighbouring countries (i.e. Turkey, Albania, Kosovo, Ukraine, south-western regions of the Russian Federation) since 2000 (Maltezou et al., 2010), justify the consideration of CCHFV as an emerging risk. Given the wide distribution of CCHF vector, the numerous animal species that can serve as hosts, and the favourable climate and environmental conditions (altering the tick's growth pattern or redirecting the migration routes of birds that host the affected ticks to areas newly warmed), one cannot exclude the possibility of a further expansion of the disease occurrence, especially in European countries bordering the Mediterranean sea (Maltezou et al., 2010).

### **Influenza A H1N1 virus**

Influenza A viruses are important human and animal pathogens with high impact on public health and animal husbandry. They may infect humans and various other animal species, including pigs, birds and poultry (EFSA, 2010C), and frequently present new subtypes of varying pathogenicity. In 2009, a new human influenza A virus subtype H1N1 was reported in Mexico and the United States and spread worldwide within a few months, causing disease in humans and other animal species, including pigs (Collignon, 2011). Although the epidemic spread purely among humans, the pig played an important role in the virus ecology due to its ability to support replication of influenza viruses from avian, swine and human species. Overall, over 18,449 deaths in humans were recorded worldwide (WHO, 2011).

It is justified to consider that this virus emerged, since this subtype was not previously described and contained a combination of gene segments not previously reported in swine or human influenza viruses (Garten et al., 2009). It also spread quickly around the world (Collignon, 2011), causing the World Health Organisation to raise its pandemic alert (WHO,



2011). Pandemic plans were triggered internationally. But, even though huge efforts were made to contain the spread of the virus and large amounts of resources were expended, they appear to have had little influence on the virus' spread and the prevention of infection (Collignon, 2011).

As was evident during the 2009 epidemic, coordinated surveillance of human and animal influenza viruses is vital. Rapid detection of human infections with new influenza viruses and timely identification of new virus variants in swine, can lead to an effective response to the emergence and spread of a novel influenza virus in humans (Lindstrom et al., 2012). Further new reassortments of the influenza A virus are to be expected in the future with possible change in pathogenesis. Already in March 2013, an A(H7N9) virus of avian origin which had not previously been seen in people, was found in China. Since then, infections in both humans and poultry have been observed, however sustained human-to-human transmission has not been reported (Chen et al., 2013; Wang et al., 2014; WHO, 2014).

### ***Coxiella burnetii***

*Coxiella burnetii* is an intracellular bacterium causing Q fever, a worldwide zoonosis. The bacteria has a wide distribution in domesticated and wild animals, but transmission to humans is mostly associated with sheep and goats (van der Hoek et al., 2012). Humans get infected mainly through inhalation of contaminated aerosols. In around 60% of cases, human infection with *C. burnetii* remains asymptomatic (Roest et al., 2011).

The incidence of human Q fever has increased considerably over the previous years (Munster et al., 2012). Prior to 2007, the disease was uncommon in Europe (ECDC, 2010), except for some local outbreaks (e.g. Germany, 2005) (Munster et al., 2012). However, from 2007 to 2009, the Netherlands faced large seasonal Q fever outbreaks, with the highest peak in 2009 (van der Hoek et al., 2012). The origin of these outbreaks has been in question. Despite the

suggestion of goat manure as their source (Hermans et al., 2014), their true origin remains unclear (van den Brom et al., 2015). The outbreaks resulted in an increase of the number of human cases, which reached 3,523 notified cases in the country (Schimmer et al., 2008), the highest number reported in the literature (Munster et al., 2012). Even though Q fever is a notifiable disease (WHO, 2015), it is known to be under-diagnosed and therefore under-reported (Coulombier, 2010). Belgium, Cyprus and Germany also reported an increasing number of cases since 2007, albeit to a smaller extent (ECDC, 2010).

The first documented (Karagiannis et al., 2007) outbreak of Q fever in 2007 and those that followed until 2009, showed some divergence from the general epidemiology of Q fever seen in the EU as a whole (EFSA, 2010B). In this case, human infections occurred over consecutive years, most victims were not occupationally related to domestic ruminants and an unusually high number of human infections were reported. The above suggests that Q fever may be regarded as a disease that emerged (EFSA, 2010B; USDA, 2010).

The reasons for the emergence of this outbreak(s) in the Netherlands are not clear and no specific source could be formally identified. The disease did not spread (by the airborne route) from the Netherlands to neighbouring countries (i.e. Germany, Belgium) (ECDC, 2010).

Overall, it is justifiable to consider Q fever as a disease with minimal general public health impact in the EU, but there are circumstances in which the associated risk is significantly elevated (from either direct (occupational) exposure to Q fever infected animals, or community based exposure caused by an elevation of *C. burnetii* in the wider environment).

### ***Streptococcus suis***

*Streptococcus suis* is recognised as a major swine bacterial pathogen. Since the first human case in Denmark (1968), human cases have been reported worldwide, from North and South America, Asia and Europe (Wertheim et al., 2008). They are more often reported, though,

from countries where pig-rearing is common and especially Southeast Asian countries (Palmieri et al., 2011).

Serotype 2 is considered to be the most pathogenic for both humans and pigs and is the most common cause of the disease in humans (Wertheim et al., 2008). *S. suis* is generally considered as an occupational disease (Palmieri et al., 2011). There is also evidence of potential food-borne transmission (EFSA, 2007B) in Southeast Asia, via consumption of local delicacies (e.g. undercooked pig tonsils, intestines, uterus and fresh pig blood) (Wertheim et al., 2008; Huong et al., 2014).

In 2005, the largest outbreak of human infection caused by *S. suis* serotype 2 (SS2) so far reported, occurred in Sichuan Province of China (more than 150 cases and 30 reported deaths), while a smaller outbreak had previously occurred in 1998 (Palmieri et al., 2011; Kerdsin et al., 2011). These severe outbreaks posed serious concerns to public health. On the one hand, because they challenged the conventional conception that opportunistic infections of SS2 in humans represented only sporadic cases; on the other, because they were characterised by more rapid disease progression and higher rate of mortality, due to streptococcal toxic shock syndrome, a presentation of illness previously only associated with *Streptococcus pyogenes* (Wertheim et al., 2008; Feng et al., 2009, 2010). From 2005 onward, the number of reported *S. suis* infections in humans has increased significantly worldwide, also in countries where the infection had been rarely or never previously reported (Palmieri et al., 2011; Gottschalk et al., 2010). Indicatively, from 2007 to 2009 the total number of *S. suis* reported cases increased from 409 to over 700 (Wertheim et al., 2008). For these reasons, *S. suis* has been suggested as an emerging zoonotic agent.

In general, currently, *S. suis* is a rare disease in humans (with the exception of China and Thailand), probably underdiagnosed, that occurs sporadically. Whilst more common in Asia,

it is a disease with increasing number of human infections (including deaths) and, therefore, of global public health concern, especially in countries with extensive pig farming; thus, the importance of hygiene on pig farms should be highlighted (EFSA, 2007B). The pathogen receives growing attention not only for its role in severe and increasingly reported infections in humans, but also for its involvement in drug resistance (Palmieri et al., 2011; Callens et al., 2013).

### **Livestock associated methicillin-resistant *Staphylococcus aureus* clonal complex 398 (LA-MRSA 398)**

*Staphylococcus aureus* is a zoonotic and human pathogen that is characterised by an increasing proportion of drug-resistant strains, including methicillin-resistant *Staphylococcus aureus* (MRSA).

In the past, MRSA was mainly considered as a nosocomial pathogen, but since 2000, the majority of infections are community-acquired (van Loo et al., 2007; Feingold et al., 2013). Recently, it has become apparent that animals, particularly pigs and also veal calves and broiler chicken, can constitute an MRSA reservoir and be the source of a “novel and rapidly emerging” type of MRSA in humans, namely MRSA clonal complex (CC)398 (LA-MRSA CC398) (Lewis et al., 2008). LA-MRSA CC398 was first detected in the Netherlands in 2003 and, as of 2010, it accounted for over 40% of the MRSA human isolates in the country (Huijsdens et al, 2009; Feingold et al., 2013).

Even though the disease was first detected in 2003, it has been suggested as emerging in the years since then. One of the reasons why, is that it was found with low (van Cleef et al., 2010; EFSA, 2009B) yet increasing frequency (van Loo et al., 2007; Lewis et al., 2008; van Rijen et al., 2008; de Jonge et al., 2010) in human patients on a worldwide scale. In addition, new information on LA-MRSA has been provided by several studies. For instance, recent evidence

suggests that humans represent an important source of new pathogenic strains affecting livestock (Fitzgerald, 2012) and that some other livestock (i.e. bovine) *S. aureus* strains may have the capacity to colonise humans (Fitzgerald, 2012; García-Álvarez et al., 2011; Laurent et al., 2012). The latter is potentially of public health importance, as it may lead to the emergence of new LA-MRSA strains in humans (Fitzgerald, 2012; van der Mee-Marquet et al., 2011). Therefore, it is suggested that targeted surveillance is required to allow early identification of animal clones that have moved into human populations (Fitzgerald, 2012), and is a convincing case demonstrating the importance of the “one-health” approach.

## **DISCUSSION**

The majority of the biological agents transmitted between livestock and humans that were identified as emerging risks in this review include RNA viruses (WNV, RVFV, CCHFV, Influenza A(H1N1) virus), most of which are vector-borne (WNV, RVFV, CCHFV) and pose mainly an occupational risk. No food-borne agent of zoonotic (livestock) origin was identified as emerging risk, however the review process revealed ample documentation that the burden of viral food-borne illness is significant.

The accumulated, albeit incomplete, knowledge gained from emerging diseases of the past (e.g. on type and special characteristics of agent, transmission route, drivers of emergence) can trigger an early identification of new risks and of changes in influential sectors or drivers which may give a first indication of potential emerging risks. For instance, due to the high mutation rate of RNA viruses (Drake et al., 1999; Parrish et al., 2008), such viruses carry a higher risk of potential emergence (compared to most DNA viruses). Additionally, drivers such as increased human and animal mobility and environmental change have made vector-borne diseases not just a problem of the tropics, but a global issue, irrespective of limited resources and poor surveillance (Pfeffer & Dobler, 2010). A greater understanding of the

population dynamics of reservoir species due to ecological changes (e.g. deforestation linked to Nipah emergence in human populations in Malaysia in 1998 (Chua et al., 2002)) and the role of wildlife, coupled with the study of human behaviour (e.g. use of bushmeat and traditional burial practices linked to Ebola spill-over to humans and spread among them in Africa (Alexander et al., 2015)), would be useful for predicting the possibility of emergence.

The knowledge gained from past experience also includes the lessons learnt in terms of outbreak control and risk management. The detection of what went right and what went wrong on national and international level (e.g. in terms of coordination, financial resources, availability of diagnostic tools, human resources, time until vaccine development) can prove very useful for a rapid and more efficient containment of potential threats in the future and the minimisation of their impact. On the basis of experience from the recent response to H1N1 pandemic, it can be said that the world was relatively well prepared for it, as pandemic preparedness plans and strategies had already been created to combat the previous H5N1 pandemic, leading to improved infrastructure and surveillance capacity (FAO/OIE/WHO, 2011). However, the vaccination campaign, which was rolled out after the peak of the epidemic, did not have a favourable cost-benefit ratio (Collignon et al., 2011; Klenk et al., 2011). Focussing on the Q fever control in the Netherlands, the Dutch government's approach to controlling the disease with the mass cull of all pregnant goats on positive farms was perceived as controversial (Lubick, 2010). Yet, the close cooperation eventually achieved between the human and veterinary fields in knowledge exchange and improvement of diagnostic tools and methodology, was essential for responding to the outbreak and demonstrated the benefits of the One Health approach (Roest et al., 2014).

The results of this review are based on the screening of a limited number of journals, but we believe that they provided us with the necessary data, given their high impact factor and high publication rate in the areas of interest. In case a journal had not published any article on these

agents with a content relevant to this review (i.e. related to an agent's emergence), it was considered that this agent was not identified as an emerging risk during the screening of this journal (Table 2), even though the journal might have published articles on this agent from a different perspective.

The excluded articles fell mainly into two categories. The first and larger included articles on agents that met most but not all criteria set for this review. Such agents cause for instance: non-zoonotic vector-borne human diseases (e.g. Chikungunya virus), zoonotic diseases transmitted between humans and animal species other than livestock (e.g. Usutu virus from birds, Marburg and Ebola viruses from non-human primates or bats, Middle east respiratory syndrome (MERS) from dromedary camels and possibly bats), zoonotic diseases transmitted between humans and livestock in areas remote from Europe (e.g. Hendra and Nipah viruses). Into the same category fell articles on food-borne agents without (e.g. Noroviruses) or not proven (e.g. *E.coli* O104:H4) zoonotic origin. The second category included articles where terminology (i.e. emerging, emergence, emerge) was used for known agents to which no new exposure or susceptibility was observed at the time of the research (e.g. often the case for antimicrobial resistance of *Salmonella* spp, *Campylobacter* spp and *Listeria* spp or VTEC non O157). The terminology was used with caution in the majority of articles screened, following the principles of risk communication. These principles suggest a careful selection of terminology in order to avoid unnecessary scares due to risk overestimation or a lack of measured response due to a risk underestimation (EFSA, 2012D).

Experience has shown that the next major emerging risk is unlikely to be identical to its predecessors. It is therefore necessary to move forward flexibly, using new strategies, along with those already known to be effective (FAO/OIE/WHO, 2011). Further research in capture and trend analysis of drivers, disease surveillance and monitoring procedures could increase the likelihood of bringing new risks to light. This would include surveillance informed by

evidence-based risk assessments combined with climate change and societal aspects, development of early warning systems and continuous monitoring of sporadic zoonotic diseases for changes in transmission patterns. New horizons have also opened with the use of new technologies, such as satellite monitoring of land and ecosystem changes or the use of mobile phones to facilitate the real-time reporting of unusual events. Development and implementation of a specific prioritisation method of emerging risks is also a necessity to ensure a more appropriate subsequent assessment of these risks. Last but not least, a better understanding of the human-animal interface and disease emergence requires a strong leadership and real efforts to engage different disciplines (FAO/OIE/WHO, 2011). Expecting the unexpected is crucial, but preparing for the unexpected is fundamental, and can only be achieved successfully within a multidisciplinary, collaborative context which operates at the field, local, national and international levels.

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## LIST OF FIGURES AND TABLES

**Table 1.** Criteria set for the selection of biological agents suggested as “emerging risks” in the literature review

**Table 2.** Number of articles retrieved, number of articles that were subject to a second screening and number of biological agents suggested as emerging risks identified, for each journal screened.

Legend: <sup>a</sup> The search string implemented in the search engines was formulated as: (unknown OR emerging OR new) AND (zoonosis OR microbiological) AND (livestock OR cattle OR goat OR horse OR pig OR poultry OR sheep); <sup>b</sup> Journals screened concurrently; <sup>c</sup> The “Emerging Infectious Diseases” journal was screened issue by issue.; <sup>d</sup> Some agents were identified in more than one journal.

**Table 3.** Information collected in the Excel database on the zoonotic biological agents suggested as emerging risks (2007-2013)

Legend: <sup>a</sup> The information provided in this column(s) corresponds to the respective criteria set (Table 1) <sup>b</sup> Novelty refers to whether the hazard, source, or route of contamination/exposure is new; <sup>c</sup> Scale refers to the number of people and Member States exposed to this hazard; <sup>d</sup> RNA refers to the ribonucleic acid; <sup>e</sup> gram + or – refers to the gram staining (positive or negative).

**Table 1.**

<b>Criteria set for the selection of biological agents (namely)</b>	<b>Description of the agents' criteria</b>
i. Disease transmission to humans	<b>Zoonotic</b> , transmitted between <b>livestock</b> animals and humans via one or more of the following ways: <ul style="list-style-type: none"><li>• by vectors or rodents;</li><li>• through direct or close proximity with infected livestock;</li><li>• through the environment (e.g. contaminated water);</li><li>• through consumption of contaminated food or drinking water.</li></ul>
ii. Time range	Have been the causative agents for incidents of human disease that occurred from 2007 until 2015.
iii. Geographic range	Occurrence anywhere in the world is considered, if there is a potential European perspective (e.g. linked to climate change or the globalisation of trade).
iv. Criteria of an “emerging risk”	The biological agent: <ul style="list-style-type: none"><li>• constitutes a hazard identified for the first time since 2007 which was recurrently reported until 2015, representing an increased exposure to it, or</li><li>• constitutes a known hazard (that is before 2007) to which an unexpected new or increased exposure and/or susceptibility occurred or was occurring until 2015.</li></ul>

**Table 2.**

<b>Scientific journal</b>	<b>Articles screened (1<sup>st</sup> screening)<sup>a</sup></b>	<b>Articles included (2<sup>nd</sup> screening)</b>	<b>Number of biological agents suggested as emerging risks</b>
International Journal of Food Microbiology & Food Microbiology <sup>b</sup>	431	67	1
Eurosurveillance	133	27	5
Emerging Infectious Diseases	NA <sup>c</sup>	80	7
Clinical Infectious Diseases & Journal of Infectious Diseases <sup>b</sup>	309	69	2
PLOS ONE	260	58	5
Transboundary and Emerging Diseases	108	18	4
Total	1241 <sup>c</sup>	319	7 <sup>d</sup>

**Table 3.**

Biological agent suggested as emerging risk	Type	Susceptible species (criterion i) <sup>a</sup>	Transmission to humans (criterion i) <sup>a</sup>	Health implications to humans	Novelty <sup>b</sup> (criteria ii, iv) <sup>a</sup>	Scale <sup>c</sup>	
						Areas Affected (criterion iii) <sup>a</sup>	Reported human cases
West Nile Fever virus (WNV)	Virus (RNA)	Humans, horses, birds	1. Mosquito borne 2. Via organ transplantation, blood transfusion 3. Exposure to blood or tissues of infected animals (horses) (occupational)	Asymptomatic or mild febrile disease (most commonly); meningitis and encephalitis (~1%) (severe form of disease)	Increased exposure due to geographic expansion of the virus into new areas (from 2008 onwards)	Worldwide; emerged in Spain, Italy, Greece	130 probable and confirmed autochthonous cases in the EU and 207 in neighbouring countries (June-November 2011) (DEFRA, 2012)
Rift Valley Fever virus (RVFV)	Virus (RNA)	Humans, domestic ruminants (cattle, sheep, goats)	1. Mosquito borne 2. Exposure to secretions of infected animals 3. Exposure to tissues of infected animals (occupational)	Unapparent infections, or with mild, influenza-like symptoms (in most cases); haemorrhagic fever, with hepatitis, thrombocytopenia, icterus, and multiple haemorrhages (most severe form).	Increased exposure due to geographic expansion of the virus into new areas (from 2000 onwards)	Widespread in Africa and re-emerging (especially 2006-2008); emerged in Yemen and Saudi Arabia (2000); Has not reached Europe.	Saudi Arabia, 2000: fatality rate reached 14%; Sudan, 2007-2008: 738 human cases officially reported, including 230 deaths (Chevalier, 2010)
Crimean-Congo haemorrhagic fever virus (CCHFV)	Virus (RNA)	Humans, domestic ruminants (cattle, sheep, goats), horses, hares	1. Tick borne 2. Exposure to blood or tissues of infected animals (occupational) or humans 3. Nosocomial transmission	High fever of sudden onset, malaise, severe headache and gastrointestinal symptoms; prominent haemorrhages may occur in late stages of the disease.	Increased exposure due to geographic expansion of the virus into new areas (from 2000 onwards)	Worldwide; increased number of outbreaks in EU and neighboring countries; first time in Greece (2008)	CCHF outbreaks have a case fatality rate of up to 40% (WHO, 2013)

Influenza A H <sub>1</sub> N <sub>1</sub> virus	Virus (RNA)	Humans, pigs, other species e.g. turkeys	1. Air borne 2. Exposure to secretions of infected animals (occupational) or humans 3. Via contaminated fomites	Mild disease, mainly affecting the respiratory tract; acute respiratory distress syndrome requiring intensive care treatment for a significant number of predominantly young or middle-aged patients	Novel virus, containing a combination of gene segments not reported before 2009	Worldwide	Over 18,449 laboratory-confirmed deaths in humans worldwide (WHO, 2011) with an estimated range between 151,700 and 575,400 deaths (Dawood et al., 2012) during the first year the virus circulated.
<i>Coxiella burnetii</i>	Bacteria (gram <sup>-d</sup> )	Humans, domestic ruminants (cattle, sheep, goats)	1. Air borne 2. Exposure to infected animals 3. Exposure to products from infected animals (occupational)	Acute infection: non-specific symptoms, most commonly flu-like (incl. high fever, headache and cough, atypical pneumonia or hepatitis); chronic: circulatory effects, chronic hepatitis	Increased exposure and susceptibility (2007-2009)	The Netherlands	Confirmed human cases: 168 (2007), 1,000 (2008), 2,357 (2009); hospitalization rate: 50% (2007), 20.9% (2008), 19.7% (2009) (EFSA, 2010B)
<i>Streptococcus suis</i>	Bacteria (gram <sup>+d</sup> )	Humans, pigs	1. Exposure to contaminated pigs (occupational) 2. Exposure to pig meat (occupational)	Meningitis and sepsis are the most common clinical manifestations of <i>S. suis</i> infection; hearing loss is a frequent complication.	Increased exposure (from 2005 onwards)	Worldwide, including 14 EU countries (more common in Asia)	1,600 human cases worldwide by 2012, most of which originating in Southeast Asia and 10% of which were in the European region (Huong et al., 2014). From 2007 to 2009, the total number of <i>S. suis</i> reported cases increased from 409 to over 700 (Wertheim et al., 2008)



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Livestock-associated meticillin-resistant <i>Staphylococcus aureus</i> clonal complex 398 (LA-MRSA 398)	Bacteria (gram +)	Humans, pigs, cattle, poultry, horses	Exposure to infected animals (occupational)	LA-MRSA 398 usually causes colonization; has, albeit rarely, been associated with deep- seated infections of skin and soft tissue, pneumonia and septicaemia in humans.	Increased exposure (from 2003 onwards)	Worldwide	LA-MRSA represent only a small proportion of the total number of reports of MRSA infections in the EU (EFSA, 2009A), but its frequency in human patients has been increasing (Cuny et al., 2015)
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