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What to expect from a viral emerging epidemics: the Brazilian experience with the Zika virus

O que esperar de uma epidemia viral emergente: a experiência brasileira com o vírus Zika

Qué esperar de una epidemia viral emergente: la experiencia brasileña con el virus Zika

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ABSTRACT

Introduction: The transformations that the world population has been going through as a result of the processes of globalization and urbanization have also changed the dynamics of transmission of many infectious diseases, as well as their epidemiological profiles. In this context, this work proposes a reflection on the evolutionary aspects of emerging viral pathogens and factors that can contribute to reemergence events. **Outline:** This article brings reflections from the authors about the scientific literature, addressing ecological and evolutionary factors that may occur in cases of viral emerging pathogens according to the experience acquired after the Zika epidemic in Brazil. **Results:** The evolutionary mechanism by which viral agents evolve and acquire new structural and pathological properties also contributes to the decline in the number of cases in conjunction with preventive measures; and the biological diversity of vectors and possible candidates for intermediate hosts represents a factor that can contribute to the occurrence of epidemic events of reemergence. **Implications:** Analyzes focusing on the evolutionary aspects of viral agents can contribute to the early recognition of new symptoms, and identification of possible candidates for reservoir hosts, consequently, contributing to the prevention of reemergence events.

DESCRIPTORS

ZikV; Biological Evolution; Emergent viruses; Epidemics.

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INTRODUCTION

The zika virus, is a biological entity that belongs to the viral genus flavivirus which currently possesses substantial medical concern due to the last outbreak in the Americas of an acute viral disease known as zika fever which is transmitted by the mosquito *Aedes aegypti* and has been associated to numerous outbreaks of microcephaly in many countries of South America, mainly in Brazil, being considered a public health problem due to the amplitude of the distribution of the vector.[1]

In Brazil, the fever caused by the zika virus became a disease of compulsory notification since the decree of the ordinance 204 from February 17th of 2017 by the Health Ministry[2], reinforcing the World Health Organization recommendations from 2016 [3] Demonstrating national and international concern regarding the new features added to the natural history of the disease, including transmission routes, clinical severity, congenital malformations, autoimmunity, and neurological complications, along with the absence of information about the risk factors, periods of disease (incubation, disease, transmissibility and cure periods), pharmacological treatments options, the ambiguity of the laboratorial tests for the diagnosis, strategies for vaccine development, interactions of the zika virus with other arboviruses and control of the vector.

Highlighting, that some of the gaps raised by the world health organization such as microcephaly and neurological disturbances related with the zika have been reported by several scientists that demonstrated by molecular assays, animal models and clinical/pathological analysis, the association between these conditions and the virus.[4-7] In this context, this work aims to present perspectives on the driving forces of evolutionary processes and what to expect from a viral epidemic or pandemic in a large and genetically diverse population such as the Brazilian concerning the viral evolution.

ZIKA FEVER EPIDEMIOLOGY IN BRAZIL

According to secondary data from the Vigilance in Health from Brazil, [2] 210,886 zika fever cases were registered in 2016 and 15,518 cases in 2017, with the highest number of cases recorded in 2016 in the Southeast n=91,340, Northeast n=72,972 and Midwest n=33,661 regions, and the lowest in the South n=821 and North n=12,072. While in the year 2017, the highest number of cases were recorded in the Midwest region n=5,569, followed by the Northeast n=4,562, Southeast n=2,878 and North n=2,438 regions, remaining the South region n=71 with the lowest number of registered.

However, the number of cases is not a very safe indicator for the analysis of disease distribution in each region of the country, since it is a parameter that considers only the frequencies of cases, disregarding the size of the populations in each region. What makes the incidence an epidemiological measure more appropriate for the formulation of information about the new cases of zika fever in the population of each Brazilian region in the time interval analyzed, also becoming more suitable for the formulation of the hypothesis regarding the outbreak in Brazil.

In the year of 2016, the incidence of zika fever in the country per 100,000 inhabitant was 102.3, and the Brazilian regions with the highest incidence were the Midwest, with a value of 214.9, Northeast with 128.2 and Southeast with 105.8, and those with the lowest incidence were North with 68.2 and the South with 2.8, while in the year 2017 the incidence per 100,000 inhabitant in the country fell to 7.5, with the highest rates in the Midwest 35.6, North 13.8 and Northeast 8 regions, and the lowest incidence values were recorded in the South 0.2 and Southeast 3.3 regions.

These secondary epidemiological data suggest that a genetic or environmental protective factor against the infection might exist in the population

from the South region such as addressed by Karlsson et al. and Costa et al.[8-9] regarding the resistance and susceptibility to infection, what should be better investigated. In addition, it is possible that the epidemiological services from this region might have had problems with under notification of cases, as reported in the northeast region mainly regarding the States of Bahia and Pernambuco in the year of 2015.[10]

Highlighting that the immunological responses of the host against the pathogen represent a driving force for the biological evolution as addressed by the hypothesis of the red queen that describes the co-evolution of pathogens and their hosts in a cyclic dynamic where the infectious agent evolves to overcome the host immunity, and the host evolve to resist the pathogen.[11] In this sense, the epidemiological data show that the zika virus had numerous opportunities to evolve.

DRIVING FORCES OF THE BIOLOGICAL EVOLUTION

The zika virus is known as the etiological agent of a febrile disease of vectorial transmission which is in most of the cases self-limiting and does not imply risks to the life. However, after the outbreaks in the years of 2015-2017 in the American continent, many cases of microcephaly and Guillain-barre syndrome post-viremia were reported as well as different routes of transmission which include the sexual route, the vertical from mother to child and from blood transfusion.[12]

Along with this new features observed in the natural history of the zika disease, many molecular differences between the viral genome and protein structures of strains before and after the outbreak were detected, evidenced by mutation seen in phylogenetic analysis,[13] as well as in studies showing new proprieties of proteins such as the E-protein as resistance to temperatures from the order of 40°C due mutations resulting in the formation of hydrogen bond between the residues Gln350 and Thr351;[14] In addition, biochemical studies demonstrated accentuated neurotropism in the zika virus because of a glycosylation of the residue Asn154,[15] as well as increased ability to evade the immune response due to mutations in the NS1 protein, which enhanced the ability of the virus to infect the human organism.[16]

These new biochemical and pathological properties can be seen through an ecological and evolutionary perspective, where the competition between different arboviruses for human hosts might be considered an important biological factor that could have promoted evolutionary processes responsible for the features of the cases observed of zika fever in Brazil.

According to Waggoner and Pinsky,[17] the ZIKV presents distribution throughout areas of the world where DENV is common (including Brazil), and the association between ZIKV and microcephaly can probably be a consequence of its introduction into a ZIKV-naive population, or in a population with unique patterns of flavivirus immunity due to prior exposure to the DENV or other flaviviruses that may act modulating the ZIKV pathogenesis.[12]

Still following the same line of reasoning, it is significant to point out that an Asian strain of CHIKV was introduced into the Americas through the Caribbean in 2013, and the first autochthonous Brazilian cases were reported, and, in the same year, other strain of CHIKV from the east, central and south regions from Africa were detected in the State of Bahia, then both strains (African and Asian) were detected in different Sates from Brazil[18], highlighting that the ZIKV epidemic occurred in concomitance with the outbreak of CHIKV in the country.

In this sense, in countries such as Colombia, the French Polynesia and New Caledonia, cases of ZIKV co-infection with other arboviruses such as DENV and CHIKV have already been reported,[19] emphasizing that the ZIKV co-circulation and co-infection with other viruses represents a factor of inevitable and unpredictable impact on the host immune system response. Moreover, it also represents a challenge in the diagnosis and vaccine development to the control

of the disease due to the substantial genetic and biochemical similarities among the flaviviruses,[20] and the evolutionary pressure the immune system impose over the viral pathogens.

On the other side, the ecological interaction of the zika virus, the vector, and the host; where different viruses also competing for the same vector should be addressed as other process in favor of the biological evolution of the organisms involved in the trio described, thus possibly impacting the transmissibility rates.

According to an experimental study performed by Göertz et al.,[21] it is demonstrated that the mosquito *Aedes aegypti* is competent to transmit both viruses- chikungunya, and zika- simultaneously, but the insect is more efficient in transmitting the zika virus, due to the salivary gland of the mosquito that functions as a stronger barrier to chikungunya and a weaker one to ZIKV at the moment the insect is feeding, giving suitability to the hypothesis that the introduction of the ZIKV in the America required some degree of genetic adaptation from the ZIKV to the vector, also providing a positive effect in the transmission to humans.

In this context, it is possible to observe this positive effect by the different values of basic reproductive number (R0) of the ZIKA, as calculated in a Brazilian state where the DENV is endemic (In Rio de Janeiro ZIKV R0= 2.33; DENV R0= 1.70),[22] as well as values higher than 1.0 found in different localities such as Salvador with a mean Ro of 4.3, Suriname with Ro of 6.0,[23] and in the Barranquilla in Colombia where a value of R0 equal to 3.8 was estimated.[24]

Highlighting that there are experimental demonstrations that the virus can infect non primates, and South America has a huge diversity of non-human primate[25-26], mainly in Brazil[27], where the susceptibility of these animals to infection by the ZIKA implies the possibility of re-emergence events due to the role of these animals as reservoirs of disease.

MOLECULAR EVIDENCE OF THE ZIKA VIRUS BIOLOGICAL EVOLUTION

Once inside the host, the virus binds to its cells through the envelope E protein, which is the largest surface protein of the virion and has the function of adhesion, internalization, fusion, and entry of the virus into the cell membrane, being this protein arranged on the surface of the viral capsid with anchorage mediated by transmembrane helices in the external portion of the phospholipid bilayer derived from the host cell that surrounds the capsid, giving it a spherical shape when observed by electron microscopy.[28,13]

In this context, the E protein presents three-dimensional conformation composed of three distinct domains rich in beta-sheet, which are: The domain I that possesses a ß-barrel type motif; the domain II presents itself as an elongated finger and has a coil of 48 residues that connects the ectodomain ZIKV-E stably folded with the C-terminal transmembrane anchor; and the domain III that is similar to an immunoglobulin.[29] Existing different glycosylation profiles between the viruses of the family Flaviviridae and between the strains of ZIKV.[13] Pointing out Kostyuchenko et al[14] that glycosylation in the position Asn154 makes the Zika virus phylogenetically closer to neurovirulent viruses such as the Japanese encephalitis virus and the virus from the west of the Nile.

In this sense, it is important to note that the Zika virus has a high capacity for homologous recombination, that is, it is a virus capable of producing numerous variants of the same protein but conserving its structure, however, giving it new functional properties[13] that can increase its adaptability to the vector or increase the virulence towards the host.

Therefore, the widespread occurrence of microcephaly in the American continent suggests the possibility of mutations involving glycosylations as described by Kostyuchenko et al.,[14] or phenotypic variations of the E protein with properties similar to

those observed in the E protein of other viruses with greater neurotropism.

In this context, Wang et al.[13] detected mutations conserved among the genomes of Zika strains, and mutations which are specific in determinate strains, such as the mutations in the positions 550, 1143, 1209 and 2831 that are present in the strains variants of the Asian strain ZIKV2015; and the Brazilian strain NatalRGN possesses unique mutations in the positions 940, 1027 and 2831, and the ZIKV strain BeH823339 that has mutations specific in the positions 337, 354, 358, 545, 984, 1440, and 2800. Indicating that after the entry of the pathogen in Brazil, the virus differentiated from the primary strain and acquired new structural and pathological properties. What is confirmed by other phylogenetic analysis of different strains isolated in the Latin American that revealed diversification of the virus into at least five different genetic clusters, been also found substitutions of amino acid found in the E protein and the membrane protein.[30]

Kostyuchenko et al.[14] also demonstrated that a mutation resulting in the insertion of Ala340 at the terminal position of the domain III enables the protein to form hydrogen bonds between the Gln350 and Thr351 residues between the CD-loop portions close to the domain III, which provides greater thermal stability to the E protein at temperatures close to 40°C, maintaining the viability of Zika virus in hostile environments such as saliva, semen, and urine, allowing the possibility of sexual transmission due to maintenance of the viability of the viral particles after the febrile episode, especially in the testicles where the immunological nature of the organ enables the virus to be transmitted sexually. Highlighting that there is also the report of transmission through breastfeeding.[10]

Emphasizing that the mutations and phenotypic variations detected in the E protein of the zika virus are relevant since this protein is responsible for binding the virus to the target cells and also for activating the inflammatory response, which is the cause of the symptoms, where the regulation of the adaptive immune response, mediated by the presentation of antigens by leukocyte with subsequent production of antibodies and cytokines may be associated with the Guillain-barré syndrome, while the activation of the modules responsible for the apoptosis regulation in glial cells may be associated with microcephaly.[13]

WHAT TO EXPECT FROM EPIDEMIC EVENTS OF VIRAL PATHOLOGIES

Considering the points exposed above highlighting that in Brazil other arboviruses compete for the same vector, the host population is large and has great genetic diversity, in the case of an emerging virus such as the ZIKV during the epidemic from 2015 to 2017, It is expected the generation of new variants of greater virulence and pathogenicity in the course of the epidemic event.

Because naturally, the viruses in their replication process generate mutants which in most of the cases are incapable of being transmitted and to cause disease between hosts. These mutants are eliminated from the viral population by stochastic events called bottlenecks, which initially reduce the viral diversity by genetic drift mechanism when the bottleneck is narrow in the host population. What ensures the exclusive interaction between variants with high transmissibility and pathogenicity to the host (and vectors in the case of arboviruses), then these variants are subject to refinement processes through the selection imposed by environmental factors, the immune responses of the host population, environmental stresses, as well as competition with other infectious agents.[31-32]

Moreover, it also should be noted that when the bottleneck in the host population widens, there are cumulative increases of defective mutations due to the mullers ratchet effect,[31] that along with factors such as reduction of susceptible individuals to infection in the population because of death or

acquired immunity and behavioral changes, that contribute to the end of an epidemic.[9]

However, in the evolutive course of a virus during an epidemic in a large population such as the Brazilian population, considering the competition of the emerging viral pathogen with other endemic viruses, it is also expected the possibility of the emergence of viral quasiespecies that can find new hosts in populations of wild or domestic animals, and thus initiate events of reemergence of disease.[33]

RESUMO

Introdução: As transformações pelas quais vem passando a população mundial em decorrência dos processos de globalização e urbanização também alteraram a dinâmica de transmissão de muitas doenças infecciosas, bem como seus perfis epidemiológicos. Nesse contexto, este trabalho propõe uma reflexão sobre os aspectos evolutivos de patógenos virais emergentes e fatores que podem contribuir para eventos de reemergência. **Delineamento**: Este artigo traz reflexões dos autores sobre a literatura científica, abordando fatores ecológicos e evolutivos que podem ocorrer nos casos de surgimento de patógenos virais emergentes de acordo com a experiência adquirida após a epidemia de Zika no Brasil. **Resultados**: O mecanismo evolutivo pelo qual os agentes virais evoluem e adquirem novas propriedades estruturais e patológicas também contribui para a diminuição do número de casos em conjunto com medidas preventivas; e a diversidade biológica de vetores e possíveis candidatos a hospedeiros intermediários representa um fator que pode contribuir para a ocorrência de eventos epidêmicos de reemergência. **Implicações**: Análises com foco nos aspectos evolutivos dos agentes virais podem contribuir para o reconhecimento precoce de novos sintomas, e identificação de possíveis candidatos a hospedeiros reservatórios, consequentemente, contribuindo na prevenção de eventos de reemergência.

DESCRITORES

Zika virus; Evolução Biológica; Vírus emergente; Epidemias.

RESUMEN

Introducción: Las transformaciones que ha venido atravesando la población mundial como consecuencia de los procesos de globalización y urbanización también han alterado la dinámica de transmisión de muchas enfermedades infecciosas, así como sus perfiles epidemiológicos. En este contexto, este trabajo propone una reflexión sobre los aspectos evolutivos de los patógenos virales emergentes y los factores que pueden contribuir a los eventos de reemergencia. **Diseño**: Este artículo trae reflexiones de los autores sobre la literatura científica, abordando factores ecológicos y evolutivos que pueden ocurrir en casos de aparición de patógenos virales de acuerdo con la experiencia adquirida después de la epidemia de Zika en Brasil. **Resultados**: El mecanismo evolutivo por el cual los agentes virales evolucionan y adquieren nuevas propiedades estructurales y patológicas también contribuye a reducir el número de casos en conjunto con las medidas preventivas; y la diversidad biológica de vectores y posibles candidatos para huéspedes intermediarios representa un factor que puede contribuir a la ocurrencia de eventos de reemergencia epidémica. **Implicaciones**: Los análisis que se centran en los aspectos evolutivos de los agentes virales pueden contribuir al reconocimiento temprano de nuevos síntomas, y en la identificación de posibles candidatos para huéspedes reservorios, en consecuencia, contribuyendo a la prevención de eventos de emergencia.

DESCRIPTORES

Virus Zika; Evolución Biológica; Virus emergente; Epidemias.

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