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Disease ecology and the concept of *emerging infectious disease*: its impact on the epidemiology of rabies virus, 1990s-2010s*

Abstract

In the beginning of the 1990s, the concept of "emerging infectious disease" (EID) was elaborated in the United States in order to trigger institutional as well as conceptual changes in the fight against infectious diseases at national and international scales. For this reason it has been described as an "active concept" by sociologists Lorna Weir and Eric Mykhalovskiy (Weir & Mykhalovskiy 2010). The impact at the institutional level of the EID concept has been described in detail, but the concrete consequences of this concept at the level of research, on the agenda of researchers, remain poorly explored by historians, philosophers and sociologists of biology and medicine. One of the major consequences of the EID concept at the research level relies on the re-conceptualization of infectious disease emergence as a complex and multifactorial phenomenon, taking place inside a "dynamic and complex global ecology" (Satcher 1995, p.4). Taking rabies epidemiology as a case study, I illustrate how epidemiologists deal with the "global ecology" of this neglected old viral disease that is present everywhere on Earth except in Antarctica and still claims more than 55,000 lives annually. I further investigate the extent to which the complexity of rabies ecology is or is not perceived as an argument against the feasibility of rabies elimination or even eradication. Finally, this paper shows that (1) the EID concept, finding its roots in the tradition of disease ecology, significantly impacts rabies epidemiology and (2) despite its complexity, rabies ecology is not always perceived as an insurmountable obstacle to rabies elimination or eradication.

Key words: emerging infectious diseases, virus, rabies, history of epidemiology, disease ecology, elimination, eradication

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Introduction: “Emerging infectious disease” as an active concept

The 1990s saw the entrance of the concept of emergence into the realm of public health thinking and epidemiology of infectious[1] diseases. Formulated in the United States, the concept of emerging infectious disease (EID) was progressively internationalized (Section 1). “Emerging” is a broad term, a “loosely defined category” (Kilbourne 1996, p.159) that could encompass many various situations, including the emergence of a (new) *disease agent*, the emergence of a (new) *disease* or the emergence of *knowledge* about a previously unknown disease agent. Many typologies of emerging infectious diseases exist[2] (e.g. Lederberg 1992, Grmek 1993, Morse 1993, Kilbourne 1996), but all of them underline the fact that emerging does not always mean “new”. Infectious diseases may qualify as emerging for several reasons.

1) A new germ, previously totally unknown, is identified inside a given population or territory. In this case, the germ may or may not have properly “emerged” inside this population or territory, as it could have been already present and yet unnoticed. Emergence here essentially refers to the “emergence of knowledge” about a given germ. One example of such an emergence is the emergence of SARS (Severe Acute Respiratory Syndrome) in Southern China at the end of 2002 and beginning of 2003. The causative agent, SARS coronavirus (SARS-CoV), was previously unknown. It was subsequently identified as a member of the family *Coronaviridae* (Abraham 2004).
2) A preexisting germ strongly increases in incidence inside a given population where it was already present. This meaning of emergence as “increase in incidence” makes it difficult to distinguish between emergence and epidemics. This difficulty, among others, has recently led some authors to underline the fact that sometimes the “significance and scope of [the concept of emergence] remains obscure” (Méthot & Fantini 2014, p.226). Ebola epidemics are one example of this kind of emergence. Once introduced inside a human population, the prevalence of the virus may rapidly increase thanks to the various transmission routes allowing the virus to easily infect other humans (Section 3).
3) A preexisting germ enters a new population or territory. The germ may either be introduced inside a human population from an animal population (the disease is

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[1] At the beginning of the 1990s, “Infectious” diseases in a broad sense essentially referred to diseases caused by bacteria and viruses, but also included “parasitic” diseases, whose causative agents are eukaryotic microorganisms such as protozoans, helminthes and fungi (Lederberg et al. 1992, p.VI; for details about the current distinction between infectious and parasitic diseases, see for instance Guégan & Choisy 2009). Today, infectious diseases in a strict sense refer to bacterial and viral diseases, but also include other infectious entities – e.g. viroids, prions – that were either unknown or the subject of intense debates regarding their nature during the 1990s.

[2] Despite great similarities between these typologies, they mainly differ through their emphasis on germs, diseases, or knowledge. However, the existence of multiple typologies underlines the difficulty to grasp such a complex phenomenon as emergence inside a single and simple typology.

then qualified as a zoonosis), or from a human population to another one. The case study described in this paper, rabies, is a zoonosis. If the germ is introduced inside a given species for the first time, then the disease is "truly new to man [or to another species]" (Kilbourne 1996, p.159) and this kind of emergence is an emergence of disease (for other cases of *disease* emergence – as a identifiable entity, as nosological entity – see Grmek 1993).

4) A strain of a preexisting germ evolves towards a significantly different strain, able to produce until yet unknown symptoms into its host. Paradigmatic examples of this "evolution *de novo*" (Morse 1993, p.12) of a new germ or, more precisely, of a new variant, are the annual epidemics as well as the occasional pandemics associated with Influenza A viruses (Lederberg et al. 1992, Webster et al. 1992, Morse 1995).

According to this typology of emerging infectious diseases and agents, a germ is absolutely new only in case 4, and a disease is new only if it is for the first time acknowledged. Emerging is then far from being synonymous with new. This coincides with the fact that the primary goal of the EID concept was not to establish an inventory of new germs and new diseases. "Emerging" essentially emphasizes the fact that infectious diseases can almost never be absolutely put under control – by hygiene measures, drugs, vaccination strategies or vector control – or circumscribed to a given population or territory (Section 1). Emergence is part of the "life" of infectious diseases[3]: it is the rule rather than the exception.

Conceptualizing emerging infectious diseases as a reality and a persistent threat to human health is what makes the concept of emergence original (for the historical roots of the EID concept, see Section 1). It is also the reason why it has been described as an "active concept" (Weir & Mykhalovskiy 2010, p.29). The EID concept motivated great institutional changes, funding policies, as well as new collaborations at the national and international levels. The elaboration of the 1996 World Health Organization (WHO) strategic plan, "Emerging and other communicable diseases" (WHO 1996), as well as the launching of the free online journal *Emerging Infectious Diseases* in 1995 are important institutional heritages of the EID concept. One of the primary goals of the EID concept relied in the implementation of global surveillance systems and networks. The WHO's global influenza surveillance network established in 1952 was one the possible models that "may offer lessons for the design of such a network" (Lederberg et al. 1992, p.6).[4]

The EID concept did raise some important critics (e.g. Farmer 1996, King 2004, see also Méthot & Fantini 2014, p.226-229) – some of these critics are discussed later in this paper. Nevertheless, its productivity at the institutional level is beyond question. However, it is not

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[3] The core of the EID concept finds some echoes in the work of French biologist Charles Nicolle (1866-1936). Nicolle described the "life" of infectious diseases not as a metaphor but as a true life. Like a living organism looking for all the possible ways to perpetuate itself, "the infectious disease, a biological phenomenon […], tends to perpetuate itself and, for this, to modify itself according to the circumstances. An infectious disease changes, perpetually evolves" (Nicolle 1930, p.30).

[4] Since 2011, this network has a new name: Global Influenza Surveillance and Response System (GISRS). http://www.who.int/influenza/gisrs_laboratory/en/

straightforward to see how the EID concept did – and still does – modify the research agenda of epidemiologists. The concrete impact of the EID concept on this agenda has not been examined in detail by historians and philosophers of biology and medicine – for exceptions, see the work of Mirko D. Grmek on HIV/AIDS (Grmek 1995) or the work of Pierre-Olivier Méthot & Samuel Alizon on the interpretations of the 1918-1919 Influenza pandemic (Méthot & Alizon 2014).

This paper shows that the EID concept significantly transformed the ways researchers investigate infectious disease (re)emergence, taking rabies epidemiology as a case study. I first demonstrate how the EID concept's emphasis on the need to understand the "dynamic and complex global ecology" (Satcher 1995, p.4) of infectious diseases (Section 1) is translated in rabies epidemiology (Section 2). I then describe how elimination and eradication of rabies are discussed by epidemiologists in a context where the complex ecology of rabies makes it highly difficult to prevent rabies reemergence (Section 3). Because rabies is a zoonosis – an animal disease that can be naturally transmitted to humans – that is present everywhere except in Antarctica, it is an interesting case study to explore the way the "complexity of factors contributing to disease emergence" (Satcher 1995, p.4) challenges the very feasibility of eradication – or even elimination[5] – of rabies.

1. The EID concept and the "global ecology" of infectious disease emergence

1.1. Act of birth and progressive internationalization of the EID concept

The EID concept was first formulated in the United States, in a context where it became obvious that new diseases could appear, and old diseases could resurrect from their ashes. The growing awareness of the threat of emerging infectious diseases followed the successive emergence or reemergence of several diseases, like tick-borne Lyme disease (1975), hemorrhagic fevers associated with Marburg and Ebola viruses, whose first detection respectively occurred in 1967 and 1976, Legionnaire's disease (1976), or Acquired Immunodeficiency Syndrome (1981). Already in the first part of the 20th century, famous researchers like Charles Nicolle (1939) had argued that "new" infectious diseases were always going to appear. "Plagues are as certain as death and taxes", argued Richard Krause in his 1981 book, *The Restless Tide: The persistent challenge of the Microbial World* [6], only a few years after the great success of smallpox's eradication. Nevertheless, it took another decade after Krause's book before the threat of emerging infectious disease became institutionally acknowledged. "Concerns over the appearance of new diseases", historian of

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[5] For the distinction between elimination and eradication, see Section 3., Box 1.
[6] Quoted in Morse 1993, p. XVIII

science Nicholas B. King argued, “are centuries old, and the term ‘emerging diseases’ can be identified in the medical literature at least as far back as the 1960s. However, not until the 1990s did emerging diseases appear as a coherent concept and the intellectual kernel of a broad public health campaign” (King 2004, p.64).

In May 1989, epidemiologist, public health officer and virologist Stephen Morse chaired a conference held in Washington D.C. on “Emerging Viruses, The Evolution of Viruses and Viral Diseases.” The year before, Morse had convinced molecular biologist Joshua Lederberg of the necessity to organize such a conference (Weir & Mykhalovskiy 2010, p.32). This conference, before being published in 1993 under the title *Emerging Viruses*, led to the formation of an Institute of Medicine (IOM) Committee on “Emerging Microbial Threats to Health” in 1991, co-chaired by Lederberg and virologist Robert E. Shope. The Committee published its report in 1992, resulting in a book entitled *Emerging Infections. Microbial Threats to Health in the United States*, directed by Lederberg, Shope and public health officer Stanley C. Oaks. To many, this book represented a “landmark” in the history of infectious diseases management (Weir & Mykhalovskiy 2010, p.31) and the act of birth of the EID concept. More precisely, the 1989 conference, as well as the 1992 and 1993 books, were altogether critical in conceptualizing emerging infections as a *threat*, thereby questioning existing national and international infectious diseases control arrangements.

Notions of threat, of risk and of vigilance are central to the EID concept and partly explain why the EID concept is original. On the one hand, the EID concept found its roots in the tradition of disease ecology (see Anderson 2004) and the idea that risk is a natural component of “civilization” (Rosenberg 1998). Indeed, it conceptualized risk *ecologically* and *sociologically*, as a natural outcome of “the dynamic balance between humans and their environment” (King 2004, p.66). On the other hand, the EID concept was nevertheless original for at least two reasons. First, “Morse’s work was notable”, King argued, because it emphasized the fact that such a dynamic balance between humans, other species and the environment was not only “ the *cause* of new risks but also as the source of their *solutions*” (King 2004, p.66, see also Beck 1992, see also Morse 1991 & 1993). Second, the idea of vigilance, Weil and Mykhalovskiy argued, constitutes “a great revision in public health thinking” (Weir & Mykhalovskiy 2010, p.2-3), because it modified the temporal dynamics of public health surveillance and intervention. The goal of “global emergency vigilance” associated with the EID concept invited public health officers as well as epidemiologists to “contain public health emergencies *prior to* their spread across international boundaries” (*Ibid.*, p.3. Emphasis added). *Potential* emergence events, and not only *actual* ones, became the target of public health “vigilance.”

A US-Canada alliance forged around the EID concept (Lac Tremblant Declaration 1994) represented the first step towards the internationalization of the EID concept, the next step being the reception of this concept at WHO in 1994 and 1995, culminating in the 1996 WHO strategic plan (WHO 1996). The internationalization of the EID concept appears retrospectively as a logical development, as this concept precisely emphasized the ability of germs to travel across national boundaries – an idea that is made explicit in the famous "cliché" (Roemer 1994): microbes *know no borders*.[7] Drawing lessons from HIV/AIDS pandemic, Lederberg, Shope and Oaks opened the preface of their 1992 book by stating that "in the context of infectious diseases, there is nowhere in the world from which we are remote and no one from whom we are disconnected" (Lederberg et al. 1992, p.V). However, the "dilemmas of global interconnectedness" (Weir & Mykhalovskiy 2010, p.34-35) were not new to the late 20th century. From 1851 to 1894, International Sanitary Conferences already discussed infectious diseases in the context of a "shrinking and boundless world" (Huber 2006, p.35). Nevertheless, the EID concept was not a simple reformulation of these old dilemmas. Formulated in a context of growing international travel, the EID concept reflected a quantitative change in the vulnerability of humans to infectious diseases. "The Institute of Medicine coined the term 'emerging and reemerging diseases' to explain that the world had enter an era in which the vulnerability to epidemics in the United States and globally was greater than ever" (Snowden 2008, p.9). Additionally, as previously said, the EID concept was also original because it insisted on the role of humans in the dispersal of infectious diseases and agents, and on the necessity to *anticipate* emerging events by measuring *risks*, thus creating a "world on alert" (Weir & Mykhalovskiy 2010).

1.2. Revisiting the "germ side" of infectious diseases and epidemics

The EID concept was forged as a reaction against a progressive neglect of or "complacency" towards infectious diseases (Lederberg et al. 1992, p.V). To some extent, these diseases were no longer viewed as a main challenge for epidemiologists and public health officers of the United States and more generally in the "Global North" (Weir & Mykhalovskiy 2010). Chronic diseases progressively replaced infectious diseases as a primary cause of mortality, and then as a primary target for public health and epidemiology. In the context of such an "epidemiological transition" (Tulchinsky & Varavikova 2000, p.42-43) from infectious to chronic diseases in many Northern countries, the HIV/AIDS pandemic of the 1980s was sometimes treated as an "exception" (Weir & Mykhalovskiy 2010, p.32). Supported by the power of antibiotics against bacteria and of antiviral drugs and strategies against viruses, the belief that the "end of infectious diseases" seemed closed (Snowden 2008) was also reinforced by the successful eradication of smallpox in 1977 (Fenner et al. 1998).

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[7] Despite the "global" and worldwide scope of the EID concept, it has sometimes been noticed that, even if infectious diseases know no borders, politics do (see King 2004 on "The Scale Politics of emerging diseases").

However, the hope for the complete eradication[8] or at least control of infectious diseases soon faced several difficulties. Growing bacterial and viral resistance to (respectively) antibiotics and antivirals (for the history and epidemiology of antimicrobial resistance, see for instance Cohen 1992, Barrett et al. 1998) progressively led to the conclusion that germs are not static entities but constantly evolve. As Weir and Mykhalovskiy noticed, it is rather surprising that the evolution of germs had not been properly integrated into public health thinking before the 1990s, since bacterial genetics[9] on the one hand and viral genetics[10] on the other hand had clearly established that these infectious entities properly evolve.

The EID concept, through its formulation in the books of Lederberg, Shope and Oaks (Lederberg et al. 1992) on the one hand, and of Morse (1993) on the other hand, was instrumental in bringing bacterial and viral genetics to the attention of public health officers and epidemiologists. Infectious agents were no more seen as generally static entities: "[These two books] formulated a new programme for public health governance that drew on accepted science in microbiology and molecular genetics. In both [books] microbes are understood as genetically mutable rather than as fixed entities. From its inception the EID concept has been conceptually coordinated with contemporary genetic approaches to microbiology and molecular biology, aligning public health thinking and practice with genetic knowledge" (*Ibid.*, p.33). In this regard, the EID concept was an invitation to reconsider the "germ side" of infectious diseases in the light of the genetics and evolution of germs.

The germ side of emerging infectious diseases goes however far beyond the sole evolution of germs. Their ecology also plays a great part in their ability to emerge at a given time and in a given place. "Microbial adaptation and change" is indeed only one of the six factors involved in infectious disease emergence, the others being "human demographics and behavior", "technology and industry", "economic development and land use", "international travel and commerce" and the "breakdown of public health measures" (Lederberg et al. 1992). All these other five factors, because they affect the environment surrounding the

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[8] The project of eradicating most of the infectious diseases had endured severe critics in the past from researchers like Emile Duclaux (1902; see also Debru 1991, Morange 2006). Section 2 discusses the feasibility of elimination and eradication of rabies.

[9] In particular, the work of molecular biologist Joshua Lederberg and geneticist Edward Lawrie Tatum on bacterial genetics in the 1940s and 1950s clearly established the fact that bacteria evolve. Either by a process of conjugation (transfer of genetic material between bacteria by direct contact or through a bridge-like connection) or by a process of transduction (transfer of genetic material between bacteria using bacteriophages as intermediates), bacteria were shown to evolve and adapt. Surprisingly, the work of Lederberg and Tatum did not lead to question the immutability of germs, despite the Nobel Prize Lederberg received in 1958 (Weir & Mykhalovskiy 2010, p.32).

[10] Despite the fact that virology was still a relatively new scientific discipline before the 1990s, having branched off from bacteriology in the 1950s and 1960s (Méthot forthcoming, Helvoort 1994, Chastel 1992), viral evolution was a well-known phenomenon, given the major role viruses – especially bacteriophages (viruses of bacteria) – played in the emergence of molecular biology (Cairns et al. 1966).

germs, strongly participate to the dissemination of microbes. Morse (1991) coined a term to designate this multifactorial dissemination: “microbial traffic.”[11]

Surprisingly, Lederberg, Shope and Oaks noticed that the role of viral (and more broadly microbial) traffic was often underestimated for the benefit of evolutionary studies at the genetic level.

> In discussions about the emergence of “new” diseases, considerable debate has centered on the *relative importance* of de novo evolution of agents versus the transfer of existing agents to new host populations (so-called microbial traffic). It is sometimes presumed that the appearance of a novel, disease-causing organism results from a change in its genetic properties. This is sometimes the case, but there are many instances in which emergence is due to changes in the environment or in human ecology. In fact, environmental changes probably account for most emerging diseases. For example, despite the fact that many viruses have naturally high rates of mutation, the significance of new variants as a source of new viral diseases has been hard to demonstrate, and there appear to be relatively few documented examples in nature. (Lederberg et al. 1992, p.42-43. Emphasis added)

As a consequence, the EID concept did not only emphasized the evolution and genetics of microbes, but also their complex ecology. Ecology being the study of the interaction of a given population with other populations and with its environment, a proper understanding of the germ’s ecology depends on a precise understanding of its hosts’ ecology.[12]

1.3. Revisiting the “host side” of infectious diseases and epidemics

Despite their importance, ecological, but also – at least when humans are concerned – social and cultural factors were only implicit in the 1992 list of six factors involved in disease emergence – e.g. “human demographics and *behavior*.” Indeed, the 1992 list rather insisted on economic and political aspects of disease emergence – “technology and industry”, international travel and commerce”, “economic development and land use”, “breakdown of public health measures.” In the mid-1990s, critics raised against the possible underestimation of the role of social and ecological determinants of disease emergence (e.g. Farmer 1996)[13], leading to eight additional factors being included in the list: climate and

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[11] Initially used in the context of viral emergence, the term “viral traffic” referred to the multiple ecological pathways a virus may take to emerge in a given population at a given time (Morse 1991). The scope of this term was subsequently enlarged to include all microbes, resulting in the term “microbial traffic.”

[12] For a more precise description of ecological studies of infectious disease emergence, see Section 2.2.

[13] Paul Edward Farmer is an American anthropologist and physician. Since 2007, he is also the editor of the peer-reviewed journal *Health and Human Rights*.

weather, changing ecosystems, poverty and social inequality, war and famine, lack of political will, and intent to harm (Smolinski et al. 2003). Furthermore, understanding the "social determinants of health" is now one of the top priorities of the WHO (2009).

Such an emphasis on social and ecological factors of infectious disease emergence was not completely new. Before the elaboration of the EID concept, these factors were already part of the agenda of "modern epidemiology", which has been substantially influenced by social medicine since the 1930s (see for instance Pemberton 2007) and by the tradition of disease ecology (Anderson 2004). Nevertheless, the EID concept clearly reminded epidemiologists of the limits of a strictly "medical model"[14] (Duffin 2009), which would essentially target the germ using drugs or vaccination strategies, while undermining the importance of ecological and social factors. In a context where ecological changes, public education and behavioral change were often neglected by public policy and scientific efforts in the United States, Lederberg, Shope and Oaks reminded that "it is often only by changing patterns of human activity – from travel, personal hygiene, and food handling to sexual behavior and drug abuse – that the spread of disease can be halted" (Lederberg et al. 1992, p.14).[15] This claim found some echoes in historian of medicine Charles E. Rosenberg 1992 book *Explaining Epidemics*. "What we need", Rosenberg argued, "is an ethnography as well as an ecology to explain the network of interactions underlying the appearance, diminution, or recrudescence of particular infectious ills" (Rosenberg 1992, p.303-4).

Listing numerous factors involved in infectious disease emergence and emphasizing the complex interactions between them, the EID concept encouraged researchers to better understand the "dynamic and complex global ecology" of infectious disease emergence (Satcher 1995, p.4). In the first issue of the free online journal *Emerging Infectious Diseases*, David Satcher from the Centers for Disease Control and Prevention (Atlanta, Georgia, USA) used the term "ecology" in a broad sense, including all factors – and not only the ecological ones – inside such a global ecology.

The next section investigates the way epidemiologists deal with such a dynamic and complex global ecology in the case of rabies. The choice of a virus as case study has been first dictated by the important role viruses have played and still play in the understanding of infectious diseases and epidemics. Viruses are often seen as emblematic of the fear inspired by infectious diseases. "From AIDS and influenza to smallpox and zoster (shingles), many of the deadliest and most feared diseases – as well as some of the most common – have been

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[14] Insisting on the role of individual and collective behavior in the emergence, maintenance and transmission of infectious diseases, hematologist and historian Jacalyn Duffin describes the limit of a strictly "medical model" of infectious disease and treatment, that would undermine the importance of social components of disease: "Syphilis continues to be sensitive to the 'magic bullet', penicillin, but the disease has not been eradicated, nor has it been controlled. The medical model treats infection inside the organism; however, prevention and eradication rely on the more difficult task of interfering with behavior" (Duffin 2009, p.172).

[15] One year later, Morse came to the same conclusion. "Because people are so important in [viral] traffic, close collaboration between biomedical and social scientists will be indispensable, and interdisciplinary approaches should be encouraged" (Morse 1993, p.24).

viral" (Morse 1993, p.VII). Furthermore, several reasons contributed to the particular choice of rabies virus. First, rabies is a zoonosis – an animal disease that can be naturally transmitted to humans. As a consequence, its management poses specific challenges, because the disease is not limited to human populations and involves at least three main actors: the virus, the reservoir host and human beings. Second, elimination of rabies has been successful in Western and Central Europe, whereas rabies is still present all over the world – except in Antarctica – and still claims more than 55,000 deaths annually. These contrasts make rabies an interesting case to discuss the feasibility of regional elimination – and of global eradication – as a function of a particular ecological context. Third, rabies is a vaccine-preventable disease but also a neglected one. This means that researchers also have to develop cost-effective strategies to control, eliminate or eradicate the disease.

2. Understanding the "global ecology" of rabies

Rabies is an old disease that results in an inflammation of the brain (encephalitis). Rabies was already known in the ancient Greece under the names *Lyssa* or *Hydrophobia* – because "the sick person is tormented at the same time with thirst and the fear of water" (Steele 1975, p.1; for a history of rabies, see Baer 1975, Chapter 1). The disease is characterized as a zoonosis because rabies is an animal infectious disease that can be naturally transmitted to humans from terrestrial mammals. These animals are the reservoir hosts[16] of rabies virus.

Rabies is a vaccine-preventable disease. Prophylaxis and treatments exist since the end of the 19th century. In 1885 Pasteur successfully immunized for the first time a rabid patient, a young boy named Joseph Meister, with an attenuated vaccine (Jackson 2013, p.3). Improved methods to prepare vaccines were developed throughout the 20th century (Jackson 2013, p.7). These efforts culminated in large oral rabies vaccination (ORV) programmes that completely freed vast areas of Western and Central Europe from red fox-mediated rabies (Müller et al. 2015). However the virus persists in many places – everywhere except in Antarctica and in the above mentioned parts of Europe – where it circulates among animal populations, ranging from non-flying terrestrial mammals (dogs, raccoons, skunks among others) to flying terrestrial mammals (particularly bats).

Such a persistence is the source of repeated reemergence events of rabies among other mammalian species, and notably humans. These cross-species transmission events resulting

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[16] A reservoir host is "a host species where the parasite predominantly multiplies" (Guégan & Choisy 2009, p.35). A reservoir host is something different from a *vector*, which corresponds to a host species that disseminates the infectious agent. However, numerous situations may blur the distinction between vector and reservoir host – e.g. a reservoir host acting as a vector. The reservoir host, also qualified as the "natural" host, generally does not suffer from infection, but there are many exceptions to this rule. Rabies virus is a very good example of this. Except in the case of bats who seem not to suffer from the presence of the virus, its natural hosts generally die as a result of brain inflammation.

in sporadic cases of disease without further transmission (Holmes et al. 2002) are termed "spill-over events." This means that rabies regularly *emerge* in human populations or in cattle populations, but is not maintained inside these populations. In other words, the human species acts as a dead end for rabies virus. Nevertheless, 35,000 to 59,000 human deaths are caused by rabies each year, especially among children under 15 years of age in Asia and Africa (WHO coverage of World Rabies Day 2015[17], Bourhy et al. 1999). To control and anticipate rabies reemergence, researchers need to identify the various factors involved in such reemergence, to estimate the weight of each factor and the interactions between them. Indeed, evaluating the feasibility of rabies control, elimination or eradication depends on a precise understanding of the "complexity of factors" (Satcher 1995, p.4) associated with rabies reemergence.

2.1.The weight of genetic factors: rabies virus as an exception

Rabies virus (RABV) is a RNA virus that belongs to the genus Lyssavirus (genotype 1, family *Rhabdoviridae*), which groups together enveloped, negative and single-stranded RNA viruses (Baer 1975).

Genetic factors are often critical to understand – and possibly control – the (re)emergence of RNA viruses. Since these viruses lack an error-correcting polymerase activity – a "proofreading" activity able to correct the errors made during the replication of the genetic material – RNA viruses tend to rapidly accumulate mutations. Such a high mutation rate per generation results in a very high evolutionary rate. Each new generation brings up a new "repertoire of variants" or "mutant clouds", a process termed "quasi-species evolution" (Domingo et al. 2012, p.159). The existence of such a great number of variants favors the possibility for a new strain of a given RNA virus to rapidly emerge and disseminate into a given host population. Mutation (antigenic drift) is thus particularly relevant for the epidemiology of RNA viruses, but other genetic factors such as reassortment (antigenic shift)[18] – in the case of segmented RNA viruses – or genetic recombination[19] may be equally important.

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[17] http://www.who.int/rabies/en/

[18] Rabies viruses are not segmented viruses. But Influenza viruses – genus Orthomyxovirus (Webster et al. 1992) – are well-known examples of the risk associated with reassortment events. Reassortment, also named antigenic shift, relies on the segmented aspect of the genome of some RNA viruses, including influenza viruses. Each viral genome consists in a defined number of segments. In the case of multiple infections inside the same host, gene segments from diverse origins – avian, human, equine for instance – can combine together to form original reassortments of the parental sequences. Antigenic shift can greatly facilitate the "jump" of species barriers, and is thus the subject of many investigations trying to anticipate potential influenza outbreaks (e.g. Ferguson et al. 2005).

[19] Genetic recombination consists in the exchange of genetic information between two DNA or RNA molecules, leading to a new combination of alleles, thus increasing the genetic variation of populations.

The critical importance of genetics factors in RNA viruses biology thus encouraged researchers to look for strategies able to contain or anticipate the emergence of RNA viruses by targeting their genetic variability. Surprisingly, no mutation has been found to be associated with rabies virus emergence or reemergence events (Bourhy et al. 1999, Holmes et al. 2002).

In a 1998 paper, researchers from the Pasteur Institute of Paris in France (Rabies Unit, Lyssaviruses Laboratory, Infection & Epidemiology department), from the National Veterinary Research Institute and the National Institute of Hygiene in Poland, from the National Veterinary and Food Research Institute in Finland, and from the Wellcome Trust Centre for the Epidemiology of Infectious Disease in the UK (Department of Zoology, University of Oxford), compared nucleotide sequences of the nucleoprotein (N) and glycoprotein (G) genes[20] from distinct groups of rabies viruses circulating in Europe. This study aimed at understanding the spread of rabies inside Europe and its successful emergence from dogs populations to foxes and raccoon dogs populations. Researchers thus looked for one or several mutations associated with the emergence of rabies virus inside these new host populations.

However, the results did not allow any firm conclusion: "strikingly, both the G and N proteins are generally conserved with few amino acid replacements accumulating among the strains studied. In particular, very few amino acid changes were found to accompany the change in transmission from dogs to foxes or raccoon dogs, although it is also possible that key mutations reside in other genes" (*Ibid.*, p. 2555). Later studies (e.g. Holmes et al. 2002) confirmed that no mutation seemed to accompany the emergence of rabies into these new host populations.

As a consequence, rabies emergence and reemergence seem to essentially result from factors others than genetic ones, namely ecological, economic, social and cultural factors. Nevertheless, genetic data remain critical for at least two reasons. First, they enable epidemiologists to quantify the spatial and temporal dynamics of rabies by tracing the virus in its host populations (see below, 2.2.). Second, genetic data are used to characterize various lyssaviruses able to cause rabies. However, different host populations – e.g. bats or wolves – are not equally susceptible to a given lyssavirus. This differential susceptibility between host species enables epidemiologists to evaluate the risk of rabies (re)emergence in areas where *potential* rabies reservoirs cohabit with the *actual* circulation of a given lyssavirus in other species. If the potential reservoir species is strongly susceptible to the rabies virus variant that circulates among other species – a conclusion that can be inferred from experimental studies infecting the potential reservoir with the rabies virus variant – then the risk of rabies reemergence in this potential reservoir is high. On the contrary, if the potential reservoir is less susceptible to the circulating virus variant, then the risk that rabies

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[20] The N gene was chosen because it encodes an internal (functional) protein involved in the regulation of transcription and replication. As a consequence, it could be an important factor in host adaptation. On the other side, the G gene may also be important in determining host range, but for another reason: it encodes an external protein important in pathogenicity and which reacts with cellular receptors of rabies virus (Bourhy et al. 1999, p. 2546-2548).

reemerges in this particular potential reservoir is low (see for instance Müller et al. 2015, p.13).[21] Genetic data are thus critical to better understand the ecology of rabies and to evaluate the risk of (re)emergence events.

2.2. Understanding the "global ecology" of rabies

Ecology is broadly defined as the study of the interactions of populations with other populations and their environment. In the context of infectious disease emergence, ecological factors usually encompass factors as diverse as population distributions and movements, individual variability (in disease susceptibility and in the ability to transmit the disease), individual and collective behavior, landscape, climate and weather. In the case of rabies, reservoir hosts and vectors are primary targets for epidemiologists and public health officers, because they ensure the persistence and diffusion of the disease.

Carnivores (globally) and bats (mainly in the Americas) are the main reservoir hosts of the different lyssavirus that cause rabies, and are thus central nodes in the global ecology of rabies (Müller et al. 2015, p.10). Carnivores in particular are important vectors of the disease as the disease modifies their behavior, which results in long-distance movements and multiple bites. However, the precise understanding of the roles of carnivores as vectors also relies on the identification of variations among individuals and species. Species variations include for instance the differential movements and behavior of wolves and dogs. Even if rabies persists more in dog populations than in wolves populations[22], and even if dogs have many more contacts with humans than wolves, wolves cover longer distances, bite many more people and livestock, and inflict severe wounds, all of this accelerating the spread of rabies (Müller et al. 2015, p.15). Individual variations[23] among dogs for instance include heterogeneities in latency, movement patterns and biting propensity of infected individuals (Hampson et al. 2009).

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[21] One example of this relies on attempts to evaluate the risk that lyssaviruses circulating in bats – for instance European bat lyssavirus types 1 and 2 (EBLV-1 and -2) – regularly infect carnivores, turning them into vectors that could propagate rabies among animal and human populations. Experimental studies and field observations in North America showed that red foxes and skunks were highly susceptible to insectivorous bat rabies virus (RABV) variants. On the contrary, experimental studies in Europe "showed that the susceptibility of mesocarnivors [e.g. the Canidae] to EBLVs is low, resulting in abortive infection and suggesting a negligible risk of sustained EBLV spill-over from bats to terrestrial reservoir species in Europe" (Müller et al. 2015, p.13).

[22] Indeed, the social life style of wolves often contributes to the elimination of the whole packs, thus limiting the spread of the disease outside a given group of wolves (WHO 2013). "Circulation of RABV in wolves independent of other wildlife has not been demonstrated unambiguously" (Müller et al. 2015, p.15), a fact that questions the ability of wolves to act as a reservoir species.

[23] The term "superspreader" refers to individuals who may either be more infective per contact ("higher per-contact transmission" rate) or have many more contacts. In both cases, the rate of spread of the disease is greatly multiplied (Kuiken et al. 2006, p.397, see also Brunker et al. 2012, Lloyd-Smith et al. 2005).

Beyond species and individual variations among carnivores, another important challenge to better grasp the ecology of these reservoir hosts and vectors relies on a quantitative determination of the impact of the landscape on their movements. Despite the fact that multiple landscape features limiting the spread of rabies viruses and infected or susceptible hosts are often identified, “quantifying these effects can be challenging” (Archie et al. 2008, p.27). Genetic data resulting from the sequencing of rabies viruses found in carnivores in various locations may provide such a quantification of physical barriers to host movements – an approach termed “landscape genetics.” For instance, a study led by Erin E. Rees and colleagues from Canada (Natural Resources DNA profiling & Forensic Centre and Wildlife Research and Development Section at Trent University; Department of Geography, Queen’s University; Cissec Corporation) used landscape genetics and computer simulation to predict and assess the impact of Niagara river on the movements of raccoon populations – and therefore on the movements of rabies viruses. Comparing the simulated population genetic structure with the actual population genetic structure based on mitochondrial DNA from 166 raccoons, Reed and colleagues estimated that Niagara river represented a barrier preventing 50% of raccoons from crossing from one side to the other (Rees et al. 2008). Landscape genetics thus offers a mean to quantify landscape factors. For this reason, it has been described as “a new frontier in disease ecology” (Archie et al. 2008[24]; on the integration between landscape epidemiology[25] and landscape genetics for “a more real-world understanding of infectious disease dynamics”, see also Brunker et al. 2012). Interestingly, rabies epidemiology – rabies in domestic dogs in particular – has been described as a “model” for the integration between landscape epidemiology and genetics in RNA viruses (Brunker et al. 2012).

Beyond the ecology of its wildlife reservoirs and the effect of landscape on this ecology, one major aspect of rabies’ global ecology relies in the close connection of man and one important reservoir host, namely domestic dogs. “Rabies is present worldwide, but the greatest burden of the disease is in developing countries, where dog-mediated rabies cause approximately 74,000 deaths annually, in particular in Asia and Africa” (Müller et al. 2015, p.10; WHO 2013). Effective control and possible elimination of dog-mediated rabies require to identify factors defining domestic dogs’ ecology. Humans and human-related activities play a great role in such an ecology. For instance, road distances proved to be of critical relevance to predict dogs movements. Using genetic data to trace the spread of rabies virus in North Africa – an approach termed phylodynamics – an international collaboration between researchers[26] demonstrated that rabies spread in North Africa was largely human-

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[24] The complete title of the paper is the following: “Infecting epidemiology with genetics: a new frontier in disease ecology.”

[25] Landscape epidemiology is defined as the study of the causes and consequences of spatial variation in disease incidence or risk across heterogeneous landscapes (Brunker et al. 2012).

[26] This work is the result of the collaboration of researchers from France (Pasteur Institute), Belgium (Rega Institute), the United States (Departments of Biomathematics and Human Genetics, David Geffen School of Medicine, University of California ; Department of Biostatistics, School of Public Health, University of California ; Fogarty International Center, National Institutes of Health, Bethesda, Maryland ; Department of Geography,

mediated. “Road distances proved to be better predictors of the movement of dog RABV than accessibility or raw geographical distance, with occasional long distance and rapid spread within each [of the examined] countries” (Talbi et al. 2010, p.1).

Beyond human infrastructures, social and cultural factors[27] are also critical to control rabies spread. Public education is essential to enable people deciphering dog behavior and identifying signs associated with rabies contamination. Furthermore, dog owners are encouraged to take care of their animals and to vaccinate them. “Every dog owner is concerned”, as WHO infographic for 2015 World Rabies Day reminded (Figure 1).

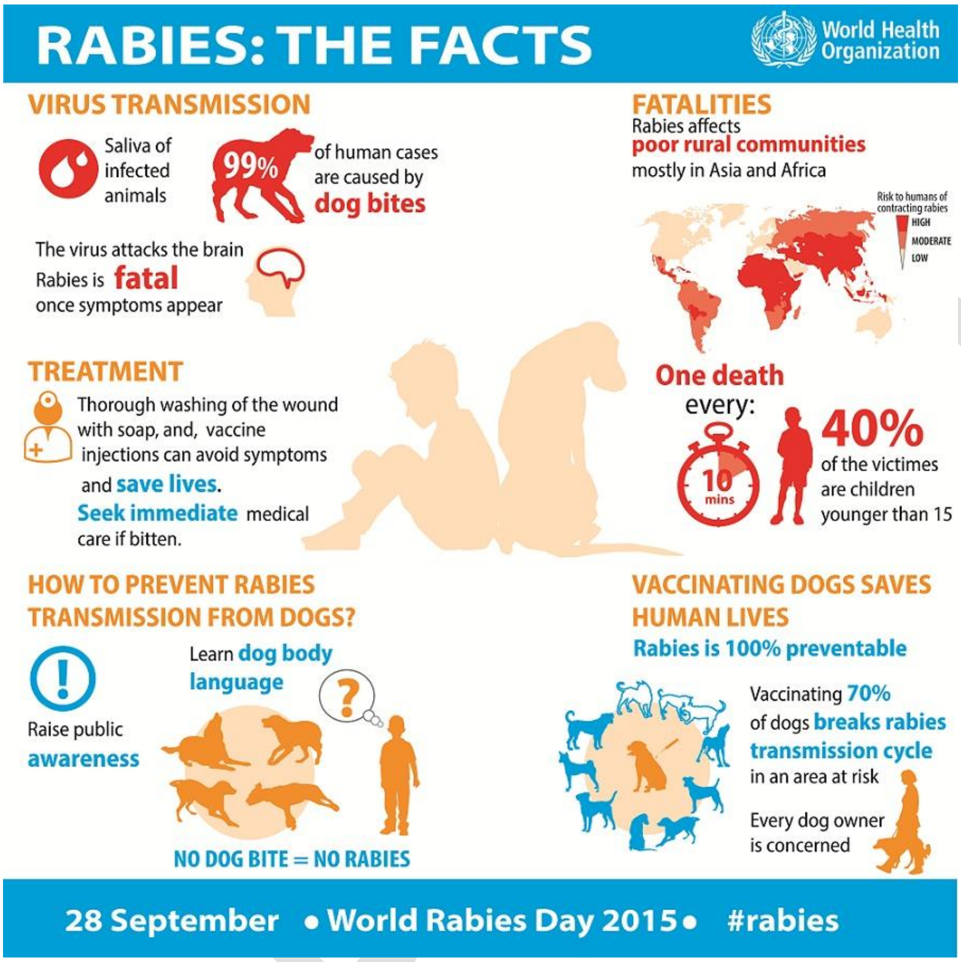

Figure 1. WHO infographic for World Rabies Day 2015[28] reminds the public of the main aspects of rabies and provides advices to identify a rabid animal, to adopt the appropriate behavior to prevent the spread of the disease, and to rapidly react in case of bite.

University of Florida ; Emerging Pathogens Institute, University of Florida ; Center for Infectious Disease Dynamics, Department of Biology, The Pennsylvania State University), Algeria (Algeria Pasteur Institute, Rabies Unit, Research and Diagnosis), Morocco (Morocco Pasteur Institute, Medical Virology Unit, Casablanca), Spain (Instituto de Salud Carlos III, Diagnostic Microbiology Service, Madrid) and the United Kingdom (Institute of Evolutionary Biology, University of Edinburgh).

[27] Social and cultural factors refer to the rules, values and believes that human beings adopt when they live together.

[28] http://www.who.int/topics/rabies/rabies-infographic-2015.jpg?ua=1

Finally, economic factors are also part of control or elimination strategies of rabies, as "the disease disproportionately affects poor, low-resource communities, particularly children with 4 out of every 10 human deaths by rabies occurring in children younger than 15 years" (WHO website, http://www.who.int/rabies/en/). Targeting dogs is often described as a sustainable and cost-effective strategy for the control and possible elimination of rabies in many countries. "Control of canine rabies at the animal source would lead to almost complete prevention of human rabies cases and major economic benefits, in particular for developing countries, which are often least capable of dealing with the disease" (Müller et al. 2015, p.10). More precisely, vaccination of dogs is now acknowledged by the WHO to be the most cost-effective strategy for preventing rabies to (re)emerge in animal and human populations.[29]

Rabies "global ecology", in the broad sense of the word (Satcher 1995), thus involves various factors that epidemiologists identify and quantify and take into account in order to better control the disease. However, the multiplicity of factors as well as the constantly changing global ecology of rabies could interfere with rabies control, elimination or eradication. The next section investigates the impact of rabies global ecology – including ecological but also other factors – on the feasibility of rabies control, elimination and eradication.

3. Eliminating rabies? Rabies in Europe and in Africa: a comparative analysis

Researchers distinguish between different strategies to manage infectious disease (Klepac et al. 2013).

- "Control" means "reduction of disease incidence, prevalence, morbidity and/or mortality to a locally acceptable level" (*Ibid.*, p.5). Control requires continued intervention measures to maintain the reduction.
- "Elimination" is synonymous with interruption of transmission and refers to the "reduction to zero incidence of infection caused by a specific established pathogen in a defined geographical area, as a result of deliberate efforts" (*Ibid.*, p.5). Maintaining elimination may require continued actions to prevent the reemergence of the disease agent.
- "Eradication" takes place at a larger scale as elimination, because eradication means global elimination of a given disease incidence in a human, animal or plant population – ideally, with "no more risk of reintroduction" (*Ibid.*, p.5).

Box 1. Definitions of control, elimination and eradication. Adapted from Klepac et al. 2013

Current rabies epidemiology relies on the precise identification, quantification and articulation of different factors, many of them being listed in the 1992 and 2003 tables of

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[29] "Vaccinating dogs is the most cost-effective strategy for preventing rabies in people" (WHO Fact Sheet N°99, September 2015). http://www.who.int/mediacentre/factsheets/fs099/en/

factors involved in infectious disease emergence (Lederberg et al. 1992, Smolinsky et al. 2003). This complex set of heterogeneous factors constitutes the "global ecology" of rabies. However, it is not straightforward to determine whether such a complexity could prevent or impede the difficult tasks of eradicating or eliminating rabies. In this section, I describe how such a complexity of factors affects epidemiological discussions about the feasibility of elimination or eradication of rabies. I first contrast discussions dealing with the elimination of rabies in Europe and in Africa to determine whether rabies ecology could prevent elimination of rabies (3.1. & 3.2.). Then I describe contrasted opinions about the relative value of sustained control of rabies *versus* elimination or eradication.

3.1. Rabies ecology and the challenge of durable elimination in Western and Central Europe (1970s-2010s)

Initiated at the end of the 1970s, rabies elimination programmes in Western and Central Europe are often quoted as an example of successful elimination (e.g. Freuling et al. 2013). Notably, such a success put into question one of the main assumptions underlying eradication and elimination programmes, namely the belief that eradication and elimination are not feasible if one of the main reservoirs of the disease agent is found in wildlife. "Indeed, the lack of a wildlife reservoir is considered a prerequisite for a disease to be considered eradicable" (*Ibid.*, p.1-2; see also Cochi & Dowdle 2011). The explanation of this is that the implementation of oral vaccination programmes in wildlife populations is particularly difficult and expensive. However, rabies was successfully eliminated from Western and Central Europe, despite its main reservoir being found in wildlife. This success proved that the complex ecology of rabies, due to its wildlife reservoir, did not prevent elimination to be successful, provided oral vaccination programmes were used strategically.

Indeed, the choice of the most appropriate strategy, based on the specificities of rabies ecology, was far from being straightforward. In other words, it was not straightforward to see how the accumulated knowledge about rabies ecology could serve the ultimate goals of controlling and even eliminating the disease from Europe. Initial efforts to reduce fox-associated rabies using increased hunting, poisoning, trapping, culling of cubs and den gassing, were controversial as they paradoxically contributed to enhance the spread of the disease. "Disruption of the fox population structure resulted in increased migration, enhanced contacts and thus increasing spread of the disease" (Müller et al. 2015, p.11). Such an offensive strategy proved to be counterproductive. On the contrary, more preventive strategies, notably oral vaccination campaigns, proved to be successful. Pioneered in North America (Baer 1975), oral vaccination using aerial and sometimes hand distribution of replication-competent infectious viruses – and not inactivated viruses – was used in combination with baiting strategies. Such a strategy aimed at inducing an immune response in foxes, thus protecting the animals from developing the disease when exposed to contaminated animals.

As a consequence, reported rabies cases substantially decreased, “from a peak in 1984 (24,315 cases) to 5,242 cases in 2013” (WHO Rabies bulletin 2014, in Müller et al. 2015, p.11). The implementation of ORV programmes in twenty-four countries ended with large parts of Central and Western Europe becoming rabies free (Freuling et al. 2013).[30] In the end, and in this particular case, a minor perturbation of rabies ecology – using oral vaccination and baits – proved more effective than a greater perturbation of the disease ecology – disrupting the reservoir host ecosystem by killing most of the individual potential reservoirs, namely foxes.

However, researchers from Germany and France[31] underlined in a 2015 paper that such a success story could still end up with an unhappy end, as risks of reintroduction and reemergence of rabies are important (Müller et al. 2015). The authors identified risk factors of ecological, economic, administrative and/or cognitive nature.

Ecological factors include for instance the possible reintroduction of rabies from bats to carnivores, the legal or illegal movements of pets as a response to growing demand for cheap dogs that make it difficult to control the spread of potentially infected or susceptible animals, and the potential for several carnivore species (e.g. the golden jackal, the small Indian mongoose) to become a reservoir host for lyssaviruses – in particular rabies virus (RABV). Another ecological factor relies on the possible or actual introduction in Europe of potential reservoir species (arctic foxes and raccoon dogs respectively) from outside Europe, due to climate changes.[32] Factors associated with rabies ecology are critical to assess the risk of rabies reintroduction and reemergence. However economic, administrative and cognitive factors could delay or impede the management of rabies ecology.

Economic factors include the coordination of multinational[33] and national efforts, as well as the ability to ensure long-term financial commitment. Long-term financial commitment, covering the various phases of the elimination programme *and beyond*, is essential since

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[30] The World Organization for Animal Health (OIE) “requires that no case be detected for a two-year period before countries can be officially declared free from rabies” (Freuling et al. 2013, p.6). From 1978 to 2010, nine countries have been declared rabies free: Finland and the Netherlands (1991), Switzerland (1998), Belgium and Luxemburg (2001), the Czech Republic (2004), Germany and Austria (2008), France (2010) (*Ibid.*, p.6).

[31] Institute of Molecular Virology and Cell Biology, and Institute of Epidemiology, Friedrich-Loeffler Institut, WHO Collaborating Centre for Rabies Surveillance and Research, OIE Reference Laboratory for Rabies, Germany ; Laboratoire de Microbiologie, Lyon University, France ; Fondation Mérieux, France; IDT Biologika GmbH, Germany.

[32] The precise interplay between climate changes and species migrations is however hard to estimate and predict. The case of arctic foxes well illustrates the ambivalent role of climate. Increasing temperatures could either allow European red foxes and raccoon dogs to migrate further north and propagate the disease, or they could on the contrary prevent animal movements by reducing ice masses that currently enable the passage between Europe and Arctic (Müller et al. 2015, p.11).

[33] At the beginning of the 1990s, the European Union declared rabies elimination a high priority and started co-financing control efforts, even in countries outside the EU (Demetriou & Moynagh 2011).

"the final phase of elimination is disproportionately the most costly" (Müller et al. 2015, p.11-12), a fact that has already been observed in the case of smallpox and poliomyelitis elimination programmes (Freuling et al. 2013, p.11, see also Klepac et al. 2013). The reason why this final phase is so costly is because of the intense reconfiguration of rabies ecology during the preceding phases of the elimination programme. Once incidence has been reduced by 90 per cent, isolated "clusters of infection are able to persist and spread" (Freuling et al. 2013, p.11). These clusters are particularly hard to identify and target, precisely because of their isolation. Yet, "even small pockets of law coverage can compromise success and considerably extend the time of elimination" (*Ibid.*, p.11), because these pockets are the source of potential reemergence of rabies in areas previously freed from the virus.

The specific temporal and spatial dynamics of rabies ecology and rabies reservoirs during and after the course of elimination programmes is also what makes it necessary to constantly re-adapt vaccination strategies to changing environmental conditions. However, administrative and cognitive factors may prevent such a re-adaptation. The complexity of administration procedures, the risk of inadequate planning of future activities and changing priorities, and the risk of ORV programmes becoming automatic, "self-perpetuating processes" more and more disconnected from the field are all factors that could prevent the "flexible execution" and "adjustment of ORV strategies to changing epidemiological conditions" (Müller et al. 2015, p.13).

Finally, the ever changing ecology of rabies is what makes *durable* elimination of the disease in Western and Central Europe a challenging goal. Durable elimination does not require mere passive maintenance of existing control measures. It necessitates active and flexible surveillance and intervention to adapt to the perpetually evolving rabies ecology, and to minimize the burden of disease as well as costs associated with durable elimination.

3.2. Eliminating rabies from Africa: dealing with epidemiological constraints (1990s-2010s)

In a 2010 paper, an epidemiological study, published in the journal *PLOS Neglected Tropical Diseases* and partly[34] supported by National Institutes of Health/National Science Foundation Ecology of Infectious Diseases Programme (NSF/DEB0225453), described the common reasons given to explain the lack of effective control of rabies in Africa and the

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[34] This work was also supported by the Wellcome Trust, National Science Foundation (DEB0513994), Pew Charitable Trusts award (2000-002558), Lincoln Park Zoo, the Disney Conservation Fund and Fauna and Flora International, the Tusk Trust, the Department for International Development Animal Health Programme, the RCVS Trust and Intervet.

seeming impossibility to eliminate rabies from this continent (Lembo et al. 2010).[35] This paper aimed at determining whether there are insurmountable obstacles to rabies control and elimination. One of the major reasons given for the impossibility to eliminate rabies from Africa relies on the virus ability to persist in several species in Africa, thus leading to sustained infection cycles in wildlife that could prevent complete and durable elimination of the disease (Cleaveland & Dye 1995, Bingham 2005). The issue was thus to determine whether such sustained infection cycles in wildlife *exist* or not, if they are *possible*, and if they could *prevent* rabies elimination in Africa.

Taking fox-mediated rabies elimination in Europe as an example, the authors first argued that the existence of wildlife rabies *per se* should not prevent rabies elimination. Indeed, rabies elimination in Western and Central Europe has shown that an infectious disease can be eliminated even if it has a wildlife reservoir, provided “disease control efforts [are] targeted at the maintenance population” (*Ibid.*, p.4). In Africa, domestic dogs are the “maintenance population”, that is the main reservoir species of rabies in Africa. Following the example of rabies elimination in Europe, it should then be possible to eliminate rabies from Africa if domestic dogs are the target of vaccination strategies. However, targeting domestic dogs would probably not be enough to eliminate the disease if rabies infection cycles can be *maintained* in wildlife species. In other words, it is the existence of *sustained* infectious cycles of rabies in wildlife – and not the presence of rabies in wildlife *per se* – that makes rabies elimination problematic.

Taking a wildlife-rich ecosystem – the Seregenti ecosystem in Tanzania – as a case study, the authors however showed that, even in such a species-rich environment, “domestic dogs are the only population essential for [rabies] maintenance” (*Ibid.,* p.4). This claim was first based on phylogenetic data showing that only a single southern Africa canid-associated variant (Africa 1b) circulated among different hosts. In other words, these data suggested that dogs are the main reservoir of this *canid*-associated variant, and that other host species are essentially infected *from* dogs. It is then probable that there are no sustained infectious cycles in wildlife. Furthermore, the authors underlined that transmission networks analyses and statistical inference were also in favor of domestic dogs being the essential maintenance population, because they suggested that within-species transmission could not be sustained for wildlife hosts (*Ibid.,* p.4). This suggests that wildlife species, because they seem to be unable to maintain within-species transmission, could be free of rabies if they were not constantly re-infected from dogs. Finally, the fact that “domestic dogs are the only

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[35] According to the authors, the four main obstacles to rabies elimination mentioned in the literature are (1) low prioritization as a result of a lack of awareness of the disease burden, (2) epidemiological constraints “such as uncertainties about the required levels of vaccination coverage and the possibility of sustained cycles of infection in wildlife” (Lembo et al. 2010, p.1), (3) operational constraints, notably “accessibility of dogs for vaccination and insufficient knowledge of dog population sizes for planning of vaccination campaigns” (*Ibid.*, p.1), and (4) lack of resources. Here I focus on the impact of epidemiological constraints, in order to describe how the complex disease ecology is considered by epidemiologists as something that could or could not prevent rabies elimination from Africa.

maintenance population in such a species-rich community", the authors argued, "suggests that elimination of canine rabies through domestic dog vaccination is a *realistic* possibility, and provides grounds for optimism for wider-scale elimination efforts in Africa" (*Ibid.,* p.5). Furthermore, the authors continued, even if local sustained infection cycles in wildlife existed in Africa, combined strategies – wildlife rabies control strategies in conjunction with dog vaccination – could be used to attempt rabies elimination.

Such an "optimism for wider-scale elimination efforts in Africa" is shared by other researchers, some of them even arguing in favor of a *global* elimination – *id est* eradication – of canine rabies (e.g. Hampson et al. 2009). However, doubts regarding the feasibility of rabies elimination from Africa persist because "the emergence of new variants maintained in wildlife also remains a possibility, as shown in the USA, where wildlife rabies now dominates since elimination of canine rabies" (*Ibid.,* p.5; see also Velasco-Villa et al. 2008). Given the complexity of rabies ecology, it is hard to predict with certainty whether rabies elimination in dogs in Africa could favor the emergence of wildlife variants as in the case of the USA, or, on the contrary, lead to rabies durable elimination as in the case of Western and Central Europe. The impact of intervention strategies cannot be exactly predicted *a priori*, that is before elimination programmes are instantiated. "For Africa, these questions are likely only to be resolved with large-scale intervention involving mass vaccination of dogs" (*Ibid.,* p.5).

Finally, the comparative analysis between rabies elimination attempts and discussions in Europe and in Africa shows that rabies complex ecology – in particular the presence of a wildlife reservoir – is not something that *absolutely* prevents rabies elimination. Yet, rabies ecology makes durable elimination problematic (Europe) and prevents epidemiologists to predict with certainty the outcome of elimination programmes (Africa and North America). The constant reconfiguration of rabies ecology brings potential reservoir species in contact with infected species, thus favoring chances of rabies (re)emergence. Furthermore, the maintenance of rabies virus variants in wildlife could allow the emergence of these rabies virus variants after the elimination of a given virus variant. The "vacated niche" left by the eliminated rabies virus variant could then be occupied by another rabies virus variant, as illustrated in North America (for a discussion about vacated niches and pathogen eradication, see Lloyd-Smith 2013). In the end, elimination is neither impossible nor certain. Given such a disappointing conclusion, epidemiologists adopt contrasted opinions on the benefits of elimination (or even eradication) attempts. In the last section of this paper, I describe these contrasted opinions.

2.3.3. Contrasted opinions on the benefits of elimination attempts

Beyond the particular case of Africa, there are reasons to question the feasibility of rabies elimination in other parts of the world. The existence of a plethora of rabies virus variants, of susceptible hosts, and of potential reservoirs, as well as the presence of rabies everywhere in the world except in Antarctica make it hard to predict rabies elimination or to claim with certainty that rabies *can* be regionally eliminated or even globally eradicated (Rupprecht et al. 2008).

Despite these obstacles, rabies has been identified as a key One Health Issue by the World Organization for Animal Health (OIE), the WHO and the Food and Agriculture Organization of the United Nations (FAO) (Pastoret et al. 2014, p.509). In other words, several international institutions consider that the existing reasons to doubt the feasibility of rabies elimination should not prevent rabies – and canine rabies elimination in particular – to become a *priority* for international and national public health services (Rupprecht et al. 2008). "Society must recall that despite the recent recognition of other important emerging infectious diseases, none exceed the case fatality rate of rabies. Given the clear relevance of rabies in public health, agriculture, and conservation biology, substantive international progress must continue towards enhanced public awareness, human rabies prevention, wildlife rabies control, and *canine rabies elimination*, with renewed collaborative vigour" (Rupprecht et al. 2008, p.95. Emphasis added). Canine rabies global eradication or regional elimination may not be *achievable goals*, because of the complex disease ecology and costs associated with its management. Nevertheless, the OIE, the WHO and the FAO insist on the fact that rabies elimination and eradication should be goals for international and national public health services.

International directives are nevertheless counterbalanced, or at least qualified by the "lessons" offered by past examples of successful or unsuccessful elimination of rabies. In particular, elevated costs associated with the final phase of elimination need to be taken into account before any elimination programme be launched. The interruption of elimination programmes before elimination is complete could favor rapid re-emergence of the disease in a context of highly modified disease ecology. Such reemergence events would be associated with tremendous costs, not to mention the associated human and animal deaths (Freuling et al. 2013). Moreover, elimination of a rabies virus variant may favor the emergence of other rabies virus variants, as in the case of the United States (Velasco-Villa et al. 2008). Finally, even successful eliminations are challenged by the constantly evolving rabies ecology. As a consequence, the success of elimination strategies is never *a priori* warranted.

In spite of these uncertainties, the majority of rabies epidemiologists, along with the international institutions like the WHO or the OIE, argue in favor of the elimination of (at least) canine rabies, a strategy that may save many human and animal lives and prove more cost-effective in the long run than the sole control of rabies. "We know it can be eliminated", researchers from the OIE and the National Reference Laboratory on Rabies explained. "By combating rabies at its source in animals and vaccinating 70% of dogs, we can eradicate it" (Pastoret et al. 2014, p.509).

4. Conclusions

This paper first described the concept of "emerging infectious disease" (EID) elaborated in the beginning of the 1990s. Section 1 demonstrated that this concept, forged as a reaction against a progressive neglect in the Global North towards infectious diseases, emphasized the difficulty to control, eliminate or eradicate infectious diseases. Because infectious diseases have a "life" of their own and may regularly emerge or reemerge, they are complex phenomena having their proper "dynamic and complex global ecology" (Satcher 1995, p.4).

Section 2 shows how rabies epidemiology deals with the multiplicity of factors involved in rabies (re)emergence events. The conceptual heritage of the EID concept in rabies epidemiology is apparent not only from the vocabulary used by rabies epidemiologists – investigating rabies "emergence" or "reemergence" – but essentially from the fact that the (1992 and 2003) list of factors associated with infectious disease emergence are systematically explored by rabies epidemiologists in order to understand the global ecology of rabies.

Section 3 explores how an ecological understanding of rabies, insisting on the complex and dynamic global ecology of the disease, impacts discussions about the feasibility of rabies elimination or eradication. One interesting result is that the complex and changing ecology of rabies – in particular the presence of wildlife hosts and of multiple rabies variants – is often not perceived as an insurmountable obstacle to rabies elimination, nor to rabies eradication.

Discussions about rabies ecology and the possibility to eliminate or eradicate the disease find some echoes in early discussions about eradication, e.g. the contrasting views of Fred Soper and René Dubos on vector and disease eradication (Litsios 1997). The disease (and its hosts and vectors) ecology makes it impossible to "extract a disease from nature's web through a direct, surgical-like, approach" (*Ibid.,* p.138). Interfering with rabies ecology is a perturbation of a given equilibrium, the evolution of which is hard to predict. It seems that rabies epidemiologists would agree with Dubos to say that any management of infectious diseases must be ecologically-minded, and that all elimination and eradication efforts are context-dependent[36]. However, Soper's claim that "one really begins to learn the important ecological facts, those which render eradication difficult only when the great bulk of the species density has been removed and points of resistance begin to appear" (quoted *in*

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[36] Yet, this "context-dependent" characteristic of infectious disease management does not prevent to learn from particular cases. Epidemiologists regularly draw "lessons" from past (successful or not) elimination or eradication attempts (e.g. Klepac et al. 2013). The success or failure of a given elimination programme may be hard to evaluate, despite the use of mathematical models (on the use of models in epidemiology in the context of eradication programmes, see Klepac et al. 2013, p.8 and the associated references). Yet common challenges associated with the elimination of infectious diseases can be identified (Klepac et al. 2013).

Litsios 1997, p.140) also finds some echoes in the current emphasis of rabies epidemiologists on the “endgame” challenge. Moreover, eradication programmes are far from being perceived as “social utopias” by epidemiologists, thereby contradicting Dubos’ prediction that eradication programmes would “eventually become a curiosity item on library shelves” (Dubos 1965, *in* Litsios 1997, p.148).

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