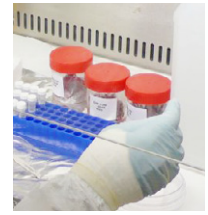


Animal models of emerging diseases: An essential prerequisite for research and development of control measures



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Implications

- Infectious diseases represent a life-threatening menace for human and animal populations. The emergence of new diseases from animal reservoirs, as well as the re-emergence of “old” diseases, requires well-adapted responses from the scientific community to provide accurate data for controlling the pathogen dissemination and its consequences. In this article, we will review the use of animal models as tools for our understanding of the physiopathology of emerging or re-emerging infectious diseases and possibilities of diagnosing them, the evolution of pathogens virulence and host spectrum, and the definition of vaccine or therapeutic targets and the testing of their biosafety and efficiency. We will illustrate these achievements through various examples from the literature and from the experience of coordinating the European infrastructure project NADIR, the Network for Animal Disease and Infectiology Research for European animal facilities.

Key words: animal models, animal facilities, biosafety, emerging diseases, host immune response, livestock diseases, pathogens, zoonosis

Introduction

Every human society is under the Damocles glaive of infectious diseases, which represent a life-threatening menace. According to WHO and OIE estimations, 70% of human diseases originated from animals during the last 30 years. Examples among largely mediated diseases affecting human populations are the AIDS epidemic originating from African monkeys, the bovine spongiform encephalopathy disease transmitted to humans from contaminated bovine meat, and avian influenza, vehiculated by domestic chicken as well as by wild species (Greger, 2007). These zoonoses are regrouped as emerging diseases. However, the concept of emerging diseases should be enlarged to i) old- or re-emerging diseases with animal reservoirs, such as tuberculosis, and to ii) animal diseases that are not transmissible to humans, such as the recent bluetongue and Schmallenberg viral diseases of ruminants that disseminated in several months throughout Europe. In addition, the concept of emerging disease is linked to the considered geographic area: a number

of diseases that are endemic in countries bordering the European frontiers would be considered as emerging as soon as they would circulate in the more developed countries. The prototype of such potentially emerging diseases in Europe are the Rift Valley fever, the West Nile disease, or the Horse African fever, which are all vectorized and could be transmitted in European countries as soon as infected insects are able to disseminate, for example through transports and/or in relationship with the warming climate, which favors invasion of northern countries by insects from the warmer areas.

Consequently, “exotic diseases” should not still be considered as such and should be studied to get a better understanding of transmission modes, reservoirs of pathogens, and pathophysiology to develop diagnostic and prevention tools and thus shorten the delay of applying adapted measures at the very early phases of epidemics, a number of them being expected, although not easily predicted. Careful analysis of epidemiological data and collection of pathogen isolates submitted to sequencing analysis allow us to follow their circulation and evolution. However, these data need to be completed by virulence tests and host spectrum definition, which as prevention tools, necessitates the use of animal models. Thus, animal models cannot be overlooked even if they can be reduced to the infection of animal cell lines in a few well defined cases, mainly linked to studies of the mechanisms of host-pathogen interactions at the cellular level.

In this article, we will review the use of animal models as tools for our understanding of the physiopathology of emerging or re-emerging infectious diseases and possibilities of diagnosing them, the evolution of pathogens virulence and host spectrum, and the definition of vaccine or therapeutics targets. Moreover, testing of innocuity and efficiency of preventive tools that include vaccines, therapeutics, and even selection of genetically resistant hosts necessitates the use of adapted animal models. We will illustrate these achievements through various examples from the literature and from the experience of coordinating the European infrastructure project NADIR, the Network for Animal Disease and Infectiology Research for European animal facilities.

Modeling Infectious Diseases

Reproducing the key events of the infectious process is the aim of any modeling approach. When possible, the reproduction of these key events in cell culture or on model/laboratory species such as zebra fish or mice is of great value, but in many circumstances, this is not feasible or at least needs to be compared with the infection of the natural host(s). Highly confined animal facilities allow these experiments to be

performed in various farm animal species, which can be considered as target species or animal models, accordingly to the experimental conditions and to the host spectrum of the considered disease. For example sheep are a target species for pathogens inducing brucellosis, tuberculosis, or Q fever but can also be considered as a model species for preliminary studies of the same pathologies in bovines, a much more expensive host species for infection experiments that require highly confined facilities (barrier safety level 3, **BSL3**). Experimental conditions refer to the contamination route and dose, which should be as close as possible to natural contamination. Use of parenteral route of infection, for example, only models the pathogen dissemination through lymph and blood but does not take into consideration the invasion step, for example, at the level of intestinal or respiratory epithelia.

Validation of animal models refers to comparisons with the natural infectious process, and should confirm their reproducibility and similarities with events observed in the natural host during natural disease transmission.

Physiopathology and Diagnosis of Emerging or Re-emerging Infectious Diseases

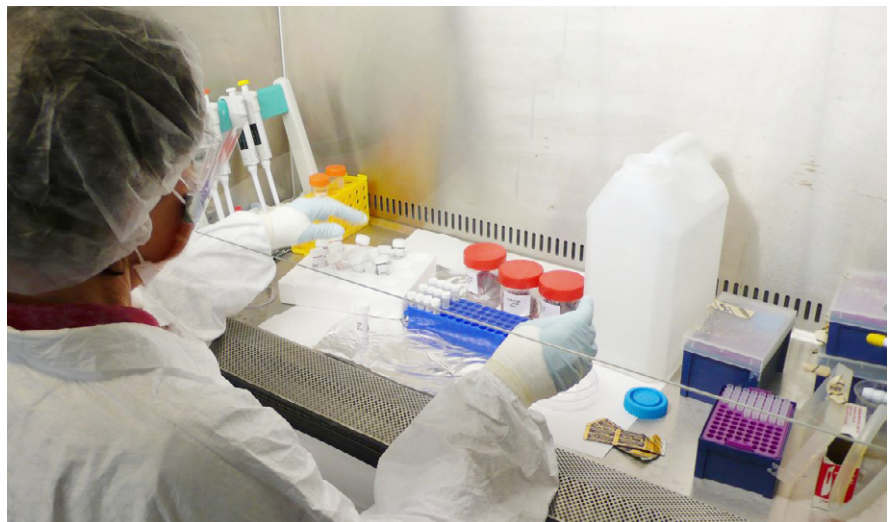
This is the main area animal models contribute. The infectious process can be considered as a succession of delimited steps such as invasion, lymphatic and then systemic dissemination, colonization of target tissues, and persistency or recovery. The understanding of factors, from the pathogen, the host, or the environment, which influence the issue of each step, and hence the infection evolution, is crucial for an improved surveillance and control of the disease transmission.

Oral contamination by pathogens such as non-typhoidal *Salmonella enterica*, mainly by serovars Typhimurium or Enteritidis, has been used to show the role of chicken as a reservoir of these pathogens (Barrow et al., 2012; Parsons et al., 2013) that are responsible for foodborne human infections causing diarrhea and possibly severe dehydration, systemic infection, and death worldwide. Persistency of *Salmonella* in chicken flocks is the cause of environment contamination and transmission to human populations through contaminated eggs and carcasses, with a number of cases in the 1990s. Experimental infection of adult birds has shown that egg infection occurs both internally, as a consequence of the ovary infection of the hen, and externally, through intestinal colonization and excretion in feces. Surveillance and vaccination in chicken breeding units and industry has allowed for decreasing both chicken frequency of infection and transmission to humans in many developed countries since the epidemics of the 1990s, but more efficient tools are needed for a better control of salmonellosis worldwide. Research is oriented toward understanding mechanisms of cellular invasion and persistency (Velge et al., 2012), improved and cheap vaccines, and improved innate resistance of chicken lines (Calenge et al., 2011). The role of the host intestinal flora is also being studied as a barrier to salmonella colonization, which requires the animal facility to maintain chicken in isolators, as the only way to avoid uncontrolled microbial contamination (Merino et al., 1996).

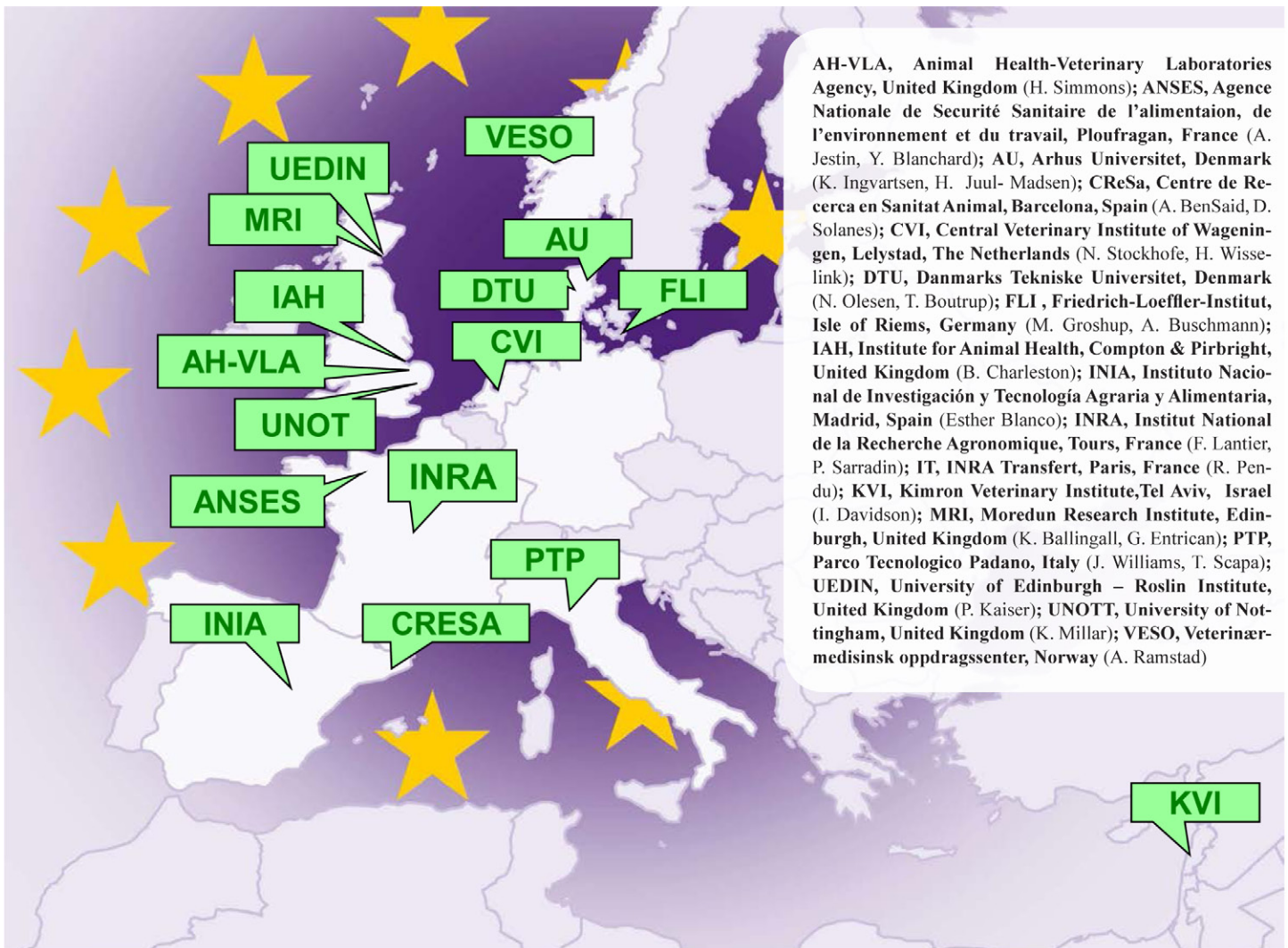
The bovine spongiform encephalopathy (**BSE**) crisis expands from 1996 — BSE was identified as a prion

disease similar to the sheep and goat scrapie in 1986, but confirmation of human contamination through infected bovine carcasses only occurred 10 years later. At that time, the pathogenesis of a “naturally” occurring prion disease was hypothetical. Experimental infections of susceptible species were crucial for evidencing the oral route of infection (Andréoletti et al., 2000; van Keulen et al., 2008; Franz et al., 2012) and establishing the list of tissues “at risk” for human consumption (Foster et al., 2001, Lacroux et al., 2012). This list varies according to species and increased as techniques of detection improved through the use of immunological techniques and thanks to the experimental infection of transgenic mice with the sheep, bovine, or human gene encoding the prion protein (Padilla et al., 2011), the degradation-resistant isoform of which has been identified in the early 1990s as the agent of spongiform encephalopathies (Prusiner, 2012). The BSE epidemics almost disappeared in domestic cows and have been observed in rare occasions in small ruminants thanks to the ban of meat and bone meal incorporation in mammalian food in most countries and to efficient control measures and surveillance. Other prion diseases remain an issue in small ruminants and in American wild deer, although their transmission to humans has not been observed. However, the large financial support provided to research the transmissible spongiform encephalopathies (**TSE**), and particularly animal model developments, has allowed efficient diagnostic and control measures to be applied and considerable progress in our knowledge of these diseases, with important consequences for research on other neuropathologies affecting humans, such as Alzheimer and Parkinson diseases, with numerous similarities to TSEs.

Two outbreaks of viral diseases have more recently affected ruminant populations throughout Europe. They were caused by arboviruses transmitted by insects and particularly by the small suckling fly *Culicoides* (Rasmussen et al., 2013a; Veronesi et al., 2013). Although non-pathogenic for humans, rapid spread of bluetongue (**BTV**) and Schmallenberg (**SBV**) viruses caused economic losses on cow, sheep, and goat farms. For example, the cost of the unexpected rapid expansion in 2006 to 2008 of BTV serotype 8 from northern Europe, is likely to exceed €1 billion (Carpenter et al., 2013). In the case of BTV, control measures are based on prevention through classical vaccines based on an inactivated virus (Zientara and Sanchez-Vizcain, 2013). Primary infection induces adaptive immune responses and protection against reinfection with



Laboratory treatment in safety cabinet of sheep samples infected with BSE for the detection of prion through immunochemical techniques (Western blotting).



Location of institute partners of the European infrastructure network NADIR (7th European Framework).

the homologous virus serotype (reviewed by Maclachlan et al., 2013). Improved vaccines based on recombinant protein are now screened by means of a mouse model that uses mice deficient in the antiviral protein interferon α (Anderson et al., 2013; Ortego et al., 2013), but co-infection with two serotypes, transplacental infection, or evaluation of vaccine efficiency had to be studied through experimental infection of the natural hosts, cattle, sheep and goat, as a rodent model would likely have different responses due to the particularity of ruminant placenta and to the specificity of their immune system (Anderson et al., 2013; Dal Pozzo et al., 2013; Rasmussen et al., 2013b; Martinelle et al., 2013).

The SBV emerged in Germany, the Netherlands, and Belgium in summer 2011 (Hoffmann et al, 2012; Larska et al., 2013), crossing across through the European continent in 1 year (Balseiro et al., 2013). It is responsible for fetus malformation and abortion in ruminants, at variable rates according to the physiological status of animals at the onset of contamination. Although ruminant populations self immunized against the virus, the contamination of semen needed to be investigated for exportation purposes and evaluation of the risk of bulls to cow transmission. This was allowed through experimental infection of bulls, which also allowed for observa-

tions of mild clinical signs of the disease at the time of contamination (van der Poel et al., 2013).

These examples of pathophysiology investigations in model and target species provide evidence for the role of animal experiments for determining the route of entry and the dynamics of the pathogen dissemination into the host. Although these investigations remain basic in the sense that they use historical microbiology techniques, they can be considerably improved through the use of molecular biology tools, imaging technologies, and the power of continuous data registration with telemetry devices and computer analysis of data. And they are essential for our understanding of new diseases and, in a number of cases, dealing with our ignorance of transmission conditions from animal to human of most common diseases such as tuberculosis and influenza.

Evolution of Pathogen Virulence and Host Spectrum

Evolution of pathogens is continuously following the one of their host and environment. Although a topic of numerous discussions, survival and dissemination potential are the motors of pathogen evolution, as for most

living organisms. Influenza viruses represent the perfect examples of this co-evolution as they adapt to the host immune response by antigenic drift, which results from the accumulation of point mutations in their envelope encoding genes. Another escape mechanism, noticed as antigenic shift, results from the introduction of new strains or from reassortments of genes from different influenza viruses, eventually originating from different species, that are co-infecting a single host (Schrauwen et al., 2013), for example pig, as it express receptors for both avian and human viruses. Reassortment is the most likely mechanism for the creation of new viruses with a pandemic potential as they may cumulate virulence/adaptation to multiple bird and mammalian hosts and a high degree of virulence and transmissibility. The H5N1 virus, which is enzootic in poultry, thus represents a potential pandemic threat for human (Anderson et al, 2010). Its broad range of host species, domestic and wild, explains its dissemination and persistency in the environment (Kaplan and Webby, 2013). Evaluation of pathogenesis, host response, and transmission potential is thus needed for a large host range, from poultry to passerines and birds of prey, to obtain the knowledge needed for active surveillance. This is why colleagues from the NADIR animal facilities acquired the know-how required to safely infect in high-confinement species from the wild, such as deer, boars, badgers, or falcons (Bertran et al., 2012), and in this later species, evidenced viral shedding with both low- and high-virulence influenza virus after infection through the respiratory and oral route as well. This kind of information is crucial for our understanding of influenza, and accordingly, a FAO-OIE-WHO joint technical consultation recommended “more research to address questions of mode of transmission, behaviors associated with increased risk, virological and ecological aspects, and viral persistence in the environment to better elucidate specific human exposure risks,” thus requesting a major contribution of animal infectious disease experts to the “one health” approach. Although risk linked to influenza is highlighted above as an example of host adaptation through genetic modification of the viral genome, similar approaches and conclusions apply to other emerging or re-emerging diseases, however less prone to pandemic occurrence, such as West Nile disease (Pello and Olsen, 2013) or Rift Valley fever, or even bacterial diseases provoked by *Borrelia* (Lyme disease) *Coxiella* (Q fever), or mycobacteria (tuberculosis).

Definition of Vaccine or Therapeutic Targets

Aside from stamping out policies for controlling animal infectious disease, vaccination is the cornerstone of control programs in livestock as therapeutics are in many cases too expensive or may contribute to the development of resistance. Vaccination with inactivated or living attenuated strains can be applied to a number of viral and bacterial animal infectious diseases of economic or public health importance (e.g., Marek’s disease of poultry, foot and mouth disease, Q fever, and brucellosis in mammals).

In livestock, tuberculosis is presently re-emerging in a number of developed countries, disseminating in and from wild fauna, which is now considered as a reservoir of *Mycobacterium bovis*, the agent of bovine tuberculosis, and may also support replication of other mycobacteria, including *M. tuberculosis* (Miller and Olea-Popelka, 2013). Two billion people are considered infected worldwide by tuberculosis, although about 10% will develop the disease. The question of animal reservoirs is amplified by the emergency of mycobacteria resistant to a number of antibiotics, as humans may contaminate domestic and wild animal populations with multi-resistant strains. At present, human populations

are more or less correctly vaccinated using the now well-known living Bacillus Calmette–Guérin (BCG) vaccine, an attenuated *M. bovis* strain. The question of vaccination of livestock and wild fauna has been raised. Classical killed vaccines and living BCG have been shown to induce various degrees of protection in badgers, the main animal reservoir in the UK (Corner et al., 2011; Robinson et al., 2012) or in possum in New Zealand (Tompkins et al., 2013). But second-generation vaccines are crucially needed to avoid the drawbacks of these classical vaccines; that is, low efficiency of a killed vaccine, risk of environmental contamination by living mycobacteria, inability to discriminate infected animals from vaccinated ones, and the risk of infection of vaccinated animals, thus becoming silent disease propagators.

Although the capacity of recombinant vaccines to elicit an immune response can be tested through mouse models, their efficiency to restrict infection needs to be evaluated against the virulent challenge in target hosts, including wild species, and with each of the potential animal and human mycobacterial pathogens. The objective is to stimulate the mechanisms of cellular immunity that are the most efficient to avoid intracellular persistency of mycobacteria and the formation of granulomas. Such well-defined animal models needs living rooms adapted to the concerned animal species and very high containment, as well as the expertise of animal caretakers and scientists involved in the monitoring of these long-lasting experiments. In addition, the development of new, well-adapted diagnostic tests and measurement of the induced cell immune response are crucially needed and have to be tested through the same animal models (Aranday-Cortes et al., 2012; Churbanov and Milligan, 2012).

Testing for the Safety and Efficiency of Preventive Tools

Although culling of infected animals for eradication purposes is often the selected policy in developed countries, information on the prevalence of most infectious diseases is scarce in the developing world, positioning vaccination as the only practicable possibility. Thus, *Brucella* vaccines have been used worldwide in bovine, sheep, and goats. The difficulty to distinguish vaccinated and infected animals among serology positive individuals is one of the problems raised by vaccination, at least if eradication is the objective. The second obstacle is the existence of wild reservoirs. Development of new vaccines allowing the definition of the vaccinated or infected status of individuals and applicable to the wild fauna is crucially needed (Godfroid et al., 2011; Osen, 2013). Such vaccines need to be deeply evaluated for their safety and efficiency in a first step using highly confined animal facilities as *Brucella* resist in the environment and are able to infect any potential host with doses as low as 1 to 10 infectious bacteria.

The use in highly confined units of adapted animal models with validated reproducibility is also indispensable for the functional characterization of genetically resistant animal lines that could be commercially developed as an alternative to medication. Such possibility has been successfully applied in sheep to reduce the number of scrapie cases (Fediaevsky et al., 2010; Hagens et al., 2010) and is presently evaluated in a number of situations [e.g., scrapie in goat (Corbière et al., 2013), salmonellosis in poultry (Calenge et al., 2011), bovine tuberculosis (le Roex et al., 2013), and bacterial and viral fish diseases (Quillet et al., 2001; Verrier et al., 2012)].

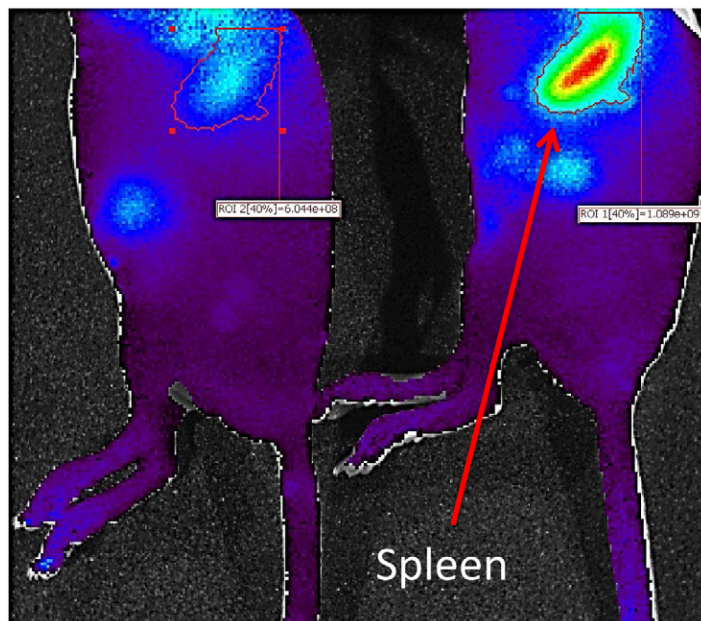
Finally, the efficiency of classical medication such as antibiotics need to be evaluated against the challenge of the natural host with virulent pathogens. The careful monitoring of such experiments, which may

result in excretion of virulent microorganisms (according to the efficiency of the tested drug), thus require the use of confined facilities to avoid any dispersal of infectious particles and biosecure conditions of experiments avoiding any contamination of the personnel.

Conclusion

The recent history of animal epidemics unequivocally demonstrated that developed countries are vulnerable to new and emerging diseases of livestock. The unpredictability and speed of spread mean that only transnational cooperation can cope with these emergencies and speed up measures necessary to control these disease incursions. Indeed, the emergence in Europe of BTV disease, and more recently, SBV epidemic, has demonstrated spreading over borders in very few months. Rapid setup and exchange of survey/diagnostic tools and reagents, epidemiological data, surveillance networks to anticipate threats, and common policies over borders to tackle spreading are key factors. Optimization and coordination of resources, not only reagent exchanges, but also procedures, evaluation criteria, and ethical standards, are the key to success, underlining the need for strategic governance and communication committees and for direct links with epidemiologic networks. In Europe, these networks should allow the transfer from the national to European level the priorities for experimental/research capacities and how to tackle health emergencies at an operational level including dialogues with non-European countries experiencing the same epidemics.

Within the EU and worldwide as well, there are a limited number of high-containment facilities for livestock. The high-containment facilities are staffed by experts in the use animal models and disease containment. Such a platform of BSL3 facilities thus have the ability to sustain the sharing of the specialized technologies of the partners, especially linking associated partners with animal facilities having up-to-date capabilities. Such capabilities are disseminated through networking as well as through peer-reviewed publications to make them accessible for the whole community.



In vivo detection of Salmonella in spleen of anesthetized mouse using optical imaging (IVIS Spectrum; PerkinElmer, Waltham, MA) of fluorescent labelled bacteria.

Similarly, based on the high cost of maintenance and upkeep of animal facilities, BSL3 platforms and capacities cannot be multiplied over countries without leading to suboptimal usage, inefficiencies, high energy costs and significant environmental impact. Cooperation and rationalizing expertise to provide a complementary network without unnecessary duplication would be a key mission for a strategic committee in dialogue with national governmental decision makers and international organizations.

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