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REVIEW

Disease Risk Assessments Involving Companion Animals: an Overview for 15 Selected Pathogens Taking a European Perspective

J. M. Rijks*, F. Cito†, A. A. Cunningham‡, A. T. Rantsios§ and A. Giovannini†

** Dutch Wildlife Health Centre, Faculty of Veterinary Medicine, Utrecht University, Yalelaan 1, Utrecht, The Netherlands, † Istituto Zooprofilattico Sperimentale dell'Abruzzo e del Molise, Teramo, Italy, ‡ Institute of Zoology, Zoological Society of London, Regent's Park, London, United Kingdom and § National School of Public Health, Athens, Greece*

Summary

Prioritization of companion animal transmissible diseases was performed by the **C**ompanion **A**nimals multisectoria**L** interprofessiona**L** **I**nterdisciplinary **S**trategic **T**hink tank **O**n zoonoses (CALLISTO) project. The project considered diseases occurring in domesticated species commonly kept as pets, such as dogs and cats, but also included diseases occurring in captive wild animals and production animal species. The prioritization process led to the selection of 15 diseases of prime public health relevance, agricultural economic importance, or both. An analysis was made of the current knowledge on the risk of occurrence and transmission of these diseases among companion animals, and from companion animals to man (zoonoses) or to livestock. The literature was scanned for risk assessments for these diseases. Studies were classified as import risk assessments (IRAs) or risk factor analyses (RFAs) in endemic areas. For those pathogens that are absent from Europe, only IRAs were considered; for pathogens present throughout Europe, only RFAs were considered.

IRAs were identified for seven of the eight diseases totally or partially absent from Europe. IRAs for classical rabies and alveolar echinococcosis found an increased risk for introduction of the pathogen into officially disease-free areas as a consequence of abandoning national rules and adopting the harmonized EU rules for pet travel. IRAs for leishmaniosis focused on risk associated with the presence of persistently infected dogs in new geographical areas, taking into consideration the risk of disease establishment should a competent vector arise. IRAs for Crimean–Congo haemorrhagic fever and West Nile fever indicated that the likelihood of introduction via companion animals was low. IRAs for bluetongue paid no attention to the risk of introduction via companion animals, which was also the case for IRAs for foot-and-mouth disease, the only disease considered to be absent from Europe.

RFAs dealing with the risk factors for companion animals to become infected were identified for eight of the 14 diseases found in Europe or parts of it. RFAs for leptospirosis were most numerous (four studies). The host related risk factor 'age' was identified as significant for dogs in at least two RFAs for cystic echinococcosis and giardiasis. Among husbandry and healthcare related factors, 'eating (uncooked) offal', 'being free roaming' and 'poor deworming practice' were associated with risk for dogs in at least two RFAs for cystic echinococcosis, while 'having received recent veterinary treatment' was identified as a risk factor in at least two studies on infection with extended spectrum beta lactamase-producing bacteria, one in horses and the other in dogs and cats. Finally, although the environmental factors 'season' and 'hydrological density' were identified as significant risk factors for dogs in at least two RFAs for leptospirosis, the inconsistent case definitions used in those studies made comparison of study results problematic.

RFAs considering the risk of people becoming infected from companion animals were identified for eight of the 14 diseases found in Europe or parts of it. RFAs for human campylobacteriosis were the most numerous ($n = 6$). Most studies made an assessment as to whether keeping a pet *per se*, or keeping a pet with supposed or known risk factors, was a risk factor for people relative to other risks. This allowed some studies to report

Correspondence to: A. Giovannini (e-mail: a.giovannini@izs.it).

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the population attributable risk or population attributable fraction of the incidence of human disease due to companion animals (for campylobacteriosis, salmonellosis and toxoplasmosis), which is a measure that is easy to perceive for laymen and policy makers. No RFAs were found that dealt with the risk to food animals from companion animals for any of the 15 pathogens investigated.

Few risk method-based studies were identified that provided information on risk factors for companion animals and on their role as a source of these 15 selected diseases, indicating a clear knowledge gap. There were not enough assessments for any of the 15 diseases to allow meta-analyses, whether these assessments dealt with companion animal disease risk or companion animal-associated human disease risk. Important method and technology gaps were the lack of harmonization in the case definitions used for a given disease and the lack of good diagnostics allowing pathogen identification to taxonomic levels that are meaningful for risk analysis. Molecular epidemiology studies on zoonotic pathogens, which included companion animals among the potential human risk factors, were not found, although such studies would provide good preliminary insights without requiring any tracing of people or any interviews. In addition to performing further risk studies that take into account these issues, there is a need for responsible pet ownership and continued education of professionals in companion animal zoonoses. Additional risk assessment studies should allow more targeted actions to reduce the risk of zoonotic diseases transferred via companion animals and provide information that will promote risk-awareness in healthy human–animal relationships.

Keywords: companion animal; import risk assessment; risk factor; risk method

Contents

Introduction

The CALLISTO (**C**ompanion **A**nimals multisectoria**L** interprofessiona**L** and **I**nterdisciplinary **S**trategic **T**hink tank **O**n zoonoses) project was a coordination and support action within the 7th Framework Program of the European Union. The CALLISTO mission was 'to provide an overview of the current situation with regard to the role of companion animals as a source of infectious diseases for people and food animals, to identify knowledge and technology gaps for the most important zoonoses and propose targeted actions to reduce the risk of zoonotic diseases transferred via companion animals. Stakeholders and the general public are informed of CALLISTO results to contribute to the uptake of the proposed actions and to promote risk-awareness in healthy human–animal relationships.'

Companion animals, as defined in the framework of the CALLISTO project, comprise any domesticated, domestic-bred or wild-caught animals permanently kept by people for company, amusement, work (e.g. support for blind or deaf people, police or military dogs) or psychological support, including dogs, cats, horses, rabbits, ferrets, guinea pigs, reptiles, birds and ornamental fish. Companion animals, therefore, also include pet pigs and hobby sheep and goats, which may play a very important role as a source of infection for, or from, farm animals.

To achieve its mission, the CALLISTO project prioritized diseases harboured by companion animals that are transmissible to man and farm animals. Viral, bacterial and parasitic diseases were scored using criteria relating to public health risk and economic impact (Cito *et al.*, 2015). The five top scoring diseases in each aetiological category (i.e. viral, bacterial and parasitic) were retained, with priority in rank given to zoonotic diseases. The 15 diseases retained were Crimean–Congo haemorrhagic fever (CCHF), West Nile fever (WNF), foot-and-mouth disease (FMD), classical rabies, bluetongue, campylobacteriosis (*Campylobacter jejuni*), leptospirosis (*Leptospira interrogans* sensu lato), salmonellosis (*Salmonella enterica*) in reptiles, cat scratch disease (*Bartonella henselae*), infection due to extended spectrum beta lactamase (ESBL)-producing bacteria, cystic echinococcosis (*Echinococcus granulosus* sensu lato), leishmaniosis (*Leishmania infantum*), toxoplasmosis (*Toxoplasma gondii*), alveolar echinococcosis (*Echinococcus multilocularis*) and giardiasis (*Giardia* spp.) (Cito *et al.*, 2015).

However, there was no good overview of disease risk in companion animals or of their role as a source of these 15 selected diseases for people and food animals. Therefore, we scanned the literature for published risk assessments for these diseases to summarize the current knowledge on the risk of occurrence and transmission of these diseases among companion animals, and from companion animals to man (zoonoses) or to livestock. During the analysis performed on these risk assessments, special attention was given to summarizing the study designs, because these strongly affect the study results. In addition, such information could serve for future companion animal disease risk assessments in Europe.

Materials and Methods

Literature Search

In 2012, for each selected pathogen, searches were made in PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) for peer-reviewed papers and also in the general Google search engine (http://www.google.com) for risk assessment reports. In each search engine, one search was performed using the name of the pathogen followed by the words 'risk assessment' and another using the name of the disease followed by the words 'risk assessment'. To increase the sensitivity of the search, no Boolean operators were used between the two words 'risk' and 'assessment', so that any paper dealing with risk assessment or risk or just assessment for the pathogen/disease under investigation was captured. The search was then refined manually to select only publications relevant to the study.

In addition, a general search was performed in PubMed using only the words 'companion animals risk assessment'. Searches in PubMed were addressed to all fields of the database. There were no restrictions in terms of the time frame covered, but only risk assessments available in English were considered. The papers listed in the results of the searches were downloaded.

Selection and Classification of Papers

Papers were selected if they incorporated companion animals, as defined in the framework of the CALLISTO project, in the pathogen risk assessment and they were classified as import risk assessments (IRAs) or risk factor analyses (RFAs) in endemic areas. The rationale is that, when a disease is absent from an area, it is relevant to assess the risks of importation and establishment of the disease into the area; while in an area where the disease is present, it is more relevant to assess the risks for companion animals of becoming infected and their role in transmission of the disease to man or farm animals. For those pathogens exotic to all EU countries, only IRAs were considered. For those pathogens present only in part of Europe, the focus was on analysis of both IRAs and RFAs. For those pathogens present throughout

Europe, only RFAs were considered. Among the RFAs, a distinction was made between RFAs dealing with risk factors for the infection of companion animals and RFAs determining the role of companion animals in transmission of the disease to man (or to food animals). In describing the IRAs, we followed as far as possible the terminology of the last edition of the World Organisation for Animal Health (OIE) Terrestrial Animal Health Code (OIE, 2014).

Studies on diseases clearly not relevant to the project were discarded, with the exception of some assessments involving non-companion animals that were of interest in terms of methodology or disease risk in general. Studies that had not adopted a specific risk factor methodology were also discarded.

Analysis of the Papers

The selected papers were examined for information on prevalence and risk factors. Study design and risk factors examined were summarized, because they affect the outcome of the study and can be relevant for future work. Where similarities in risk factors were identified across studies in a given category, these were highlighted.

Further, some of the RFAs that looked into the role of companion animals in zoonotic transmission provided a measure for the proportion of disease risk in the human population due to companion animals. This measure was the population attributable fraction (PAF), defined by Rockhill *et al.* (1998) as 'the proportional reduction in average disease risk over a specified time interval that would be achieved by eliminating the exposure(s) of interest from the population while distributions of other risk factors in the population remain unchanged.' Specific attention was paid to the PAF (or population attributable risk [PAR] if expressed in numbers instead of a fraction), because it is a measure that is easy to perceive for laymen and policy makers.

On-line Map Videos of Events Reported to the World Organisation for Animal Health for the 15 Diseases

Ten of the 15 diseases studied by CALLISTO are reportable to the OIE. Data on the annual reporting to the OIE in domestic or wild animals were obtained for these 10 diseases from the OIE for all countries in the world, mapped per year, and then compiled into a video.

On-line Table of Published Epidemiological Importance for Species Susceptible to the 15 Diseases

Data on the epidemiological importance of domestic (companion and farmed) or wild animals were assembled for these 15 diseases in an on-line table (Supplementary Table). Associated with the table is the published literature from which data were collected.

Results

Viral Diseases

Crimean–Congo Haemorrhagic Fever. CCHF virus is transmitted to man through tick bites, mainly by *Hyalomma* spp., or through contact with body fluids of infected animals (Vescio *et al.*, 2012). CCHF virus can infect numerous domestic and wild animal species. Ruminants are considered amplifying hosts, developing viraemia but showing no clinical signs (Gale *et al.*, 2010). In Europe, CCHF is endemic in the Balkans (www.who.it; accessed 24/1/2015), although this is not apparent from 2005 to 2012 OIE data (Supplementary on-line map video 1: CCHF). One study identified the pathogen in ticks on deer in Spain (Estrada la Pena *et al.*, 2012).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Three IRAs that considered the role of companion animals were identified (Gale *et al.*, 2010; DEFRA, 2011; Hoek *et al.*, 2012). Two of these qualitative studies performed an entry assessment, an exposure assessment and a consequence assessment (Gale *et al.*, 2010; Hoek *et al.*, 2012). With regards to entry, Hoek *et al.* (2012) considered that companion animals could be a risk in terms of importation of the pathogen and competent ticks into the Netherlands, because the movement of pets is regulated but not always monitored. A *Hyalomma* spp. tick was imported into the UK on a horse (Jameson and Medlock, 2009). Additionally, the lack of a specific test to detect CCHF viraemia in livestock was highlighted (Hoek *et al.*, 2012). However, overall it was expected that the role of pets in CCHF virus epidemiology was very limited, and that infected *Hyalomma* ticks on migratory birds would be the most probable route of entry for CCHF virus into Western Europe (Gale *et al.*, 2010; DEFRA, 2011; Hoek *et al.*, 2012).

One RFA examined environmental and climatic data for risk factors for CCHF occurrence in people in Bulgaria (1997–2009), using a zero-inflated negative binomial model (Vescio *et al.*, 2012). There were no RFAs of risk factors for infection of companion animals, or the role of companion animals for disease risk to man, in the areas where CCHF is endemic.

West Nile Fever. West Nile virus (WNV) can infect birds, mammals (including man), reptiles and

amphibians. Some species of wild bird are the main amplifying host species (Hubálek and Halouzka, 1999). WNV infection can cause severe disease and death in horses and natural infection has been identified in domestic cats. Experimental infections suggested that horses were dead-end hosts (Campbell *et al*., 2002) and that cats and dogs were unlikely to contribute much to WNV transmission (Austgen *et al*., 2004). WNF outbreaks occur sporadically in several European countries, specifically in Southern and South-Eastern Europe (Supplementary on-line map video 2: WNF).

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Three IRAs were identified. One addressed the risk of importing WNV through horses and poultry into the UK (Roberts and Crabb, 2012). This qualitative study concluded that horses and poultry exhibit low and short-lived viraemia and would not contribute to the transmission cycle. Two other IRAs considered importation via migratory birds and mosquitoes into the UK (Brown *et al*., 2012) and Barbados (Douglas *et al*., 2007). In these quantitative studies, companion animals were not considered.

Four RFAs examined human infection risk factors in areas where the disease is endemic (USA or Canada) or reoccurs repeatedly (EU) using GIS software generating static maps (Cooke *et al*., 2006; Winters *et al*., 2008; Epp *et al*., 2011; ECDC, 2013), and three RFAs examined the determinants of seasonal WNV time of emergence and activity in the USA using GIS software to generate dynamic maps (Tachiiri *et al*., 2006; Zou *et al*., 2007; Konrad and Miller, 2012). Risk factors examined included environmental, climatic and vector-related data, and models were validated mostly using bird and human infection status data. Companion animal data were used neither as a risk factor nor to validate the models.

Foot-and-mouth Disease. FMD is primarily a disease of domestic and wild artiodactyls. The disease has been eradicated from Europe, but it still occurs in Russia and Anatolia, other parts of Asia, Africa and in South America. There were 37 reintroductions into Europe in the period 1985–2006 (Valarcher *et al*., 2008) and two since 2006 (OIE website May 2013; Supplementary on-line map video 3: FMD). Some of these epidemics led to important economic losses. Their exact origin often remained unknown (Valarcher *et al*., 2008).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

One qualitative and six quantitative IRAs dealt with the risk of FMD importation via legal or illegal trade of livestock or livestock products or fomites (EFSA, 2006a; Wooldridge *et al*., 2006; Asseged *et al*., 2007; Hartnett *et al*., 2007; Adkin *et al*., 2008; Lin *et al*., 2009; Miller *et al*., 2012). The qualitative report assessed introduction pathways into the EU (EFSA, 2006a). It classified countries worldwide into nine risk categories and concluded that there is a persisting risk for the import of FMD into the EU via live animals originating from the Middle East and via legal or illegal meat or meat products from Asia (EFSA, 2006a). It also concluded that the main route for subsequent dissemination in the EU was likely to be the movement of infected live animals. Neither this IRA, nor any of the six other quantitative IRAs, specifically addressed the risk of introduction and dissemination of FMD via cloven-hoofed species kept as companion animals. Quantitative and qualitative information regarding cloven-hoofed animals imported or kept as pets in the EU would be required for this. Noteworthy in this context is an effort by Marshall *et al*. (2007) to examine husbandry practices reported by owners of miniature swine that could be relevant to the risk of FMD in the USA.

Classical Rabies. Rabies is a disease of mammals, including man, caused by neurotropic viruses of the genus *Lyssavirus* of the family Rhabdoviridae. The focus of the CALLISTO project was classical rabies virus (genotype 1) and not the genetically distinct bat lyssaviruses that only sporadically cause human disease. Classical rabies virus is responsible for almost all human rabies cases and it is distributed worldwide. The virus causes encephalomyelitis and is maintained in mammalian reservoirs, mainly domestic and wild carnivores and, in the Americas, also in bats (Warrell and Warrell, 2004). Dogs represent the major rabies reservoir in developing countries. In Western Europe, the red fox (*Vulpes vulpes*) and the (introduced) raccoon dog (*Nyctereutes procyonoides*) are, or have been, the main reservoir hosts (Cliquet *et al*., 2010), although fox rabies has been recently eradicated from several west European countries. Domestic animals, primarily domestic dogs and cats, forge the link between infected wildlife and man (Rupprecht *et al*., 2000). Classical rabies is endemic in a number of European countries. In those European countries that are officially free from classical rabies (UK, Ireland, Sweden and Malta), the rabies control legislation is stricter than that in force in the remainder of the EU. Indigenous human cases still occur in Eastern Europe (e.g. Ukraine and Russia) while cases in rabies-free countries are due to virus

importation (Supplementary on-line map video 4: Rabies; this video includes rabies caused by classical rabies virus as well as by other lyssaviruses).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Three IRAs assessed the rabies risk faced by the four officially rabies-free countries (EFSA, 2006b) or by the UK only (Wilsmore *et al.*, 2006'; Goddard *et al.*, 2010 and associated report Det Norske Veritas, 2011), including assessing the effectiveness of the wider EU rules for the importation of dogs, cats or other mammals with regards to rabies. One study was a qualitative report (Wilsmore *et al.*, 2006), while the others were quantitative (EFSA, 2006b; Goddard *et al.*, 2010; Det Norske Veritas, 2011). The results of the three IRAs, assuming 100% compliance with all EU regulations, indicate that abandoning the current regulations specific to rabies-free countries to comply only with the wider EU regulations would increase significantly the annual risk of rabies introduction.

Despite classical rabies being endemic in several European countries, we were unable to find RFAs addressing the risks of companion animals becoming infected with rabies in Europe, or RFAs addressing the risks of human infection from companion animals in Europe.

Bluetongue. Bluetongue virus (BTV) can infect most species of domestic and wild ruminants. Ruminants kept for hobby purposes or as pets may be at risk of infection and disease, and can in theory be a source of infection and of introduction of BTV. The main route of transmission of this non-contagious disease among ruminants is via bites of female *Culicoides* spp. midges. In addition to ruminants, carnivores may become infected with BTV through the oral route and from midge bites. In 2007 and 2008, BTV serotype 8 infection caused disease and death in two Eurasian lynxes (*Lynx lynx*) in Belgium, presumably through infection via the oral route (Jauniaux *et al.*, 2008). In 2011, a study performed in Morocco after a BTV outbreak showed circumstantial evidence of the susceptibility of dogs to BTV-1 infection transmitted by natural vectors (Oura and El Harrak, 2011). It remains questionable as to whether carnivores develop levels of viraemia able to infect midges, but if they do, dogs and cats that are transported from BTV endemic to non-endemic countries without any pre- or post-importation testing could present a BTV risk to the destination countries (Oura and El Harrak, 2011). During the last decade, almost all Western and Central European countries have been affected by BTV. Serotypes involved were 1, 2, 4, 6, 8, 9 and 16 and 11, 14, 25, 27. By 2012, however, most Northern and Central European countries were again free from BTV, although virus circulation still remains in parts of Southern Europe (Supplementary on-line map video 5: BT). BTV is not a zoonosis.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Four IRAs focused on quantifying the risk of virus introduction into new areas via infected hosts or vectors (entry assessments). One modelled the risk of BTV importation from Canada into the UK through infected cattle (Kelly *et al.*, 2000). With export from Canada occurring only between 2nd February and 15th April (when there is no vector activity), and under a regime of pre-export serological testing and quarantine, it was 90% certain that there was only a 0.004%–0.473% chance of introducing BTV into the UK each year. Another IRA focused on the risk related to the introduction of vaccinated ruminants from restricted zones into BTV-free territories (Giovannini *et al.*, 2004). The last two IRAs dealt with BTV introduction via infected vectors, modelling the risk of wind-borne spread of infected *Culicoides* spp. from the continent into the UK in 2007 (Gloster *et al.*, 2007a, b) and the risk of introduction of infected *Culicoides* spp. via transport and trade networks from Northern European countries into Spain in 2007 (Napp *et al.*, 2013). None of the IRAs gave specific consideration to ruminant companion animals or focused on the possible role of domestic carnivores in the spread of BTV from endemic to free areas.

The risk for BTV transmission amongst ruminants, including those kept for hobby purposes or as pets, depends largely on the presence of competent BTV vectors. Consequently, RFAs focused mainly on identifying climatic and environmental conditions suitable for maintaining *Culicoides* spp. populations and enhancing BTV transmission. These were performed using data from Spain extrapolated to the EU (Wittmann *et al.*, 2001), from Iberia and Morocco (Baylis *et al.*, 2001), from Italy (Conte *et al.*, 2003, 2004; Purse *et al.*, 2004; Conte *et al.*, 2007a, b), from Austria (Brugger and Rubel, 2013) and the EU (Guis *et al.*, 2012). They used *Culicoides* trapping data, ground-collected climatic data or remote sensing data, and GIS software. Differences in heliophily and ombrophily among *Culicoides* spp. were observed that were likely to impact on their ability to transmit BTV (Conte *et al.*, 2007a, b). The more recent studies attempted to produce dynamic predictive maps of the abundance of vectors, considered a proxy of the risk of infection transmission, with a view to adjusting surveillance efforts seasonally and geographically (Guis *et al.*, 2012; Brugger and Rubel, 2013).

In addition to these RFAs, the risk of BTV overwintering by horizontal transmission was modelled by Napp *et al.* (2011) and the risks of BTV persistence in Italian ruminant populations under different vaccination regimes were modelled by Giovannini *et al.* (2004).

Results were that, given the relative abundance of the three susceptible ruminant species considered, a vaccination campaign should cover at least 80% of all domesticated susceptible ruminants to be successful.

Bacterial Diseases

Campylobacteriosis. Dogs and cats are well-known carriers of *Campylobacter* spp., including *C. jejuni*, but *Campylobacter* spp.-associated disease in these species is uncommon (Fox *et al.*, 1983; Burnens *et al.*, 1992; Wieland *et al.*, 2005). *Campylobacter* spp. infection also occurs in other companion animal species, but prevalence has not been studied systematically and the infection has only rarely been associated with disease (Harvey and Greenwood, 1985; Gardner and Young, 1987; Skirrow, 1994; López *et al.*, 2002; Hurcombe *et al.*, 2009). Birds are natural hosts for *C. jejuni* (Wieland *et al.*, 2005) and *Campylobacter* spp. is likely to be common in poultry kept as pets or by hobby farmers. *Campylobacter* spp. infections are endemic in all European countries.

Only two RFAs were found that focused on the risk factors for companion animals (i.e. dogs, cats and birds) to become infected. These were performed in Argentina (López *et al.*, 2002) and Switzerland (Wieland *et al.*, 2005). These studies were surveys (cross-sectional studies), with cases being defined as animals with *C. jejuni*-positive faecal cultures. Analysis involved univariable and multivariable logistic regression (López *et al.*, 2002; Wieland *et al.*, 2005). Prevalence of *C. jejuni* in the faeces of examined companion animals was high: dog 17% (95% CI: 13–22%; López *et al.*, 2002) and 41% (95% CI: 37.3–45.1%; Wieland *et al.*, 2005); cat 16% (95% CI: 8–27%; López *et al.*, 2002) and 42% (95% CI: 37.9–46%; Wieland *et al.*, 2005); pet birds (i.e. chickens, pigeons, parrots, sparrows, canaries and other caged birds) 19% (95% CI: 5–42%; López *et al.*, 2002). Risk factors examined in both studies for dogs and cats included the host factor age category, husbandry factors related to contact with other animals and degree of confinement, and the environmental factor season. In multivariate analysis, none of these factors was a consistent risk factor in both studies.

Six RFAs addressed risk factors for people to become infected through companion animals. These studies were performed in the UK (Adak *et al.*, 1995), Denmark (Neimann *et al.*, 2003), Sweden (Carrique-Mas *et al.*, 2005), Switzerland (Buettner *et al.*, 2010), the USA (Friedman *et al.*, 2003) and Australia (Stafford *et al.*, 2008). They were mostly case–control studies, a case being defined as a person with diarrhoea and positive bacterial culture (and, in four studies, in a certain age category). Tens to hundreds of exposure factors, including exposure to pets, were examined using questionnaires. In addition to other exposure factors not related to pets, the risk for disease in man was significantly associated with owning or having contact with a dog (Carrique-Mas *et al.*, 2005), a cat or another pet (Buettner *et al.*, 2010), in particular if this was a young animal (kitten, Neimann *et al.*, 2003; puppy, Friedman *et al.*, 2003; Stafford *et al.*, 2008), or an animal with diarrhoea (Adak *et al.*, 1995). In addition, the relative risk that companion animals pose to man seemed to differ according to the age category of the people. The PAF of the identified companion animal-related risk factor was mostly significant, but relatively low compared with other risk factors for people older than 6 years of age (PAF 'had a pet puppy' = 5%, Friedman *et al.*, 2004; PAR 'having a dog that is not older than 6 months' = 3%, Stafford *et al.*, 2008; PAF 'pet contact' = 8%, Buettner *et al.*, 2010), but relatively high for people under 6 years of age (PAR 'having a dog' = 30%, Carrique-Mas *et al.*, 2005).

*Leptospirosis (*Leptospira interrogans *sensu lato)*. *Leptospira interrogans* sensu lato can infect man and many domestic and wild animals. The pathogen is shed in the urine of infected animals, and can survive in moist environments. The bacterium occurs in all European countries (Supplementary on-line map video 6: Leptospirosis); however, there are more than 200 different *L. interrogans* serovars, each with one or more reservoir hosts, and different serovars predominate in different animal species and in different areas.

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Four RFAs and associated studies addressed the risk of dogs becoming infected with *L. interrogans*. These were performed in the USA (Ghneim *et al.*, 2007; Raghavan *et al.*, 2011, 2012a, b), Canada (Alton *et al.*, 2009), or both countries (Ward *et al.*, 2002; Ward, 2002a, b). All risk factor studies were case–control studies; however, the studies differed in their case definitions, in particular with regards to the cut-off for serological tests. For example, dogs with microscopic agglutination test (MAT) titres of 100 were defined as cases in one study (Alton *et al.*, 2009) and controls in others (Ghneim *et al.*, 2007;

Raghavan *et al.*, 2011). Analyses involved univariable and multivariable logistic regression (Ward *et al.*, 2002; Ghneim *et al.*, 2007; Alton *et al.*, 2009; Raghavan *et al.*, 2011, 2012a, b). Temporal or spatial patterns, or both, were detected using scan tests (Ward, 2002a; Alton *et al.*, 2009), the Cochran–Armitage test for trends in proportions (Alton *et al.*, 2009), time-series analysis (Ward, 2002b) and GIS (Ghneim *et al.*, 2007). Prevalence of clinical leptospirosis in dogs was low in the USA and Canada in the period 1970–1998 following the introduction of leptospirosis vaccination in the 1970s (37/100,000 dogs at veterinary teaching hospitals), but started to increase from 1983 onwards (Ward *et al.*, 2002). This was in due in part to infections with serovars not included in vaccines (Ward, 2002a; Glickman *et al.*, 2006; Alton *et al.*, 2009). The factors examined in two or more studies included host factors, such as age category, gender and neuter status and breed category (Ward *et al.*, 2002; Ghneim *et al.*, 2007; Alton *et al.*, 2009), and environmental factors such as urban or rural surroundings (Ghneim *et al.*, 2007; Alton *et al.*, 2009; Raghavan *et al.*, 2011), hydrological density (Ghneim *et al.*, 2007; Raghavan *et al.*, 2012a) and season (Ward, 2002b; Alton *et al.*, 2009). Among these, there were consistent positive effects of hydrological density (hydrological density OR = 2.80; 95% CI: 1.58–4.96, Raghavan *et al.*, 2012a; hydrographical density expressed as the total length of hydrological features within an area of 0.5 km radius from the home of the dog OR = 375.15; 95% CI 19.88–13303, Ghneim *et al.*, 2007). Moreover, a consistent pattern of cases peaking in the autumn in the Northern Hemisphere was found (August to November, Ward, 2002b; October to December, Alton *et al.*, 2009). However, findings relating host factors or urban or rural surroundings were not consistent. Ward *et al.* (2002) found that a greater risk was associated with intact male dogs of working or herding breeds, but Alton *et al.* (2009) found no indication that host factors played a role. Two studies (Alton *et al.*, 2009; Raghavan *et al.*, 2011) found dogs in urban environments were more at risk, which was contrary to univariate analysis and GIS results in the study by Ghneim *et al.* (2007). In addition, Ward (2002a) found evidence for temporal–spatial clustering of cases, while Alton *et al.* (2009) found no evidence for spatial clustering, possibly due to an effect of scale.

Two RFAs addressed risk factors for people becoming infected with leptospirosis through exposure to companion animals. These were performed in Mexico and in Switzerland (Leal-Castellanos *et al.*, 2003; Barmettler *et al.*, 2011). Both were seroprevalence studies. The study population were householders in a rural area in the Mexican study (Leal-Castellanos *et al.*, 2003) and persons exposed to clinical cases of canine leptospirosis in the Swiss study (Barmettler *et al.*, 2011). The serological tests used for the detection of cases and identification of serovars were MAT (cut-off at a titre of 80; Leal-Castellanos *et al.*, 2003) or a complement fixation test (CFT) followed by MAT (Barmettler *et al.*, 2011). In the Swiss study, none of the people had antibodies to *L. interrogans*, so risk factors could not be examined. In contrast, in the Mexican cross-sectional study, 441/1,169 (37.7%) of the householders had antibodies to *L. interrogans*, predominantly to serovars *hardjo* and *bratislava*. In the multivariable model, which controlled for host age, gender and socioeconomic status, the risk factors examined included occupation, presence of domestic animals, handling of animal tissues, contact with animal excreta, water in puddles near the home, foot skin cuts or abrasions during flooding, type of footwear, presence of rodents in the home, choluria in the previous year and dengue infection in the previous year. In this setting, risk was associated with being a farmer (OR = 1.95, 95% CI 1.03–3.71), presence of pigs, cattle, or both (OR = 1.87, 95% CI 1.29–2.72), contact with animal excreta without protection and with skin cuts or abrasions (OR = 2.25, 95% CI 1.10–4.56), foot skin cuts or abrasions during flooding (OR = 4.23, 95% CI 3.12–5.75), open footwear (OR = 1.80, 95% CI 1.32–2.45) and choluria in the previous year (OR = 2.19, 95% CI 1.23–3.90). The risk associated with presence of dogs, cats, or both (OR = 1.31, 95% CI 0.96–1.80) or of rodents in the home (OR = 1.30, 95% CI 0.98–1.73) was not significant (Leal-Castellanos *et al.*, 2003). This study highlighted the link between serovar, reservoir species and risk factors.

Salmonellosis. In the context of the CALLISTO project, the focus was only on *S. enterica* infections of reptiles. *S. enterica* occurs in the intestinal microflora of reptiles throughout Europe. *S. enterica* infection in reptiles is mostly without clinical disease (Supplementary on-line map video 7: Salmonellosis; not specific to reptiles).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Only one RFA addressed the risk of reptiles becoming infected with *S. enterica* (Pfleger *et al.*, 2003). It was a 3-year longitudinal study performed in a vivarium in Austria, where 103 reptiles belonging to 23 different species and 35 amphibians belonging to five species were kept in terrariums under conditions

simulating different ecosystems. Faecal samples were taken for bacterial culture and isolation on average every 49 days. Risk factors examined included the host factor suborder to which the host belonged, the husbandry factors diet (e.g. plants, insects and/or mice) and duration of stay in captivity, and the environmental factor climate (e.g. arid, mesic, humid or aquatic). Analysis was descriptive and also used logistic regression. None of the sampled animals showed clinical signs of *Salmonella* spp. infection. Prevalence in reptilian faeces (51/301 = 17%; in 13 of 23 species) was significantly higher than in amphibian faeces (3/75, 4%; in one of five species; $P < 0.05$). Prevalence in snakes was 24%, in lizards 17% and in turtles 3%. Permanent excretion was never observed and co-housed animals often excreted different serotypes. Some animals never became infected. The relative risk of infection increased by 2.91 per year in captivity. Animals feeding on mice were more at risk than those that did not feed on mice ($P < 0.05$). On 20 occasions the outside and inside walls of the terraria were swabbed, but *S. enterica* was never isolated.

Four RFAs addressed the risk of people becoming infected through contact with pet reptiles. These were performed in the USA (Ackman *et al.*, 1995; Mermin *et al.*, 2004; Jones *et al.*, 2006a, b) and in the UK (Aiken *et al.*, 2010). They were case–control studies (Mermin *et al.*, 2004; Jones *et al.*, 2006a, b) or case–case studies, the latter to avoid notification bias (Ackman *et al.*, 1995; Aiken *et al.*, 2010). They were sometimes matched (Ackman *et al.*, 1995; Jones *et al.*, 2006a, b). In three RFAs, cases were patients of all ages (Ackman *et al.*, 1995; Mermin *et al.*, 2004; Aiken *et al.*, 2010), but one RFA restricted the study to infants <1 year of age (Jones *et al.*, 2006a, b). Cases were patients with salmonellosis caused by all serotypes other than *Salmonella typhi* (Jones *et al.*, 2006a, b) or by all non-typhoidal serotypes (Aiken *et al.*, 2010), non-typhoidal B or D type serotypes (Mermin *et al.*, 2004) or *S. enterica* serotypes that are predominantly cultured from reptiles and are called reptile-associated serotypes (Ackman *et al.*, 1995). Effort was made to exclude outbreak cases (Mermin *et al.*, 2004; Jones *et al.*, 2006a, b). In the case–case studies, the controls were patients suffering from other enteric diseases, either shigellosis (Ackman *et al.*, 1995) or *Campylobacter* spp. infection (Aiken *et al.*, 2010). The questionnaires included questions about recent reptile exposure. All studies found that cases had significantly higher odds of being exposed to reptiles than controls, although there is some circular reasoning between case definition and risk factor, in particular in the Ackman *et al.* (1995) study. Young age was a risk factor in the three RFAs where patients were of all ages (Ackman *et al.*, 1995; Mermin *et al.*, 2004; Aiken *et al.*, 2010). Mermin *et al.* (2004) found that the PAF for reptile or amphibian contact was 6% for all sporadic *Salmonella* spp. infections and 11% for people under 21 years old, and concluded that reptile (and amphibian) exposure is associated with 74,000 *Salmonella* spp. infections annually in the USA. Aiken *et al.* (2010) found the PAF of reptile exposure among patients with non-typhoidal serotypes was lower (0.95%), accounting for approximately 12,000 of the cases reported in England and Wales in 2007. Jones *et al.* (2006a) found that in infants, reptile exposure was a risk factor for salmonellosis caused by all serotypes other than *S. typhi* (OR = 5.2, 95% CI 3.4–7.9), with the highest PAF (17.4%) of all risk factors examined.

*Cat Scratch Disease (*Bartonella henselae*).* Domestic cats are the natural reservoir of *B. henselae*. People, dogs and horses are more likely to be accidental hosts. *B. henselae* has been found in all European countries where it has been looked for.

One RFA addressed the risk factors for cats becoming infected with *B. henselae* (Chomel *et al.*, 1995). The survey was performed in the USA. In a convenience sample of cats, *B. henselae* was cultured from the blood of 39.5% of the animals and seroprevalence was 81%. Multivariate logistic regression demonstrated that bacteraemia was less likely in cats that were 1 year of age or older (OR = 0.34, 95% CI 0.16–0.73) and in cats kept indoors (OR = 0.18, 95% CI 0.06–0.54).

Two RFAs addressed the risk of people becoming diseased with *B. henselae* (Zangwill *et al.*, 1993; Sanguinetti-Morelli *et al.*, 2011). One was a matched case–control study performed in the USA; cases being defined as persons with unexplained lymphadenopathy, owning a cat in the 3 months before disease onset (Zangwill *et al.*, 1993). Analyses were univariable and bivariable. The study found that ownership of a kitten was a risk factor, in particular receiving a scratch from it (Zangwill *et al.*, 1993), and suggested a role for fleas in transmission. The other study was a survey performed in France to identify seasonality of risk (Sanguinetti-Morelli *et al.*, 2011) using lymph node biopsy samples, which were tested by real-time polymerase chain reaction (PCR) for the presence of *B. henselae*. Most cases occurred from September to April rather than in summer.

Infection with Extended Spectrum Beta Lactamase-Producing Bacteria. Extended spectrum beta lactamase (ESBL)-producing bacteria can be important zoonotic pathogens as they are resistant to many

antibiotics. They are transmitted by the faecal–oral route, direct contact or fomites. They have been found in all European countries where they have been looked for.

Two RFAs addressed the risk factors for companion animals carrying ESBLs. There was a cross-sectional study on 627 horses recruited by randomly selected veterinary clinics in the UK (Maddox *et al.*, 2012), and one on 174 dogs and 202 cats visiting or living in randomly selected nursing homes or brought to veterinary practices for routine vaccination in Switzerland (Gandolfi-Descristophoris *et al.*, 2012). Both studies identified cases based on faecal sampling. In the UK study, horses were considered cases when ESBL-producing *Escherichia coli* could be isolated from their faeces, while in the Swiss study dogs and cats were considered cases when ESBL-producing Enterobacteriaceae could be isolated from their faeces. Prevalence was adjusted for clustering at source in both studies. Adjusted prevalence was 6.3% for ESBL-producing *E. coli* in the horses in the UK study, and it was 2.5% (9/376; 95% CI 1.3–4.6) for ESBL-producing Enterobacteriaceae in dogs and cats in the Swiss study. The ESBL-producing Enterobacteriaceae isolated in the latter study were *E. coli*, *Klebsiella pneumoniae* and *Enterobacter* spp., and no difference in carriage of ESBL bacteria between dogs and cats was detected. The risk factors examined in both studies included host factors, such as species or breed, age (category) and gender, healthcare related factors, such as veterinary treatments, and environmental factors concerning the nature of the premises where the animal was kept and contact with other animals (Maddox *et al.*, 2012; Gandolfi-Descristophoris *et al.*, 2012). In both studies, multivariable analysis showed a clear link to recent healthcare events. In the horses, the most significant risk factors were hospitalization of the case within the last 10 days (OR = 15.96, 95% CI 4.08–62.4, $P < 0.001$) and within the last three months (OR = 8.33, 95% CI 1.74–39.9, $P = 0.008$; the reference being hospitalized more than 6 months ago). In the dog and cat study, antibiotic treatment in the 3 months prior to the investigation was the only significant risk factor identified (OR = 7.8, 95% CI 2.2–26.9, adjusted for gender, age category and species). In the horse study, there were also significant premises-related risk factors. These were staying on the premises with a recently hospitalized horse (OR = 3.90, 95% CI 1.05–15.3, $P = 0.04$), type of premises being a 'field only' premises (OR = 3.78, 95% CI 1.06–13.5, $P = 0.04$) or a 'racing yard' premises (OR = 7.24, 95% CI 1.06–49.4, $P = 0.04$), and mixed land use in the surroundings (OR = 11.82, 95% CI 1.92–72.7, $P = 0.007$).

There were no RFAs addressing the risk of people becoming infected by ESBL-producing bacteria carried by companion animals. A review article published in 2012 (Ewers *et al.*, 2012) focused on the genetic comparison of strains isolated in livestock, companion animals and humans beings. Its contents could be very useful in the planning of studies on the risk factors for the transmission from companion animals to humans beings, but the article does not deal with the specific problem of risk factors.

Parasitic Diseases

Cystic Echinococcosis. *Echinococcus granulosus* sensu lato is a cestode parasite. Dogs are definitive hosts and shed eggs in their faeces, which infect intermediate hosts. These are generally ungulates, such as sheep, in which they develop into larval cysts, which in turn infect the definitive hosts when ingested. People can also be infected by eggs and develop cysts (i.e. cystic echinococcosis or hydatidosis). The endemic area of *E. granulosus* sensu strictu in Europe covers southern and south-eastern Europe and Wales. *E. intermedius* (a strain of *E. granulosus*) is prevalent in the Baltic countries, Poland and southwards to Romania (this is not apparent on Supplementary on-line map video 8: Cystic and alveolar echinococcosis, which combines cases of cystic and alveolar echinococcosis).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Three RFAs focused on the risk factors for dogs becoming infected by ingesting larvae. Two were performed in Wales (Buishi *et al.*, 2005a; Mastin *et al.*, 2011) and one in Libya (Buishi *et al.*, 2005b). The Welsh studies followed a FMD outbreak (Buishi *et al.*, 2005a; Mastin *et al.*, 2011). All three surveys examined faecal samples of dogs to determine prevalence and used questionnaires to identify the risk factors for infection of the dog. Analyses involved univariable and multivariable logistic regression; in addition, Buishi *et al.* (2005a, b) used multilevel modelling to account for spatial clustering of cases. Prevalence of *E. granulosus* in faeces of dogs in Wales was around 10%, and the proportion of farms with at least one positive dog around 20% (Buishi *et al.*, 2005a; Mastin *et al.*, 2011). The factors examined in two or more studies included: host factors such as age, gender and type; husbandry and healthcare related factors such as the nature of the dog feed, whether the dog was confined or free roaming and deworming practice; environmental factors such as on site (sheep) slaughtering or not, offal disposal practices; and human knowledge about *E. granulosus* and occurrence of

human cases on farm. The risk factor standing out in all three studies was free roaming of the dog (Buishi *et al*., 2005a, b; Mastin *et al*., 2011). Other factors significant in at least two studies were dog age <5 years, dog eating (uncooked) offal, and poor deworming practice (absent, or at >4 months intervals) (Buishi *et al*., 2005a, b).

Two RFAs focused on the risk factors for people becoming infected. These were performed in Spain (Campos-Bueno *et al*., 2000) and in Wales (Dowling and Torgerson, 2000). The first was a case–control study (univariable and then multivariable conditional logistic regression analysis), the second a survey (cross-sectional study; univariable and then multivariable logistic regression analysis). A case was defined as either a person that had been diagnosed surgically or through radiology with cystic echinococcosis (Campos-Bueno *et al*., 2000) or a person that had been treated for it (Dowling and Torgerson, 2000). In the first study, controls were other radiographed persons. To identify risk factors, tens of questions were asked, covering personal data, ownership or contact with dogs, eating habits, work and family environment. The variables included in the multivariable analysis in the first study were owning dogs fed on uncooked offal or carrion, family environment of livestock–ranching type, size of the place of birth and of usual residence (number of inhabitants) and living in rural dwelling; and in the second study, age, gender, owning a farm, keeping dogs, deworming dogs, keeping sheep, wintering lambs away, having a vegetable plot, dogs allowed inside house and dogs not allowed inside house. The only significant risk factor in the first study was having a dog that was fed on uncooked offal or carrion (OR = 3.985; 1.936–8.203). There was no significant factor in the second study.

Leishmaniosis. *Leishmania infantum* is a zoonotic protozoal parasite, with dogs as the reservoir host. Sandflies are biological vectors. Infection is usually through the bite of a *Phlebotomus* spp. sandfly. Leishmaniosis is currently endemic only in some Southern European countries (Supplementary on-line map video 9: Leishmaniosis).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Two IRAs were found, both of which focused on gathering data on the *Leishmania*-infected dog reservoir in non-endemic countries, a reservoir that is mostly due to dog imports from, or travel to, endemic countries. The studies had in mind the implications of such a reservoir for the establishment of leishmaniosis in non-endemic countries should a competent vector arise. Both studies involved diagnostics and a questionnaire, and analysis was only descriptive. One study was performed in the UK in 2005–2007 (Shaw *et al*., 2009) and the other in Germany in 2004–2009 (Menn *et al*., 2010). The first established the presence of several hundred cases in the UK, in particular in southern and central England. The majority of cases with a complete travel history (176/183, 96%) had stayed in endemic areas for >6 months and some (26/183, 14%) were known to have leishmaniosis when they were imported (Shaw *et al*., 2009). The second study examined 4,681 dogs with a travel or import history, more than two-thirds of which involved movement to or from endemic areas. This study found that 12.2% (569) had antibodies against *L. infantum*, indicating their exposure to the parasite.

Two RFAs aimed at predicting the occurrence of canine leishmaniosis in southern France (Chamaille *et al*., 2010, Hartemink *et al*., 2011). The first looked into environmental and climatic factors that could explain leishmaniosis maintenance and emergence in the south of the country (Chamaille *et al*., 2010). The study used a regular 5 × 5 km grid and considered a cell to be endemic for canine leishmaniosis if it contained a least one locality with at least one canine leishmaniosis case, based on studies from 1965 to 2007. The cases included were confirmed by parasitological, serological or molecular techniques. Imported cases were excluded from the database. Using principal component analysis (PCA) followed by hierarchical ascendant classification (HAC), these cells were characterized in environmental (i.e. forest cover, dog density and human density) and climatic terms (i.e. altitude, temperature and rainfall) and two distinct environments ('ecological niches') were identified: one inland in the Cévennes region and one on the Mediterranean coastal plain. The authors hypothesized that these may correspond to the favoured environments of two sandfly species. For each environment, an 'ecological niche' model (Maxtent model) was then used to predict the potential sandfly distribution on canine leishmaniosis. The second study (Hartemink *et al*., 2011) focused on predicting outbreaks by using sandfly trapping and satellite data to model vector abundance, and combining this with literature and expert-derived estimates of variables and parameters, to create an R0 map for leishmaniosis.

Toxoplasmosis. Felids are the definitive hosts for *T. gondii*. Generally, cats only shed *Toxoplasma* spp. oocysts in their faeces for a few weeks following infection. All warm-blooded vertebrates are potential intermediate hosts. People, like other intermediate hosts, are infected either by sporulated oocysts, bradyzoites in

meat or tachyzoites via the intra-uterine route (Dabritz and Conrad, 2010; Elmore *et al.*, 2010; Lindsay and Dubey, 2011). *T. gondii* is endemic across Europe (this is not clear from Supplementary on-line map video 10: *Toxoplasmosis*, presumably due to lack of reporting of cases).

Supplementary video related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

Four RFAs addressed risk factors for people becoming infected with *T. gondii* directly or indirectly through exposure to companion animals. These studies were performed in France, across six European countries, Brazil and the USA (Baril *et al.*, 1999; Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009). All four studies were case–control studies, matched or not. The French and the European studies specifically addressed the risk of women becoming infected during pregnancy and, accordingly, the population section investigated was limited to pregnant women (Baril *et al.*, 1999; Cook *et al.*, 2000). In the French study, a single control was matched using gestational age and area of residence (Baril *et al.*, 1999), while in the European study the controls were the next four women testing negative with the same screening tests in the same laboratory (Cook *et al.*, 2000). The USA study concerned only persons aged 18 years or older. Neither the Brazilian nor the USA studies focused on pregnant women, but took gender and age class into account in the analysis (Jones *et al.*, 2006a, b, 2009). Case definitions were based on serological test results indicative either of primary or recent infection with *Toxoplasma* spp. This was defined by a negative test for *Toxoplasma*-specific IgG and IgM, followed by a positive test, confirmed on a further serum sample (Baril *et al.*, 1999; Cook *et al.*, 2000), or presence of *Toxoplasma*-specific IgM and IgG in high or rising titres (Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009), in combination with *Toxoplasma*-specific IgA and IgE titres (Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009). Significance levels in the univariable analyses (adjusted in the study by Cook *et al.*, 2000 for testing centre, maternal age, time between diagnosis and interview) were used to identify factors for multivariable (conditional) logistic regression analyses (Baril *et al.*, 1999; Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009). The risk factors examined covered demographic and social characteristics, as well as 'historical factors' in the month preceding the estimated date of *Toxoplasma* spp. infection of the case, in particular concerning preparation and consumption of meat and other food, soil and vegetable-related exposure, and exposure to cats, kittens, cat litter or other animals. Baril *et al.* (1999) and Cook *et al.* (2000) also examined women's awareness of the infection and how they had been informed. In the final multivariable analyses, all four studies identified the consumption of raw, undercooked, dried or frozen beef (Baril *et al.*, 1999; Cook *et al.*, 2000; Jones *et al.*, 2009), lamb (Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009) or other meat (Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009) as a significant risk factor. In the European study, between 30% and 63% of infections in pregnant women could be attributed to meat consumption (PAF for pregnant women between 0.3 and 0.63; Cook *et al.*, 2000). Soil and vegetable-related exposure was also a fairly consistent risk factor, involving frequent consumption of raw vegetables outside the home (Baril *et al.*, 1999), contact with soil (Cook *et al.*, 2000) or working in a garden (Jones *et al.*, 2006a, b). In the European study, between 6% and 17% of infections in pregnant women could be attributed to soil contact (Cook *et al.*, 2000). With regards to cats, in the USA study, taking care of one or two kittens as opposed to none was not a significant risk factor, but taking care of three or more kittens as opposed to none was, and this accounted for approximately 10% of the risk (Jones *et al.*, 2009). In the French study, having a pet cat was borderline significant (OR = 4.5, 95% CI 1.0–19.9; Baril *et al.*, 1999), while none of the other cat-linked factors in the European and Brazilian studies were associated with significant risk (Cook *et al.*, 2000; Jones *et al.*, 2006a, b, 2009). Pregnant women in the European study perceived raw meat, raw unwashed vegetables and fruit and cat contact as risk factors, but rarely soil contact (Cook *et al.*, 2000). There were a few other consumption and environment-related risk factors, such as travel outside Europe or the USA (Cook *et al.*, 2000) or the consumption of raw shellfish or unpasteurized goats milk (Jones *et al.*, 2009). Oysters, clams and mussels are filter feeders that concentrate *T. gondii*, as has been shown under experimental conditions, and *T. gondii* has been identified in a California mussel by PCR and DNA sequencing. The seawater in California is thought to be contaminated by *T. gondii* oocysts that originate from cat faeces, survive or bypass sewage treatment and travel to the coast through river systems. Both in the Brazilian and the USA studies, demographic characteristics were significant confounders in the model (Jones *et al.*, 2006a, b, 2009), highlighting the importance of accounting for demographic factors in the selection of the controls.

Alveolar Echinococcosis. *Echinococcus multilocularis* is a tapeworm for which foxes are the primary definitive hosts. Domestic dogs, the wolf and the raccoon dog are other definitive hosts with high reproductive

potential of *E. multilocularis*. Intermediate hosts are usually small mammals, but eggs can also infect other species, including man. Human alveolar echinococcosis (AE) has an incubation period of 5–15 years and is usually fatal if untreated (Eckert and Deplazes, 1999). Domestic dogs may play an important role in the transmission to man (Deplazes *et al*., 2011). In Germany, approximately 13,000 domestic dogs were considered to be infected annually (Dyachenko *et al*., 2008). In contrast, domestic cat infections are characterised by low egg excretion and infected cats are estimated to play an insignificant role in environmental contamination with *E. multilocularis* eggs (Hegglin and Deplazes, 2013). In Europe, *E. multilocularis* is endemic in parts of France, Belgium, the Netherlands and northern Italy and in all central and eastern European countries (including Slovenia, Romania and the Baltic States) (Eckert *et al*., 2000). Furthermore, foci exist in Denmark and Sweden. Infection-free countries in Europe currently include the UK, Ireland, Malta and Finland. The Supplementary on-line map video 8: Echinococcosis, combines cases of cystic and alveolar echinococcosis, so these details are not apparent.

Four IRAs assessed the risk of importing this parasite into one or several of the infection-free countries via infected dogs and sometimes also via cats (Bødker *et al*., 2006; EFSA, 2006c; Torgerson and Craig, 2009; DEFRA, 2010). The studies were qualitative or semi-quantitative. All found the risk of import was greater than negligible when the disease was present in wildlife in the area of origin. Risk was influenced by the prevalence in wildlife in the area of origin and by the timing of deworming of imported animals. Only treatment with praziquantel 24–48 h before pet entry in the country was able to reduce the risk of *E. multilocularis* importation to a negligible level (EFSA, 2006c). A fifth IRA pointed out the possibility of disease introduction via intermediate hosts, although the host in that particular study was not a pet (DEFRA, 2012) but a wild animal, the Eurasian beaver.

Three RFAs addressed the risk of people developing AE in Europe through infection from companion animals. They were case–control studies performed in Austria (Kreidl *et al*., 1998), Germany (Kern *et al*., 2004) and France (Piarroux *et al*., 2013). Cases were patients diagnosed with AE using one or several diagnostic techniques (histopathology or PCR on suspect tissue, serology, morphological imaging techniques such as ultrasound, radiography, computed tomography or magnetic resonance imaging) (Kreidl *et al*., 1998; Kern *et al*., 2004; Piarroux *et al*., 2013). The French study had 180 cases, the Austrian 21 and the German 40. In all studies, there were three or four controls per case. In the Austrian and German studies, controls were matched by age and place of residence in (part of) the 10 (Kern *et al*., 2004) or 20 (Kreidl *et al*., 1998) years preceding the diagnosis of the case. All studies performed univariable analysis, followed by multivariable (conditional) logistic regression (Kreidl *et al*., 1998; Piarroux *et al*., 2013) or a scoring system (Kern *et al*., 2004). Risk factors investigated related to exposure to the sylvatic cycle via occupation or food consumption habits, or to exposure to companion animals. In the French study, which was performed nationwide, having residence or not in a high-risk department (i.e. department with clusters of human cases) was taken into account. Companion animal risk factors examined in more than one study were dog ownership (Kreidl *et al*., 1998; Kern *et al*., 2004; Piarroux *et al*., 2013) and cat ownership (Kreidl *et al*., 1998; Kern *et al*., 2004). Risk factors relating to the way dogs or cats were kept were investigated only in the German study. The study outcomes differed. The German and French studies found the strongest association of human cases to be with farming in areas where the disease occurs. Dog ownership was a significant risk factor in the univariable analysis (Kern *et al*., 2004; Piarroux *et al*., 2013). Having 'cats eating mice' and 'cats left unattended outdoors' were risk factors, while cat ownership *per se* was not (Kern *et al*., 2004). In contrast, the Austrian study found that disease was associated significantly neither with farming nor dog ownership, but with hunting in the forest and with cat ownership (Kreidl *et al*., 1998). A fourth RFA, which did not look at risk factors for human AE related to companion animals, found a significant association with vole density (Burlet *et al*., 2011).

Giardiasis. *Giardia* spp. are common enteric protozoal parasites of domestic animals. There are different *Giardia* assemblages, including the zoonotic assemblage A (*Giardia duodenalis*) and the dog-specific assemblages C and D (*G. canis*).

Two RFAs addressed prevalence and risk factors for *Giardia* spp. infection in dogs. These were performed in Belgium (Claerebout *et al*., 2009) and the UK (Upjohn *et al*., 2010). The surveys were performed in different dog populations. In both studies, a case was defined as a dog with *Giardia* spp. antigens in faeces. To detect the antigen, the first study used a direct immunofluorescence assay (Claerebout *et al*., 2009), while the second used a commercially available enzyme-linked immunosorbent assay (ELISA)-based test kit (Upjohn *et al*., 2010). True prevalence was calculated from apparent prevalence corrected for test sensitivity and specificity using the

Table 1
Number of IRAs and RFAs taking into account companion animals that were identified (CA) and number of IRAs and RFAs discussed in terms of method or disease risk in general (Other)

	CA				*Other*		
	IRA role CA	*RFA CA infection*	*RFA CA to human*	*RFA CA to food animal*	*IRA*	*RFA occurrence*	*RFA human infection*
(A) Pathogens absent from Europe (IRAs)							
Foot-and-mouth disease virus	NAD	NA	NA	NA	7*	NA	NA
(B) Pathogens partially absent from Europe (IRAs, RFAs)							
Congo–Crimean haemorrhagic fever virus	3* (dog, cat, horse)	NAD	NAD	NAD	NA	NA	1
West Nile virus	1 (horse)	NAD	NAD	NAD	2	3	4*
Rabies virus	3* (dog, cat, other mammals)	NAD	NAD	NAD	NAD	NAD	NAD
Bluetongue virus	NAD	NAD	NA	NAD	4	11	NA
Echinococcus granulosus sensu lato	NAD	3 (dog)	2 (dog)	NAD	NA	NA	NA
Leishmania infantum	2 (dog)	2 (dog)	NAD	NAD	NA	NA	NA
Echincoccocus multilocularis	4* (dog, cat)	NAD	3 (dog, cat)	NAD	1*	NA	1
(C) Pathogens present wherever investigated (RFAs)							
Campylobacter jejuni	NA	2 (dog, cat, pet bird)	6 (dog, cat, unspecified pet)	NAD	NA	NA	NA
Leptospira interrogans sensu lato	NA	4 (dog)	2 (dog, cat)	NAD	NA	NA	NA
Salmonella enterica	NA	1 (reptile, amphibian)	4 (reptile)	NAD	NA	NA	NA
Bartonella henselae	NA	1 (cat)	2 (cat)	NAD	NA	NA	NA
ESBL-producing bacteria	NA	2 (horse, dog, cat)	NAD	NAD	NA	NA	NA
Toxoplasma gondii	NA	NAD	4 (cat)	NAD	NA	NA	NA
Giardia spp.	NA	2 (dog)	1 (dog, cat)	NAD	NA	NA	NA

CA, companion animals; NA, not applicable; NAD, no available data.
*Some studies are not peer-reviewed articles, but reports.

Rogan–Gladen formula (Rogan and Gladen, 1978). The factors examined varied slightly per population investigated. They included host factors such as age, gender and breed and, in the Belgian study, also husbandry and healthcare-related factors such as the number of other dogs present, cleaning and deworming practices. True prevalence varied greatly among the dog populations examined: household dogs 9.3% (95% CI 5.5–13.1) (Claerebout *et al.*, 2009); breeding kennel dogs 43.9% (95% CI 37.8–50.0) (Claerebout *et al.*, 2009); dogs with gastrointestinal disorders 18.1% (95% CI 13.1–23.1) (Claerebout *et al.*, 2009); and rescue shelter dogs on day of entrance 21.0% (95% CI 16.7–25.4) (Upjohn *et al.*, 2010). In all populations, (very) young age was consistently found to be a risk factor for *Giardia* spp. infection in dogs (Claerebout *et al.*, 2009; Upjohn *et al.*, 2010). However, because the diagnostic tests used in the case definition did not distinguish between *Giardia* spp., prevalence in dogs did not translate to zoonotic risk in different dog populations. This requires genotyping, which was performed in both studies. The zoonotic assemblage A predominated in household dogs (Claerebout *et al.*, 2009), contrary to kennel dogs and clinically affected dogs (Claerebout *et al.*, 2009) and rescue shelter dogs (Upjohn *et al.*, 2010), where the host-specific *Giardia* assemblages C and D predominated.

A single study addressed risk factors for people becoming infected through exposure to companion animals (Chute *et al.*, 1987). This study took place in the USA, and was a case–control study with matching based on age, gender and year of the infection (four controls for one case). Analysis was performed per variable using unconditional logistic regression, with the matching variables included in the model. The questionnaire included topics such as day care centre exposure, household exposure to giardiasis, drinking from a shallow well, foreign travel, camping, or having a household dog, a household cat or farm animals. The first four were identified as risk factors for giardiasis, but not dog, cat or farm animal contact (Chute *et al.*, 1987).

Discussion

The CALLISTO project prioritized 15 companion animal diseases of zoonotic or economic importance (Cito *et al.*, 2015). Among these, we distinguished those that were absent from Europe ($n = 1$), those present only in part of Europe ($n = 7$) and those found everywhere they were looked for in Europe ($n = 7$). We searched for IRAs in the first two situations and RFAs in the second two, considering only studies with a specific risk factor methodology (Table 1). We found few relevant studies and concluded that overall there is a lack of information on risk factors for companion animals and their role as a source of these diseases for people and food animals.

IRAs were identified for the disease considered absent from Europe, FMD, and for six of the seven diseases partially absent from Europe, namely CCHF, WNF, bluetongue, classical rabies, alveolar echinococcosis and leishmaniosis. No IRAs were found for cystic echinococcosis.

In the cases of classical rabies and of alveolar echinococcosis, the risk of disease introduction via companion animals was the main risk assessed. IRAs for classical rabies and alveolar echinococcosis concluded that there was an increased risk for introduction of these pathogens into officially disease-free areas as a consequence of abandoning national rules and adopting the harmonised EU rules for pet travel. This highlights the need for responsible pet ownership, which, as defined by the CALLISTO project, includes minimizing the potential risk that pets may pose to the public, other animals or the environment. This requires proper advice from professionals, which is not self-evident (Davidson and Robertson, 2012), and the support of policy makers. The CALLISTO project not only recommends education of owners and promotion of the concept of responsible pet ownership, but also continuing education of relevant professionals in companion animal zoonoses and associated regulations.

In the case of leishmaniosis, the risk of disease introduction via companion animals was the main risk assessed; the IRAs for leishmaniosis focused on risk associated with presence of persistently infected dogs in new geographical areas. This differed from IRAs (and RFAs) performed in the context of the three other vector-borne diseases (CCHF, WNF and bluetongue), which often explored the presence of conditions favourable to development and infection of the vector. Such geographical and ecological conditions are crucially important in the assessment of the possible pathways of spread, and their consideration would also be important for leishmaniosis.

In the case of CCHF and one of the three IRAs related to WNF, the risk of introduction via companion animals was one of several risk factors assessed. The assessments estimated a low likelihood that the pathogens would be introduced via companion animals, but a limitation of these studies was the sparse data available.

The IRAs relating to the last two diseases (FMD and bluetongue) paid no attention to the risk of introduction via companion animals. Although there are

plausible reasons for this, the facts presented in this paper also provide examples of subjects where more insight is required before continuing to leave companion animals out of consideration in the analysis of risk. For example, in the case of bluetongue, evidence for infection of domestic carnivores is quite recent and still poorly explored. This could explain the lack of IRAs examining the potential role of domestic carnivores as a means for bluetongue introduction. However, to rule out the importance of domestic dogs and cats in bluetongue disease risk, more studies on the potential role of domestic carnivores in the long-distance transmission and persistence of BTV would be needed (Oura and El Harrak, 2011).

Another plausible reason for paying little attention to the risk of introduction due to companion animals is the main use made of animal species by man. Information on risk associated with companion animals may not be perceived to be a necessity or a priority when an animal species is used primarily for food production, such as a ruminant or a pig. Published risks are likely to relate to animals kept for economic purposes, and the role of individual subjects of the same species kept as companion animals is likely to be neglected. This was the case for the IRAs for FMD and bluetongue. To take into account artiodactyls kept as companion animals would require qualitative and quantitative information on numbers of cloven-hoofed animals imported and kept as pets in the EU, and on their conditions of import and rearing. The collection of robust data on the numbers and distributions of companion animals was one of the recommendations of the CALLISTO project. The study by Marshall *et al.* (2007) details husbandry practices by owners of miniature swine that differ from those applied to swine kept for food production, and these could affect FMD risk.

RFAs dealing with the risk factors for companion animals to become infected were identified for six of the seven diseases found across Europe (campylobacteriosis, leptospirosis, salmonellosis, cat scratch disease, infection with ESBL-producing bacteria and giardiasis) and two of the seven diseases partially present in Europe (cystic echinococcosis and leishmaniosis). There were not enough RFAs for any of these diseases to allow meta-analyses. Risk factors identified in at least two studies for a given disease included: host factors such as age (cystic echinococcosis and giardiosis); husbandry and healthcare related factors such as eating (uncooked) offal, being free roaming, poor deworming practice (cystic echinococcosis) or having received recent veterinary treatment (infection with ESBL-producing bacteria); and environmental factors such as season and hydrological density (leptospirosis).

Meta-analyses can be used to integrate data from different published papers to obtain an overarching evidential framework. However, to do this robustly, a degree of harmonization in the case definitions used for infection or for disease across different studies is necessary (Hajarizadeh *et al.*, 2012). For some diseases we found case definitions to be fairly consistent (e.g. campylobacteriosis), but this was clearly not the case in others; for example, for leptospirosis, cases in one study would have been controls in another.

Using and developing genetic techniques to distinguish among species, subspecies and serovars of pathogens is another important point that needs to be addressed to enable more-meaningful risk factor studies to be performed. One example relates to giardiasis. Without the use of diagnostic tests differentiating *Giardia* spp., the specific risk factors for dogs becoming infected with zoonotic *Giardia* spp. will remain undetermined. Another example relates to leptospirosis. It is known that reservoir hosts differ for *Leptospira* serovars. This difference will affect risk factors, as exemplified by the outcome of the human leptospirosis risk factor analysis performed in Mexico (Leal-Castellanos *et al.*, 2003). Vaccines are now used to protect dogs from clinical disease, but cross-protection against all serovars is not achieved. Appropriate tests are necessary to identify the emerging serovars in dogs and the adaptations to be made in vaccines. If risk studies would also differentiate between serovars, risk factors specific to emerging serovars could be identified and mitigation strategies could be better defined.

We did not find RFAs dealing with the risk factors for companion animals becoming infected for the ubiquitous disease toxoplasmosis or the five partially present diseases CCHF, WNF, classical rabies, bluetongue and alveolar echinococcosis. This was surprising for diseases such as classical rabies for which there is, contrary to bluetongue, clear knowledge on the importance of companion animals in disease epidemiology. Evidence for infection of domestic carnivores is centuries old, and the way the infection can be transmitted among animals and to man has been explored extensively. It is possible that the need for additional information is not perceived. However, the CALLISTO project highlighted the re-emergence of rabies in foxes in Eastern Europe and the fact that the underlying reasons for this are currently not yet understood. Pet husbandry and healthcare practices and environments continually evolve. Changes in pet travel (Glaser and Gothe, 1998; Honey, 2014) and in distribution of wildlife reservoir species (Vos *et al.*, 2012) have been documented. Such changes may modify the relative risk for rabies.

RFAs considering the risk of people becoming infected from companion animals were identified for six of the seven diseases considered to be endemic in Europe (campylobacteriosis, leptospirosis, salmonellosis, cat scratch disease, toxoplasmosis and giardiasis) and two of the seven diseases partially present in Europe (cystic echinococcosis and alveolar echinococcosis). All studies made an assessment as to whether keeping a pet *per se*, or keeping a pet with supposed or known risk factors, was a risk factor for people relative to other risks. This allowed some studies to report the PAR or PAF of the incidence of human disease due to companion animals (campylobacteriosis, salmonellosis and toxoplasmosis).

As with the RFAs dealing with risk factors for companion animals becoming infected, there were insufficient RFAs considering the risk of people becoming infected from companion animals to perform a meta-analysis of the results of published papers. For cat scratch disease, we found only a few studies and these had been performed during a limited time just after the discovery of the disease. All were aimed at identifying the source of infection for man. Once the disease had been linked to cats, all investigations (or their publication) ceased. The only recent study is one on seasonality by Sanguinetti-Morelli *et al.* (2011).

As with companion animal disease risk, meta-analysis of human disease (or infection) risk requires more harmonized case definitions without sources of bias (e.g. in the case of salmonellosis) and good diagnostics so that pathogens are identified to taxonomic levels that are meaningful for risk analysis (e.g. toxoplasmosis; Lindsay and Dubey, 2011).

In some cases, risk factors for people were integrated with the risk factors for pets, defining a single risk factor reflecting both components. An example is the human risk factor for cystic echinococcosis from 'owning a dog that is allowed to eat offal or carrion'. This demonstrates how an understanding of infection risk factors for companion animals improves our understanding of risk factors for man.

Risk factors need to be formulated precisely enough to capture zoonotic risk. Understanding a disease cycle can contribute to identifying more specific risk factors. The risk factor 'taking care of three kittens or more' is a good example of trying to capture in a risk analysis for toxoplasmosis in man, a factor that is relevant, given what is known of the cycle of toxoplasmosis. It captures well the short time a cat is infectious.

We did not find RFAs dealing with human disease risk via companion animals for infection with ESBL-producing bacteria or for four partially present zoonotic diseases (CCHF, WNF, classical rabies and leishmaniosis). Also, surprisingly, no RFAs were found that dealt with the risk to food animals from companion animals for any of the 15 pathogens investigated.

The method used to search for information might have contributed to the apparent lack of information on risk factors for companion animals and on their role as a source of the selected diseases for people and food animals. This includes not only the search machines and terms used, or the language limit set to English articles only, but specifically also the restriction to studies with specific risk factor methodology. Most review articles on animal diseases also contain some information on the possible risk factors for becoming infected or for the spread of the disease. These articles were excluded from analysis due to the restrictions imposed on the search. However, we strongly favour the use of a risk methodology-based approach. The application of these methods allows us to go beyond speculation on risk factors, and often provides quantitative information, with measures such as PAR, putting risk factors into perspective. Of course, the analyses are only as good as the underlying data.

Many analyses of human risk factors assessed in this study were based on the classical case–control approach. The essence of the case–control study design is to select a group of cases and a group of non-cases (i.e. controls), and compare the frequency of the exposure factor in the cases with that in the controls. The cases are the study subjects that have developed the disease or outcome of interest, while the controls have not developed the disease or outcome of interest at the time they are selected (Doho *et al.*, 2003). Information on exposure is often acquired through questionnaires, interviews and observation.

A different approach that does not require any tracing of people or any interviews is the use of molecular epidemiology. This approach is based on the collection and sequencing of isolates of a pathogen from human beings and from animal, food and environmental samples and comparison of the sequences in order to obtain, for each human isolate, a probability of association with each of the possible sources considered. Part of the sequences (usually the sequences from animals, food and environmental sources) may be retrieved from published data. This second approach has been used in different countries; for example, to assess the role of different potential sources of *Campylobacter* spp. for human campylobacteriosis (Wilson *et al.*, 2008; Mullner *et al.*, 2009; Boysen *et al.*, 2014). No such study including companion animals among the potential human risk factors was found during our literature search. This type of approach could be easily modified to include companion animals and could be very useful for the

first stage of assessing the risk attributable to companion animals as a source of human infection. Subsequently, however, classical case–control studies would be required to assess which factors (e.g. behaviours or life styles) are associated with the transmission of the infection between companion animals and man.

To conclude, CALLISTO has proposed a set of recommendations for the various stakeholders involved in the companion animal sector. The following are the main recommendations relating to epidemiology and risk factors:

- Performance of studies to identify risk factors for companion animal infection or colonization with pathogens known to have a relevant role in human disease.
- Performance of studies to characterize the transmission dynamics of infections moving between companion animal, human and production animal populations.
- Initiation of multicentre case–control studies to evaluate the role of companion animals as a source of infection for people by determining the PAF of disease due to companion animals. Such studies should be based on standardized case definitions and should incorporate molecular analyses for the identification of strains/clones of pathogens shared between man, companion animals and food animals.
- Performance of specific targeted investigations to assess the potential human pathogenicity of pathogens associated with companion animals for which there are currently few data on zoonotic risk.

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Conflict of Interest Statement

The authors do not have any financial or personal relationships with other people or organizations that could inappropriately influence (bias) their work.

Supplementary Data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.jcpa.2015.08.003.

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