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EDITORIAL 10.1111/j.1469-0691.2010.03444.x

# Of mice and men: defining, categorizing and understanding the significance of zoonotic infections

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**Article Published online:** 9 December 2010

The increasingly anthropocentric model by which humans have grown to theoretically view the surrounding world is often tested in practice, be it climate changes and global warming, the complex consequences of natural disasters, or the outcomes of interaction with the rest of living creatures. In medicine, this anthropocentric model of thinking is nowhere more obvious than in the case of zoonotic infections, the burden and significance of which are constantly under-appraised. Zoonotic infections remain an ever-growing unsolved puzzle, serving typically as an umbrella term under which numerous infectious diseases are shelved, in order to ignore not only their medical and veterinarian-related burden, but also, and more importantly, their major socio-economic correlations, which pertain to global and regional political ethics, and thus should preferably remain unnoticed.

## In Search of a Definition

What is a zoonotic infection and is there any reason for having such a classification? What do we conclude about an infectious agent by terming it as zoonotic? Zoonosis is a complex Greek word deriving from the words '*ζώον*' (zoon), which means animal, and '*νόσος*' (nosos), which means disease. In broad terms, a zoonotic infection is one that can be transmitted by animals to humans. A definite clarification of the term though does not exist, and one may wonder whether we need one, apart from the broad characterization offered above. But a definition is needed, because it will allow for proper grouping of appropriate pathogens and direct understanding of their correlations and broader, non-medical parameters. A proper definition would further allow for functional targeting of the factors that allow for the continuing prevalence of zoonotic infections through public health strategies and adaptations of social, medical and veterinarian policies that affect the impact of zoonoses.

The initial World Health Organization (WHO) definition of zoonotic infections in 1951 referred to any disease naturally transmitted between vertebrate animals and humans, either way, but excluded, crucially, experimental transmissions and toxin-mediated transmissions, and further excluded indirect participation of animals or vectors in the disease transmission chain. The term 'anthroponoses' (from the Greek word '*άνθρωπος*', which stands for human) had been coined to characterize diseases whose source was an infectious human, and the term 'sapronoses' (from the ancient Greek word '*σαπρός*', which means putrescent or degradable) referred to diseases whose origin was an abiotic substrate [1]. Zoonoses were further characterized as anthropozoonoses, when transmitted from animals to humans, and zooanthroponoses when transmitted *vice versa*. The term 'amphixenoses' (the Greek words '*αμφί*', which means bi-, and '*ξένος*', which means host) was also limitedly used to describe zoonotic infections that are transmissible either way. All these sub-terms were subsequently abandoned by WHO expert committees. Our anthropocentric view of nature means that in general the term 'zoonoses' refers to disease transmissible to humans, while the inverse remain a subject localized to the interest of environmental specialists.

## In Search of a Categorization

This widely accepted definition not only underlines the extent of the zoonotic impact on human health, but also underscores the categorization issues that emerge: for example, influenza A (H5N1) virus, the most alarming avian influenza strain, is a typical zoonotic infection because it demands close human contact with animal hosts for the infection to spread to man. On the other hand, the novel swine influenza A (H1N1) virus is also typically a zoonotic infection, transmitted from swine hosts to humans; however,

the ensuing direct human to human transmission was the signifying characteristic of the pathogen and the major factor leading to the 2009 pandemic. Despite being strictly a zoonotic infection, sharing initially certain socio-political characteristics with other typical zoonotic viral infections regarding its birth and initial contact with humans, its spread dynamics and human morbidity potential are irrelevant to its zoonotic nature. The same could be said about HIV, the simian origin of which would allow for a zoonotic characterization, and SARS-CoV, which originated in horseshoe bats [2].

Categorization is further blurred when considering agents usually transmitted from human to human through an arthropod vector (for example dengue), agents though that require for their lifecycle an invertebrate animal host: these are not strictly zoonoses, because the animal host is invertebrate, but they do share certain socio-ecological characteristics with the typical zoonotic infections. Moreover, a number of pathogens require a vertebrate host but can replicate in and infect humans through contact with abiotic material: often referred to as 'saprozoonoses' [1], these agents are not unanimously considered to be of a zoonotic nature.

## Why Zoonoses Matter

One may wonder why a categorization is needed in the first place. Furthermore, one may wonder why we discuss zoonoses; there are numerous reasons, ranging from those that are historical and philosophical/teleological to pure pragmatism.

### The historical perspective

Zoonoses preceded humanity, adding fuel to a non-anthropocentric view of their existence, their interaction with the human race, and their re-emergence. Hippocrates, among others, has written extensively about this interaction [3], and the common effect of infectious agents in livestock and humans can be traced as far back as the Ten Plagues of Egypt. 'It will become fine dust over the whole land of Egypt, and festering boils will break out on men and animals throughout the land' [4], says Exodus 9, describing an airborne infection causing disease in livestock and humans. The Old Testament also carries the description, in the First Book of Samuel, of a lethal outbreak of 'groin tumors' in Philistines, in conjunction with the presence of rats, a possible early description of bubonic plague or tularemia and its association with rodents [5]. Awareness of this interaction was not lost through the ages: in 1796, Edward Jenner commented that man 'has familiarized himself with a great number of animals which may not, originally, have been intended for his associates', and thus this deviation 'seems to have proven to him a prolific source of diseases' [6].

### The pragmatist perspective

In a courageous attempt to classify existing human pathogens, Taylor *et al.* [7] demonstrated that the majority of these pathogens are zoonotic, comprising 61% of the total of 1415 species. Furthermore, they managed to demonstrate that the vast majority of emerging diseases are caused by a zoonotic pathogen, the percentage reaching 75%. Although the categorization as zoonotic for some of the pathogens by Taylor and colleagues may be doubtful (many being theoretically only zoonotic), and although some of the species implicated are of historical or isolated significance for human health, there still exists an enormous burden of zoonotic agents causing major human morbidity. As discussed in the reviews by Christou and Akritidis in the present issue of Clinical Microbiology and Infection ('The global burden of bacterial and viral zoonotic infections' and 'Parasitic, fungal and prion zoonoses: an expanding universe of candidates for human disease', respectively), the global impact of zoonotic infections is far more significant than indicated by public health and eradication campaigns and scientific research. This underestimated burden is even more troublesome because it transcends the strict medical field, extending to the veterinarian and public health field, and reaching, as will be discussed later, issues of society, state, economy and regional and national and global politics of all sorts. To put it simply, millions of new cases of zoonotic infections are registered annually worldwide, often in clusters irrespective of the disease, with a major morbidity toll that may lapse to chronicity, and considerable mortality. One can anticipate the future to hold an enhanced morbidity burden of zoonotic infections: not only are we able to recognize them better through advanced diagnostics, but medical progress has also created a vast reservoir of potential candidates for infection; in particular, immunocompromized patients build up such a patient pool, developing a wide spectrum of opportunistic infections, many of which were previously considered harmless zoonotic agents, typical examples being human cryptosporidiosis, unknown 40 years ago, and toxoplasmosis or listeriosis in AIDS patients.

### The globalization perspective

The world now has become a huge village; extensive population movements take place annually, be it for tourism, leisure or work, or even through military operations. Outbreaks of zoonotic infections in travellers abroad have been increasingly reported, ranging from leptospirosis in adventurous athletes [8], to leishmaniasis and Q fever in troops deployed in Iraq and Afghanistan [9,10]. Voluntary or war-related

immigration further serves as a vehicle for zoonotic infection migration: this has been demonstrated repeatedly regarding brucellosis kinetics [11].

**The socio-economic perspective**

Zoonotic infection control is a complex issue. Control of human disease, either by eradication or through elimination, may prove futile due to the lack of (and the projected non-development of) efficient vaccines for most of the significant zoonotic pathogens. One can presume that control should be an issue of veterinarians, identifying and eliminating disease in animal hosts. This is not the case though, because numerous zoonotic agents are recognized in wildlife, which is out of veterinary jurisdiction. Even for pathogens that emerge from domestic animals though, control is often unattainable due to inadequate planning or inadequate implementation of relevant campaigns: taking into account that this is often the case in the industrialized world (again the example of brucellosis control in the European Union [12] can serve as an instructive case study), one can imagine how futile such a target is in developing countries with absent or poorly developed medical, veterinary and public health infrastructure. The latter countries are the ones which serve as vast zoonotic reservoirs though: zoonoses have been recognized as diseases of the poor, and this has obvious implications for the way they are confronted by science, health-related project funding bodies and politics. Again using brucellosis as an obvious example for the author (an experience though that could be generalized for numerous other zoonotic agents and various countries, industrialized or not, the US-Mexico border [13,14] being a prime example), a minor outbreak (<10 cases) of foodborne brucellosis in a suburb of the capital, Athens, a few years ago, resulted in extensive media coverage; on the other hand, a rather extensive (more than 80 cases) subsequent outbreak in a rural island of northern Greece [15] went unnoticed by the media, despite exhibiting significant evidence of all sorts of policy misdemeanours (illegal animal importation, inadequate implication of preventive policies and subsequent testing, inadequate notification of preceding cases that should serve as an alarm, and so on). The fact that zoonotic control is a political issue though is a rather easy conclusion: the instructive story of a bovine spongiform encephalopathy (BSE) outbreak and its enormous consequences for the economy not only of the affected country but also of numerous others, underlines how a peculiar and vaguely understood zoonotic agent can affect global politics. However, terming zoonoses control as a political issue is also a too broad term to start with: As discussed in the review by Cascio and colleagues in the present issue of Clinical Microbiology and Infection (The socio-ecology of zoonotic infections), approaching the evolution of zoonotic infections should ideally be an interdisciplinary task that should comprise an intelligent political approach with all sorts of medical, veterinarian, public health, animal biology/


**FIG. 1.** Certain zoonotic outbreaks of the last decade. BSE, bovine spongiform encephalopathy.

entomology/ornithology-related, environmental, ecological, evolutionist and socioeconomic parameters. Even if all these parameters are harmonized, one needs to be assured that the public will be receptive: a direct relationship of zoonotic disease prevalence with the health literacy of the public has been demonstrated for certain zoonoses, including brucellosis and rabies [16,17]. In this vein, introducing novel control strategies and campaigns that may directly affect the economical status of livestock owners may result in opposition or unwillingness to co-operate by the public, thus cancelling any control effort at the beginning [18].

**The philosophical perspective**

Once more regarding our anthropocentric view of the universe, we tend to forget that humans are a rather late link in the vertebrate evolutionary chain, preceded by numerous existing animal species, as well as certain zoonotic agents [19]. Modern man has in general attempted to overrule nature: modern man may have a lizard as a pet (to remember the aforementioned Jenner quote), may taste all sorts of raw delicacies, imported or in the field, may travel in all sorts of virgin environments to recognize true nature (and its true habitats, which are often zoonotic agents of major morbidity and mortality), may interfere with nature's equilibrium by eliminating wildlife that could serve as an infectious reservoir for domestic animals that man himself located near wildlife, and so on. Essentially it's the human that invades and disrupts nature's equilibrium, and naturally nature fights back. A non-anthropocentric view would thus consider man a true virus of nature, one that the universe tries to eliminate using all sorts of weapons, zoonotic bacteria being its antibodies, and zoonotic viruses its natural killer cells.

**The teleological perspective**

It is therefore not surprising that the vast majority of infectious disease outbreaks reported in recent decades have been of zoonotic nature or at least of zoonotic origin [20] (Fig. 1), including the major infectious threats of the 21st century, SARS-CoV, avian influenza, the pandemic 2009 influenza, and the West Nile Virus US outbreak. It is further not surprising that all bar one (smallpox) of the Category A listed potential biological weapons [21] and the majority of the Category B listed biological agents [22] are of zoonotic nature. The end of humanity by a zoonotic infectious agent has been a common and increasingly popular scenario in films [23]; the recent outbreaks have demonstrated that it is also a plausible scenario, one which raises the question of whether a zoonotic pathogen will eventually be the human race's nemesis.

The recent global outbreaks of novel infectious diseases originating in animal species underline that we should anticipate more such outbreaks in the future. We should further take into account that chronic, currently considered idiopathic, diseases may ultimately be attributed to a zoonotic agent: the typical example here is the constantly evaluated potential relationship between *Mycobacterium paratuberculosis* and Crohn's disease [24]. Understanding the complexity of zoonotic infections, and tracing the aetiology of their resurgence back to their roots is far from the concept of surveillance/diagnosis/eradication and elimination campaigns. It is foremost a concept of understanding nature as an organic system within which humans serve as a non-integral part, as a part of a chain that can recycle its integrity by expelling humans.

'The single biggest threat to man's continued dominance on the planet is the virus', commented Joshua Lederberg, PhD, Nobel laureate, as cited in the closing credits of the 1995 film Outbreak: few doubt that such a virus would be of zoonotic origin [25].

## Transparency Declaration

The author has no conflicts of interest to declare.

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