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The socio-ecology of zoonotic infections

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Abstract

The resurgence of infectious diseases of zoonotic origin observed in recent years imposes a major morbidity/mortality burden worldwide, and also a major economic burden that extends beyond pure medical costs. The resurgence and epidemiology of zoonoses are complex and dynamic, being influenced by varying parameters that can roughly be categorized as human-related, pathogen-related, and climate/environment-related; however, there is significant interplay between these factors. Human-related factors include modern life trends such as ecotourism, increased exposure through hunting or pet owning, and culinary habits, industrialization sequelae such as farming/food chain intensification, globalization of trade, human intrusion into ecosystems and urbanization, significant alterations in political regimes, conflict with accompanying breakdown of public health and surveillance infrastructure, voluntary or involuntary immigration, loosening of border controls, and hierarchy issues in related decision-making, and scientific advances that allow easier detection of zoonotic infections and evolution of novel susceptible immunocompromised populations. Pathogen-related factors include alterations in ecosystems and biodiversity that influence local fauna synthesis, favouring expansion of disease hosts or vectors, pressure for virulence/resistance selection, and genomic variability. Climate/environment-related factors, either localized or extended, such as El Niño southern oscillation or global warming, may affect host–vector life cycles through varying mechanisms. Emerging issues needing clarification include the development of predictive models for the infectious disease impact of environmental projects, awareness of the risk imposed on immunocompromised populations, recognition of the chronicity burden for certain zoonoses, and the development of different evaluations of the overall stress imposed by a zoonotic infection on a household, and not strictly a person.

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Speaking in (billions of) Dollars

The two distinct characteristics of zoonotic infections, their landscape epidemiology and their dynamic nature, have long been recognized but massively underevaluated [1].

The burden of zoonotic infections worldwide exceeds involves more than sheer morbidity and mortality, which are analysed for different zoonotic agents in other reviews in the present issue. The effect of zoonoses on various parameters of human life can be quantified, e.g. by estimating the economic impact of zoonotic epidemics, which, for the period between 1995 and 2008, exceeded 120 billion dollars [2]. Typical examples of the immense financial strain exerted on a country or a region by a zoonotic outbreak include the following: the effect that a plague outbreak in Surat, India in 1994 had on the country's trade and tourism, let alone the inner population immigration waves observed, with an estimated total cost of $2 billion, according to the WHO; the economic burden of cystic echinococcosis, which exceeds $1.2 billion annually regarding only the economics of human disease [3]; the effect that the outbreak of bovine spongiform encephalopathy had on the UK economy, exceeding $5 billion, and also on international trade agreements; the effect that a zoonotic agent that spread to humans and then from person to person had on a localized economy in

Toronto, Canada, resulting in a loss of 0.5% of the city's gross domestic product; and, finally, the enormous, still being evaluated, cost of the novel H1N1 influenza virus (another zoonotic agent that, after jumping species, evolved the capability for direct interhuman transmission) 2009 pandemic. One must not forget also that the majority of the category A and category B potential biological weapons [4] are of a zoonotic nature, and the costs of research and response preparedness for these agents are also significant.

The majority of recent infectious disease outbreaks in recent years have been zoonotic (either only in origin or in general behaviour) [5]. The extent of the zoonotic disease burden on human health is outlined in other reviews in this issue, and approaches hundreds of thousands of annual deaths and tens of millions of annual infectious episodes; however, these estimates comprise novel cases, and for certain widespread zoonoses, chronicity of infection with severe sequelae has been documented, and adds further to the morbidity/mortality burden. It has been widely acknowledged that dealing with the problem of zoonotic infections is a task that is beyond medical and public health specialists alone, and should include understanding of veterinary and environmental parameters, issues regarding human social behaviour and political changes, basic science-related aspects of pathogen life-cycles and evolution, and (for many of the zoonotic agents of importance) aspects related to vector life cycles and behaviour [6]. Understanding zoonotic infections as a multifactorial issue is critical, predominantly for preventing their expansion, in terms of geographical and social prevalence. Factors associated with this (either *de novo* or resurfacing) expansion can roughly be categorized as factors related to the pathogens and factors related to human behaviour. These factors are not independent: modifications of human behaviour result in modifications of pathogen ecology and life cycle in more than one pathway. Fig. 1 depicts the rough categorization of these factors and the interplay between them.

Factors Associated with Human Behaviour

These can be further subdivided into factors related to direct individual human activities, factors related to generalized trends in socio-economic and political status, factors related to scientific advances, and factors related to the indirect effect of human behaviour through environmental and climate alterations.

Individual human practices that predispose to zoonotic infections have been increasingly recognized in recent years as means of exposure to zoonotic agents. Such factors are often consequences of globalization and the ease of international travel. A typical example would be the expanding industry of ecotourism: urban citizens of the developed world who visit developing countries or rural areas of the developed world and engage in activities such as forest camping, river rafting, or bat cave exploring, are prone to zoonotic infections such as vector-borne rickettsioses, leptospirosis, and haemorrhagic fevers or lyssavirus-related illness, respectively [7–9]. Hunters are increasingly recognized as an important target group for zoonotic infections, through direct exposure to agents existing in the soil of forests/hunting areas in general, or through direct contact with and consumption of infected wildlife meat products [10]. A parallel situation may develop in zoos, aquaria, and agricultural fairs

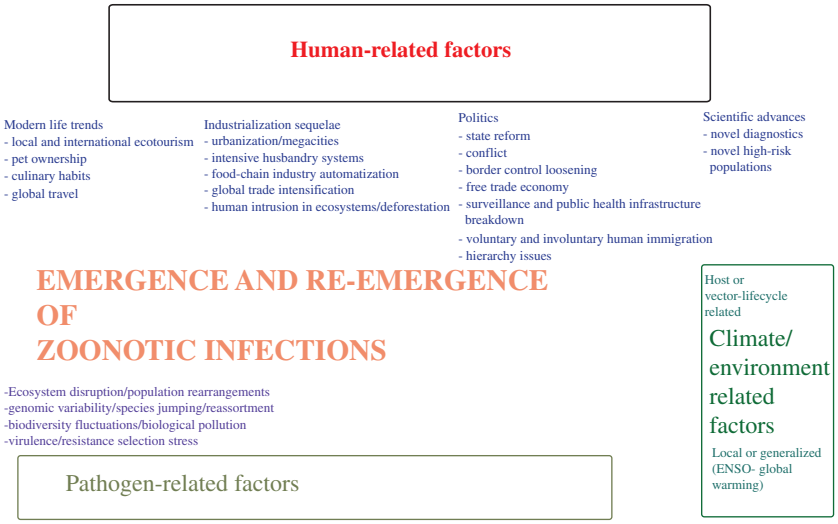

FIG. 1. Factors influencing the resurgence of zoonotic infections and their interplay. ENSO, El Niño southern oscillation.

(the latter being traditionally linked with *Escherichia coli* O157:H7 outbreaks in the USA).

Exposure to the culinary customs of developing countries (or rural regions of the developed world) often results in exposure to typical and non-typical (such as *Brucella*) foodborne pathogens [11]. Culinary practices that have emerged as fashionable in recent years, e.g. raw fish or even bushmeat consumption, have led to exposure of unsuspecting connoisseurs to unusual infectious bacteria and parasites [12,13]. The increased trend for pet ownership results in increased exposure to zoonotic pathogens, particularly with regard to non-traditional pets such as lizards and primates: the typical examples here would be the monkeypox outbreak in the USA, which was minimal in its impact on humans but extremely instructive about the pathways that zoonoses use to expand their horizon, and the increased incidence of transmission of *Salmonella* infections to children and young adults by reptilian pets—it was estimated that 11% of *Salmonella* infections in the under-21-year age group could be attributed to ownership of unusual pets [14]. One should also remember that animals that are illegally imported or inadequately screened during importation may actually be the norm [15]; that pets of healthcare personnel have been implicated in zoonotic healthcare outbreaks [16]; and that the effect of pet ownership on humans with particular predisposition to the development of zoonotic infections (see below) has not been adequately evaluated.

Socio-economic and political alterations in human behaviour have affected the prevalence of zoonoses through multiple pathways. The population of the world has been constantly increasing, resulting in increased demands for food, including meat; the industrialization of animal raising for food purposes and the intensive husbandry systems applied have resulted in the development of vast animal reservoirs in which an infection can spread from one animal to another and then jump species (a pathway that was theoretically implicated in the genesis of both SARS and pandemic influenza outbreaks); this is also the rule for the extensive, sanitarily challenged animal markets of the East. The need for increased livestock production also leads to the expansion of farming in previously non-inhabited areas, through deforestation for farm development or common breeding areas for livestock and wildlife species carrying a disease. The first was implicated in the pathogenesis of the Nipah virus outbreak in Malaysia, where the increased needs of the swine industry led to expansion of the industry to non-inhabited areas, bringing swine as amplifier hosts (and subsequently humans as dead-end hosts) in contact with a hitherto unrecognized bat virus [17]. The latter has been consistently demonstrated as the means of the continuing re-emergence of brucellosis in US cattle in the Yellowstone area through contact with infected elk [18].

In a similar mode, the need for more food has led to industrialization of the relevant sector, and this in turn correlates with the re-emergence of certain foodborne zoonotic pathogens [19]; the fragility of the food production chain as a geographically amplifying vector of zoonotic outbreaks is demonstrated by many of such recent episodes.

Apart from increased demands, however, industrialization, the development of megacities and generalized urbanization (2008 was the first year in which the majority of the human population was urban) [20] have led to a continuous encroachment of humans into previously uninhabited areas: this not only affects the ecology of wildlife habitats, unleashing dynamics that allow for zoonotic pathogen or vector predominance, as will be discussed later, but also directly brings essentially 'virgin' human populations into contact with a novel environment (including its zoonotic agents); thus, entering the Amazon forest or central African jungles leads to novel zoonotic outbreaks, some of which, as in the case of Ebola or Marburg virus, carry major mortality rates. The effect of human behaviour on climate change and environmental pollution is another example of a human-mediated pathway to zoonosis re-emergence that will be discussed subsequently.

Politics also exert a direct effect on the prevalence of zoonotic infections. The typical example here is the transition of numerous countries in recent years from communist, strictly state-controlled economies to free trade. This has led to the resurgence of numerous zoonotic agents, owing to less strict veterinarian and public health surveillance, but also to the recognition of hitherto undetermined/underevaluated zoonotic foci. Furthermore, when political transition was associated with conflict, as in the cases of the Balkan peninsula, the social substrate for zoonotic outbreaks became stronger, aided by factors such as famine, involuntary immigration of large human populations, and total breakdown and delayed redevelopment of public health and medical infrastructures: the Kosovo tularaemia outbreak, the entry of Crimean-Congo haemorrhagic fever into the area and the Balkan brucellosis resurgence are all typical examples where these factors coalesce [21–23]. Moreover, the end of the Cold War meant that borders were loosened, leading to easier illegal trading of infected animals, and thus zoonotic agents, through borders, and also to the resurgence of obscure agents becoming continental priorities: annual European Union (EU) trichinellosis rates, for example, almost tripled after the inclusion of Romania [24] in the EU, leading to the development of

novel priorities for the EU in terms of zoonoses. Adapting to novel realities is often not easy for the state: thus, the development of surveillance networks and interdisciplinary infrastructures that can adequately evaluate zoonotic trends and risks to human health often terminates in a 'who's in charge' question [6]. Even in politically stable states, politics exert an indirect effect: the relationship of socio-economic status with zoonotic disease prevalence has been repeatedly demonstrated, and extends far beyond the illustrative H5N1 avian influenza prevalence in rural areas where humans and poultry share the same space—even in the developed settings of the EU or the USA, a correlation of brucellosis incidence with gross domestic product [23] and an alarming, under-recognized prevalence of certain zoonotic infections in impoverished urban minorities [25], respectively, have been observed.

Immigration dynamics are of paramount importance in this respect: immigration, voluntary or not, is always a political issue related to socio-economic deprivation or conflict. However, the influx of novel populations with distinct epidemiological backgrounds results, when consistent and massive enough, in alteration of the epidemiological profile of the host country, and leads to new infectious disease burdens in unexpected settings: this is a trend that is constantly demonstrated, whether related to pathogens of major morbidity, as in the case of trypanosomiasis influx into Europe and the USA [26] or brucellosis prevalence in immigrants of Turkish origin in Germany [27], or to pure seroprevalence fluctuations, as in the case of toxoplasmosis in Greece and elsewhere [28]. Immigration finally serves as a vehicle for further indirect zoonotic importation; the first US victim of the novel H1N1 pandemic was a Mexican child visiting relatives.

Scientific advances are directly correlated with the increased zoonotic significance in various ways. Progress in diagnostics has allowed the recognition of novel agents that might have remained uncharacterized otherwise; these agents are often of borderline significance to human health, as is the case with obscure parasitic and viral causes of fever in Africa, but others demonstrate an increasing impact on humans. It has been shown that, for certain zoonoses at least, actual emergence is factitious, and what is really observed is diagnostic emergence (in either case, recognition of significance is the issue).

Science has succeeded in battling various other diseases and prolonging life-expectancy: thus, novel populations have emerged, and these populations, e.g. the elderly, immunocompromised patients treated for malignancies, patients who have undergone xenotransplantation, or AIDS patients, all belong to groups at high risk for certain zoonotic infections that otherwise would cause isolated cases of human disease. The absence of preventive policies for such patients (or patients with prosthetic devices) is a major public health and preventive medicine shortfall that will be dealt with in the final part of this review.

Factors Associated with Pathogen Characteristics

Each species of zoonotic origin that is able to induce human disease has a predetermined niche in its ecosystem, and a specific life cycle in which humans are usually intruders before being transformed into accidental hosts. Disruption of the ecosystem equilibrium is rarely, if ever, the outcome of direct pathogen characteristic alterations: typically, environmental, climate-related or human intervention factors are implicated, and the consequence of such intrusions is an amplification of the zoonotic agent's virulence, or population, or geographical effect—a schematic model would recognize thresholds for pathogen survival, persistence and amplification in a given ecosystem [29], with external factors modulating the survival tactics of the agent.

Environmental factors that might affect a zoonotic agent's prevalence and significance include alterations in biodiversity: it has been demonstrated, for example, that avian biodiversity exhibits an inverse correlation with West Nile virus (WNV) incidence in the USA, as the abundance of species that are similar to the natural host of the virus minimizes the possibility of vector contact with the virus, the so-called 'dilution effect' [30]. 'Biological pollution', on the other hand, the homogenization of fauna of diverse areas through human-induced animal translocation, has been a significant factor minimizing biodiversity in recent years [31]. However, biodiversity may act inversely on the long-term prevalence of zoonoses, by creating a niche that favours reassortment and species jumping.

The only pathogen-related factor that can be considered to be intrinsic is genomic variability, and this is particularly relevant to viral zoonotic agents, and specifically RNA viruses: their enormous mutation rate is essentially a factory producing the species that are most potently pathogenic for humans [32]. In the case of non-viral pathogens, environmental or human pressure can be exerted for selection of strains that are more virulent or resistant to available treatments (a characteristic that is also known for species jumping and is thus favoured by pathogen biodiversity), through the wide, often uncontrolled, use of antibiotics in veterinary medicine, and the non-selective, non-rotational use of pesticides (in the case of zoonotic vectors) [29].

Human intrusion in any ecosystem is disruptive, and the resulting disequilibrium may create a conservatory for zoonotic agents: deforestation is the most typical procedure implicated, drastically altering the geological, hydrological and biological characteristics of a given space, often replacing it with plantations with different ecological correlations, grazing fields, or rice plantations, or even new-built suburban housing. In each case, changes in the synthesis of the local fauna may result in significant increases in the population of a definite zoonotic agent host, which in turn may increasingly come into contact with humans (deforestation needs humans): an example is the resurgence of leishmaniasis in certain areas of Brazil, where replacement of natural forest with paper industry-suitable trees resulted in an ecosystem with different thresholds for previously existing species, and allowed the amplification of fox populations, which, in turn, served as natural *Leishmania* reservoirs, causing human disease in workers or recent settlers in the area [33]. Similar observations have been made for other pathogens, including the zoonotic *Plasmodium knowlesi* (a zoonotic potential has also been suggested in Brazil for *P. vivax* and *P. malariae*). An inverse procedure, reforestation, has been also implicated in Lyme disease emergence: this is not surprising, as reforestation is essentially another form of ecosystem disruption, allowing, according to its individual characteristics, the influx of specific animal populations, e.g. white-tailed deer in a particular case [34]. One has to remember that human 'developmental' intrusions need not be grand in scale to interrupt the balance of a specific ecosystem. Even simple road construction can have such an effect, through alteration of the hydrological characteristics and the ensuing creation of stagnant ponds that may act as zoonotic conservatories (e.g. favouring snail adaptation) [33].

The effect exerted by climate changes on zoonotic pathogen ecosystems is discussed in the following section.

Climate Change and Zoonotic Infection Resurgence

The effects of climate change can be local, regional (as in the case of El Niño southern oscillation), or generalized, as in the case of global warming.

A typical example of a local climate effect is the emergence of Sin Nombre virus in the USA: disproportionately heavy rainfall in a given area resulted in disproportionate vegetation growth, which in turn served as a dietary amplifier for a specific rodent population, thus leading to human exposure to large numbers of rodents and the emergence of haemorrhagic pulmonary syndrome [35]. Excessive rainfall and climate variability in general have been systematically demonstrated to precede Rift Valley fever outbreaks or haemorrhagic fever outbreaks in China [36]. Numerous other examples exist, but space limitations preclude further analysis.

Alterations in climate conditions on larger geographical scales have been recognized as inducers of zoonotic outbreaks, both in the case of El Niño southern oscillation [37] (which, in practice, also induces most of the local events described above), and for continental alterations, such as for fascioliasis or leptospirosis [38–40].

Global warming is an ecological emergency, but its implications for human disease caused by infectious agents remains understudied: It is well known that the mosquito life cycle is affected by temperature [33], meaning that a slight (1–2°C) increase in average summer temperature may allow mosquitoes to inhabit temperate zones, often carrying with them zoonotic agents for which they serve as vectors. Bird migration may be affected by global temperature alterations: birds seeking novel migratory routes may also transfer a novel zoonosis to a previously non-endemic area. The WNV 2010 outbreak in Greece may have been caused in this way, as a potential westward deviation of avian migratory routes, related to temperature alterations of aerial streams or modifications of temporary transitional niches, could explain both the past Romanian outbreak and the present one (one cannot expect these changes to develop year after year). In any case, zoonotic infections exhibit a tendency to move their ecological landscape westwards (this is typical for certain European emerging zoonoses, and also applies to WNV) and polewards, because of the gradual narrowing of the traditional temperate zones [41].

Projections for the Future

We can be certain that, as all of the aforementioned factors are unlikely to be moderated but will be probably intensified in the near future, the majority of future infectious disease outbreaks, caused by either novel or 'renown' agents, will be zoonotic, at least in origin. Is prevention therefore an issue? Regarding *de novo* agents, prevention is a paradox: going into the jungle to discover the next potential human plague means exposing humans to this potential plague. Regarding agents whose behaviour we are familiar with, one has to remember the need for a multidisciplinary approach that, as outlined above, extends to politics. Politics are strangely ignored when proposals for zoonotic control are brought forward; but it is politics that would regulate socio-economic fluctuations associated with disease resurgence, that would implement strict surveillance policies and public health

campaigns, and that should recognize the emergence of certain zoonoses and ensure the necessary funding for basic and applied scientific research.

Certain issues that need urgent clarification and further attention can be outlined:

1. Recognition of the need for pre-emptive studies on the effects of massive or smaller developmental projects on local animal fauna and local zoonotic reservoirs. This is an inadequately explored idea that was partly introduced by McSweegan many years ago [42], the so-called 'infectious diseases impact statement'. Environmental studies are compulsory in such projects, but almost never extend to/always fail to predict an outcome that is typically associated with zoonotic (or infectious disease in general) emergence.
2. Recognition and enhancement of the health literacy of special populations that are at increased risk for the development of zoonotic infections [43]—these populations need information about the precautions that they should take regarding their dietary practices, potential pet ownership, and exposure to diverse ecosystems in the form of minor rural vacations or international travel. It is disheartening that, even today, most patients with a prosthetic heart device or an underlying cardiac anatomical disorder are unaware of the risks posed by raw dairy product consumption or direct contact with sheep and goats in areas endemic for brucellosis and Q-fever (G. Pappas, unpublished data).
3. Recognition of the major long-term burden induced by certain of these diseases with a chronic phase: a person exposed to *Echinococcus granulosus* in his native land as a child, who then migrates for socio-economic reasons to a developed country, may need decades to exhibit any symptoms, and is unlikely to be diagnosed accidentally, as annual medical check-ups are not included in the usually poor/non-existent healthcare of illegal immigrants; this person is likely to seek medical attention only in an emergency (hydatid cyst rupture) or when the hydatid cyst is too large to not cause space-occupying symptoms. Clinicians in country that is non-endemic for cystic echinococcosis should be prepared to recognize the long history evolving in such patients and the extreme costs, mentioned in the introductory section, that will be passed on to the host countries.
4. Planning any intervention is difficult, for financial and scientific reasons. The burden of many of these diseases remains unrecognized, as disability is often mentioned in anthropocentric units; instead, any zoonosis imposes a threat to the family as a unit—exposure is likely to be common for members of a household, particularly in agricultural settings, and animal loss (owing to the disease or state regulations for sick animals) may have a significant impact on the economy of the household, which is further worsened by the often observed inadequate access to appropriate medical treatment for the human patients themselves (imagine the scenario in any impoverished or conflict-active region of Africa or Asia). The disability-adjusted life-year is not always a suitable unit [44]. Also, ambitious eradication campaigns are not always feasible when all of the aforementioned issues have not been taken into account, and neither are successful elimination campaigns, as these may have temporary positive results but subsequent surveillance degeneration, leading to zoonotic resurgences, usually with some twists.

Transparency Declaration

Conflicts of interest: nothing to declare.

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