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Viral Evolutionary Ecology: Conceptual Basis of a New Scientific Approach for Understanding Viral Emergence

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1. Introduction

Kilbourne first applied the term of Molecular Epidemiology in 1973 in a paper on influenza [1], since then the term has been extensively used for other diseases caused by viruses [2-4], bacteria [5-7], parasites [8-10] and even non-infectious diseases [11, 12]. Molecular epidemiology was subsequently accompanied by a more integrative definition of eco-epidemiology [13, 14] with little impact in scientific literature.

Although molecular epidemiology and eco-epidemiology are important in the understanding of disease and disease emergence [15, 16], we postulate here that the medical science community needs to consider a new conceptual approach to epidemiological studies of emerging infectious diseases (e.g. viral diseases). Emerging viral diseases are mainly caused by RNA viruses whose transmission cycles involve the ecological interaction with several actors and the evolutionary responses through time.

The new approach called Viral Evolutionary Ecology (VEE) [17, 18] combined with epidemiology will help us to better explain many emerging viral diseases by encompassing the complex interface between such factors as genetic structure, evolutionary biology and ecology of pathogens [19], and environmental aspects such as biodiversity, society, and human impact on natural ecosystems, all of them closely interplaying in ways often as yet unknown [20, 21]. This complimentary approach has been previously considered under the field of Evolutionary Epidemiology [22-24], however, the impact in the study of viral emergence needs to be highlighted.

Under the VEE framework where the real actors are the viruses instead of human beings, we can recognize our main role in disturbing the environment and offering conditions for new

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viruses to emerge. Viruses do not live for causing disease to humans, animals, plants or other organisms, they are simply naturally selected to increase their viral fitness, a process in which ecology and evolutionary biology play the main role, so viral emergence and disease are mere consequences of this dynamic.

In this sense, public health problems (e.g. several viral diseases) are the unexpected consequence of new ecological niches promoted by human actions on natural systems. In Luria's words "…each virus disease is potentially a different form of virus life…" [25]. Over the last 10 to 15 thousand years, humankind has been changing the planet, triggering the "Butterfly Effect" with dramatic alterations [26], producing new ecological landscapes called emerging or novel ecosystems [27], and the subsequent emergence of viral diseases.

Today, emerging viral diseases caused by respiratory, encephalitic and haemorrhagic viruses, and others like AIDS, have a severe impact on public health and economy not only in developing countries but also worldwide [28]. It is necessary to integrate current knowledge on VEE, with epidemiological and surveillance programmes to assess new public health policies.

2. The study of risk factors and eco-epidemiology

Epidemiology is a field focused on estimation of distribution and frequency of risk factors, prediction of the public health impact, and finally, offering control and prevention strategies for reducing the effects of disease in human populations [29]. In a restricted sense, the emphasis of this scientific discipline is directed to the study of factors, in a closer contact among the infectious agent with humans, such as social, cultural, biological, environmental, etc.

The causes underlying the rise of disease are at macro (socio-cultural) and micro (cellular and molecular) levels, but they are indeed acting over the individuals, populations and communities [30, 31]. There are several lines of evidence on the relationship between natural ecosystems intervention and re/emergence of diseases produced by bacteria, parasites and viruses [32-37]. Specifically, for understanding viral emergence it is important to understand the sylvatic cycle of viruses, the transition to human populations, the relationship between vectors, pathogens and reservoirs in wildlife ecosystems, the change in the distribution of vectors and reservoirs after natural habitat fragmentation, and how these conditions are generating potential new roles and ecological niches for species.

Wild ecosystems historically disturbed by agricultural and industrial activities with changes in biotic and abiotic factors (water bodies distribution, soil profiles, plant coverage, breeding microclimate, vertebrate and invertebrate populations, etc.) [38], constitute new selective pressures for pathogens and therefore new opportunities for adaptation [39]. It allows vectors/reservoirs to exploit the new resources, favouring viral contact with potentially new host populations (humans). In fact, evidence of distribution and abundance of mosquitoes in intervened areas demonstrates the high frequency of endophilic species and parasites transmission [34, 40-42].

For instance, blood-sucking mosquitoes may constitute the connectors between real and potential transmission cycles as they allow arboviruses (Arthropod-borne Viruses) to

circulate in different geographical regions [43], involving human and wild reservoir species (mainly Rodentia and Didelphimorphia) [44-46].

On the other hand, Eco-epidemiology has been defined in two ways: first, as a paradigm that can integrate multiple levels of causes to reconsider the risk factors for disease in a human population [14, 30]; second, as the study of ecological effects perceived as having adverse effects on populations, ecosystems and the services provided by nature [13, 47, 48]. Despite the breadth of the eco-epidemiological approach, interactions of the virus-vector-host triad, their complex cycles, incidence and prevalence of diseases in geographic areas, ecological dynamics and historical (evolutionary) factors must be considered using a more integrative approach that helps us to predict the pathogen distribution and potential emergence of disease.

When a virus is introduced into a new host population, or quickly expands its range with a corresponding increase in cases of the disease, it is considered an Emerging Virus [36, 49]. There are three ways for a virus to emerge: *De novo* evolution of a new virus; the introduction of an existing virus from another species; and spread of a virus from a smaller population in which the virus may have previously emerged or have been introduced [50]. In any case, emerging viruses are descents from those lineages that circulate naturally.

The study of emerging viruses is often invoked by Molecular Epidemiology, using phylogenetic methods to infer the origin, emergence, spread and disease dynamics [16, 39, 51]. Evolutionary and ecological dynamics of emerging viruses are so linked that viral diversity is correlated with the epidemic dynamics [52].

Although Epidemiology considers the risk factors and Eco-Epidemiology introduces ecological factors under causal thought, it is still necessary to include the evolutionary variable, which is the goal of the VEE approach.

3. Viral evolutionary ecology

Viruses are not considered living beings but biological entities that evolve [53], and depending on the population size, their evolution can be determined in a higher or lower proportion by genetic drift or natural selection, respectively. Considering a natural transmission cycle of a virus between hosts, maybe involving an invertebrate vector, it is expected that adaptive evolution allows an efficient replication of the virus in such an environment [54]. If the ecosystem is stable and the transmission cycle has been established for a long time, it is expected that the rate of infection and mortality does not critically affect the host population [55]. The genetic background of current viruses evolved in such conditions possibly reflects the interaction of their ancestors with the whole environment, being better explained by an evolutionary ecology approach.

Ecology studies contemporary interactions, while Evolutionary Biology is concerned with historical issues. In this sense, Evolutionary Ecology is focused on the integration of these two disciplines to understand the most complicated issues, for example the causes of abundance and distribution of organisms, in relationship with abiotic and biotic dynamical variables [56-58].

VEE studies the impact of the evolutionary response of viruses to the hosts, and other interacting environmental factors, which are shaping their observed diversity and distribution patterns [18]. Although the role of evolutionary processes in driving viruses to new or more severe outcomes of diseases is known, the study of ecological and historical scenario, in which pathogen–host interaction evolves, is not always so well considered. VEE is becoming necessary for understanding and explaining the different patterns of disease in the human population, like acute-to-chronic [59], asymptomatic-to-lethal infections [55, 60] and the emergence of new viruses in humans [61, 62].

Under VEE, the virulence of pathogens is conceived as a process, in which a specific genotype or lineage is selected, which is translated into differential fitness and expansion of the disease [63]. The potential change in virulence resulting from selective pressures imposed by changes in host ecology has motivated the introduction of a new dimension within the objectives of epidemiology, incorporating ideas from the evolutionary ecology of parasites [64].

Viruses necessarily use the cellular machinery for their life cycles, however, the cell is only one component of the whole environment a virus has to face. Depending on the virus, a specific life history commonly involves replication in a specific cell type and tissue, the survivorship of viral particles in the external environment and specific transmission mode (e.g. aerosols, arthropod vectors, etc.) [65]. These features are some of the components of the Hutchinsonian niche of a virus allowing adaptation through time [66]. If every feature above is taken into account, virus-derived problems to humans could be easily understood, not like a virus-derived but a human-derived virus-driven problem (disease and/or disease emergence).

Several processes, such as transmission, host-shift, co-evolutionary arms race, resource tracking, competitive interactions and life histories, highlight the importance of ecology to explain past and current variation and distribution of viruses. Variables, such as host species, host density, competition with other viruses, genetic trade-offs on adaptation and physicochemical conditions, determine transmission and the final success of a virus in a specific host [67].

At present, the geno/phenotype of viruses is being challenged to overcome new changes, such as new host availability and loss of the original ecosystem. Thinking about the high diversity and adaptive potential of viruses, mainly because of their high mutation rates, large population sizes, short generation times and population dynamics [68-70], we expect from novel host and/or vector availability the adaptive evolution of new genetic variants in viral populations capable of exploiting the new environments and emerging in new transmission cycles involving new actors like humans, domestic and even wild animals.

Let us consider the AIDS epidemic whose responsible viruses are HIV-1 and -2. It was estimated that SIVs (Simian Immunodeficiency Viruses) had been circulating in African monkeys for at least 32,000 years [71] and HIV probably originated from them in the 1930s, with the most common recent ancestor (MRCA) estimated by mean of molecular clock analysis and coalescence theory, and the jump of species barrier probably due to the confluence of several factors [72].

Several hypotheses have been postulated to explain the emergence of HIV epidemic in humans. The first one related to hunters killing monkeys, natural reservoirs of SIV in a non-pathological relationship. The increase of dead monkeys in the forest and several events in Africa such as civil wars, human displacements, sexual violence, poverty and prostitution, could have produced an increase in size of SIV populations, contact between monkeys, their products and humans, altogether leading to the jump of SIV to human beings and originating the pandemic virus of the Twentieth Century [73].

On the other hand, not all SIV strains in Africa are closely related to posterior epidemic HIV strains. It was recently found that several GUD (Genital Ulcers Diseases, like syphilis, chancroid and lymphogranuloma venereum), prostitution and possibly lack of circumcision in African human populations, could have favoured the jump of species barrier or host-shift of SIV from monkeys to humans [74].

It could be more comprehensible using an illustration that represents the multidimensional space (hyper-volume) of environmental factors, that affect the performance of a species, as postulated by Evelyn Hutchinson [75]. In Figure 1, these n-dimensions are converted into only three coordinates for clarity. Performance of a viral species or genotype can be represented by a mountain (adaptive peaks in Simpsons' conception [76]), in which every peak corresponds to the maximum viral fitness of every viral species, or the maximum number of viruses produced by that specific genotype or species. Taking into account that fitness is a relative measure, viral fitness could change through evolutionary time as environmental conditions also change. Viral species in this model move over the surface of the adaptive landscape. If adequate environmental factors converge, the species could have real existence.

In our example, there are two mountains representing two viral species (Species A and Species B), existing in two different lapses of evolutionary time and infecting two different hosts (Sigma and Phi), respectively. Species A is the ancestor and could have originated Species B by successful adaptation after colonization of a new host. The probability of Species A exploiting the new host species (Phi) could be null (zero) or maximal (one). When environmental conditions dramatically change, as mentioned above with SIV, the probability of the Species A jumping to the host species Phi and the opportunity for adaptation to this new host are very high. The resulting virus (Species B) playing a new role in the ecosystem (new ecological niche) can be considered an emerging virus.

The trajectory of the virus jumping from one species to another could be represented using a curved arrow, in which fitness decrease is associated with poor adaptation to the new host at the initial contact [77]. After this process the adaptation allows a gradual fitness increase up to the highest peak, in which the phylogenetic nearness of the donor and the recipient host species is extremely important [78].

Figure 1 has the limitation of assuming that Species A disappears once the adaptation to the new host occurs. This is not always true as this ancestral virus could continue infecting the original host (Sigma) and co-exist with the descent virus (Species B) in evolutionary time. The same has occurred with emergent HIV and contemporary SIV strains, closely related to the ancestor of HIV.

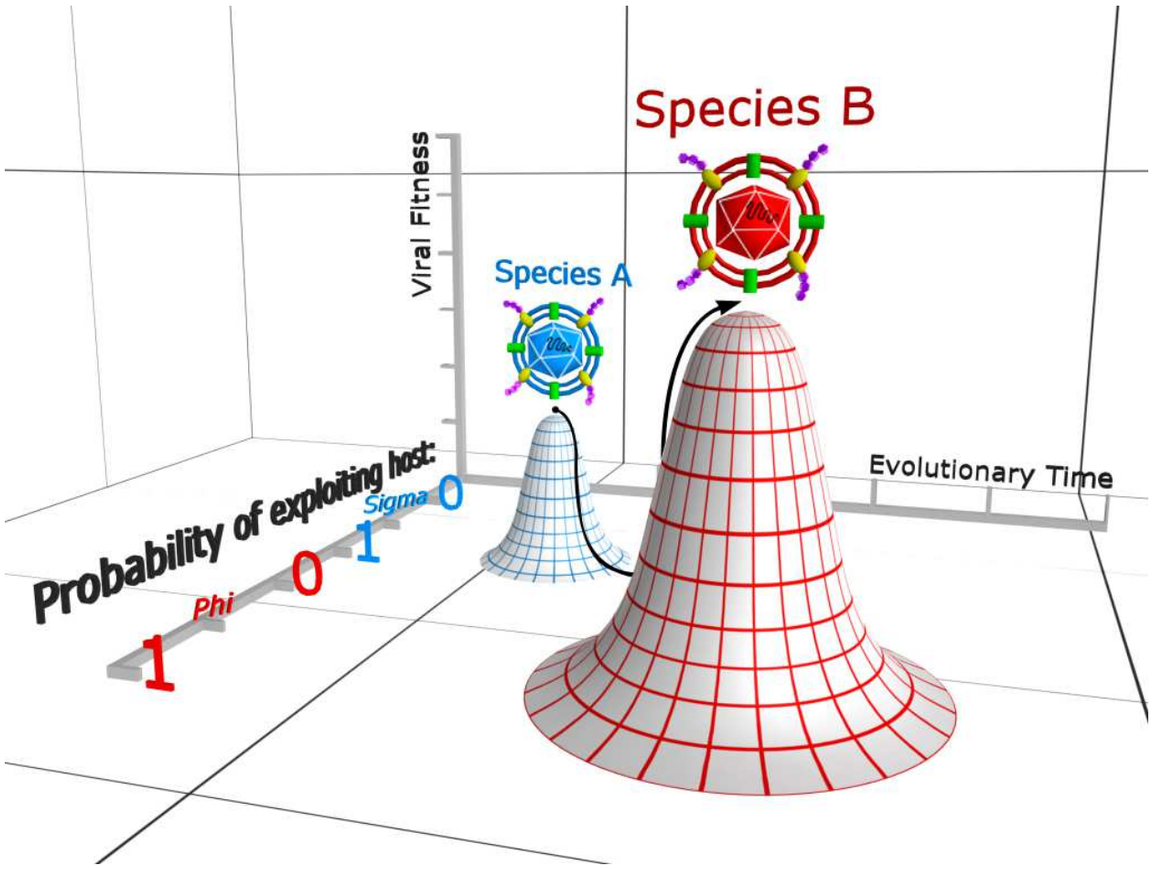

Fig. 1. Ecological niche, adaptive landscape and the jump of species barrier: adaptive landscape representing the fitness of two viral species (A and B) in their specific hosts (Sigma and Phi, respectively). Species A is the ancestor of B, generated after colonization of a new host species (Phi). The probability of Species A exploiting host Phi could be null (zero) or maximal (one) and depends on n-dimensions of the environment. Viral emergence occurs when species B originates from adaptation of the species B to the new host, with a new ecological niche.

4. The new multidisciplinary and integrated approach: Viral emergence using the VEE framework

Over the last 50 years of virological research, many fine details in the cellular and molecular biology of viral infection, immunology, viral morphogenesis and other topics have been elucidated. In spite of these tremendous advances, the interface between intra-host and inter-host dynamics has not been so well addressed. The causes and process of emergence of viral diseases have to be necessarily studied at the genetic and ecological levels in which several factors related with the ecology and evolutionary biology of pathogens, hosts and the pathogen-host relationship are undeniable.

In natural ecosystems, many viruses have natural transmission cycles, involving vectors and wild reservoirs, however, transformation of the landscape leads to changes in their

abundance and distribution [79, 80]. With these changes, some viral species could exploit the ecological resources, adapting to new hosts (e.g. humans), making possible the emergence of viruses [78, 81].

Viruses exist in a high variety of ecosystems, in which numerous elements are implied in their trafficking and disease dynamics [80]. An important group of viruses implied in emergent and re-emergent diseases belong to the families *Togaviridae* (genus *Alphavirus*), *Flaviviridae* (genus *Flavivirus*) and *Bunyaviridae* (genera *Orthobunyavirus* and *Phlebovirus*) [32, 35-37]. These viruses are transmitted by haematophagous arthropods, mainly mosquitoes (Diptera: *Culicidae*). The family *Culicidae* of insect vectors is often associated with sylvatic areas, historically modified by human activities like artificial landscapes (agriculture, livestock, mining, house building and urbanization) [32, 35-37].

Viral diseases are the evolutionary consequence of our historical landscape alteration. Considering the very ancient origin of SIV (several thousands of years), the recent emergence of HIV (1930s) and the Acquired Immune Deficiency Syndrome (AIDS) as a new pathological entity, viral disease emergence can be considered as an evolutionary event, precipitated by changes in landscape ecology, due to human activity after the rise of agriculture (10 to 15 thousand years ago) [82]. If the ecological niche for species A (in Figure 1) is represented by the corresponding mountain, then new variables will be shaping the ecological niche for species B.

SIV has been infecting monkeys in Africa over thousands of years and HIV has recently arisen by SIV jumping and adapting from monkeys to humans. In this sense, the HIV epidemic could have been due to successful colonization and virus adaptation to the new host, and several other factors mediating transmission in the last host, all of them allowing the generation of a new ecological niche.

It is important to establish the phylogenetic relationship between virus isolates from different geographical regions (phylogeography), emphasizing the fact that ecological factors could explain the presence of a virus in the ecosystem and the necessary interactions for potential emergence (niche). Landscape ecology studies how landscape structure affects the abundance and distribution of organisms [83-85]. Combining landscape ecology with VEE will be a powerful tool for understanding the epidemiology of viral diseases that have devastating effects on the human population.

For epidemiology, it is important to identify any emergent pathogen for establishment of public health policies. It is worrisome that viral diversity in wild tropical areas is almost unknown. It is necessary to establish new and fast tools for taxonomic identification of both viruses and their arthropod vectors [86]. The study of ecologic variables mediating the transmission cycle (viral trafficking) will be useful in finding patterns and predictive factors for the emergence of new viruses.

VEE studies the responsible elements for maintaining viral circulation in wild ecosystems, as well as the patterns generated from ecosystem perturbation, which determine the convergence of conditions (ecological and evolutionary) in the new or emergent ecosystem favouring the co-existence of viruses, reservoirs and vectors [79, 87], and mediating viral disease emergence.

5. Conclusion

Emerging viral diseases are seriously affecting human populations and our current epidemiological tools are insufficient to explain the emerging process. Viruses are not living organisms, but they have genomes and their evolution is governed by the same factors driving evolution in all other living beings. The emergence can be well understood as a biological process by applying concepts of evolutionary biology such as adaptation. If we also consider the environmental changes enabling new selective pressures (novel ecosystems), we can expect the appearance of new virus-host interactions (ecological niches). Therefore, epidemiological and evolutionary ecology studies must be integrated to obtain a better explanation of viral emergence and establishment of measures for the prediction and control of these devastating diseases.

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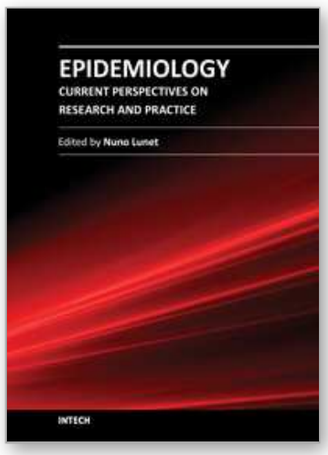

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This special issue resulted from the invitation made to selected authors to contribute with an overview of a specific subject of their choice, and is based on a collection of papers chosen to exemplify some of the interests, uses and views of the epidemiology across different areas of research and practice. Rather than the comprehensiveness and coherence of a conventional textbook, readers will find a set of independent chapters, each of them of a great interest in their own specialized areas within epidemiology. Taken together, they illustrate the contrast between the attempt to extend the limits of applicability of epidemiological research, and the "regular" scientific activity in this field or an applied epidemiology. Epidemiologists with different levels of expertise and interests will be able to find informative and inspiring readings among the chapters of this book.

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