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FINAL REPORT

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CALLISTO

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TABLE OF CONTENTS

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1. CALLISTO PROJECT

This document is the final report of the EU Framework 7-funded project entitled CALLISTO (Companion Animal multisectoriaL interprofessionaL and interdisciplinary Strategic Think tank On zoonoses), which has investigated zoonotic infectious diseases transmitted between companion animals and man and food producing animals.

The work of the CALLISTO consortium was structured as seven Expert Advisory Groups (EAGs) working within five project work packages over three cycles of one year each (2012 – 2014).

The stated objectives of the CALLISTO Project, and the cycles during which they were addressed, were:

1. To develop a detailed overview of the role of companion animals as a source of infectious diseases for man and food animals, including available information on disease incidence and geographical distribution in these host categories (cycle 1).

2. To identify knowledge and technology gaps in the management of the most important zoonoses transmitted by companion animals (cycle 2).

3. To propose targeted actions that contribute to reducing the risk for infectious disease outbreaks in man and food animals associated with keeping companion animals (cycle 3).

4. To disseminate the results of CALLISTO to relevant stakeholders to contribute to the uptake of the CALLISTO-proposed actions and to promote risk-awareness in healthy and balanced human/animal relationships (cycles 1 – 3).

1.1
WHAT IS A COMPANION ANIMAL?

Companion animals are any domesticated, domestic-bred or wild-caught animals, permanently living in a community and kept by people for company, enjoyment, work (e.g. support for blind or deaf people, police or military dogs) or psychological support – including, but not limited to dogs, cats, horses, rabbits, ferrets, guinea pigs, reptiles, birds and ornamental fish.

1.2
WHAT ARE THE DEMOGRAPHICS OF COMPANION ANIMAL OWNERSHIP IN THE EU?

CALLISTO has gathered available data on the very large and growing number of companion animals estimated to be kept within EU countries and the economic contribution made by the associated industry (e.g. breeding, sales, pet food, insurance, pharmaceutical and veterinary support). There are an estimated 66 million cats, 61 million dogs, 39 million ornamental birds, 6 million horses and 9 million aquaria in the EU and the estimated annual spend on petcare products alone is € 25.7 billion. It is also recognized that there are great challenges to obtaining accurate data of this type, particularly for other exotic animal species being kept and certain regions of Europe.

1.3
WHAT ARE THE SOCIETAL BENEFITS OF COMPANION ANIMAL OWNERSHIP?

Companion animals make crucial contributions to human society. In addition to working roles (e.g. dogs for visually or hearing impaired people), some companion animals afford profound benefits in areas as diverse as human health and childhood development. The positive influence of owning a companion animal has further benefit by reducing human healthcare spending.

1.4
WHAT IS RESPONSIBLE PET OWNERSHIP?

CALLISTO recognizes that the societal benefits of keeping pets comes with accepting responsibility for the health and welfare of these animals. Acceptance and promotion of the concept of responsible pet ownership (RPO) is required in order to reduce the risks of transmission of zoonoses from companion animals to man or production animals.

CALLISTO recommends adoption of the following definition of RPO: *Responsible Pet Ownership (RPO) is a duty of care based on the principle that animals are sentient beings having intrinsic value, are dependent on humans for their health and welfare, and are part of the ecosystem. RPO aims to maintain a good level of animal health and welfare, to maximize physical and psychological benefits to humans and to minimize the potential risk that pets may pose to the public, other animals, or the environment. This duty starts with responsible acquisition and continues with providing appropriate care and protection for pets and their offspring.*

1.5 WHAT ARE THE CHALLENGES RELATED TO COMPANION ANIMAL ZOONOSES?

Despite these unquestionable benefits, there are risks that human owners may contract zoonotic infectious diseases directly or indirectly from companion animal species. Moreover, as traditional livestock species now increasingly serve a role as companions, there are disease transmission risks from these animals to farmed animals of the same species. An increase in the keeping of exotic and wild animals as companion animals also presents a potential novel risk as sixty percent of emerging infectious diseases are zoonotic with over 70% of those originating in wildlife, presenting an increasing and significant threat to global health.

Currently within Europe there is little co-ordination between the numerous groups that represent the interests of pet owners, farmers or the horse-owning community. The general public has little understanding or concern about zoonotic infectious disease.

With few exceptions (e.g. canine rabies virus infection) there is little serious attempt to monitor the prevalence, emergence or re-emergence of zoonotic pathogens arising from companion animal species (i.e. infectious disease surveillance) and this is generally limited to more traditionally kept companion animals (e.g. dogs and cats) With the exception of the EU Pet Travel scheme (again focussed on canine rabies) there is little legislative awareness of the scale or significance of companion animal zoonoses.

The monitoring and control of companion animal zoonoses is a prime example of where a 'One Health' (joint human and veterinary medical and public health) approach is essential.

1.6 WHAT ARE THE MAJOR COMPANION ANIMAL ZOONOSES?

CALLISTO has thoroughly reviewed the spectrum of companion animal zoonoses and identified 15 'paradigmatic' diseases that formed the basis for more detailed risk analyses related to those diseases and their spread between companion animals, man and farmed animals. The 15 paradigmatic diseases are listed in Table 1.

Of the 15 CALLISTO paradigmatic diseases, seven are currently notifiable to OIE; nine are notifiable to ECDC and three to both OIE and ECDC. Two paradigmatic diseases are not notifiable to ECDC or OIE (those caused by Toxocara canis/cati and Bartonella henselae).

Campylobacteriosis and salmonellosis were the most commonly reported zoonosis with 220,209 and 95,548 confirmed human cases, respectively, but the role of companion animals in the transmission of these pathogens to food-producing animals and people is not clear and needs further investigation. Most of the 15 paradigmatic pathogens are linked to the more commonly kept companion animal species of cats and dogs. Only eight of the pathogens are also relevant to other species.

Table 1
CALLISTO Paradigmatic Pathogens

VIRAL PATHOGENS
Crimean-Congo haemorrhagic fever virus
West-Nile virus
Foot-and-mouth disease virus (non-zoonotic)
Rabies virus
Bluetongue virus (non-zoonotic)
PARASITIC PATHOGENS
Echinococcus granulosus sensu lato
Leishmania infantum
Toxoplasma gondii
Giardia species
Toxocara canis/cati
BACTERIAL PATHOGENS
Campylobacter jejuni
Leptospira interrogans sensu lato
Salmonella enterica
Bartonella henselae
Extended Spectrum Beta-Lactamase (ESBL) producing organisms
BITE WOUND INFECTIONS
Bite wound infections are included in the priority list.

The **"Strategy Report of the First Cycle"** includes detailed information on issues presented in the paragraphs above.

2. "PARADIGMATIC" PATHOGENS AND RISK ASSESSMENTS

In the following paragraphs, contents and main finding of the Second Cycle of CALLISTO research activities concerning risk assessments are described. "Paradigmatic" infections of viral, bacterial and parasitic origins are detailed as well as risk factors for transmission of such pathogens.

2.1 WHAT ARE THE CALLISTO PARADIGMATIC VIRUS INFECTIONS?

The viral pathogens that were ranked most important for human health risk were rabies virus, Crimean-Congo haemorrhagic fever virus (CCHFV), cowpox virus, hantavirus and lymphocytic choriomeningitis virus (LCMV). The human case fatality rates of these viral infections range from very low (cowpox) to nearly 100% (rabies). However, prompt postexposure prophylaxis will almost always prevent disease from rabies.

Route of transmission, companion animals involved and occurrence in Europe differ between these viruses. Rabies virus is transmitted mainly by the bites of infected carnivores. The main reservoir in Europe is the red fox, but domestic dogs and cats are the primary source of human infections. Although rabies in foxes is largely under control in Europe through oral vaccination, recent reports of rabid foxes in southern Europe highlight the risk of re-emergence of rabies in Europe.

CCHFV is transmitted to humans by infected ticks, mainly of the genus Hyalomma. CCHFV may infect many different species of wild and

domestic birds and mammals, including domestic dogs. CCHFV is not present in most of western Europe; however, it is considered as emerging based on its occurrence in 2002 in Turkey with an increasing number of cases thereafter, specific foci in the Balkan region, and the detection of the virus in ticks in Spain. Importation of CCHFV-infected animals is a potential route of introduction into CCHFV-free countries.

Cowpox virus, hantavirus and LCMV are transmitted to humans by contact with infected animals, or contact/inhalation of infected faeces/urine. Wild rodents, including house mice and voles, are commonly infected, and act as the main source of human infection in Europe. Companion animals (e.g. domestic cats, hamsters, guinea pigs and pet rats) may become infected by wild rodents, putting their owners at risk.

The viral pathogens that were ranked most important for livestock production risk were bluetongue virus, African swine fever virus, foot-and-mouth disease virus and influenza virus. The livestock in large parts of Europe are currently free of these important pathogens and incursion would have major impacts on the livestock industry and international trade. For these viruses, ruminants, pigs and poultry kept as companion animals may be relevant. The main concern regarding companion animals is introduction into countries that are currently free of these viruses, either by importation of infected animals kept as pets or feeding of infected food waste to pet pigs. Rabies virus was also considered important for livestock production, because it infects a variety of domestic animals, including cattle, sheep and goats.

The viral pathogens that were ranked most important for fish production risk were cyprinid herpesvirus-3 (Koi herpesvirus), viral haemorrhagic septicaemia virus, infectious pancreatic necrosis virus, spring viraemia of carp virus and grass carp haemorrhagic virus. These viruses are transmitted mainly through water and typically occur in multiple fresh water and marine fish species, although cyprinid herpesvirus-3 and grass carp haemorrhagic virus appear restricted to carp species. The main concern is that these viruses can cause epidemics with high mortality in both farmed fish and wild fish populations. There is little to no information on the prevalence of these viruses in ornamental fish, which therefore form a potential weak spot in control measures against these viruses.

2.2 WHAT ARE THE CALLISTO PARADIGMATIC BACTERIAL INFECTIONS?

The bacterial pathogens that received the overall highest score for human health risks were *Campylobacter jejuni, Leptospira interrogans, Salmonella enterica, Bartonella henselae, Chlamydophila psittaci* and *Escherichia coli* producing extended spectrum beta-lactamase (ESBL). The diseases associated with these six selected zoonotic pathogens are all endemic in EU Member States and have been associated with specific companion animal species. Dogs and cats appear to be the main companion animal sources of campylobacteriosis; *B. henselae* infection (e.g. cat scratch disease) has been traditionally associated with cats, although dogs have recently been recognized as reservoirs of other *Bartonella* species of zoonotic potential; exotic companion animals, such as reptiles and birds are the main sources of salmonellosis and psittacosis, respectively; in theory any animal species may be considered as a potential reservoir of ESBL-producing E. coli, but among companion animals the main zoonotic risks are likely associated with dogs, cats and horses, as a consequence of the widespread use of antibiotics, especially broad-spectrum antibiotics, in these domestic animals. Dogs and possibly rats are the main reservoir of leptospirosis among companion animals, but their role in transmission of leptospirosis is unclear. Although evidence of dog-to-human transmission has only once been reported in the scientific literature, leptospirosis was included in the list of priority diseases because of the high impact of this disease on human health as well as of the lack of studies analysing the risk factors for human infections, which makes it difficult to assess the risk of zoonotic transmission from dogs.

With the exception of *B. henselae* and *C. psittaci*, the same pathogens were also ranked as the most relevant in relation to possible economic impact on animal production. The ranking was slightly different since S. enterica was scored as the most important pathogen in this context, followed by *C. jejuni, L. interrogans*, meticillin-resistant *Staphylococcus aureus* (MRSA) and ESBL-producing *E. coli*. Based on the current knowledge, the role played by companion animals in transmission of these pathogens to food animals appears to be limited to Salmonella and Campylobacter.

Bite wound infections were included in the list of priority diseases due to their relatively high incidence and possible serious consequences for human health. However, these infections were not included in the risk assessment since they are not associated with a specific pathogen.

2.3 WHAT ARE THE CALLISTO PARADIGMATIC PARASITIC INFECTIONS?

The parasitic pathogens that were ranked as having the overall highest score for human health risks were *Echinococcus granulosus* sensu lato, *Leishmania infantum, Toxoplasma gondii, Echinococcus multilocularis* and *Giardia* genotypes. With the exception of *L. infantum*, humans are infected with these pathogens by the oral route, frequently by exposure to infected faeces, food, soil or water. *Leishmania infantum* is a vector-borne pathogen transmitted by the bite of female sand flies. The five diseases associated with these zoonotic pathogens are endemic in EU Member States, with variable prevalence rates in different regions. Leishmaniosis is endemic in Southern Europe where vector sand flies are abundant, while *E. multilocularis* infection causing alveolar echinococcosis is more prevalent in central, eastern and northern Europe. *Echinococcus granulosus* sensu lato and *L. infantum* are associated with dogs as the main reservoir, while *E. multilocularis* is associated with foxes, but may also be transmitted by domestic dogs. *Toxoplasma gondii* is excreted in cat faeces and can be transmitted by ingestion of felid faecal material, but is also frequently transmitted by eating contaminated meat of intermediate hosts, notably undercooked meat. Dogs and cats are also hosts of *Giardia* species, but transmission of these pathogens may often be anthroponotic (e.g. human to human), which makes it difficult to assess the risk of zoonotic transmission from pet animals.

Four of the five highest-scoring zoonotic pathogens are also in the group of the five highest-scoring pathogens with animal health relevance. These are *E. granulosus* sensu lato, *Giardia* genotypes, *T. gondii* and *L. infantum*. However, *Neospora caninum*, which ranked as the highest-scoring parasitic disease relevant for animal health is not a zoonotic agent. The dog is the definitive host and cattle are the main intermediate hosts, suffering from reproduction losses mostly by vertical transmission.

Based on the current knowledge, companion animals play an important role in the transmission of parasitic diseases to food animals. The fact that four of the five highest scoring parasitic diseases that threaten human health in Europe are also ranked among the highest scoring diseases impacting on animal health in Europe stresses the importance of preventing these diseases in coordinated One Health efforts which include veterinary as well as human health officials and resources.

2.4 WHAT ARE THE RISK FACTORS FOR TRANSMISSION OF THE CALLISTO PARADIGMATIC PATHOGENS?

The second cycle of CALLISTO focused on the assessment of risk factors for spread of these diseases within companion animal populations or to human beings. These risk assessments were based on an analysis of relevant published literature identified by interrogation of PubMed and Google. Papers were subdivided into (1) those relating to import risk assessments (IRAs) for regions where a disease was absent, and (2) evaluation of risk factors in endemic areas for a disease. For diseases present throughout Europe, IRAs were considered not to be relevant and only evaluation of risk factors for endemic areas were considered. For diseases exotic to all European countries, evaluation of risk factors for endemic areas was considered not relevant and only IRAs were considered.

Import Risk Assessments

Four of the 12 evaluated diseases (CCHF, rabies, leishmaniosis and alveolar ecchinococcosis) were considered to be emerging in at least some EU countries. Most IRAs were focused on the risk of introduction and not to the risk specifically posed by companion animals. However, all IRAs showed that the set of measures in place, if properly implemented, would be effective in reducing the risk to negligible values. The only relevant route of introduction remaining was the smuggling of infected animals.

In the case of vector-borne diseases, geographical and ecological assessments were crucially important in the assessment of the possible pathways of spread.

Evaluation of Risk Factors

All 12 considered diseases were endemic in at least part of the EU. For 10 of these 12 diseases a study of risk factors was performed. Risk factors for infection of pet animals were evaluated for nine diseases. The main risk factors included pet intrinsic factors such as age (campylobacteriosis, leptospirosis, cat scratch disease, cystic echinococcosis and giardiosis) or gender (leptospirosis); lifestyle related factors such as going outdoors, deworming, having been stray, killing game, being a working dog (camplyobacteriosis, leptospirosis, cat scratch disease and cystic echinococcosis) or being kept for long time in captivity (salmonellosis); health-related factors, such as having fleas (cat scratch disease), having been hospitalized (ESBL)

or not having received antihelmintic treatment (cystic or alveolar echinococcosis); or environmental factors such as season and land use (leptospirosis), presence of vectors (leishmaniosis), or density of other key hosts involved in the cycle (leptospirosis, campylobacteriosis).

Risk factors for infection of humans were evaluated for eight diseases. Most studies made an assessment as to whether keeping a pet per se, or keeping a pet with known risk factors, was a risk factor for humans relative to other risks (campylobacteriosis, leptospirosis, salmonellosis, cat scratch disease, campylobacteriosis, toxoplasmosis and alveolar echinococcosis). This allowed some studies to report the population attributable fraction (PAF) of the incidence of human disease due to companion animals (campylobacteriosis, salmonellosis, toxoplasmosis). The PAF is the percentage of total cases that may be attributed to the action of a specific risk factor (e.g. the ownership of a companion animal or the consumption of a specified food item). In some cases (for example cystic and alveolar echinococcosis) risk factors for pets and risk factors for humans were integrated, defining a single risk factor reflecting both components (e.g. owning a dog that is allowed to eat offal or carrion). For the two viral diseases considered, there was no published information on risk factors for either pets to get the infection or for humans to get the infection from pets. In the case of vector-borne diseases, geographical and ecological assessments were important in the assessment of the possible pathways of spread.

The most important conclusions drawn from these analyses were:

1. In the case of studies performed in Europe, the results are directly applicable by decision makers, while in the case of studies performed in third countries only the methodologies are applicable to Europe.
2. For a proper evaluation of the levels of risk posed by companion animals, the estimation of the PAF and the use of source attribution methods are of crucial importance.
3. Ecological assessments are useful, especially for vector-borne diseases, but are not limited to these (e.g. ecological risk factors have been studied for leptospirosis in the USA).
4. All IRAs considered were general and were not specifically aimed at evaluating the risks posed by companion animals.
5. Companion animals may be reservoir or source of infection for humans (i.e. toxoplasmosis or alveolar echinococcosis). These two scenarios must be clearly separated.

The **"Strategy Report of the Second Cycle"** includes detailed information on the issues presented in this chapter.

3. WHAT ARE THE CALLISTO RECOMMENDATIONS ON COMPANION ANIMAL ZOONOSES?

The CALLISTO final recommendations are grouped into five strategic areas:

1. Demographics and tracing/movement of companion animals
2. Education and communication
3. Surveillance and infection control
4. Risk assessment
5. New tools for diagnosis, prevention and therapy

The recommendations are categorized as those related primarily to policy, those related primarily to scientific research and those applicable to both areas. Each recommendation is prioritized using a 3-star ranking (*, ** or ***). In the more detailed descriptions of the recommendations given, the target user groups were also defined by a coding system.

3.1 DEMOGRAPHICS AND TRACING/ MOVEMENT OF COMPANION ANIMALS

*** CALLISTO recommends that more robust data be gathered on the numbers and distribution of owned and free roaming (including stray) companion animals in the EU. Such data are essential in order to be able to quantify the actual risks of zoonotic diseases attributable to companion animals and to develop sustainable interventions to prevent transmission to humans and livestock.

*** CALLISTO recommends development of systems for microchip identification of companion animals and registration of these animals in a cross-border accessible database.

** CALLISTO recommends that consideration be given to controlling companion animal movement between areas of the EU endemic for particular zoonoses and areas that are not currently endemic for that disease.

** CALLISTO recommends a specific scientific study of the reasons underlying the re-emergence of rabies in foxes in Eastern Europe.

** CALLISTO recommends the implementation of schemes to assess mortality during transportation of companion animals imported into the EU.

3.2 EDUCATION AND COMMUNICATION

*** CALLISTO recommends that any message delivered about companion animal zoonoses achieves a balance between maintaining, or possibly increasing, the benefits of keeping companion animals and mitigating or eradicating potential infectious disease risks.

*** CALLISTO recommends promotion of, and education in, the concept of responsible pet ownership as defined above.

*** CALLISTO recommends that opportunities be created for the education of physicians, veterinarians, owners and other relevant professional categories in companion animal zoonoses. Specifically, from a One Health perspective, increasing the knowledge of human physicians in this area is crucial.

3.3 SURVEILLANCE AND INFECTION CONTROL

*** CALLISTO recommends the creation of a European network, linked to EFSA and ECDC, for monitoring the prevalence of known zoonotic agents in the relevant companion animal species and for early detection of new zoonotic infectious diseases using companion animals as sentinels. Such data should be obtained from veterinary practices and commercial veterinary diagnostic laboratories and captured into a computerized database for analysis.

*** CALLISTO recommends that companion animals (particularly dogs, cats and horses) be included in national surveillance programmes on antibiotic resistance.

*** CALLISTO recommends targeted scientific research to address the significance of specific pathogens for which there is currently little information about whether companion animals are sources of these infections and how transmission of these pathogens might occur between man and companion animals.

** CALLISTO recommends implementation of methods for improved reporting of companion animal zoonotic infectious diseases.

** CALLISTO recommends the introduction of systems for monitoring the movement of arthropod vectors of zoonotic infectious disease throughout the EU as climate change increases the geographical range of such vectors.

* CALLISTO recommends the introduction of systems for monitoring companion animals travelling outside of the EU for the potential introduction of exotic pathogens as these animals return to the EU.

3.4
RISK ASSESSMENT

*** CALLISTO recommends the initiation of multicentre case-control studies to evaluate the role of companion animals as a source of infection for people by determining the population attributable fraction of disease due to companion animals. Such studies should incorporate molecular genetic analysis in order to identify strains/clones of pathogens shared between humans, companion animals and food animals.

*** CALLISTO recommends the performance of studies to identify risk factors for companion animal infection or colonization with pathogens known to have a relevant role in human disease.

** CALLISTO recommends specific targeted investigations to assess the potential human pathogenicity of a group of pathogens associated with companion animals for which there are currently few data on zoonotic risk.

** CALLISTO recommends the performance of studies to characterize the transmission dynamics of infections moving between companion animal, human and production animal populations in a farm setting.

3.5 NEW TOOLS FOR DIAGNOSIS, PREVENTION AND THERAPY

*** CALLISTO recommends introduction of some form of regulation of the use of critically important antibiotics (CIAs) used in human medicine for companion animals, and the development of new alternative veterinary antimicrobials and alternative treatment strategies to manage multidrug-resistant infections in companion animals.

*** CALLISTO recommends the development of rapid field diagnostic test kits for the veterinary practice.

** CALLISTO recommends the development of new vaccines that protect against zoonotic pathogens.

** CALLISTO recommends introduction of schemes for the regulation and certification of diagnostic laboratories and definition of minimum requirements to ensure quality control of diagnostics and susceptibility testing within veterinary hospitals.

* CALLISTO recommends a series of specific targeted research programmes that address the field efficacy of some currently available companion animal vaccines.

* CALLISTO recommends the development of rapid diagnostic test kits for use in the slaughterhouse setting.

The **"Strategy Report of the Third Cycle"** includes relevant information on topics described in chapter 3 of this document.

CONCLUSIONS

There are very large numbers of companion animals throughout Europe and these animals, of varied species, play an integral role in human society, providing very real human health and welfare benefits. There is however, some risk that close human contact with companion animals may lead to the transmission of zoonotic infectious diseases of numerous different types. Companion animals may also be a source of some infections transmitted to farmed livestock. This risk must be communicated to the pet owning public in a balanced fashion by veterinary and human healthcare professionals, the pet industry and governments. The risk may be somewhat ameliorated if the owners of companion animals subscribe to the principles of responsible pet ownership.

Nevertheless, there are further policy and research actions that could be implemented by the EU and/or national governments to further reduce the risks associated with the close integration of companion animals into human society. These include the development of systems for identifying and registering the most common companion animal species and establishing surveillance programmes that capture data on zoonoses that occur in these animals. Closer attention should be paid to the health status of animals entering or re-entering the EU from third countries and the welfare surrounding companion animal cross-border movement. Data collection and pathogen assessment in the less studied exotic companion animals being kept is also needed to better understand risks. Disease and disease vector spread within Europe should be monitored and solutions found to limit such spread. The emergence of antimicrobial resistance in companion animals should be monitored. Controls should be placed on the use of human critically important antibiotics in companion animal species, but new approaches to companion animal antimicrobial therapy must be developed in parallel.etic analysis in order to identify strains/clones of pathogens shared between humans, companion animals and food animals.

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