CLIMATE CHANGE AND VECTOR-BORNE DISEASES IN SOUTHERN EUROPE

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Abstract

Vector-borne infections have always caused suffering throughout the history. The alliance of arthropods and microorganisms is hard to defeat as insecticides and drugs proved to be temporary solutions. Since our questionable victory over malaria and yellow fever in the midst of the last century, vectors gradually broaden their sovereignty in the presence of our oblivion. The infrastructure for surveillance and control of vectors is neglected and in the last decades we tend to prioritize chronic diseases rather than infections. Expanding air travel and marine transport, increasing global trade and travel provoked the globalization of vectors and pathogens. Climate change, especially the northerly stretch of temperate zone promote and sustain the incursion of exotic vectors like Aedes albopictus in Southern Europe bringing along tropical diseases like Chikungunya. Dengue becoming hyperendemic around the world is looking for a competent vector in Southern Europe while Aedes aegypti is trying to take hold in Portugal and Spain. West Nile Virus, an emerging encephalitis threat is gradually increasing its epidemic potential in Europe. The widening man-made environments and anthropogenic changes like global warming affect the behavior and population dynamics of vectors as well as the evolution of pathogens causing dramatic changes in disease prevalence and even severity. Today we may well be in the brink of resurgence of vector-borne infections so we need to assess current and future risks, and conduct effective surveillance.

Keywords: *Vector-born. Arbovirus. Mosquito. Climate change. Southern Europe*

The War we Haven't Won

Roughly since Patrick Manson's research on filaria, trying to understand their life routine followed by Ronald Ross's description of Plasmodia's association with Anopheles in 1896, a war against the arthropod vectors and pathogen microorganisms has begun (Deb-Roy, 2008).

In 1900, soon after the incrimination of mosquitoes as malaria vectors, Walter Reed confirmed that yellow fever was also transmitted by mosquitoes (Oldstone, 2010). These discoveries led to major sanitation campaigns in Americas and Europe. During the first half of 20th century, even before the advent of DDT, many regions were relieved of mosquitoes and their plagues (Roberts, 2010).

Encouraged by the retreat of malaria and backed up with the era of antimicrobials, insecticides and vaccines, WHO adopted the global malaria eradication program by the 8th World Health Assembly in 1955. Indoor residual spraying with DDT was the main implementation. By the 1970s malaria was eradicated from North America and southern Europe and the mosquito populations were largely defeated in other regions. Control programs had saved millions of lives throughout the world (Roberts, 2010).

During the 20th century accompanying these public health efforts living standards in the western world have dramatically changed. Environmental sanitation and housing conditions improved. Better nutritional status, personal hygiene and wider access to medical care were established. Changing farming practices, planned urbanization accompanied by economic development and technological advances virtually exiled the long feared infectious disease epidemics beyond the boundaries of developed world (Gratz, 2006).

In the last quarter of 20th century successful eradication efforts and modern human environment inhibiting disease transmission lulled us into a false sense of security. Eradication programs were gradually discontinued. Public health infrastructure for surveillance and control of vector-borne diseases has been neglected. De-emphasis of infectious diseases has decreased funding for research on vectors and their pathogens as epidemiologic transition to chronic diseases prevailed in the western world (Chavers and Vermund, 2007).

The past forty years has witnessed our complacency leading to the resurgence of vector-borne diseases as well as the emergence of novel ones (James, 2010). Today we have to cope with these threats under entirely different circumstances of a new world.

A Whole New World for us All

In the 21st century we live in a more crowded but much less bigger, extremely interconnected world. This intensity is further complicated with an ever speeding upheaval of ecologic disturbances, creation of new environments and treating the life on earth insolently.

Over the last 200 years world population has increased from less than a billion to over 6 billion. Half of this growth occurred in the last 40 years (Cliff et.al., 2009). It is estimated to reach 9.5 billion by the year 2050. Growing populations of the developing world have been concentrating in big cities and surrounding slum areas.

Overcrowding with serious deficiencies like access to clean piped water, proper housing and sanitation facilities is a major problem of uncontrolled urbanization (Chavers and Vermund, 2007). Escalating urbanization and population growth in the last 50 years is providing wide and rich habitats for human pathogens and vectors. While slums serve as gateways to rural interaction, urban crowds sustain the co-circulation of many microorganisms with high reproduction rates promoting genetic drift, recombination and evolution to adopt new hosts and transmission paths. Many vector species adapted to peridomestic environments also proliferate to high population densities in urban settings (Wilson, 2010).

Urbanization and technical advance led to a transition in our food production, handling and distribution customs. In a world where more than half of the population is living in cities, mass production of foods was required to meet the demands of growing populations. Intensified agricultural practices like vast areas of cash crops and industrial farms became widespread (Chavers and Vermund, 2007). The new animal husbandry practices usually involve confining large populations of domestic livestock in small quarters sometimes in close proximity to other species. These genetically similar dense host environments in contact with humans create ideal settings for cross species zoonotic transmissions. Increased transmission among reservoir hosts provokes spillover infections in humans leading to emergence of new threats (Daszak, 2009; Kimball and Hodges, 2010). There are currently 520 known arthropod borne viruses throughout the world. 100 of them are human pathogens and another 25 cause disease in domesticated animals (Monath, 1993).

During the last century long distance air transport has gradually shrunk our world by eliminating distance and time barriers. This is easily comprehended by the fact that in the late 17th century traveling from England to Australia, a distance of 12,000 miles, took nearly a year by ship whereas it took sixteen days by planes in 1930 and just one day in the year 2000 (Cliff et.al., 2009). This exponential decline in travel times accelerated the globalization by increasing international trade and travel. Air transport is expanding steadily since 1960s. The annual international tourist arrivals worldwide have increased 35 fold in the second half of the last century (Wilson, 2010). Every year more than 2 billion passengers make 28 million scheduled flights between 3700 airports in more than 23000 aircrafts. In today's world humans can reach any airport destination within 48 hours which is less than the incubation period for any vector-borne disease (Morse, 2009; Reiter, 2010).

Globalization increased the movement of humans and animals as well as food products, pests and pathogens dispersing them across the world via modern transport technology. Since the advent of containerization in international trade in 1960s, every year more than 20 million cargo containers cross the oceans and continents exchanging colossal amounts of commodities and a few arthropods now and then (Reiter, 2010).

And a Little Warm Up

CO2 and water vapor are the most important of green house gases and interestingly they are also the two main final products of burning fossil fuels. About 2.5 million years ago just about when enough CO2 had been absorbed from the atmosphere and buried underground as fossil fuels, the world stepped into an ice age that continues today. Since the Industrial Revolution in the 18th century fossil fuels have been extensively burned for energizing the modern world resulting in a CO2 increase in the atmosphere. This process can be easily traced in paleoclimatic and modern meteorological records as the CO2 concentration of atmosphere in an ice age was estimated to be 200 ppmv. In the preindustrial period it was 270 ppmv. In 1958 and 2003 they were 316 ppmv and 370 ppmv respectively. Today it is nearly 390 ppmv and rising (Maslin, 2004).

This anthropogenic change resulted in a 0.76°C increase in earth's average surface temperature since 1850. The warming is actually felt during the last few decades. The last 11 years (2001-2011) were among the top 12 warmest years in records back to 1850. Global warming has been greatest in the northern hemisphere continents especially in the mid to high latitudes. Precipitation changes accompanying warming were more variable in distribution. During the 20th century continental precipitation of the northern hemisphere has increased by 5-10% and perceived as increasing heavy rain falls. In contrast there have been decreases in precipitation in other regions mainly northern and western Africa and parts of the Mediterranean. As a result of this warming trend distribution ranges of plants and animals shifted towards higher latitudes and altitudes (Houghton, 2009).

Until the end of 21st century the global warming trend is expected to cause major climate changes. Climate change represents long term alterations in the average values of meteorological variables that are expressed over decades in contrast to climate variability which is fluctuations over periods of months or years (Cliff et.al., 2009). It is estimated that by the end of 21st century the mean global surface temperature will increase by 1.4 to 5.8°C, on average a third of a degree Celsius rise per decade (Maslin,2004). The warming will be more pronounced in higher latitudes than tropics. Global warming will intensify the hydrological cycle thus the global average precipitation will increase. The spatial and temporal distribution of precipitation won't be uniform throughout the northern hemisphere. In northern and central Europe the precipitation is expected to increase resulting in heavy rains and major floods. However the expansion of subtropical high pressure regions towards the temperate regions will cause southern Europe, Central America, South Africa and Australia to have less precipitation in the 21st century. These are the projections of climate models and the predictions on distribution of temperature rise or rainfall patterns in regional scales always have certain degrees of uncertainty (Houghton, 2009).

Climate and Vector-Borne Diseases

Temperature is a defining environmental factor on insect biology and vector-borne disease transmission. Insect vectors are cold blooded animals so their metabolism is highly dependent on ambient temperatures. The rate of their development through embryonic, larval and pupal stages to become adults is strongly determined by the climate. In temperate regions the activity of many vector species is defined seasonally by certain temperature intervals where as in the tropics and subtropics it is all year round (Becker, 2010). The timing of reproduction, biting rate and overall survival of a vector species are also affected by minute fluctuations in temperature (WHO, 2003). Moreover the extrinsic incubation period of pathogens in invertebrate hosts is highly temperature-dependant. This period is the time it takes a microorganism after entering the vector by an infectious meal, to mature, reproduce and get ready to be transferred to a new host (Unnasch, Cupp and Unnasch, 2006). It is obvious that the abundance, infectiousness and activity of vectors are enhanced by warming weather.

Precipitation is another defining factor of transmission activity as most vector species needs aquatic larval habitats to breed and humid conditions for prolonged survival. The prevalence of certain vector species is delimited by dry seasons and many of them rely on drought resistant eggs to survive until the rains come (Becker, 2010). A curious aspect of dry spells in rural settings and deprived urban areas that people tend to store large amounts of water within reach of vectors providing them excellent breeding sites. Evidently this behavior seems to sustain substantial vector populations in spite of unfavorable natural conditions (Linthicum et.al., 2010).

Vector capacity is the potential number of secondary infections produced by vectors that feed from an infectious individual on a single day. Vector capacity and duration of host infectiousness are the most important parameters predicting the vector-borne disease occurrence in a region and the former is strongly influenced by climatic conditions (Wilson, 2001).

The impact of climate variations on vector-borne diseases is best observed in endemic areas where the transmission is stationary and in unstable areas along the endemic margins where the transmission is sporadic in nature exclusively due to climatic limitations (Connor and Mantilla, 2008).

In endemic regions, changes in weather conditions may increase the population density and activity of vectors and extend their seasonal range. Consequently the disease incidence and the duration of transmission season also increase. In unstable regions of disease activity, temporary elimination of the restraining climatic variables (insufficient precipitation, low temperatures…) leads to outbreaks. In these marginal areas the emerging disease activity doesn't last long once the conditions return to normal (Connor and Mantilla, 2008).

The most convincing evidence for these effects of climate variability on vector-borne diseases came from the studies on El Nino Southern Oscillation.

El Nino Southern Oscillation is an interannual global climate variability pattern which occurs in irregular intervals of 2 to 7 years. These phenomena arise from the interactions between oceans and atmosphere causing changes in the direction and intensity of currents and winds in the Indo-Pacific region. Three possible outcomes constitute this periodic cycle, El Nino conditions, normal conditions and La Nina Conditions (Maslin, 2004). Typical El Nino conditions are characterized by a warming of sea surface temperatures of the central and eastern equatorial Pacific Ocean by 0.5°C. The prolonged warming of Pacific Ocean affects the global weather causing precipitation anomalies around the world. While increased rainfall and floods occur in certain parts of the world, in some others extended droughts are most likely to happen. The time of onset, duration and intensity of El Nino events vary widely and are hard to predict (Cliff et.al., 2009). However there has been a trend towards more frequent and intense events since 1976 (Maslin, 2004).

In many investigations El Nino Southern Oscillation has been associated with vector-borne disease outbreaks in distinct parts of the world. Drastic precipitation changes induced by El Nino episodes affect the abundance and distribution of vectors thus setting the stage for epidemics and outbreaks of enzootic diseases (Linthicum et.al., 2010).

On the other hand unlike climate variability, climate change presents a permanent shift in climatic conditions which will potentially readjust the temporal and geographic distribution of vector-borne diseases. Vectors and pathogens currently confined to lower latitudes and altitudes may extend their territory to mid latitudes and higher altitudes (Maslin, 2004; Houghton, 2009). Changing conditions may create ideal environments for the establishment of alien species of pathogens, vectors and hosts posing new threats (Cliff et.al., 2009). Transmission rates of diseases in endemic regions may be permanently increased resulting in high disease prevalence. In addition, the induced hyperendemic state may enable pathogens to evolve rapidly and they may even afford to become more virulent to their hosts, meaning more severe disease (Ewald, 1994).

climate change seems to have the potential to alter the current occurrence of vector-borne diseases across the globe. However the actual disease occurrence depends on many other factors that would promote or inhibit transmission. Most important is the conductivity of the human environment to the transmission of vector-borne diseases (McMichael, 2004). The land use practices like agriculture and forestry and urban planning that determines the environmental conditions favoring competent vector presence, the practices and behavior of human hosts that determines the extend of exposure to vectors, the vulnerability of the population to diseases determined by genetic susceptibility and immunization status, the disease burden determined by provision of adequate medical care for individuals and the presence of an effective public health infrastructure. Most of these factors are strongly correlated with the socio-economic development of a population which will ultimately shape the future events (Meade and Earickson, 2000; Houghton, 2009).

Dengue and Aedes Aegypti

Aedes Aegypti is an exclusively anthropophilic, highly domesticated African mosquito. In its original environment it had evolved to be a compatible vector for primatophilic arboviruses. Its ecological plasticity enabled it to adapt to humans and peridomestic environments. Before the era of transoceanic trade Ae. Aegypti was confined in Africa transmitting yellow fever among the native Africans. By the transatlantic slave trade in the 17th and 18th centuries Aedes aegypti and the yellow fever were introduced to the Americas (Oldstone, 2010). Dispersed by the expanding trade in the 18th century, Ae. aegypti had reached Southeast Asia. There another primatophilic jungle flavivirus, dengue adopted the new vector and traveled back to the Americas and Africa with it. First dengue epidemics occurred in Jakarta, Indonesia and Cairo, Egypt in 1779 followed by another in Philadelphia in 1780 (Lai and Putnak, 2007). At the beginning of the 19th century Ae. aegypti had already established a worldwide distribution infesting urbanized port cities and its cold intolerance was the only reason for its delimited range between the 45° north and 35° south latitudes. Throughout the 19th and early 20th centuries dengue epidemics were common in Europe and North America. In fact dengue was endemic in most of the Mediterranean countries. Major outbreaks occurred in port cities of France, Portugal, Spain and Italy. The last epidemic in Southern Europe was in Greece in 1927-28 with nearly one million cases and over a thousand deaths (Mari and Peydro, 2012).

In 1901 with the launch of a sanitary campaign to control yellow fever in Havana, a worldwide crusade against mosquitoes began (Oldstone, 2010). By the mid 20th century, Ae. aegypti was mostly eliminated from Central and South America and it was eradicated in Europe. Consequently dengue disappeared from Europe (Gratz, 2006).

However this was not the case in other parts of the world; especially in the Southeast Asia where in the same period population growth, economic development and uncontrolled urbanization led to the formation of large cities with extensive slum areas. In these semi-urban settings water storage practices and rich breeding habitats like rain water filled tin cans, pots, bottles and discarded tires facilitated the proliferation of the highly domesticated Ae. aegypti to large populations (Gubler, 2010). Aedes albopictus, another primatophilic mosquito, dwelling in the surrounding disturbed rainforests also exploited this lucrative opportunity and adapted to urban environments. Like Ae. aegypti it was used to breeding in tree holes, plant axils and rock crevices and it was also a competent dengue vector (Licia et.al., 2012).

The concentration of humans and mosquitoes in such great densities created an extremely favorable setting for the transmission of dengue. Dengue prevalence began to soar in these large cities. Gradually different dengue serotypes found their way and accumulated in these transmission pools. In such cities with populations over 5 million the simultaneous co-circulation of different dengue viruses was

easily maintained by Ae. aegypti and Ae. albopictus (Reiter, 2010). There were four distinct serotypes and sequential infections with different serotypes were common as cross-protection was insufficient (Gubler, 2010).

This hyperendemic state in Southeast Asia led to the emergence of dengue hemorrhagic fever/dengue shock syndrome (DHF/DSS), a severe form of dengue infection characterized by increased vascular permeability, hypovolemia and clotting abnormalities. It was precipitated by the immune response induced by sequential infections by different dengue virus serotypes (Holtzclaw, 2007). The first DHF/DSS epidemic was recorded in Manila, the capital city of the Philippines in 1953-1954. In the following decades DHF/DSS became a major cause of hospitalization and death among young children in dengue endemic regions of Southeast Asia (Lai and Putnak, 2007).

Following the successful vector control programs and the discovery of 17D yellow fever vaccine, Ae. aegypti lost its significance in the tropical America and a period of complacency has supervened. During the 1980s and 1990s Ae. aegypti reinvaded much of the South and Central America reaching an unprecedented distribution (Monath, 1993). In the same period Ae. albopictus was introduced to North America in cargo containers from Asia and became established widely down to South America (Reiter, 2010).

It was not just the vectors spreading all over the world; the increasing air travel in the second half of the 20th century enabled all four dengue serotypes to embrace the globe. According to the records DEN-2 used to be the only dengue serotype in the New World until the introduction of DEN-3 in 1963 followed by DEN-1 in 1977 and lastly DEN-4 in 1981 completing the four (Reiter, 2010).

By the spread of all four serotypes and having ubiquitous vectors uniquely adapted to humans hyperendemic transmission of dengue led to the worldwide emergence of DHF/DSS. Until the 1970s only Southeast Asia was hyperendemic, in the following two decades the hyperendemic state and DHF/DSS spread to India, Pacific islands, Southern China, Central and South America, Africa and Australia (Gubler, 2010).

Dengue is currently the most important arboviral disease affecting humans. It is widely distributed in the tropical and subtropical urban regions. The prevalence of dengue has been significantly rising in the last few decades. It is estimated that every year nearly 100 million people around the world contract the disease and several hundred thousand of them have DHF/DSS (Gubler, 2010). Roughly 2.5 billion of the world's population is currently at risk and this number is expected to reach 5 to 6 billion by the end of the 21th century (Holtzclaw, 2007; Cliff et.al., 2009). There are no effective antiviral drugs or vaccines available for the virus yet.

Endemic dengue is long lost in Europe. Despite every year hundreds of imported dengue cases (mostly returning tourists from Southeast Asia or Tropical America) were reported all around Europe (Mari and Peydro, 2012), the absence of a competent vector has precluded its local spread so far. However since the end of the

20th century Ae. albopictus has been smoothly infesting Southern Europe and it is much more cold tolerant than Ae. aegypti while heading north (Reiter, 2010). In 2010 the reemergence of autochthonous dengue transmission was recorded in Nice, France. The same year two more indigenous cases were reported in Greece. In both incidents Ae. albopictus was implicated as the vector (Mari and Peydro, 2012),

Ae. albopictus is still a secondary vector for dengue viruses as it is unable to maintain a stable transmission in human populations on its own. However it may enhance the vector capacity of the primary vector in endemic settings (Goddard, 2008). In Europe the re-establishment of endemic dengue is still not a threat without a primary vector like Ae. aegypti (May, 1993).

Since Ae. aegypti's disappearance from Europe in the mid 20th century, its presence has been reported sporadically in many European countries including France, Italy, Croatia and Turkey. Recently in 2005-2007, the surveys conducted in Madeira, Portugal confirmed the first reestablishment of Ae. aegypti in the Iberian Peninsula (Mari and Peydro, 2012). Very soon a little warming may encourage Ae. aegypti to come back to its former territories in Southern Europe.

Chikungunya and Aedes Albopictus

Also known as the Asian tiger mosquito, Aedes albopictus is native to East and Southeast Asia. Today it is widely dispersed beyond Asia mainly to North and South America, Southern Europe and West Africa (Lai and Putnak, 2007).

Like Ae. aegypti, Ae. albopictus is a daytime biter but it is less anthropophilic and feeds freely on other mammals and birds (Lai and Putnak, 2007). It is highly invasive and has a remarkable capacity to adapt to peridomestic environments in both rural and urban settings (Licia et.al., 2012). It is extremely hard to control as it can breed in tree holes, leaf axils as well as plastic cups and used tires. Unlike Ae. aegypti, Ae. albopictus can survive the winters of temperate regions by cold tolerant dormant eggs therefore it can reach much higher latitudes (Mari and Peydro, 2012).

In the last thirty years Ae. albopictus has spread from Asia throughout the world. It was dispersed by the international trade of used tires. The mosquito eggs inside the tires have been shipped all around the world in containers (Reiter, 2010).

Ae. albopictus was first detected in North America in 1983. The infestation was traced back to cargos imported from Japan. In three years time it was already established in the U.S. and Brazil (Reiter, 2010).

In Europe the first report of Ae. albopictus's presence was dated 1979 (Mari and Peydro, 2012). The intrusion was in Durres, Albany. The infestation broke out at a rubber factory near the city port probably out of tires imported from China. The next introduction in Europe was in Genoa, Italy in 1990. The imported tires from Atlanta, U.S. were blamed for the intrusion (Gratz, 2006). In the last two decades

Ae. albopictus has established itself in Balkans (Albania, Croatia, Monte Negro, Serbia, Greece, Turkey), Italy, France and Spain. Currently it is still expanding its range (Reiter, 2010).

Chikungunya is an enzootic alphavirus maintained by aedine mosquitoes in the forests of tropical Africa and probably tropical Asia (Chretien et.al., 2008).

In Africa during the non-epidemic periods the virus is maintained in an enzootic cycle involving monkeys, rodents and birds. In Africa many different Aedes species are involved in transmission (Licia et.al., 2012). The epidemics occur when a primatophilic bridge mosquito spills the virus over humans and Ae. Aegypti spreads it. Humans are competent hosts for the chikungunya virus as infection causes enough levels of viremia to infect mosquitoes thus humans become the reservoir during epidemics (Monath, 1993).

In Asia no animal reservoir host could be determined during the non-epidemic periods and humans appear to be the only source at all times. In tropical Asia Ae. eagypti and Ae. albopictus are the main Chikungunya vectors (Licia et.al., 2012).

The first Chikungunya outbreak was recorded on the Makonde plateau, Tanzania in 1952. Until the beginning of the 21th century chikungunya was confined to the tropics of Africa, Indian Ocean and Southeast Asia (Goddard, 2008). In the 1960s and 1990s there were many epidemics recorded in India, Sri Lanka, Thailand, Indonesia and the Philippines. The infection was a typical viral syndrome with exceptionally severe joint pains that could persist for months to years (Licia et.al., 2012).

In the last decade a seemingly ordinary chikungunya outbreak in Kenya turned out to be a pandemic. An epidemic broke out in Mombasa and Lamu on the Kenyan coast in 2004. In 2005 it spread to the western Indian Ocean islands, the Comoros, Mauritius, Mayotte, La Reunion and the Seychelles with over 200.000 cases (Reiter, 2010). In La Reunion and Mauritius islands where Ae. aegypti was scarce, the virus acquired a new adaptive mutation which promoted Ae. albopictus to be a more competent vector, a primary one (Chretien et.al., 2008; De Lamballerie et.al., 2008**)**. The vector capacity of chikungunya transmission was increased. In 2006 a massive outbreak occurred in India with over 1.25 million cases and it spread eastward causing epidemics in Southeast Asia, Indonesia and the Philippines (Reiter, 2010).

In 2007 a surprising chikungunya outbreak occurred in Italy. It was the first time ever an autochthonous chikungunya transmission was detected in a temperate region. In two villages of the Province of Ravenna, northeast Italy over 200 cases was recorded. The probable index case was a traveler who had returned from India and developed a fever two days later. The incriminated vector Ae. albopictus had already been established in the region for at least a decade. The outbreak ceased in late September when the temperatures fall (Reiter, 2010).

The pandemic virus continued to circulate in West Indian Islands, India and Southeast Asia and in September 2010 another indigenous transmission of chikungunya was reported in southeast France (Licia et.al., 2012).

The high transmission rate in the eastern tropics and the frequency of imported cases rise concerns about the outbreak risk in Ae. albopictus abundant areas of southern Europe.

West Nile Virus and Culex Pipiens

West Nile virus (WNV) is a flavivirus and it belongs to the Japanese encephalitis antigenic complex. The members of this group have birds as primary vertebrate hosts and Culex species as major vectors. They are all neurotropic viruses and they infect humans and domestic animals as dead-end hosts (Gubler, 2010).

WNV infection is usually asymptomatic, sometimes presents as a self-limited viral syndrome called West Nile fever (WNF) and rarely as a neuroinvasive disease, West Nile encephalitis (WNE) (Smith, 2007).

WNV is principally maintained in enzootic cycles involving birds, as mammals don't develop enough levels of viremia to infect a mosquito thus complete the cycle (Unnasch, Cupp and Unnasch, 2006). Ornithophilic Culex species are the main vectors in enzootic cycles and Culex pipiens is the bridge vector primarily responsible for the epidemics (Smith, 2007). Cx. pipiens is a night feeder especially active at dawn and dusk. It feeds on birds and mammals and readily breeds in clear, slightly brackish or even sewage waters (Harbach, 1988). Cx. pipiens has established a worldwide distribution in temperate zones and known as the common house mosquito.

WNF epidemics are usually triggered by avian epizootics as increased infection burden in birds inevitably spill over humans by bridge vectors (Reiter, 2010). Enzootic activity normally leads to sporadic human cases and probably many inapparent infections.

WNV was first isolated in West Nile District of Uganda in 1937 (Smith, 2007). Following its identification, the serologic surveys found that WNV infection had been wide spread in Africa (Gratz, 2006). The movements of bird populations, especially the long distance migrations had facilitated the dispersion of WNV and it was enzootic in Africa, Europe, the Middle East, Central Asia and Australia (Reiter, 2010).

There are two main phylogenetic lineages recognized. Lineage 2 strains are mainly confined in sub-Saharan Africa circulating in enzootic cycles where as Lineage 1 strains are widely distributed in North Africa, Europe, Asia, Australia and North America causing spillover epidemics with serious neurologic involvement (Smith, 2007).

The first lineage 1 epidemics were recorded in Israel and Egypt in 1951. These countries were especially prone to epidemics as they lie at the crossing of major migration routes between Eurasia and Africa (Gratz, 2006). In 1957 the first WNF epidemic with severe neurologic manifestations was recorded in Israel (Sejvar, 2003). The first serologic evidence of WNV presence in Europe was recorded in Albania in 1958 (Gratz, 2006) and the virus was isolated in France in 1963 during an outbreak (Hubalek and Halouzka, 1999). In the following decades the virus activity was determined all over Europe but large epidemics were rare. In 1975 a serologic survey in Romania found 25.5% WNV seropositivity among humans and in Greece the seropositivity was 29% in 1980 (Gratz, 2006). The continuous virus movement between Europe and Africa was maintained by migratory birds and the seasonal epizootics among birds were rarely recognized unless spillover infections among humans or domestic animals were detected (Reiter, 2010).

In 1994 an outbreak in Algeria marked the emergence of a new WNV strain. There were 20 encephalitis cases of which 8 died (Gubler, 2010). The new strain had acquired an exceptional viral fitness, inducing a 10.000 fold greater viremia in susceptible birds facilitating further spread (Brault, 2007). The increased virulence was also manifested by a higher incidence of severe neurologic disease among birds and humans (Oldstone, 2010)

The enhanced transmission spread the emergent neurovirulent strain in bird populations causing epizootics. Predictably WNF epidemics accompanied the spread. First WNF epizootics occurred in Morocco and Romania in 1996 (Smith, 2007). In Bucharest a major WNF epidemic occurred with 500 clinical cases and over 100.000 estimated infections. The case fatality rate was 10% (Gratz, 2006; Lashley, 2007). Neurologic involvement was so prominent that it was perceived as a West Nile encephalitis outbreak. Throughout 1997 and 1998 the emergent virus activity was recorded in Tunisia, Italy and Israel (Smith, 2007).

In 1999, following a five year circulation in the Mediterranean region, West Nile virus crossed the Atlantic and caused an outbreak in New York City. It was the first contact in the Western Hemisphere (Reiter, 2010). The recovered virus was genetically related to a virus isolated from a goose farm in Israel in 1998. The virus was probably introduced by a mosquito on a plane or a viremic captive bird (Cliff et.al., 2009).

WNV spread easily among the naïve bird populations of New York causing a severe epizootic with high mortality (Gubler, 2010). Concurrently a cluster of patients with viral encephalitis was reported. The initial contact resulted in 62 neuroinvasive disease and thousands of infections among humans (Sejvar, 2003).

The virus successfully overwintered in North America in 1999, possibly facilitated by hibernating infected Culex mosquitoes or persistent infections in birds. The vertical transmission of WNV in Culex pipiens was also reported (Unnasch, Cupp and Unnasch, 2006). In the following years the virus was spread by migratory birds northwards into Canada, westwards across the United States and southwards

reaching to Venezuela. WNV became widely established in the Americas (Gubler, 2010). The rapid dispersal across the U.S. led to large epizootics and epidemics in 2002 and 2003. There were nearly 3000 cases of West Nile neuroinvasive disease (WNND) and 284 deaths reported in 2002 (Gubler, 2010). WNV became the most important cause of mosquito borne encephalitis in North America.

In 2010 the second largest WNF epidemic in Europe occurred in Greece indicating an active circulation in southern Europe. There were 197 cases of WNND and 33 deaths reported (Danis et.al., 2011).

In the last decades West Nile virus evolved to enhance its transmission which led to its emergence as a serious encephalitis agent and its introduction into the Western Hemisphere. Currently it is the most widely distributed arbovirus in the world.

Conclusion

The world has never been so immense yet accessible for microbes before. Today pathogens can proliferate in larger populations of humans and domestic animals than ever before and they readily exploit the modern transportation means. The world became one large medium to circulate, multiply, mutate and evolve. Viruses, especially arboviruses are the ones most readily seize these opportunities and become emerging threats.

Transmission dynamics of vector-borne diseases are governed by complex interactions of many physical, biological and socio-economical variables. Understanding the ecology of disease, meaning gaining insight over the vector, pathogen and host interactions in relation to environmental heterogeneity is crucial for developing effective interventions. To achieve this, a multi-disciplinary collaboration involving microbiologists, epidemiologists, entomologists and public health professionals among others is needed.

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