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Chapter 3

Genetic and Geo-Epidemiological Analysis of the Zika Virus Pandemic; Learning Lessons from the Recent Ebola Outbreak

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Additional information is available at the end of the chapter

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Abstract

"Outbreak" is a term referring to a virus or a parasite that is transmitted very aggressively and therefore could potentially cause fatalities, as the recent Ebola and Zika epidemics did. Nevertheless, looking back through history, quite a few outbreaks have been reported, which turned out so deadly that essentially changed, molded and literally re-shaped the society as it is today. In the present chapter, differences and similarities between the two most recent outbreaks have been studied, in order to pinpoint and design a trace model that will allow us to draw some conclusions for the connection of those two epidemics. Due to the high dimensionality of the problem, modern and state of the art geo-epidemiological methods have been used in an effort to provide the means necessary to establish the abovementioned model. It is only through geo-epidemiological analysis that it is possible to analyze concurrently a multitude of variables, such as genetic, environmental, behavioral, socioeconomic and a series of related infection risk factors.

Keywords: genetics, evolution, epidemiology, Zika, Ebola

1. Introduction

The *Flaviviridae* is a diverse viral family of more than 100 known viral species, which has a worldwide distribution with several different viral members across the continents of our planet [1]. The first *Flaviviridae* virus outbreak was recorded in 1878 with the yellow fever virus at the city of Memphis, Tennessee, a hometown of 45,000–50,000 people that suddenly

became a ghost town [2]. At the same time, germ theory was still a state of the art concept. Researchers had no idea that the cause of yellow fever was a virus 1000 times smaller in size the human eye could detect, and they definitely had no idea that arthropod vectors were the carriers, and for this case mosquitoes in particular. Yellow fever virus was isolated for the first time in 1927, and it was not until 10 years later that an effective vaccine was developed against the fatal virus [3]. Due to the fact that *Flaviviridae* is a highly mutagenic family of viruses, in subsequent outbreaks, several new members have been identified and reported to share high similarity in structural conservation and molecular characteristics. Overall, the genus *Flaviviridae* comprises four main genera *Hepacivirus*, *Pegivirus*, *Pestivirus* and *Flavivirus* [4, 5].

The genus *Hepacivirus* is the smallest and contains the Hepatitis C Virus (HCV), one of the most fatal human pathogens in the *Flaviviridae* family [6, 7]. The genus *Pegivirus* was recently classified and includes virus species that infect mammals [4, 8]. The genus *Pestivirus* has not been classified as a zoonotic disease yet and contains the bovine viral diarrhea virus (BVD) and the classical swine fever virus (CFSV) [4, 9]. Nevertheless their impact on livestock is strongly connected with the economic and social well-being of many countries. Last but not least the genus *Flavivirus* is the largest one and contains 70 identified human and animal viruses [4] including Dengue virus (DENV), West Nile virus (WNV), Japanese encephalitis virus (JEV), Tick-borne encephalitis virus (TBEV), Yellow fever virus (YFV) and Zika virus (ZIKV) the last of which recently led to the World Health Organization (WHO) in order to declare a global public-health emergency.

Among other common characteristics, the *Flaviviridae* family viruses spread quickly and easily in a tropical environment and attribute that the researchers are now re-examining the current Zika virus outbreak [10, 11]. In fact, this is down to the way viruses pass from one species to another. The viruses within this family fall within significant medical concern as variety of diseases inflict to both humans and animals. The majority of these viruses spread by arthropod vectors such as ticks and mosquitoes and in many cases they can also be transmitted from animals to humans. *Flaviviridae* family viruses can survive for long periods in their hosts by replicating without damaging the host cell. Generally, humans are infected with these viruses by direct contact with infected blood. In America, people have been mostly infected with Zika virus through the bites of the *Aedes aegypti* mosquito [12].

The ability of the *Flaviviridae* family viruses to spread so rapidly is also due to the structure of its viral genome [4, 13]. The *Flaviviridae* are a family of positive, single-stranded enveloped RNA viruses. Their genetic material in the form of ssRNA contains all the information needed in order to make copies and it also mutates more easily [14]. Mistakes in replication can happen in both DNA and RNA, but RNA has fewer systems in place to proofread and correct mutations that may naturally arise [15]. In fact the RNA viruses do not have these correcting mechanisms at all, so the mutations remain and get passed to the next generation [14]. RNA replication has an error rate roughly 10,000 times higher than that of DNA, which means that *Flaviviridae* family viruses evolve much quicker.

Flaviviridae family genera present similarities in the organization of its genetic material, the estimate life cycle, replication and morphology of the viral particles [5]. Virions of *Flaviviridae* family viruses are spherical almost 40–60 nm in diameter. Each virion consists of a lipid envelope

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which is composed of two or three virus-encoded membrane proteins, a membrane and a small capsid. The genetic material is located within the capsid. The genome includes a single-stranded positive sense RNA molecule of approximately 9.5–12.5 kb. It contains a long open reading frame (ORF) which is found between untranslated regions (UTRs) at 5′ and 3′ ends. All the family members lack 3′ terminal polyadenylated tail. The whole genome is translated into a polyprotein, which is processed post-translationally by host and viral proteases. This polyprotein consists of minimum 10 different products, depending on the classification of the virus that can be divided based on structural and non-structural (NS) proteins [7].

2. General epidemiology

Despite the fact that the Zika virus epidemic in the Americas and the Caribbean is showing signs of a significant slow-down, Zika virus transmission is continued worldwide. To date, 148 areas worldwide related with Zika virus from which 61 areas worldwide have confirmed the transmission of Zika virus disease, 18 areas have evidence of Zika virus circulation and 69 have the potential for Zika virus future transmission [16, 17]. Moreover five countries have reported sexually transmitted Zika cases [18, 19]. There are critical knowledge gaps around Zika virus and a lack of historical reports on its vectors, transmission patterns and geographical distribution. Regardless these challenges, there is a need to better understand the epidemiology of Zika virus transmission in a given area, at a given time in order to allow an assessment of the possibility of Zika virus infection for a number of populations, and to adapt public health recommendations for residents and travelers [17].

The first isolation of Zika virus was detected in 1948 from the mosquito species *Aedes africanus* [20, 21]. Since then, there have been several new cases of Zika virus vectors reported to literature. Collectively, the most frequent mosquito vector is the genus *Aedes* including, *A. aegypti*, *Aedes furcifer*, *Aedes luteocephalus*, *Aedes vitattus* and *Aedes apicoargenteus* [22–24]. The main vector of the Zika virus in South and South-East Asia is considered to be the genus *A. aegypti* of mosquitoes, which also play a major role as the major transmission vector for Dengue virus, Yellow fever virus, Chikungunya virus and many other mosquito-borne *flaviviruses* [25]. Based on reports during the two major outbreaks in the Pacific Islands, new potential vectors of Zika virus could be *Aedes hensilli* and *Aedes polynesiensis* mosquitoes [26, 27]. Moreover, recently another member of mosquitoes within the *Aedes* genus was found to be infected, the *Aedes albopictu* [12, 28]. Zika virus replicates in mosquitoes within 7–10 days and afterwards spreads with high levels of transmission through the salivary glands. However, the superiority of either vector over others in its capacity to optimally transmit Zika virus is yet to be investigated. Despite the Zika virus reservoir is unclear, some researcher believe that Zika virus might be maintained in nature by a sylvatic cycle involving non-human primates, or in a broad members of *Aedes* mosquito's species [23, 24]. Zika virus transmission in urban areas takes place by the anthropophilic mosquitoes *A. aegypti* and *A. albopictus*, from which the *A. albopictus* is particularly worrisome from the *A. aegypti* because of its daily feeding and their custom to bite several hosts during the development cycle of their eggs which makes them very effective as a transmission vectors [21, 29, 30]. Nevertheless, serological studies

have established the presence of particular antiviral antibodies in several mammals including elephants, felines and rodents, which confirm that other reservoirs may be involved in the transmission cycle of the Zika virus [21, 31]. Therefore, there is an urgent need to identify vectors and possible vectors in vulnerable area in order to control Zika virus outbreaks.

3. Genetic and geo-epidemiological analysis of the Zika virus

Zika virus has been around since the first human case was diagnosed in 1952 [20]. It only caused sporadic human infections until the first humongous outbreak on the Micronesian island of Yap in 2007 [32]. Even then, the symptoms were reported to share many common characteristics with a mild flu symptoms including fever, rash, headaches and joint and muscle pain. However, during the Zika virus outbreak in Tahiti in 2013 and 2014, a small number of people began to show unusual symptoms that resembled another syndrome called "Guillain-Barré," a condition that causes the immune system to attack a person's nerves, resulting in muscle weakness, tingling and even paralysis [33]. Furthermore, pregnant women infected with Zika virus have also given birth to babies with microcephaly, or smaller than normal heads [34]. It is possible that these new symptoms could be a result of the Zika virus evolution [35]. Zika virus was relatively infrequent and it did not cause a lot of concern, but when new cases were identified with greater frequency and people started to see babies born with microcephaly and nervous system disorders, the public health importance of this virus had to change completely [36].

The sudden appearance and the rapid global spread of the Zika virus have caused confusion regarding the meaning of the term "pandemic" [37]. There is also confusion in the recognition of pandemics when they occur. Some believe that the explosive contagiousness is sufficient to classify a disease as a pandemic. Another opinion claims that the severity of the infection and mortality must be considered. A pandemic is an epidemic of infectious disease that has spread throughout human population across a large region such as multiple continents or even worldwide [38]. The pandemic is not related to the endemic, which is a disease that can be controlled as far as transmissibility is concerned. On the other hand, the pandemic is characterized as a lethal threat to humans, since mortality rates may overcome these wars and accidents. The main feature of the pandemic is that it is communicable.

A look back in history reveals that pandemics are so expansive and deadly that they essentially changed the course of history such as the Black Death or as well known as "Bubonic Plague" in 1339–1351, which affects both Europe and Asia [39]. Painful, egg-sized swellings on the body signaled the infected had only a week to live [40]. Being close to a sick person was enough to get infected. The total number of worldwide deaths is estimated at 75 million people and even today the WHO reports 1000–3000 cases of plague every year [41]. Furthermore, Cholera boomed during 1817–1823 in Asia, Middle East and Africa. The cholera bacterium lurks in contaminated water and infects the small intestine, causing severe diarrhea. About 40% of victims die within hours, due to dehydration. Cholera has killed at least 10 million people. An estimated 2.86 million cholera cases occur annually in endemic countries. Among

these cases, there are an estimated 95,000 deaths [42]. Nowadays, HIV/AIDS is still expanded worldwide since 1970, despite the fact that it is originated in central Africa [43, 44]. HIV virus viral genome was identified in the early 1980s, after an epidemic expand among homosexual men in western countries. HIV is transmitted through bodily fluids and blood, and destroys the immune system [45]. HIV infected people with zero immune response are easier to die of other diseases such as cancer or pneumonia, or from simple infections. Since there is no cure, anti-retroviral drugs are granted to the patients to prevent the virus from spreading and killing more immune cells. HIV and generally AIDS have killed more than half a million North Americans [46]. In Southern Africa, it is estimated that 25 million have lost their lives, with 35 million more still infected, including many children born with the virus [47].

The World Health Organization (WHO) has produced a six-stage (phasing) classification that describes the process by which a novel influenza virus moves from the first few infections in humans through a pandemic [48]. The stages do not relate to how sick the person gets or how many people are infected by the virus. Instead, they relate to where it is located and how it is spread from one area to another. Firstly, viruses circulate within animals only. No human infection has resulted from the animal virus. Secondly, if an animal virus infects humans, it means that this virus has mutated, so there is a basic level of pandemic threat. Thirdly, small groups of people in a region are infected by the virus. It is possible to transmit the virus outside the boundaries of the community if others outside that community come into contact with those humans who are infected. The next phase is when the outbreaks of the virus are increasing dramatically in many communities in a short period of time. A stage before the pandemic is when the transmission of the virus from human to human has been recorded in at least two countries. Finally, the pandemic phase means a global pandemic is underway. Illness is widespread and governments and worldwide organizations are actively working to curtail the spread of the disease, and to help the population deal with it, by using preventive measures [49].

Due to the nature of pandemics, we will never be fully protected despite any development in antivirals and viral medicine [50]. The following categories are the most ominous: Viral hemorrhagic fevers, including Ebola and Marburg Virus, have the potential to turn into pandemics. Influenza—the recent discovery of the H5N1 (Avian Flu) is an example of this. The strain was spotted in Vietnam in 2004; the ability of the virus to potentially combine with human flu viruses is a concern to scientists. Ebola—the largest Ebola epidemic the world has ever seen is still ongoing. Huge efforts have been made in order to prevent it from turning into a pandemic. Viral diseases occupy a dominant position in pandemics. The majority of deaths worldwide caused by viral pandemics, the mortality of diseases that belong to *Flaviviridae* family are shown in **Table 1**. A major problem is the immediate and prompt response for protection before a disease evolves into a pandemic. The progress of science in drug discovery is rapid, scientists replace the traditional methods of in vivo/in vitro trial error testing and focus more on techniques of rational drug design based on the structure which is efficient, fast and of lower cost [51].

To date there is neither a drug nor a specific vaccination available against Zika virus, Ebola or HIV virus. Thus there is a great need for the development of novel antiviral strategies.

Virus	Case fatality rate (CFR)	Diagnosed (per year)	Deaths (per year)
Yellow Fever (YFV)	7.5%	200.000	30.000
Dengue Fever (DENV)	40–50% (without treatment) 1–5% (with treatment)	50–528 million	20.000
Japanese encephalitis virus (JEV)	0.3–60%	70.000	20.400
Tick-borne encephalitis virus (TBE)	20–40% far Easter 2–3% E.U, U.S.A	10.000–15.000	1000
Hepatitis C virus (HCV)	9%	3–4 million	350.000
West Nile virus (WNV)	3–15%	3.000	100
Zika virus (ZIK)	—	1,5 million	18 (+71*)
	*cases of deaths with microcephaly and/or central nervous system (CNS) malformation in newborns.		

Table 1. Case fatality rate (CFR) of viruses in *Flaviviridae* family. Microcephaly and other fetal malformations potentially associated with Zika virus infection or suggestive of congenital infection, have been reported in seven countries or territories. Particularly, from October 2015 until January 2016, 4783 cases of microcephaly have been reported in Brazil. On 29 April the first American died of complications related to the Zika virus, health officials of CDC reported.

Viruses have a relatively simple structure. They contain nucleic acids in a capsid. The mechanism used for their transmission is based on the host cell. In the end, the host cell is destroyed after the creation of multiple copies of the virus. An antiviral strategy for *Flaviviridae* family is to identify which proteins/enzymes are involved in viral replication. Important enzymes are the viral helicase and viral polymerases, NS3 and NS5, respectively [52]. The knowledge that the helicase plays a key role in the translation of Zika virus leads to the establishment and the design of homologous helicase models in order to be used for the rational design of an anti-Zika pharmacophore [53]. Also it has been shown that IFN, ribavirin, 6-azauridine and glycyrrhizin have the ability to inhibit infection of VERO cells induced with IFN to be more effective [54]. Moreover, the combination of IFN and ribavirin may be more effective in the *Flavivirus* genus. Researchers have shown that propoxy derivatives are good candidates for drugs against HCV [55]. Anti-malaria hydroxychloroquine indicated inhibition of dengue virus infection and has been safely used during pregnancy as well as amodiaquine and tetracyclines [56].

Ebola virus disease (EVD) is a non-segmented, negative-sense, single-stranded RNA virus that resembles rhabdoviruses and paramyxoviruses in its genome organization and replication mechanisms. It is a member of the family Filoviridae, based upon their filamentous structure. The genus Ebola virus is divided into five species (Zaire, Sudan, Ivory Coast, Bundibugyo and Reston). Among them, the first four cause disease in humans. The disease has a high risk of death, killing between 25 and 90% of those infected, with an average of about 50% [57]. The disease was first identified in 1976 in two simultaneous outbreaks, one in Nzara and the other in Yambuku, a village near the Ebola River from which the disease took its name. The old virus differs from today by 3%. Ebola outbreaks frequently make their appearance in sub-Saharan Africa. So far the greatest epidemic ever recorded was in western Africa (December 2013–January 2016) with 11,315 confirmed deaths. Symptoms of Ebola typically include fever,

severe headache, muscle pain, weakness and sore throat. Late-stage symptoms of Ebola virus may include vomiting, diarrhea, redness in the eyes, swelling of the genitals, internal and external bleeding. Typically, symptoms appear 8–10 days after exposure to the virus, but the incubation period can span from 2 to 21 days. Recovery may begin between 7 and 14 days after first symptoms. Death, if it occurs, follows typically 6–16 days from first symptoms and is often due to low blood pressure from fluid loss [58].

Ebola virus is transmitted from human to human by close contact with infected patients and virus-containing body fluids. Specifically, it spreads through direct contact with blood or body fluids (including but not limited to feces, saliva, sweat, urine, vomit and semen) of a person who is sick with or has died from Ebola [59]. Ebola can also be spread through needle sticks and contact with objects (like needles and syringes) that have been contaminated with the virus. According to WHO, you can also contract the virus by handling a sick or dead wild animal that has been infected with it. In the countries of West Africa, transmission through infected animals has been observed, usually infecting bats or wild animals as prey. The Ebola virus is also a sexually transmitted disease, transmitted by semen (oral, vaginal and anal sex) [60]. High-risk groups, except the population of sub-Saharan Africa are people surrounded by patients either in the family or in the professional environment. Scientists observing the virus have not seen any evidence to suggest that the Ebola virus may be mutating to become more contagious.

Ebola is difficult to be diagnosed when a person is first infected because the early symptoms, such as fever, are also symptoms of other diseases. The main question doctors consider is whether the person has been in one of the countries in West Africa within the last 21 days, then tests of blood and tissues can diagnose Ebola. Laboratory diagnosis of Ebola is achieved in two ways: detection of infectious particles (or particle components) in affected individuals and measurement of specific immune responses to Ebola virus [61]. To date, no FDA-approved vaccine or medication is available against Ebola virus. Albeit, when some basic interventions are used early, they can improve the chances of survival. The basic interventions used are providing intravenous fluids (IV) and balancing electrolytes (body salts), maintaining oxygen status and blood pressure and treating other infections if they occur, medications to treat shock and pain medications.

Since no therapy has been approved, an important issue that occurs is prevention. Preventive methods are vital. WHO and other global health organizations have suggested several types of protection, some of them are wash your hands with soap and water or an alcohol-based hand sanitizer and avoid contact with blood and body fluids, isolate the patient, wear protective clothing, dispose of needles and syringes safely, use safe burial practices and avoid facilities in West Africa where Ebola patients are being treated.

To date, the largest outbreak of the Ebola virus was in West Africa. In March 2014, Guinea, Liberia and Sierra Leone were the countries where the major outbreak of Ebola appeared. In early October of the same year, the first transmission of the virus to occur outside Africa was reported, later other patients were identified in Europe and America. The numbers show the extent of the problem. In the period 2013–2015 in Liberia, Sierra Leone, Guinea, Nigeria, Mali, United States, Senegal, Spain, United Kingdom and Italy, there were 11,315 deaths with

case fatality rate of up to70–71%. The United National health agency in December 29, 2015 declared the end of the Ebola virus transmission in Guinea, Liberia and Sierra Leone, where the epidemic began killing 13,000 people [62].

Zika virus was originally isolated in 1947 from the blood of a Rhesus monkey for yellow fever research conducted in the Zika forest, Uganda, from which the disease took its name. Then the virus was recovered again from humans and mosquitoes in the countries of Central Africa and Malaysia. The Zika virus belongs to the genus *Flavivirus* of the *Flaviviridae* family. It is a single-stranded RNA virus, with a shell and the shape of a sphere. Genomic comparisons have revealed that it has two major lineages: Asian and African on the basis of their nucleotide sequences. Typical symptoms are fever, headache, maculopapular rash that starts on the face and spreads to the whole body, redness in the eyes or conjunctivitis. Symptoms are generally mild and start about 2 or 7 days after the infection. Furthermore in some cases, lack of fever and often fewer symptoms such as muscle pain and arthralgia have been observed.

The Zika virus is a vector-borne disease, transmitted by several *Aedes* (stegomyia) species of mosquitoes, having been isolated in *A. albopictus* mosquitoes and *A. aegypti*. Other reported modes of transmission are through mother to fetus, through laboratory exposure, blood transfusion and through sexual contact. Transmission through transplantation is possible but not proven. The Zika virus has been detected in human blood, saliva, semen and urine. It has been confirmed that it remains after 62 days of infection in the patient's semen and urine. A possible mode of transmission is considered to be the bite of infected animals with the virus. All these transmission modes of Zika virus make it a challenge for science and for the whole world.

Since the virus can be detected in human body fluids, various methods have been developed for diagnosing it, through saliva or urine samples that have been collected over 3–5 days after the onset of symptoms. It is possible to isolate the viral genome and detect the nucleic acid by reverse transcriptase-polymerase chain reaction. Serological tests like ELISA or immunofluorescence are also widely used. CDC had developed an ELISA technique to detect specific anti-Zika IGM during the epidemic in Yap in 2007 [63].

Currently, no specific treatment or vaccination is available for Zika virus. Treatment of symptoms may include rest, fluids, antipyretics (the CDC advice against using aspirin or other nonsteroidal anti-inflammatory medication) and analgesics. In addition, the CDC has advised that pregnant women who are diagnosed with Zika virus should be considered for the monitoring of fetal growth and anatomy every 3–4 weeks, because of Zika virus correlation with infant microcephaly. Prevent Zika virus by avoiding mosquito bites. Mosquitoes that spread Zika virus bite mostly during the daytime. Additionally, sexual transmission of Zika virus can be prevented by using condoms or not having sex.

The geographical spread of the virus Zika virus beyond Africa and Asia was reported in 2007. The first major expansion with 185 cases occurred in 2007 on the Yap Islands of the Federated States of Micronesia. Scientists assume that the introduction of the virus in Yap probably came from an infected mosquito or human from Southeast Asia. In 2013, the virus broke out again near the French Polynesia. In May 2015, the Ministry of Health of Brazil sounded the alarm

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because 14 states of the country were affected by the virus. Scientists suspect that Zika virus is the cause of 2400 cases of microcephaly and 29 infant deaths in Brazil only in 2015. Currently confirmed cases are in 31 countries of South America, 5 countries in Oceania/Pacific Islands and in Care Verde. **Figure 1** represents all counties with active Zika virus this period March 2016. The number is expected to increase due to the travel movements (holidays, Olympic Games, pilgrimage to Mecca). Furthermore, 80% of cases will not be diagnosed because they do not have any symptoms. The distribution of *A. aegypti* and *A. albopictus* has remarkable parallelisms with the spread of Zika virus.

The climate change has a great affect on the transmission of the Zika virus. *A. aegypti* is a known vector of several viruses, including dengue fever, yellow fever and Zika virus. They have identified hundreds of cases in Europe, some ended in death. Probably, it comes from Africa, having been transferred globally through trade and sailing ships. Now found in tropical, subtropical even in temperate parts. It is relatively small, with black and white patterns. A distinctive external feature is the presence of a silver lyre-shaped sign on the chest. *A. aegypti* has four stages during its life: egg, larva, nymph and adult. In the first three stages, it lives in the water and in the last in the air. Females are hematophagous. They lay their eggs in temperatures between 25 and 29°C in small water-filled containers. In order to survive in a region, they must have adequate temperature and water availability. Humidity is vital not only for the eggs but also for the adults. They prefer to host mammals ideally humans [64] and artificial ponds. *A. aegypti* populations exist in northern Brazil, Southeast Asia, India, Greece, Spain and temperate regions of North America. Another type of mosquito that transmits diseases and belongs to the same family is *A. albopictus*. It originates from the tropical forests of South-East Asia. They have the same appearance with *A. aegypti*, and the diagnostic feature is the presence of a median silver-scale line against a black background on the thorax. Their

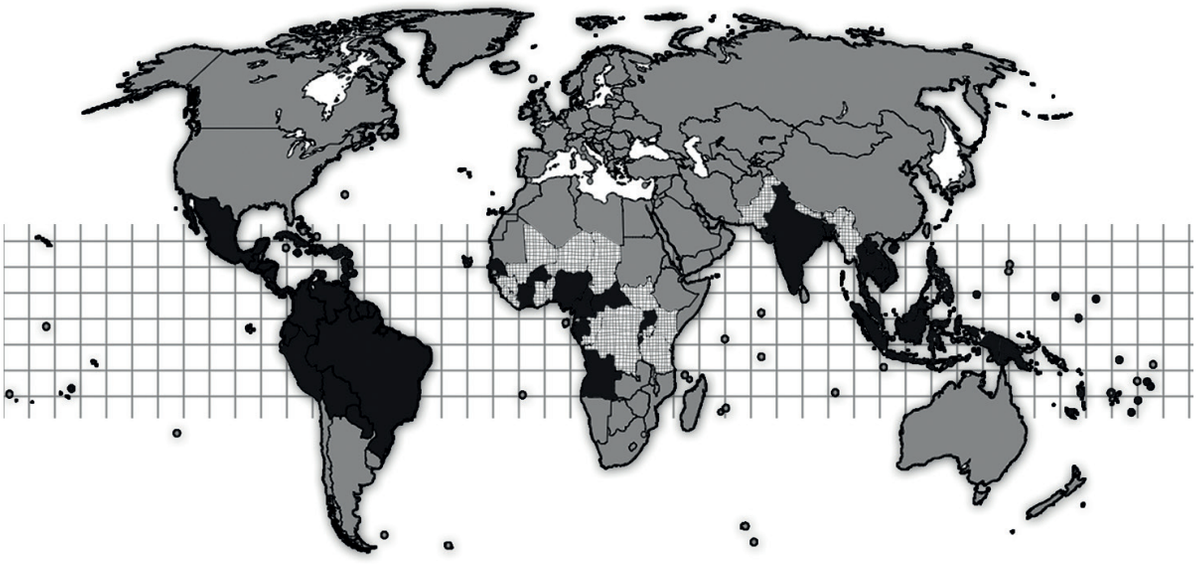

Figure 1. Areas with active Zika virus (colored dark grey, Category 1), areas with evidence of Zika virus (marked with small squares , Category 2) and areas with potential of Zika virus transmission (marked with large squares, Category 3). Figure was constructed based on WHO report of March 2017 about Zika virus.

eggs can survive at −10°C, making them more resistant compared to *A. aegypti*. *A. albopictus* populations expand geographically over the years. The main reason for the enhanced distribution of vectors *A. aegypti* and *A. albopictus* is climate change. Climate change has already changed the distribution of certain bodies of animals and is expected to influence it even further. According to the European Environment Agency, the global average temperature has increased by 0.74°C and the water level is increasing by 1.8 mm every year due to the fact that the ice in the Arctic melts at 2.7% each decade. Climate change may cause changes to the period and intensity of infectious diseases. The rise in temperature allows the survival of insects at higher altitudes. Proof of this can be malaria, which has expanded into areas, where previously it did not succeed. Dengue fever has also been seen in Puerto Rico, Florida, Gulf Coast states and Hawaii, places that had not usually been affected. Rising temperatures in the southern coast of the United States of America areas in Florida, Hawaii and the Coast state the following potential residence of *A. aegypti* together with Zika virus. The wind can reduce mosquito bites but also extend their flights. The increased rainfall creates small natural ponds, excellent conditions for reproduction and survival of mosquitoes. All these events create a clear picture that the protection of global health comes from environmental protection.

Another major factor that has an immediate effect on the transmission of the viruses is the mass population transfer from less safe areas to unaffected areas where they could find breeding ground for the expansion of the viruses [65]. The communities and the international organizations should not be negative toward the population transfer from poorer to richer countries or from countries in war to countries in peace as long as extra measures are being taken like a database for all immigrants that enter another country, On the other hand, the technological achievements of the twenty-first century have annihilated the distances and many travelers can be easily transferred all over the globe [66]. Thus, new measures are necessary for the population control in all the vulnerable continents like Europe and Asia. In addition, an online webpage should be created in order to update on a daily basis about the new crusts in each continent for every virus from the ones mentioned above. A new more detailed profile for any incoming stigma should be created for every crust. The study of every specimen for the immediate tracking of dangerous mutations of the virus and the immediate report of different symptoms from the ones expected in case of detecting a familiar virus. Phylogeography of the viruses is a new revolutionary idea through which we can comprehend and compare the nature of the viruses for the better treatment in case of random outbreaks [67].

What do Zika virus and Ebola have in common? Although both Ebola and Zika virus have been known for decades, in the last period they have been in the forefront of international attention not only for their huge spread but also for the serious consequences they induced. Ebola is characterized as a deadly and highly contagious virus. On the other hand, Zika virus is not fatal but scientists associate it with microcephaly infants and Guillain-Barré syndrome. According to the World Health Organization, both Ebola and Zika virus are infectious diseases that began and spread from animals to humans. Ebola is transmitted through infected animal and body fluids. Zika virus mainly through mosquito bites, from mother to fetus and isolated cases have reported transmission through semen and blood. The Ebola virus can only be transmitted when symptoms are present, the virus incubation period is from 2 to

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21 days. We do not know if Zika virus is transmitted asymptotically, the incubation period of Zika virus has not been calculated exactly, but probably a few days to a week. Both viruses have mutated. Ebola causes several symptoms such as fever, vomiting and excessive bleeding while Zika virus exhibits mild symptoms or none, since 80% of the cases show no symptoms. It is worth to mention that there is neither treatment nor vaccine for both Ebola and Zika virus. Ebola is characterized by high mortality rates ranging from 50 to 90%. There are similarities in how these two epidemics unfold. Both of them were reported much later, many deaths from Ebola until declared an emergency for public health, and many microcephaly cases which are believed to be associated with Zika virus. Interesting is the similarities that geographical areas have which were inflicted by the two viruses. Ebola started and was mainly reported in Guinea, Sierra Leone and Liberia. These countries have a shortage of drinking water, residents have a poor diet, living in unsightly and unsanitary conditions and made use of pesticides and chemicals. Most cases of Zika virus are found in Brazil, Columbia and El Salvador, poor countries with large rural areas, residents have a poor diet with a lack of vitamin A. In Brazil, the use of pesticides has increased and has forbidden chemicals from other countries. Similarities and differences between Ebola and Zika virus are shown in **Table 2**.

Similarities	Differences
Both of them have been known by scientists for decades.	Zika virus typically leads to mild febrile cases, with most being asymptomatic, Ebola has severe symptoms.
They are an animal origin in other words, a zoonoses.	Ebola has high mortality rate Zika virus not.
No treatment or vaccine	The incubation period of Ebola 2–21 of Zika virus few days up to a week
They spread in poor countries	Zika virus cannot be transmitted through “casual contact”, as ebola
Had a rapid spread	The Ebola can only be transmitted when symptoms are present.
They became epidemics in recent years.	
Both viruses have mutated.	

Table 2. Similarities and differences of viruses Zika virus end Ebola.

4. Conclusion

What Ebola and Zika virus should teach us is that we cannot assume that pathogenic viruses will continue to behave the same way without being mutated. Both viruses have similarities with how they spread. However, we should be mindful that there are some differences between Zika virus and Ebola based on fatality and modes of transmission. Zika virus like many of its cousins (WNV, dengue and chikungunya) will continue to exist and threaten mankind, until answers are provided to several open questions: Are there modes of transmission other than through the vector? Are mosquito species other than Aedes is involved in the urban cycle? Can person-to-person contamination occur through saliva? Can congenital or sexual transmission

occur? What is the rate of transmission by blood transfusions? Is ZIKV capable of establishing a chronic infection? Is there the generation of a long-lived protective immune response? Is there the possibility of re-infection? These questions must be urgently answered to allow the effective design of strategies to prevent and/or treat ZIKV transmission and infection and will demand a collective and coordinate basic research initiative to address these issues.

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