
VECTOR-BORNE
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Vector-Borne Diseases & Treatment

Chapter 1

Chikungunya Fever: Biology and Epidemiological Aspects

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Abbreviations

CHIKV: Chikungunya; ECSA: East/Central/South African; MCC: Maximum clade credibility; IOL: Indian Ocean Lineage; Ae.: Aedes; PHB: Prohibitin; PtdSer: Phosphatidylserine; PVEERs: mediated virus entry-enhancing receptors; GAGs: Glycosaminoglycans; PAHO: Pan American Health Organization; ZIKV: Zika virus; DENV: Dengue; RT-qPCR: Polymerase Chain Reaction using Reverse Transcriptase Reaction in Real Time; RT-PCR: Polymerase chain reaction; IgM: Immunoglobulin M; Igg: Immunoglobulin G; RT-LAMP: Real-time Accelerated ; ELISA: Enzyme Linked Immuno Sorbent Assay; IVM: Integrated Vector Management; WHO: World Health Organization; SIT: Sterile insect technique; RIDL: Release of Insects carrying a Lethal gene; IIT: Incompatible Insect Technique; CI: Cytoplasmic Incompatibility; Bti: Bacillus thuringiensis israelensis; IRS:Indoor residual spraying; Medea: Maternal effect dominant embryonic arrest.

1. Introduction

Vector-borne diseases transmitted by mosquitoes like *Aedes aegypti*, in particular Chikungunya fever, is quite alarming [1]. Chikungunya fever was first described during an outbreak in Tanzania in 1952. In the last 50 years, Chikungunya virus (CHIKV) has spread beyond

the African lands and has caused explosive outbreaks, which include millions of cases in the Indian Ocean, Asia and, most recently, in Europe and the Americas [2]. The name Chikungunya comes from the Bantu language spoken by the Makonde tribe-an ethnic group in southeast Tanzania and northern Mozambique - as a descriptive term, which can be translated as the disease that bends up the joints due to arthralgia that can last for months [2,3]. The etiological agent of Chikungunya fever is CHIKV, an *Alphavirus* belonging to the *Togaviridae* family [5].

2. Chikungunya Virus Structures

CHIKV is an enveloped virus with icosahedral symmetry, belongs to the Semliki Forest antigenic group of the genus *Alphaviridae*, which includes other arthritogenic viruses such as o'nyong-nyong, Ross River, Barmah Forest and Mayaro [5,6]. The genome, which consists of a single 11.8Kbp positive sense RNA strand, is closely related to the o'nyong-nyong virus and encodes a 2,472 amino acid non-structural polyprotein and a 1,244 amino acid structural polyprotein [7]. The polyproteins give rise to 4 non-structural proteins (nsP1, nsP2, nsP3 and nsP4) that make up the viral replication machine and 5 structural proteins (C, E3, E2, 6K and E1) [8,9].

The virion is 70 nm in diameter and consists of repeating units of the E1 and E2 transmembrane glycoproteins (240 heterodimers of E2/E1 arranged as trimeric spikes on its surface), the capsid (C), a host-derived lipid bilayer, and a single molecule of genome RNA. The genome encodes the nonstructural proteins (nsPs) at the 5' end and the structural proteins at the 3' end. The 5' end of the genome has a 7- methylguanosine cap, while the 3' end is polyadenylated [10]. The nsPs are translated from genomic RNA and the structural proteins from a subgenomic RNA (**Figure 1**) [11].

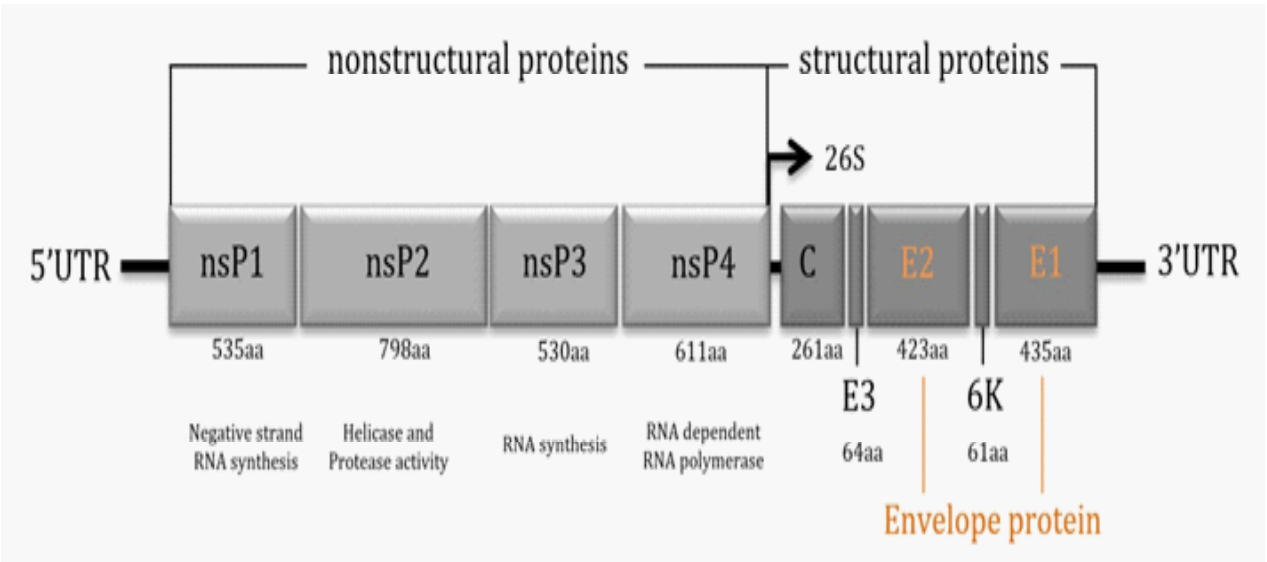

Figure 1: Schematic representation of the chikungunya virus genome. Organization of nonstructural and structural proteins throughout the genome as well as the non-translatable regions at the 5' and 3' ends. The function and size of amino acids is shown for each protein. C, capsid; AA, amino acid.

Until 2004, there were three different genotypes of CHIKV revealed by phylogenetic analysis that evolved independently in different geographic regions. The West African genotype is derived of isolates from Senegal and Nigeria. The East/Central/South African (ECSA) genotype is an enzootic genotype in Africa, and it has been related to epidemics in the Indian Ocean. The Asian genotype, including isolates from Asian countries such as Singapore, Malaysia, and Thailand has been associated with spread in the Pacific Region [12–15].

The origin of the 2005 epidemic in the Indian Ocean was initially attributed to the ECSA lineage. When the epidemic began in Kenya in 2004, the first CHIKV isolates of the La Réunion Island exhibited an alanine residue at position 226 in the E1 envelope protein, but subsequent isolates showed a replacement of alanine for valine residues (A226V). This and other substitutions gave rise to the fourthlineage, the Indian Ocean (IOL) (**Figure 2**).

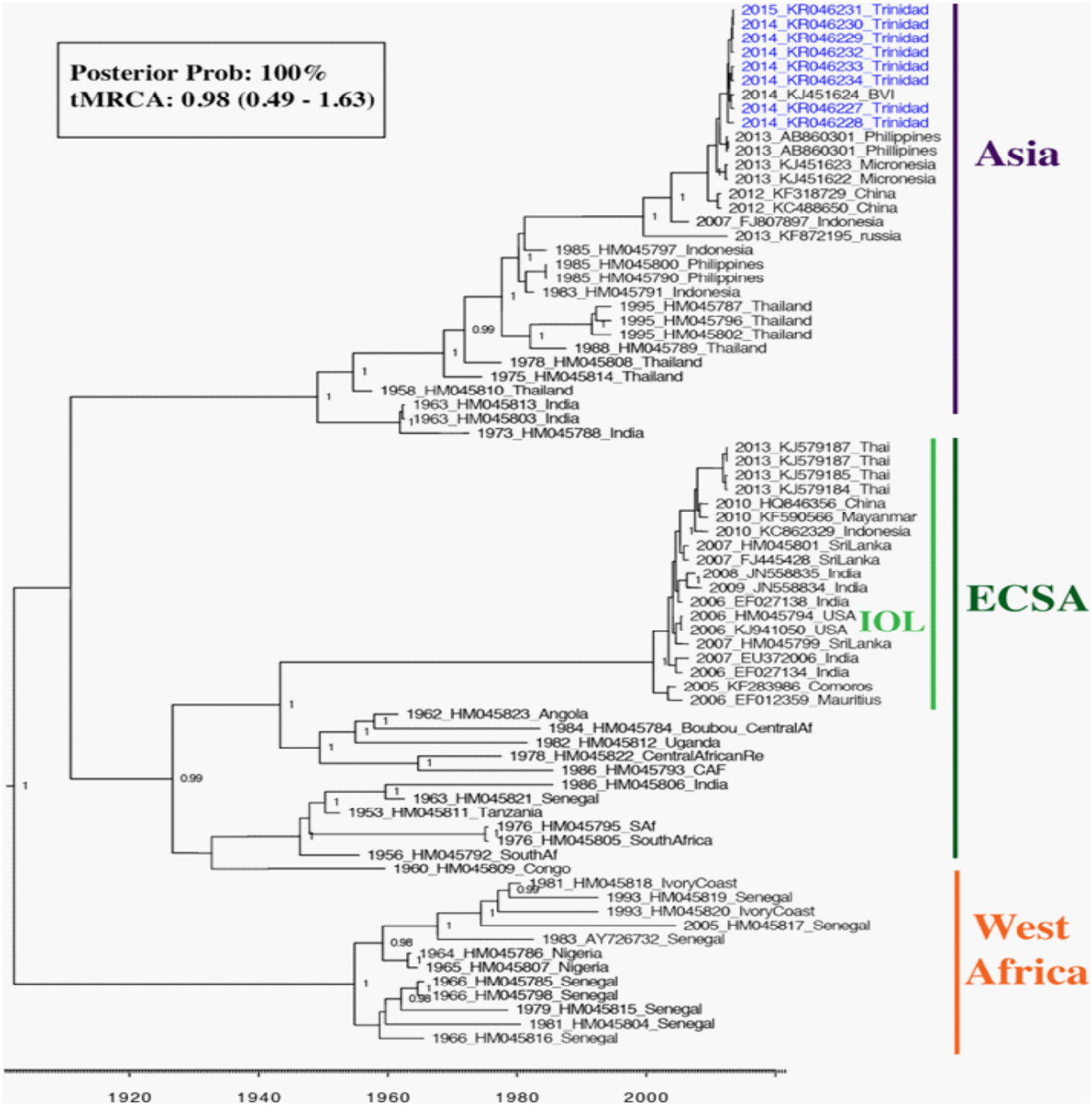

Figure 2: Maximum clade credibility (MCC) phylogeny based on the complete coding region of 74 chikungunya virus sequences. In detail, the presence of IOL representing a novel ECSA [16].

This mutation, may have contributed to the adaptation of the virus to the *Aedes albopictus* mosquito, leading to the resurgence of CHIKV in 2004. In addition, another adaptive mutation was identified and analyzed, the E2-L210Q point mutation that was identified in the E2-glycoprotein coding region. This mutation contributed to the increase in CHIKV infection in both mosquitoes and cells, and it acted mainly on epithelial cell infection [17,18]. These two mutations have been shown to cause a dramatic increase in CHIKV infectivity with spreading to Europe and the Americas due to the widespread distribution of the *Ae. aegypti* and *Ae. albopictus* vectors [16,19,20].

Like all alphaviruses, CHIKV enters the target cell by endocytosis facilitated by the interaction of the E2 envelope glycoprotein with receptors on the surface of the target cells, which may be fibroblasts, macrophages, monocytes or endothelial cells [21,22]. Some receptors (DC-SIGN, L-SIGN, heparin sulphate, laminin and integrins) are implicated in the process, but their roles are still unclear [9]. Prohibitin (PHB), phosphatidylserine (PtdSer)-mediated virus entry-enhancing receptors (PVEERs), and glycosaminoglycans (GAGs) have also been suggested as CHIKV receptor proteins in mammalian cells [23–25] and ATPsynthase β subunit in mosquito cells [26,27]. It appears that these proteins facilitate the initial interaction of CHIKV with the cell surface instead of virus absorption; even CHIKV can proceed in the absence of such proteins.

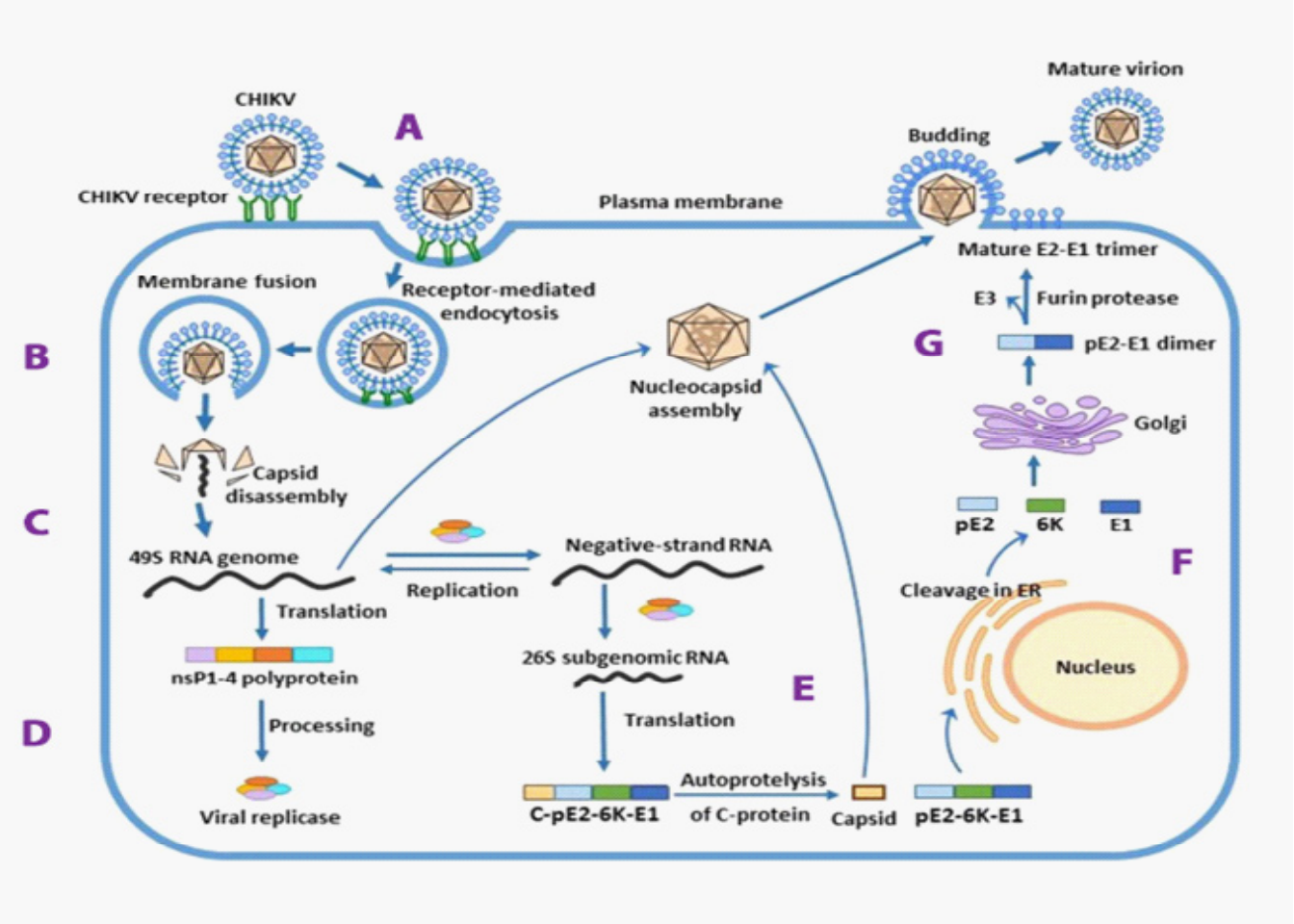

Figure 3: Schematic representation of the replication cycle of chikungunya virus.*The figure was adapted from Abdelnabiet al., 2015* [28]

CHIKV enters the cell by endocytosis following the binding of the E2 protein to specific receptor(s) on the cell surface(A). Within the endosome, conformational changes occur in viral envelope glycoproteins due to the low pH environment, allowing for fusion between the E1 envelope glycoprotein and the endosomal membrane (B) [29]. There is release of the viral nucleocapsid in the cytoplasm where it is disassembled to release the viral RNA genome (C).

There by, the viral genome is translated by the host cell machinery to generate a non-structural polyprotein that is cleaved to produce the nsP123 precursor and free nsP4 protein. The nsP123 precursor interacts with nsP4 and host cell proteins to form an initial replication complex (viral replicase) that synthesizes the negative strand RNA (D) [21]. The negative strand RNA is then used as a template to synthesize positive-stranded genomic RNA and sub-genomic RNA (26S RNA) that drives the expression of the polyprotein precursor (C-pE2-6K-E1) (E) [29,30].

The capsid protein (C) is then released from this polyprotein by its autoprotease activity, while the remaining polypeptide pE2-6K-E1 is processed in the endoplasmic reticulum (ER) (F). Glycoproteins pE2 and E1 form heterodimeric complexes that migrate to the cell membrane through the Golgi complex. During this migration to the cell surface, pE2 is cleaved by a cell furin or furin-like proteinases to form mature E2 and E3. Finally, nucleocapsid complexes collect in the cytoplasm and sprout through the cell membrane by acquiring a lipid bilayer envelope containing virus-encoded E1-E2 glycoproteins (G) (**Figure 3**) [29].

3. Transmission Cycle

There are two distinct CHIKV transmission cycles that have been characterized: enzootic/sylvatic and urban. The enzootic cycle occurs in Africa, where arboreal mosquitoes, mostly Aedes and Culex species,such as *Ae. furcifer, Ae. vittatus, Ae. fulgens, Ae. luteocephalus, Ae. dalzieli, Ae. campaxhynchites, Culex annulirostris,* and *Mansonia uniformis.* Nonhuman primates would be the main reservoirs and hosts of amplification with high seroprevalence rates and levels of viremia in response to experimental infection [31]. The main CHIKV vectors of urban cycle are *Ae. aegypti and Ae. albopictus.* The enzootic transmission cycle can spread to infect people who live near enzootic mosquito vectors that may be involved in an interhuman transmission during small outbreaks (**Figure 4**). CHIKV was introduced in urban areas through the anthropophilic vectors present at the site, initiating human-mosquito-human transmission leading to epidemics in Africa [32].

CHIKV can initiate a sustained, urban transmission cycle that only relies on *Ae. aegypti* and/or *Ae. albopictus* and human amplification hosts. This endemic/epidemic cycle results in high levels of human exposure to mosquito transmission, particularly because these vectors live in close proximity to people [32]. *Ae. aegypti* and *Ae. albopictus* are species that have some significant differences, such as the high degree of anthropophily and the preference for

more anthropic sites as well as lower vegetation cover by *Ae. aegypti,* which is the opposite of what occurs with *Ae. albopictus* [33,34]. Both species share similarities in their life cycle and mode of reproduction [22,35].

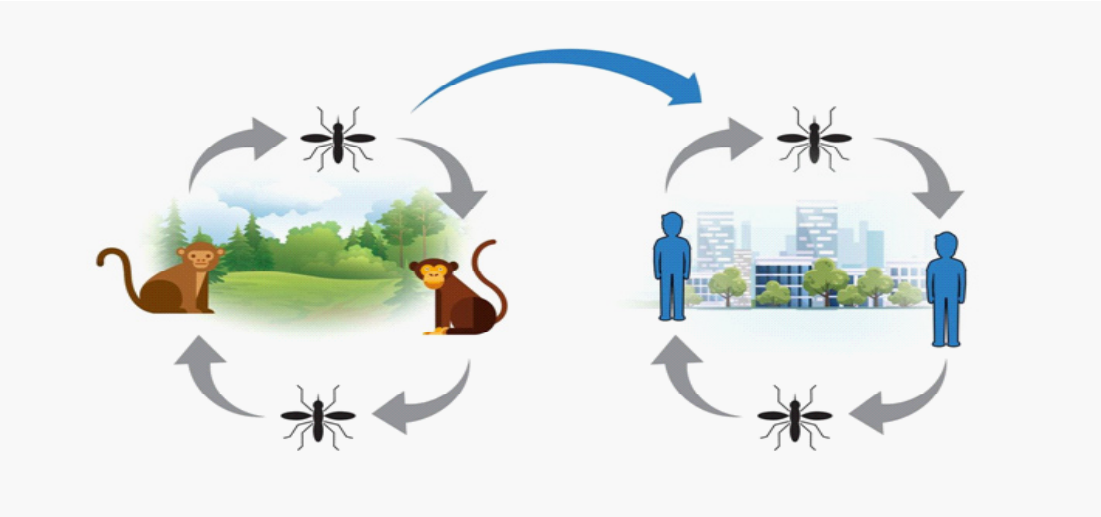

Figure 4: Life cycle of the Chikungunya virus in Africa showing the interconnection between the sylvatic cycle on the left and urban cycle on the right. The virus is maintained in a sylvatic cycle consisting of non-human primates and different species of forest-dwelling mosquitoes including Aedini mosquitoes (Ae. Africanus, Ae. furcifer-taylori, Ae. dalzieli, etc.). The urban cycle virus is maintained between the mosquitos *Ae. aegypti* and *Ae. albopictus* and humans.

The biology of *Ae. aegypti* is ideal for the development of epidemic events because this species is extremely urban and human-related. Adult females mainly feed on humans, and they are known for gonotrophic discordance (females often have several partial blood meals during a single gonotrophic cycle). This increase significantly affects the chances for virus transmission. Females tend to deposit and spread their eggs in artificial containers as preferred locations for their larvae, and they rest inside houses with ready access to human hosts [31].

The main form of dissemination of CHIKV is through the bite of infected female mosquitoes, although there are cases in which maternal-fetal transmission occurs [36] and there is the risk of transmission through blood transfusion as with other arboviruses. However, this event involving CHIKV has not yet been confirmed [37].

Ae. albopictus is zoophilic and anthropophilic, aggressive, silent, active throughout the day, and has a longer lifespan than other mosquitoes (up to 8 weeks). In recent decades, it has spread to several areas that are known to be *Aedes* free [38]. It appears that most of the new introductions of *Ae. albopictus* were caused by diapause eggs contained in timber and tires exported from Asia around the world. *Ae. albopictus* eggs can persist in diapause during low winter temperatures that are unfavorable to adult survival.

Although the infectivity of different CHIKV strains varies widely for both *Ae. aegypti* and *Ae. albopictus,* humans develop high-titer viremias that generally persist during the first 4 days after the onset of symptoms, with peaks estimated on the first day of symptoms at approximately 9 viral RNA copies/mL and infectious titers sometimes exceeding 7 PFU/mL. These titers generally exceed the oral infectious dose 50% levels for both epidemic vector species,

allowing efficient transmission among humans by mosquitoes [7]. Humans serve as a reservoir for CHIKV during urban epidemic periods, and other vertebrate hosts, such as monkeys, rodents, and birds, serve as a reservoir for the virus to keep circulating in the environment [39].

3. Global Expansion and Epidemiology

According to Diallo and colleagues (2016), some ecological factors can potentially contribute to dissemination of CHIKV, such as the temperature, which impacts human migration and the mosquito presence area range; rainfall and vegetation; the availability of breeding sites and new vector species; and human demographic changes linked to population movements due to migration, tourism, and global trade [35].

The number of countries reporting Chikungunya fever cases has increased and reflects the growing number of reported cases and people affected by this disease (**Figure 5**) [40]. The described scenario has roots in factors related to the selection of insecticide-resistant populations, climate changes, globalization and the human population´s disregard for eliminating potential mosquito breeding sites. Other factors include the absence of a specific vaccine and medication and the low efficiency of conventional methods for mosquito population control, which is caused by the precariousness of the offered services [2–5].

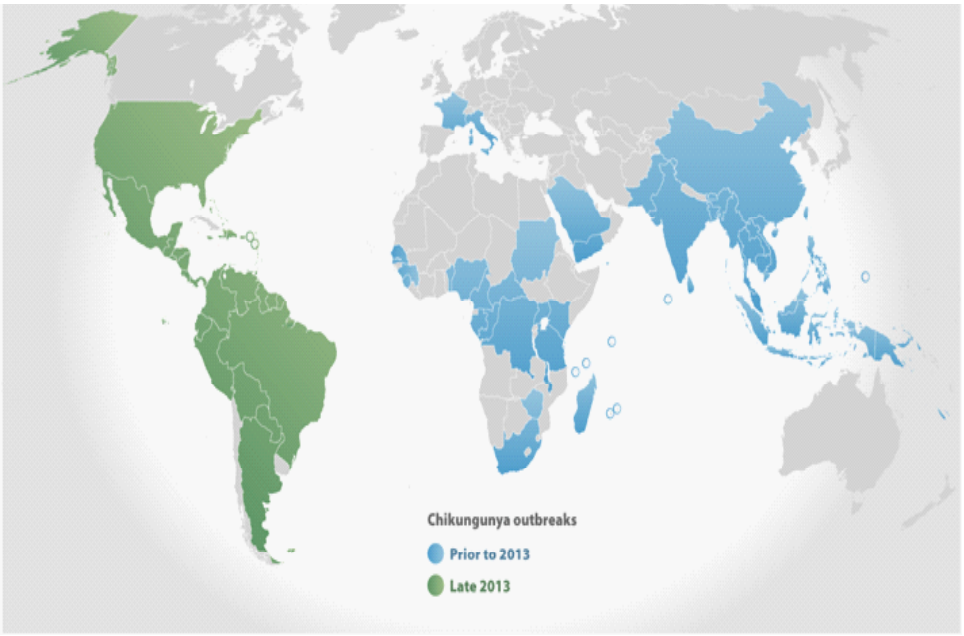

Figure 5: Distribution of chikungunya virus all over the globe, concentrating mainly on tropical and subtropical regions according to PAHO/WHO [42]

CHIKV was first isolated in 1952 after an epidemic in Tanzania [4,43,44]. Later on, other countries also started to report Chikungunya cases outside the African continent, especially in Asian countries (1958–1973) [45].

The major outbreak period was between 2004 and 2007; according to the World Health Organization (WHO), more than 272,000 people were infected during an outbreak of Chikungunya in the Indian Ocean islands, including La Reunion and Mauritius, Organization (WHO), more than 272,000 people were infected during an outbreak of Chikungunya in the Indian Oc

ean islands, including La Reunion and Mauritius, where *Ae. albopictus* was the presumed vector. This outbreak wave might have started in Kenya (after disease re-emergence), and it was later spread to the Indian Ocean Islands. A mutated CHIKV may be responsible for this rapid spread; once it improves the vector competence of *Ae. albopictus* makes this mosquito more relevant in the transmission process and not only *Ae. Aegypti* [2,19,45,46].

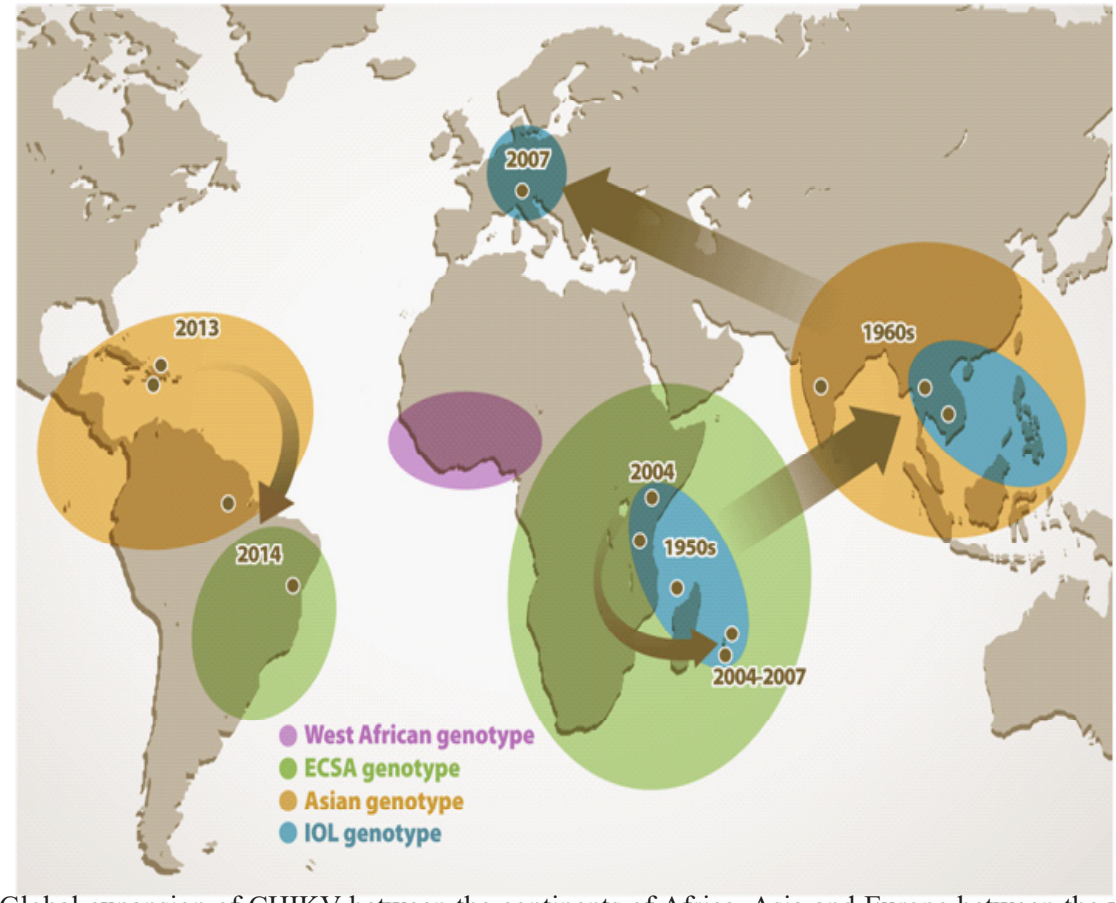

Figure 6: Global expansion of CHIKV between the continents of Africa, Asia and Europe between the years of 1950 and 2015. It originated in Africa, radiated to Asia, Europe and later to America.

The inclusion of a second species transmitting the virus allowed it to reach a wider range of areas, such as Europe during the Italian outbreak in 2007 [47]. The possible reason for the Italian outbreak was the migration of people infected with the virus, who introduced the infection in a coastal village in Italy. This outbreak (197 cases) confirmed that mosquito-borne outbreaks by *Ae. albopictus* are plausible in Europe [2]; later on, cases of Chikungunya were also reported in Croatia [48].

The Union of Comoros had, in 2005, 63% of their main island population infected with CHIKV; the entomological surveillance also detected virus circulation in the *Ae. aegypti* population [49]. In 2006, an outbreak in India had more than 1.5 million cases of Chikungunya with *Ae. aegypti* implicated as the vector [2].

The first reported/confirmed case in the Americas occurred in 2013 on Saint Martin Island [28,50,51]. However, dengue-like infections that were previously reported could have been Chikungunya instead of Dengue, which could be related to an unclear diagnostic protocol or crossed infections [44]. In 2015, the PAHO mentioned more than 690,000 suspected cases

and more than 37,000 confirmed cases of Chikungunya. From the total number of suspected cases, Colombia was responsible for around 350,000 of them with fewer than 150,000 laboratory confirmed cases. Also, Brazil contributed 265,000 suspected cases. However, in 2014, more than 1 million suspected cases were reported in the same region (**Figure 6**) [2].

4. Symptoms, Diagnostic and Treatment

CHIKV has an incubation period that usually takes between 3 and 7 days, but it may range from 1 to 12 days. The viremia period is approximately 10 days, starting 2 days after the beginning of symptoms. Approximately 70% of the infected individuals have symptoms, but they have a very low mortality rate [52].

Chikungunya fever presents in three distinct phases, the acute, subacute and chronic phases. The first is an acute or febrile phase in which the symptoms are characterized by high fever with a sudden onset and polyarthralgia, which occurs in approximately 90% of the cases and is accompanied by back pain, headaches and fatigue. Retro-ocular pain, chills and conjunctivitis may occur at this stage as well. The fever usually lasts until the fourth day [53].

The subacute phase occurs soon after. At this stage,a fever is not usually present. Severe arthralgia occurs, which can lead to immobilization of the patient; myalgia; pain affecting the head, throat and muscles; red spots; skin eruptions; constipation and conjunctivitis. During diagnosis, there are descriptions of additional symptoms, such as generalized pruritus; maculopapular rash; and the onset of purpuric, vesicular and bullous lesions. In rare cases, peripheral vascular disease and fatigue may develop [54,55].

The chronic phase corresponds to the period after 3 months from the initial symptoms, but in some cases can evolve to the chronic phase. At this stage, some symptoms may vary according to the sex and age of the infected individual and may manifest mainly as inflammatory polyarthritis and tenosynovitis [56].

Most patients remain symptom-free for approximately 4 months, but it is common to last for 20 months. In less frequent cases, the symptoms may remain for years, as in a case of a patient who had chronic rheumatism at 24 months. In addition, the presence of CHIKV-specific IgM antibodies has also been reported [57,58].

In their research, Sissoko [57] observed that those over 45 years of age are more susceptible to developing persistent arthralgia. Other factors, such as underlying disorders and severity of pain during infection, may also increase the duration of symptoms [58,59]. Other manifestations were documented during an epidemic, such as neurological, ocular and hemorrhagic complications [60].

Atypical and severe manifestations may occur when CHIKV-infected patients are also

infected by immunological viruses or during drug toxicity. In those cases, the patient may not have fever or joint pain (**Figure 7**) [61–64].

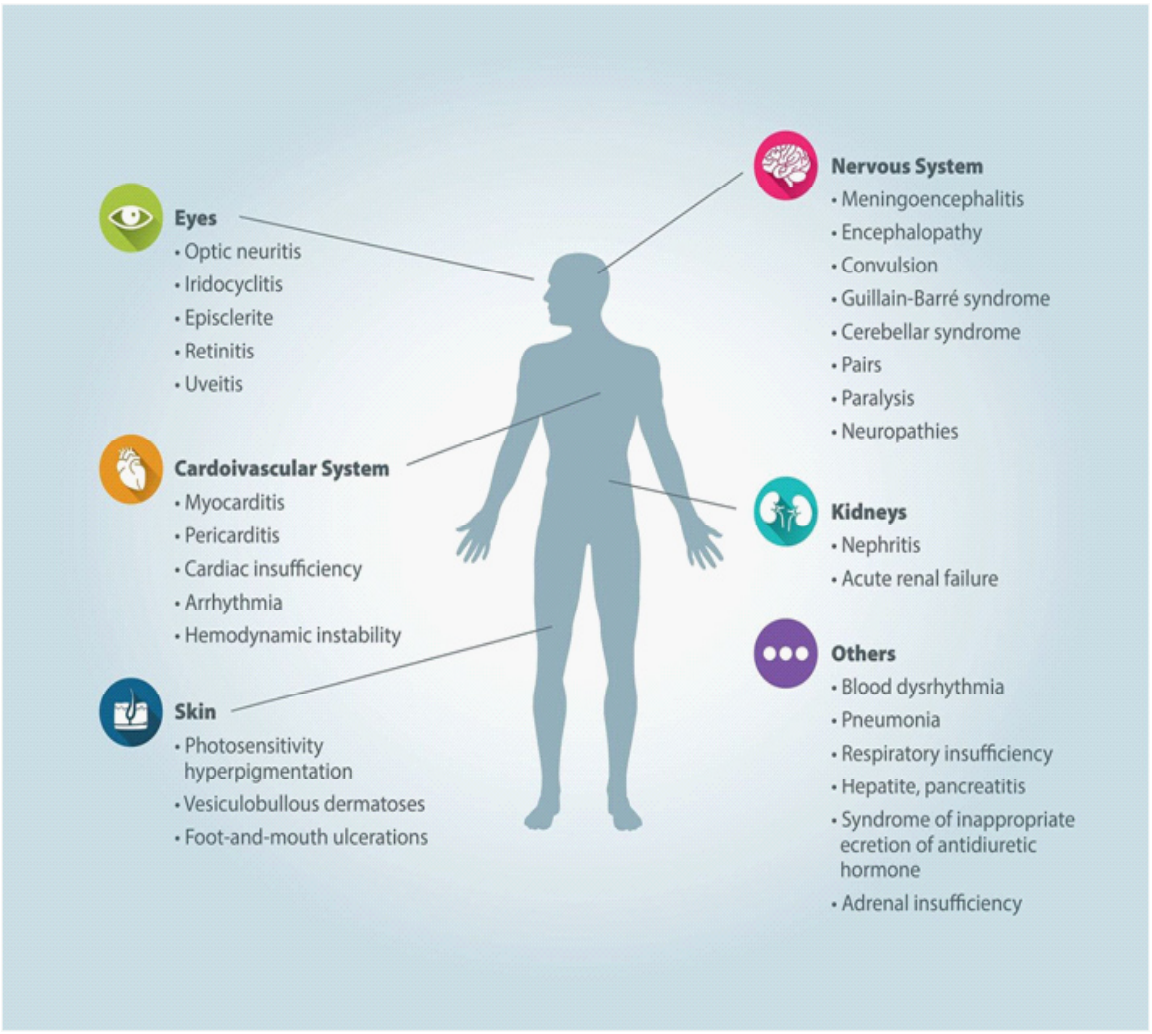

Figure 7: Atypical manifestations in CHIKV-infected patients, showing the system and organs affected as well as the resulting manifestations.

CHIKV infection is usually more severe when it occurs in newborns, children, people over 65 years old, and people with pathological comorbidities such as febrile convulsion, diabetes, asthma, heart failure, alcoholism, rheumatic diseases, sickle cell anemia, thalassemia and hypertension. CHIKV infection may also develop to a severe stage in patients using aspirin, anti-inflammatory medications and high doses of paracetamol [64].

Vertical transmission of infected pregnant women is 48%. In the first trimester of pregnancy, CHIKV infection is usually severe and may lead to fetal death [65]. Vertical transmission in pregnant women has also been documented in the last trimester of gestation. In newborns, the symptoms can appear on the fourth day after birth and may develop as a fever, difficulty feeding, cutaneous manifestations, pain and distal edema [65,66].

In severe cases, neurological complications including cerebral edema, intracranial hemorrhage, seizures and encephalopathies may occur in addition to hemorrhagic complications and myocardial involvement [67]. Children usually have the same symptoms as adults. They may have neurological manifestations, such as seizures, altered level of consciousness, blind-

ness, and acute flaccid paralysis [58,68].

It is not possible to detect CHIKV only by analyzing the clinical picture of the patients because it is easily mistaken for other arboviruses such as Dengue and Zika. Cases of double simultaneous infection of more than one arbovirus have also been reported. The Zika virus (ZIKV), Chikungunya (CHIKV) and Dengue (DENV) co-circulate in much of the tropical Western Hemisphere. Three cases of patients in Ecuador who had co infection with ZIKV-CHIKV and three cases of CHIKV were reported. The cases were diagnosed through the Polymerase Chain Reaction using the Reverse Transcriptase Reaction in Real Time (RT-qPCR) [69]. There was evidence of coinfection among DENV-CHIKV in several countries, like Angola, Gabon, India, Madagascar, Malaysia, Myanmar, Nigeria, Saint Martin, Singapore, Sri Lanka, Tanzania, Thailand and Yemen (**Figure 8**) [70,71].

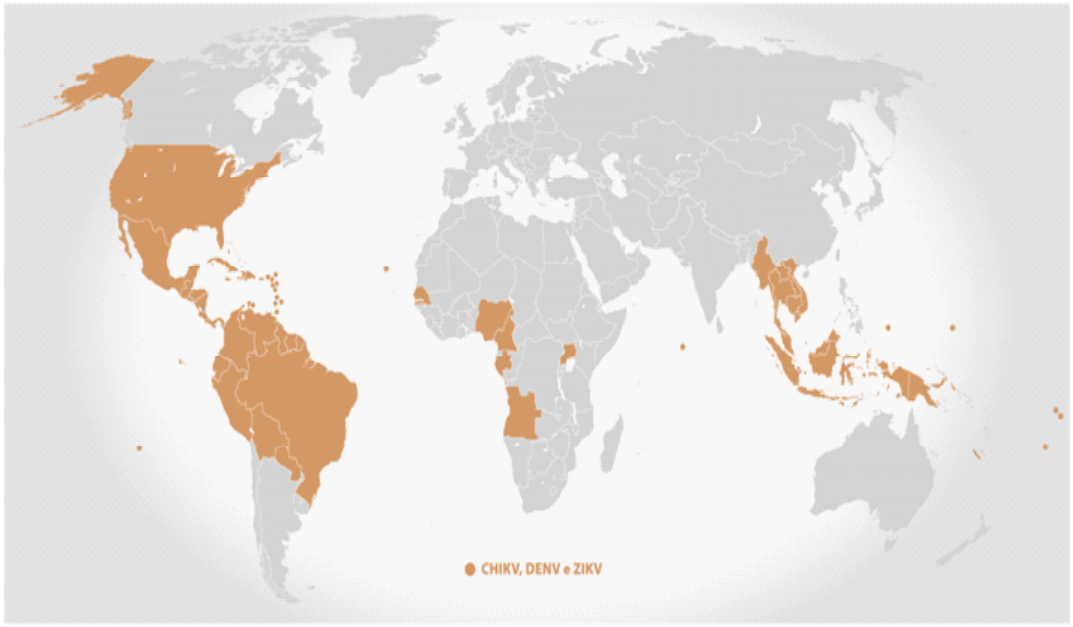

Figure 8: Countries with past or current autochthonous transmission of CHIKV, DENV and ZIKV.

Seventeen samples of CHIKV-positive sera were collected during the dengue outbreak in Delhi in 2006, and six of the 17 samples were positive for both CHIKV and DENV [72]. Another study by Wagoner et al. analyzed serum samples from 346 patients with suspected arboviral disease during the acute phase. A multiplex RT-qPCR was performed for ZIKV, CHIKV and DENV, and the detected viremia for each virus was quantified. Two hundred sixty-three patients were positive for a virus, 192 were positive for a single virus (monoinfections), and 71 were positive for 2 or all 3 viruses (coinfections). For each virus, the mean viremia was lower in coinfections than in monoinfections [69,73].

Laboratory tests are the fastest and most efficient method for diagnosing CHIKV infection. The reverse transcriptase reaction followed by polymerase chain reaction (RT-PCR) is a molecular method that can identify the genetic material (RNA) of the virus in the blood. Another method is real-time accelerated reverse-transcription-loop-mediated isothermal amplification (RT-LAMP); this method is similar to RT-PCR, but the cost of analyzing the samples is lower [74–76]. The sensitivity of the LAMP method is 2.7 copies/reaction for CHIKV, and -

no sophisticated instruments are required, which makes this method adaptive to field diagnosis and small-scale hospitals [77].

The rapid diagnostic test of CHIKV is a tool for faster virus detection. The serology test detects the presence of antibodies in the patient's blood. In this method, serodiagnostics are used for detecting immunoglobulin M (IgM) and immunoglobulin G (IgG) against CHIKV in blood and serum samples [78]. Two days after infection, it is already possible to detect the presence of IgM and IgG antibodies through an ELISA immunofluorescence assay. However, only IgG antibody remains in the serum for a longer period of time [79,80].

Virus isolation in cell culture is also used. This method can identify small levels of virus. The samples collected during the viremia period are inoculated into mosquito culture cells or in mammalian cell culture. However, because this approach requires more time, from 7 to 12 days, it is not commonly used [64].

To date, there are no vaccines or antivirals for the preservation and treatment of CHIKV. The therapy used is palliative and focuses on relieving the symptoms alone; it is used in combination with hydration and rest care. Symptomatic treatment consists of the use of analgesics, such as paracetamol; non-steroidal anti-inflammatory drugs (ibuprofen, naproxen, diclofenac, nimesulide, and acetylsalicylic acid); antipyretics and saline solution [58,64]. Aspirin is contraindicated in the acute phase because there is a risk of developing Reye's syndrome and bleeding [64].

Several studies have been performed to better understand the genomic structure, replication cycle and functions of viral loci and proteins in different alphaviruses. These studies showed that the vertebrate immune system eliminates viral infections through apoptosis in a few days, which is a very short time interval compared to invertebrates. However, CHIKV infection in humans is mainly characterized by the persistence of symptoms for a long period of time. According to recent studies, CHIKV has tropism for muscle satellite cells, which serve as a reservoir for the virus [5,71,81].

5. Vector Control and CHIKV

There is no current vaccine for CHIKV. Therefore, preventive measures to reduce transmission are a primary focus for decreasing human-vector contact and vector control [82]. Hence, the vector control associated with entomological surveillance is used to reduce and maintain the vector density below the levels of epidemic transmission [35].

To perform vector control, a methodology known as Integrated Vector Management (IVM) is used, a strategic control approach that is promoted by the WHO. According to the WHO [83], the IVM is defined as “a rational decision-making process for he optimal use of

resources for vector control," and it considers the following five elements: advocacy, social mobilization and legislation; collaboration within the health sector and with other sectors; an integrated approach to disease control; evidence-based decision-making; and capacity-building. In this sense, the IVM proposal is that control is not only a health sector, but it is a network of collaboration between the public, private and community sectors, the latter of which is a key factor to guarantee the sustainability of actions [84].

The IVM consists of several interventions with proven effectiveness, which are used separately or together, aiming at viable economic control and reducing dependence on any single intervention. This strategy also helps reduce the selective pressure of resistance to insecticides, increasing the useful life of insecticides and/or drugs [84].

IVM, as the main *Aedes* control measure, seeks to eliminate the vector in all life stages through either eliminating breeding sites, which permit the larval development, or eliminating the adult mosquitoes using insecticides [85]. The first type of control is achieved by making it impossible for mosquitoes to access these containers or by constantly emptying and cleaning them, eliminating the aquatic stages of mosquitoes using insecticides or biological control agents. Adult control involves chemical control methods that can be applied with residual surface treatments or space treatments [83]. According to the WHO [86], the control methods, which are categorized into environmental, biological and chemical, can be used separately or in combination.

5.1. Environmental methods

This strategy aims to change the environment to prevent or minimize the spread of vector and human contact with the vector-pathogen. It is based on removing, destroying, recycling or preventing the possibility of containers that accumulate water (temporary), such as bottles, disposable cups, gutters, and other potential breeding grounds. Also, permanent containers (i.e., water tanks and barrels) are covered. Additional approaches are adequate disposal of tires, installation of screens in the windows of homes and the improvement of services of adequate water distribution to the population. These actions could be the pillar of dengue vector control [86].

5.2. Biological methods

This approach is based on the use of predatory and parasite organisms of mosquitoes or competing species that reduce their populations. Some larvivorous fish and predatory copepods (small freshwater crustaceans) are examples of organisms that can be used against the immature larval stage vector. These organisms should be appropriately raised and distributed to potential mosquito breeding sites [86].

5.3. Chemical methods

This type of method can be used to target larval (larvicidal) and adult (adulticide) stages of the mosquito. Chemicals used as larvicides are restricted to containers that cannot be handled according to environmental control, except in emergency situations. Containers for water storage (i.e., water box) should be of low toxicity to other species and should not change the color, odor or taste of water (the WHO has specific guidelines on the use of chemicals in drinking water). Regarding adulticides, their use is intended to impact some parameters of mosquitoes linked to disease transmission, such as population density and longevity. Adulticides may be applied to either 'residual surface treatments' or 'space treatments'. The first one is indicated for specific routine use in real estate and concentrates many potential breeder containers. The space treatments seek to rapidly and largely destroy the vector population, and it is only recommended for control in emergencies to reduce or prevent an epidemic [86,87].

The implementation of the current vector control methodologies faces difficulties that compromise its effectiveness. These difficulties are mainly related to urban infrastructure problems, such as disordered urban growth, inefficient and deficient garbage collection, irregular occupation of areas, and an irregular water supply [88,89]. Other difficulties are the selection of resistant populations to larvicides/insecticides or the inefficiency of the insecticide in reaching the target vector during its application [87,90,91]. Faced with the challenges encountered by the control methods (traditional methods), new tools are being developed and evaluated to complement the traditional control [89,92,93].

These strategies are being called "innovative" and involve several different areas with mechanisms of action ranging from social measures, selective monitoring, different dispersion of insecticides, and new chemical/biological control compounds to molecular procedures [89,94]. The main concepts of some of these innovative approaches will be described below (**Figure 9**). Of note, they are still being evaluated in pilot tests.

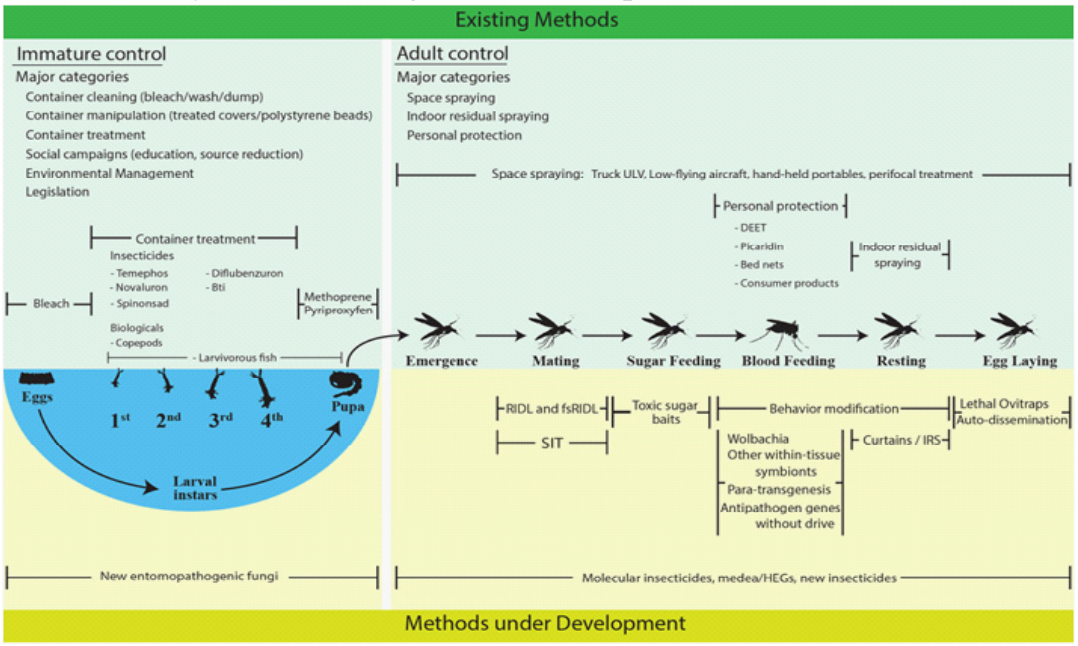

Figure 9: Examples of existing and developing *Aedes* control methods. Bacillus thuringiensis israelensis (Bti), Female-specific flightless OX36404C (fsRIDL), Indoor residual spraying (IRS), Maternal effect dominant embryonic arrest (Medea), Homing endonuclease genes (HEGs). *The figure was adapted from Achee et al., 2015* [90].

5.4. Eco-bio-social control

This approach is conducted by various sectors of the community and includes health and environmental education to avoid pesticides. Therefore, the activities focus mainly on eliminating water reservoirs and covering potential breeding sites (working not only to remove the mosquito but also correcting or minimizing the social and environmental deficiencies that favor proliferation). It also involves installing screens on windows and doors [89]. This type of strategy allows those agents, formerly mere receivers of information, to also be agents of vector control [95–97].

5.5. Autodissemination

This approach uses the mosquito itself to spread larvicide in the potential breeding sites. In this strategy, *Aedes* females are attracted to "dissemination stations" (breeding impregnated with the larvicide pyriproxyfen powder), which are distributed throughout the city. When these containers are used as breeding grounds by *Aedes* females, the larvicide will attach to the female's body. Then, when this same female visits another breeding site, the larvicide present in this female will contaminate the water there, making the container incompatible with the survival of the immature mosquito forms [89,98].

5.6. Autocidal control

In 1950, a species-specific technique for insects was developed for birth control of its own population [99]. SIT can control agricultural pests, and several species have developed their own programs. There are numerous success cases [100]. The approach involves the mass rearing of target species, sterilization (via an ionizing source or chemosterilizer) and subsequent release of sterile males. After mating this sterile male, the generation of offspring will be made unfeasible, reducing the reproductive potential of the wild population over time [99,101,102].

Other SIT-based technologies have been developed, such as the "Release of Insects carrying a Lethal gene" (RIDL) [103], and the Incompatible Insect Technique combined with SIT (IIT/SIT). The RIDL technology uses a transgenic *Ae. aegypti* strain carrying a gene responsible for conditioned mosquito lethality, which is transmitted to the offspring after copulation of the transgenic male with the wild-type female [103–105].

Regarding IIT/SIT, the technique is based on the use of a symbiont that is naturally found in populations of several species of insects, the *Wolbachia* bacteria. Males infected with

this bacterium, when copulating with uninfected females, have their offspring affected by Cytoplasmic Incompatibility (CI) that occurs at the time of embryo fertilization [106,107]. The Wolbachia, as a control tool, can be used in another approach, as well as with infected mosquito release, with the purpose of replacing the natural population of *Aedes* by a population infected with bacteria. Such an approach is based on the generated CI, which leads to infeasible offspring that considerably reduces the lifetime of an adult mosquito. Wolbachia's capacity can reduce or eliminate arbovirus transmission, including CHIKV [89,94,108,109].

The innovative approaches, such as autocidal control, will likely become viable tools soon. However, until evaluations are finalized, the focus should remain on improving existing measures [93].

According to Diallo *et al.* [35], to reduce CHIKV's chances of being a threat to public health, it is necessary that control measures are effective and sustainable. However, this goal will only be achieved if perseverance and quality work are linked to a multidisciplinary scientific network (i.e., entomology, virology, and epidemiology). Even so, the success of vector control programs requires an educated and committed community.

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Chapter 2

Chikungunya: A Neglected Re-Emerging Disease

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Abstract

Chikungunya virus (CHIKV) is a re-emerging arthropod borne virus transmitted by Aedes species of mosquitoes that causes major outbreak in more than 60 countries in Asia, Africa and more recently Europe and American continents. The re-emergence of chikungunya poses major public health burden worldwide, mostly affecting low and middle income countries. The outbreak is relatively uncommon; sporadic and affects all age groups. It is a febrile disease characterized with debilitating polyarthralgia lasting for weeks to months. Although chikungunya infection has caused millions of cases, still it is poorly documented without specific preventive and therapeutic interventions. This chapter summarizes our current knowledge about the epidemiology and clinical significance of chikungunya virus, mosquito vector, prevention and control measures.

Keywords: Aedes mosquitoes; Alphavirus; Arthropod-borne disease; Chikungunya; Vaccine

1. Introduction

Chikungunya infection is considered as a neglected debilitating disease caused by chikungunya virus. The word “chikungunya” is used for both the virus and the disease, which was derived from Makonde word meaning “to walk bent over” [1]. Chikungunya virus is an arthropod-borne virus and belongs to the genus *Alphavirus* within the family *Togaviridae* that is predominantly found in tropical and subtropical regions [2]. Since its first outbreak in Tanzania in 1952, the virus poses serious threats to humans for the last few decades. The virus was first isolated from human sera in 1953 [3]. The chikungunya outbreaks are infrequent, sporadic

and known to cause major epidemics across the globe [4]. During epidemics, humans serve as the major reservoir for the virus, whereas during non-epidemic period, monkeys, rodents and birds serve as the reservoirs. Although chikungunya is not a life threatening disease, mortality was reported in some cases [5]. The US National Institute of Allergy and Infectious Diseases (NIAID) in 2008 categorized chikungunya as 'Category C Priority Pathogen' because of the associated potential risk [6,7].

Togaviridae family comprised of two genera viz., *Alphavirus* and *Rubivirus.* The genome of chikungunya virus consists of a single stranded, linear, positive sense, ribonucleic acid of about 11.8Kb and comprised of two open reading frames encoding structural (C, E2, E3, E1) and non-structural polyproteins (nsP1, 2, 3 and 4).The structural proteins undergo post-translational modifications to form two major capsid proteins namely E1, E2 and two minor proteins called E3 and 6K [8,9]. The trimers of E1 and E2 heterodimer cover the viral surface and form the spike region. The structural proteins are involved in viral encapsidation and budding during infection. The non-structural proteins are translated from 5' region of the viral genome which is essential for viral replication and processing [10].

2. Outbreaks of Chikungunya

The chikungunya virus circulates in tropics and the primary source for pathogen transmission to humans is mainly through day biting *Aedes* mosquito viz., *Aedes aegypti* (the yellow fever mosquito) and *A. albopictus* (the Asian tiger mosquito) [11]. However, maternal–fetal transmission has also been reported in the recent epidemic [12]. The regional distribution of mosquito vector indicated the predominance of *A. albopictus* in Europe and *A. aegypti* in India. The *Aedes albopictus* is diurnal with wide geographic prevalence and the mosquito's eggs can resist desiccation. All these characteristics contribute towards the efficiency of the vector in sustaining the virus and thus spreading the disease [13].

Since 2000, chikungunya has expanded its geographic range and it has now been identified in over 60 countries in Asia, Africa, Europe and American continents [14]. In Asia, CHIKV was first reported in Bangkok, Thailand in 1958. In 1963, it was reported first time in Kolkata, India, followed by Pondicherry and Vellore (1964), Barsi (1973) [15,16]. In 2005, India has witnessed a massive outbreak of chikungunya after 32 years. The southern and central parts of India were heavily affected with more than one million cases [17]. Almost one third of the population was affected in the La Reunion outbreak in 2006. The global expansion of *Aedes albopictus* caused emergence of chikungunya cases in Europe for the first time during 2007 [18]. In 2013, the first local chikungunya case in America was diagnosed in Saint Martin. Recently, in 2015, several countries in American continent were affected and about 1.1 million cases were reported [18-20].

3. Symptoms

Usually, onset of illness occurs between 2-6 days, after the humans get an infected mosquito bite. CHIKV has an incubation period of 2-4 days and often clinical symptoms are similar to dengue infection. In many cases, dengue is misdiagnosed as chikungunya [21], however, unlike dengue, chikungunya is rarely fatal [22]. Chikungunya causes severe health burden to affected populations causing severe joint pain, rashes, fever, headache, nausea and fatigue. Severe arthralgic syndrome was reported in many cases including joint pain that may last for weeks to months [23]. Other symptoms including fatigue, asthenia, peripheral edema and conjunctivitis are also reported occasionally [24-28]. The clinical manifestations are highly variable and the treatment is purely symptomatic. The infected persons are given non-salicylate analgesics and non-steroidal anti-inflammatory drugs to alleviate viremia symptoms [29].

4. Status of Chikungunya Vaccine Development

Since 1952, CHIKV cases appear intermittently across the globe calling for the need of an effective vaccine development at earliest. During the last few years, several approaches have already been explored and substantial progress is achieved for chikungunya vaccine development. Although many vaccines are in the pipeline, still there is no effective anti-viral treatment available so far [30]. Considering these facts and the dismal figures related to disease incidence, the demand for an effective, safe and cost-effective vaccine is highly recognized.

Potential candidate CHIKV vaccines are under development and some are in clinical trials. Live-attenuated vaccines, chimeric alphavirus vaccine, DNA vaccine candidates, whole-inactivated, subunit vaccines and virus-like particle (VLP) approaches are employed to develop a safe and potent vaccine [31-37]. Among these, three vaccine candidates have shown promising results in animal models. For instance, the live-attenuated vaccine (CHIKV/IRES) projected for phase I trial protects mice from animal challenge experiments and elicits strong neutralizing antibody response. The VLP based vaccine (VRC-CHKVLP059-00-VP) has shown strong immunogenicity in animal challenge experiments. Then live attenuated measles virus-based vaccine (MV-CHIK) expressing CHIKV structural proteins elicit both humoral and cellular immune response in CHIKV challenge in mice. The Phase-I trials of the two latter vaccines have successfully completed in 2014 and 2015 respectively. However, none of the vaccine has been directly tested in humans as yet [18, 38].

5. Conclusion

Chikungunya is rapidly re-emerging as a major public threat which causes significant mortality and economic burden in affected countries. The early detection and appropriate management of infected vectors could possibly reduce the extent and range of infection. Although preventive measures including mosquito vector control strategies are implemented on priority,

there is no treatment or prophylactic vaccine available to prevent the transmission of virus. The recent chikungunya outbreaks across the globe highlight an increasing trend in the disease severity and its geographical range. The authors encourage to continue such epidemiological studies to generate baseline data of disease burden in distant geographical regions and prioritize the allocation of deliberate health resources and support for the ongoing vaccine initiatives.

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Vector-Borne Diseases & Treatment

Chapter 3

Susceptibility status of *Ornithodoros moubata* to different classes of insecticides (Acaricides) in six regions of mainland Tanzania

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Abstract

Understanding the insecticides susceptibility status of the commonly used insecticides for control of disease vectors is of paramount importance in setting up control agenda. In this chapter, the biological efficacy of commonly used insecticides (Acaricides) was evaluated under laboratory conditions against field collected populations of soft ticks (*Ornithdoros moubata*) from six regions of mainland Tanzania. The aim of this study was to assess the susceptibility status of *O. moubata* and ensure safe use of these pesticides for effective control. Six regions (namely Iringa, Morogoro, Arusha, Manyara, Shinyanga and Dodoma) with high infestations of O. moubata were selected. Within each region collections were carried out in two districts which are highly infested with *O. moubata*. Ticks collected from the community houses were transported to laboratory for rearing and insecticides susceptibility bioassays. Effectiveness of these insecticides were determined by exposing batches

of unfed 1st instar nymphs of *O. moubata* in five replicates on filter papers impregnated with serial dilutions of technical grade insecticides. The susceptibility status of eight field isolates of *O. moubata* was determined. The 24 and 48 hours mortality was higher and the insecticides were found to be effective.

The use of insecticides in control of *O. moubata* in Tanzania is seemed to have tolerance variability among *O. moubata* tested. More studies on genetic information on resistance to these insecticides should be established for each region for effective control planning for *O. moubata*.

Keywords: Tanzania; susceptibility; soft ticks; resistance; *O.moubata*

1. Background

Soft ticks of the genus *Ornithodoros* (also known as tampan ticks) belong to family Argasidae [1]. *Ornithodoros moubata,* the commonest soft tick is widely distributed in Tanzania [2-5]. These ticks inhabit mainly in human traditional huts with wall and floors with cracks, sands under trees where animals and humans often seek shelter during the day, they occur mainly in semi arid and arid areas [3]. They hide in cracks, crevices of walls and in floors with loose soils during the day and emerge at night for feeding on man or animal host present [1, 6]. They feed fast in presence of host and can survive for long duration of at least five or more years without food [1,7,8]. In Tanzania, *Ornithodoros moubata* as been found to be the vector for *Borrelia duttoni*, it has been reported that infestation rate of *Ornithodoros spp* by *Borrelia duttoni* to be more than 60% in Dodoma region where epidemics of tick-borne relapsing fever has been reported [9]. *O. moubata* are of medical importance as they cause nuisance and transmit tick borne relapsing fever (TBRF) caused by the spirochete *Borrelia duttoni*. Many cases have been reported from pregnant women (7.5% routinely attending Maternal and child health (MCH) centers in Dodoma) [4] and children, 75% and 55% in Dodoma and Mwanza regions respectively [10]. Spirochetes have been found in blood during febrile periods [11]. Transmission of TBRF by *O. moubata* is transovarial or transstadial [1,6]. Transstadial transmission occurs when immature and adult *O. moubata* suck blood from an infected host [12]. According to Service, houses infested with *Ornithodoros* species showed a remarkable density reduction when treated with insecticides (acaricides) sprays or dusts such as5% DDT, 3% Malathion, 5% carbaryl (Sevin), 0.5% Naled (Dibron), 0.5% Diazinon or 1% Propoxur [1,6].

Recently, newer acaricides with low human toxicity have demonstrated to be effective against *Ornithodoros* species both under laboratory and field conditions [13,14]. Vasil'eva and others reported that, *O. pappilipes* demonstrated reduced susceptibility with 40% mortality to Dieldrin, Malathion, Propoxur and Bendiocarb; while in DDT susceptibility was reduced to 60% mortality, and in deltamethrin mortality was observed to be 100%, completely susceptible to deltamethrin [14]. The field trial carried out in Magugu ward with Sevin powder (Carbaryl),

doom powder (Permethrin) and Doom spray (Permethrin) in houses infested with *O. moubata* in Matufa village found out that, the Permethrin formulation provided 100% mortality of the soft ticks within two weeks while Carbaryl provided 100% mortality of the ticks after three weeks [15]. Lambdacyhalothrin (Icon), used for indoor residual spray, permethrin and deltamethrin used on treated bed nets for the control of mosquitoes have been reported to reduce TBRF cases in Dodoma region in Tanzania [13].

In Tanzania, a surveys were carried out by Tropical Pesticides Research Institute (TPRI) between September 2003 and February 2004 in Dodoma, Shinyanga, Morogoro, Iringa, Arusha and Manyara regions revealed that, the communities use arbitrarily acaricides/insecticides meant for controlling agricultural, household pests and ticks of veterinary importance [16,17]. Moreover, the use of these chemicals was not based on susceptibility tests to ascertain their effectiveness. Such misuse of pesticides might have caused tolerance of Insecticides used in public health in *O. moubata* and the resistance may therefore interfere with the results of control measures in future. Also the current wide coverage and use of long lasting insecticides treated nets [18,19] have been the source of insecticides resistance to other ectoparasites observed in Tanzania mostly bed bugs [20-23]. The aim of this current chapter is therefore to report the efficacy of the commonly used insecticides (Acaricides) in controlling soft ticks *O.moubata* sampled from six regions of the mainland Tanzania.

2. Methods

2.1. Study area description

The regions involved in this study were Iringa, Morogoro, Arusha, Manyara, Dodoma, and Shinyanga. All these regions had reported relapsing fever cases before. In all infested region, a infested district was selected. In each district one ward was selected based on number of relapsing fever reported (i.e. the one with highest number of cases was prefereed) and within a ward two to three villages infested with *O. moubata* were surveyed. During the survey in each village, 20 houses were randomly selected for the assessment and collection of *O. moubata* as this is the maximum number of houses which could be managed. Samples of ticks collected from such houses provided representative samples as it was assumed that communities within the same village have similar practices and civilization. Tick surveys and collections were carried out between 2003 and 2004 while rearing of tick colonies and susceptibility tests were carried out from 2005 to 2008.

2.2. Tick collections

The regions with high infestations were selected based in the information obtained from ministry of health. In each region districts were selected and subsequently villages. From the selected houses in each village, loose soils were collected using a hand shovel from the sitting

room, bedside, kitchen (around fire place), and chicken roost areas at night. These sites were selected because people and chicken spend most of their time around while in the house, thus are preferred by ticks for easier blood meal access. The soils were taken outdoors and sieved to check for ticks as they tend to move away when exposed to light. Ticks were picked using forceps and kept in specimen tubes. Ticks were identified using morphological identification keys and subsequently reared while fed with rabbits and chicken for susceptibility tests [24]. Ticks collected from the field were divided into two batches. One batch was taken to Sokoine University of Agriculture (SUA) for parasitological work of *B. duttonii* in ticks and the other batch was reserved for rearing at Tropical Pesticides Research Institute (TPRI) for insecticides susceptibility tests.

2.3. Establishment of *O. moubata* tick colonies

The ticks (at various developmental stages) collected from the different areas in the field from six regions of Tanzania (Iringa, Morogoro, Dodoma, Arusha, Manyara, Shinyanga and Dodoma) (**Table 2**) were fed on rabbits (Chinchilla X New Zealand White breeds) or local chickens respectively. Ticks were the maintained under laboratory conditions at temperature between $28+^{0}1$C and at a relative humidity above 85% at TPRI so as to obtain adequate amounts of larvae for susceptibility tests.

2.4. Evaluated chemical products

Technical grade of pesticide classes used were organophosphates, organochlorides, synthetic pyrethroids and carbamates (**Table 1**). The pesticides chosen for the tests are either widely used for control of other vectors or are having the promise to control the tick. Serial dilutions of technical grade pesticides (**Table 1**), were prepared using olive oil and trichloroethylene (Trilene) at 1:2 ratio as recommended by FAO (Stone et al., 1962). Trilene with olive oil alone was used to impregnate untreated control filter papers. Test papers were impregnated in the complete range of concentrations and were left to dry at room temperature (in a ventilated room) for 1 hour before exposing the ticks (Stone et al., 1962).

2.5. Susceptibility tests

First instar nymphs [10-14] day old were used for the tests. Batches of [10] nymphs of *O. moubata* per concentration were exposed to filter papers impregnated with insecticides (Anon 1971). Before and after treatment ticks were held at temperature between $28+^{0}1$C and at a relative humidity above 85%. Mortalities at each concentration were determined at 24 hours and 48 hours after exposure. In discriminating the resistant population of ticks form different regions, we adopted the cutoff point method developed by World Health Organization [25]. The population found to have mortality below 90% was considered resistant after 48 hours of monitoring. In data analysis regression probit analysis was not d due to small sample of ticks

collected from houses in some areas.

2.6. Ethical clearance

Ethical and scientific approval to conduct the research was obtained from Tropical Pesticides Research Institute research ethics committee, Arusha, Tanzania. Informed consent was sought orally from the village communities, before collecting *O. moubata* in houses.

3. Results

3.1. Tick collections used to establish colonies of *O. moubata* for susceptibility tests

Ticks that were collected from Usolanga, Utosi, Hoza, Njoroki, Laghangareri and Nyabubinza villages were too few to continue the colonies, while adult ticks from Nyabubinza were fed but did not lay eggs thus their colony could not be established. Ticks collected from Endagichan could not stabilize under laboratory conditions. The number of ticks in highly infested areas were sufficiently available for use in the insecticides susceptibility test between March –June 2006 and March 2008 (**Table 2**). Ticks from less infested areas continued to be reared to increase their number to facilitate trials. The data shows that infestation of *O. moubata* in some places (Usolanga and Balang'dalalu) was as high as 80- 85% of houses (Table 2). Out of the total (3983) collected *O. moubata* collected 16% was used to raise the colonies for susceptibility tests at TPRI while the remaining ticks were used for parasitological work at Sokoine University of Agriculture. There were no ticks collected from Morogoro district.

3.1. Establishment of *O. moubata* tick colonies

Our laboratory observations shows that, it takes mean days of 18 for O. moubata eggs to develop into1st nymph instar; 10.5 days from engorged 1st nymph instar to 2nd nymph instar; 13 days from engorged 2nd nymph instars to 3rd nymph instars; 13 days from engorged 3rd nymph instars to 4th nymph instars; 13 days from 4th engorged nymph instar to 5th nymph instar; 12 days from 5th engorged nymph instar to adults and 19 days for engorged adults to lay eggs. In summary, our observations show that it takes about three months for *O. moubata* to complete one life cycle; as it took us a year to raise three generations from the few field collected ticks samples and some of them did not stabilize under laboratory conditions.

3.2. Susceptibility of *O. moubata* to commonly used insecticides

The mean mortality of *O. moubata* in a population in 24hrs and 48hrs after exposure obtained for each series of concentrations tested for each insecticide (in dosemortality) were subjected to analysis of variance one way as shown in Figures 1 to 9. In all regions higher mortalities were observed to all tested insecticides was observed. Mortalities due to Alphacypermethrin exposure for all regions was below cut off point of 90%. The mortality variation be-

tween 24 hours and 48 hours was statistically significant for each region (P<0.001). There was no statistical difference in 24hrs observation among regions (df =5, F=2, P=0.089), the same was for 48 hrs of monitoring post exposure (df=5, F=1.8, P=0.132) (**Figure 1**). Mortalities induced by exposure in Cyhalothrin were found to be statistically significant for comparison of 24 hours and 48 hours of monitoring in each region (P<0.001). There was no significant difference in mortalities among regions ticks in both 24hrs (df = 5, F=0.136, P=0.901) and 48hrs (df=5, F=1.953, P=0.101) among regions (**Figure 2**). Mortality in all regions for exposure in cyhalothrin was below 90%. In each region, the comparison of mortalities in 24 and 48 hours post exposure was significant different with more mortalities encountered in 48 hours (P<0.001) except for Manyara region (P = 0.211). The deltamethrin induced mortalities comparison in ticks among regions was statistically different in 24hrs (df = 5, F=5.4, P = 0.003) but was not statistically different 48 hrs post exposure (df=5, F=2.6, P=0.064) (*Figure 3*). Only in Manyara region mortality was above 90% in 48 hrs of monitoring. For permethrin, statistical difference were observed in each regions for mortalities in 24 and 48 hours post exposure (P<0.001). The mortalities induced by permethrin among the regions compared in 24hrs was statistically different (df=5, F=2.8, P=0.031), similar trend was observed in 48 hrs (df=5, F=6.7, P<0.001), only Manyara hours region had mortality above 90% after 48 hours while there rest were below 90% (**Figure 4**). In each region, the mortality induced by dieldrin in 24 and 48 hours was statistically different (P<0.001). There was significant responses in mortalities among the regions in 24 hrs post exposure (df=5, F=5.1, P=0.002) and similar trend in 48hrs (df=5, F=6.0, P=0.001), only Iringa and Shinyanga regions had mortalities above 90% (**Figure 5**). In each region mortality in 24 hrs and 48 hours post DDT exposure was low on no mortality at all (**Figure 6**). Mortalities varies significantly within each region (P<0.001). DDT induced low significant mortalities among regions in both 48hrs (df=5, F=5.7, P=0.001) and 72 hrs (df=5, F=7.8, P<0.001) post exposure but was not significant at 24hrs (df=5, F=2.1, P=0.097), and there was no mortality observed in Dodoma region in both 24 and 48 hrs (Figure 6). Mortalities induced by Fenithion in each region were statistically different between 24 and 48 hours of monitoring **(Figure 7**). The induced mortalities among the regions were no different statistically in 24 hrs (df=5, F=1.9, P=0.114) either in 48 hrs (df=5, F=2.43, P=0.058). Mortalities exceeded 90% only in 48 hours of monitoring in Shinyanga region (**Figure 7**). In each region, the mortality differences between 24 and 48 hrs was statistically different (P=0.01) induced by Malathion **(Figure 8**). Mortalities due to Malathion exposure among regions was not statistically different in 24 hrs (df=5, F=1.52, P=0.207) but significantly different in 48 hrs post exposure (df=5, F=3.3, P=0.006). Only Iringa region had high mortality exceeding cut off point of 90% after 48 hours (**Figure 8**). In each region the mortality different between 24hrs and 48 hrs were statistically different (P=0.001), except in Morogoro and Dodoma which were not different (P=0.209)(**Figure 9**). Low mortalities induced by Carbaryl were not statistically different among regions in 24 hrs (df=5, F=0.32, P=0.901) and also in 48hrs post exposure (df=5, F=1.95, P=0.101) (**Figure 9**).

4. Discussion

Standard test papers recommended by FAO for the assessment of ticks susceptibility was used to assess the susceptibility of *O. moubata*, the agent of tick-borne relapsing fever to a number of pesticides commonly used to control other arthropods of public health and veterinary importance. The results of most synthetic pyrethroids, organochlorines, organophosphates and carbamate insecticides used in these trials had reduced mortality efficacy in controlling *O. moubata* in the six regions, however their reduced efficacy varied from one insecticide to another in these regions which indicating different degrees of efficiency for controlling the vector in future. Similar efficacy of tested products have been observed in bedbugs tested from Manyara region [20]. The low mortality of *O. moubata* to pyrethroids (permethrin and deltamethrin) has been observed in Manyara region, this study observed high mortalities to due to low coverage of insecticides treated nets in this region during the study period, while in areas with high coverage of ITNs bed bugs and mosquitoes which have been exposed to pyrethroids for long time had low mortalities observed [21,22,26-28]. Mortalities due to fenithion and dieldrin was very high in Shinyanga region in all tested ticks tested while in Iringa region mortalities above cut of point was observed in the dieldrin and malathion 48 hours post exposure. Other insecticides observed mortalities below cut off points (i.e. below 90%). This mortalities variation observed in Iringa and Shinyanga regions might have been attributed with low usage or not used at all of these insecticides. Similar scenario of having insecticides induced mortality variations between regions has been observed in other arthropods of medical importance for similar classes of insecticides [26,29,30]. For those insecticides which have shown low mortality effect in controlling *O. moubata*, the use of similar insecticides or insecticides with similar active ingredients in public health or agriculture should be surveyed and changed or rotated for resistance management [31]. Similar scenarios of resistance to insecticides which have been used for the control of other pests of public health or agriculture have been found to be the source of pests resistance to insecticides [21-23,28,32,33]. The use of different strategies to delay or avoid insecticides resistance such as combination of insecticides, rotation of insecticide and mosaic strategy have been observed to combat insecticides resistance problem in mosquitoes and might work for other arthropods such as *O. moubata* [31]. The mixtures of acaricides/insecticide with different modes of action are suggested for use against vectors is one of the strategies could be used for delaying emergence of resistance [31,34]. Alternating the use of different classes of insecticides in community for control purposes might reduce tolerance of insecticides if well used and managed [31,34].

Laboratory trials have shown a low acaricides/insecticidal activity for most synthetic pyrethroids for *O. moubata* which has been shown with other insects such as mosquitoes [19, 35], tsetse flies [36], bedbugs [20,36] and cattle ticks [36]. Therefore application of synthetic pyrethroid insecticides on bed nets (ITNs) or long lasting Insecticides nets (LLINs) against

mosquitoes can play a significant role in controlling *O. moubata* by inducing reduced mortality due to frequent exposure to insecticides [13,21,22,37] and if not well managed can lead to insecticides resistance as observed in Tanga and coastal regions for bed bugs [21,22].

Disease Vector in human dwellings and his domestic animal as well as other insect pests are of great economic importance due to losses incurred such as death and for been sick which reduces production. The use of chemical has been one of the major method in controlling disease pests. In controlling *O. moubata*, treatments should be considered as a supplement to basic hygiene and house improvements will continue to be demployed in the near future as the principal measure for obtaining rapid and maximum control of a vector pest [38]. In delaying the emergence of resistance in soft ticks population, the use of insecticides with different mode of action in singly or in combination can be beneficial in resistance management. Cooperthion which has a mixture of acaricide and insecticide with different modes of actions for use against ticks and tsetse flies is one of the strategies of delaying emergence of resistance which have been working well in the field [39].

In public health departments, government should prepare community training manual, a package of training on house improvements which will be considered as the part of major disease vector control strategy. House types (i.e., the physical structure together with the materials and construction style that make up a human habitation) have been linked with the health negative outcomes [40-43]. The improvement and modernization of human houses construction have been found to be a major barrier in vector borne diseases, the transformation of houses from traditional houses (made of mud and thatches which are easily having cracks and dusty floor) to modern houses (houses built with blocks and concrete floor which is easy to clean) [40,41,44-47].

5. Conclusion

The findings of insecticides susceptibility status in these six regions survey have indicated that, there is reduces mortality for the insecticides classes tested against *O. moubata* in all regions. Further studies have to assess the possible ways to reinforce the management of *O. moubata* infestation and insecticide resistance. Although the findings of these studies show that, *O. moubata* can be controlled by several insecticides from Organochlorides, Organophosphates, Carbamates and synthetic pyrethroid groups; there was variation of insecticides classes used in mortality for different regions hence more efforts have to be included in house style improvement by public health officers.

6. Acknowledgement

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7.Tables

Table 1: Insecticides used for susceptibility tests of *O. moubata*

Pesticides Class	Chemical name	Purity of Technical material (a.i)
Organochlorine (OC)	DDT	10%
	Dieldrin	5%
Organophosphate (OP)	Fenthion	5%
	Malathion	10%
Carbamate (C)	Carbaryl	7.5%
Synthetic pyrethroid (SP)	Alphacypermethrin	95.7%
	Deltamethrin,	99%
	Permethrin	99%
	Lambdacyhalothrin	97%

Table 2: Collections of *O. moubata* from houses from different Regions of Tanzania for establishing colonies under laboratory conditions for susceptibility tests

Region	District	Ward	Village	No. of houses Sampled	No of houses Infested (%)	Total No. *O. moubata* collected	Total No. of ticks from the original samples allocated to TPRI
Iringa	Iringa Rural	Iddodi	Usolanga	20	16 (80%)	179	4
			Makadupa	20	9 (45%)	72	3
			Idodi	20	17 (85%)	**382**	7
	Mufindi	Sadani	Utosi	20	9 (45%)	122	5
			Igomaa	20	15 (75%)	**215**	7
Morogoro	Morogoro	Morogoro	Bonye	20	0	0	0
			Dakawa	20	0	0	0
	Mvomero	Kibati	Hoza	20	5 (25%)	55	3
			Pandambili	20	8 (40%)	314	13
Manyara	Hanang	Balang'dalalu	**Balang'dalalu**	40	27 (67.5%)	695	86
	Mbulu	Mbulu	Endagichan	20	14 (70%)	181	18
			Masieda	20	12 (60%)	440	16
Arusha	Karatu	Maleckchand	**Maleckchand**	20	5 (25%)	92	20
			Laghangareri	20	4 (20%)	72	5
	Monduli	Ketumbeine	Njoronyoki	13*	6 (46%)	330	36
			Namanga	2**	0	0	0
			Engarenaibor	1***	0	0	0
Shinyanga	Bukombe	Uyovu	**Nampalahala**	20	8 (40%)	**534**	186
			Kaniha	20	1 (5%)	**24**	9
	Maswa	Malampaka	**Gulunghwashi**	20	8 (40%)	**233**	59

			Nyabubinza	20	1 (5%)	43	19
Dodoma	Dodoma		**Makangwa**	-	Not done	**-**	100
			Mzula	-	Not done	-	20
Total				**396**		**3983**	**616**

* represents – sampled houses were 13 (coverage 65%) instead of 20 (100%) because of bad terrain which made accessibility to households difficult) and rough roads which made the survey team to spend the limited time in traveling

** and *** represents – few houses sampled due either resistance from the communities leadership, or absence of the ticks as per discussions between the team and the village leadership.

8. Figures

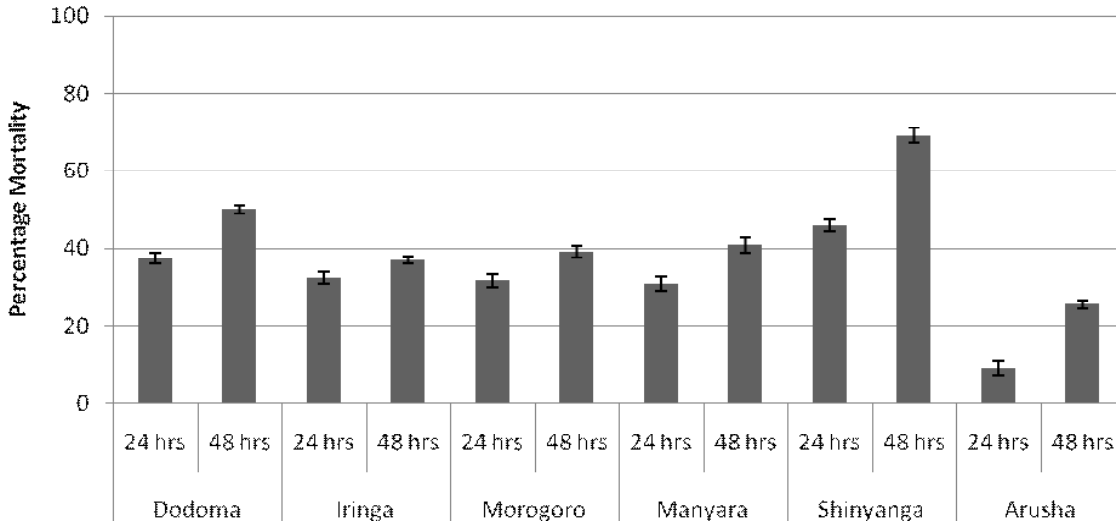

Figure 1: *O. moubata* mortality induced by Alphacypermethrin in 24 and 48 hours poste exposure

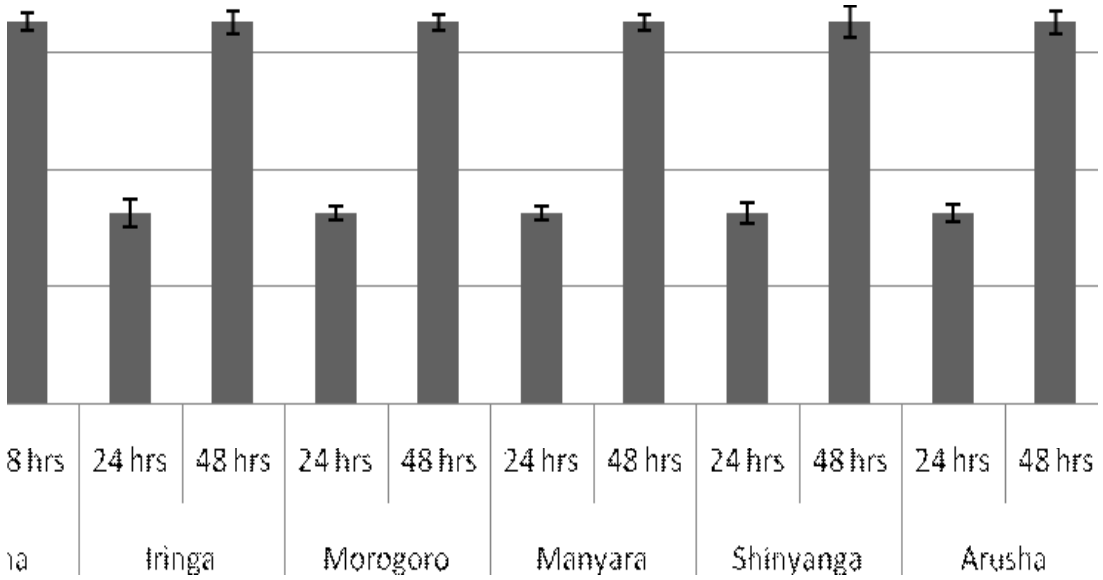

Figure 2: *O. moubata* mortality induced by Cyalothrin in 24 and 48 hours post exposure

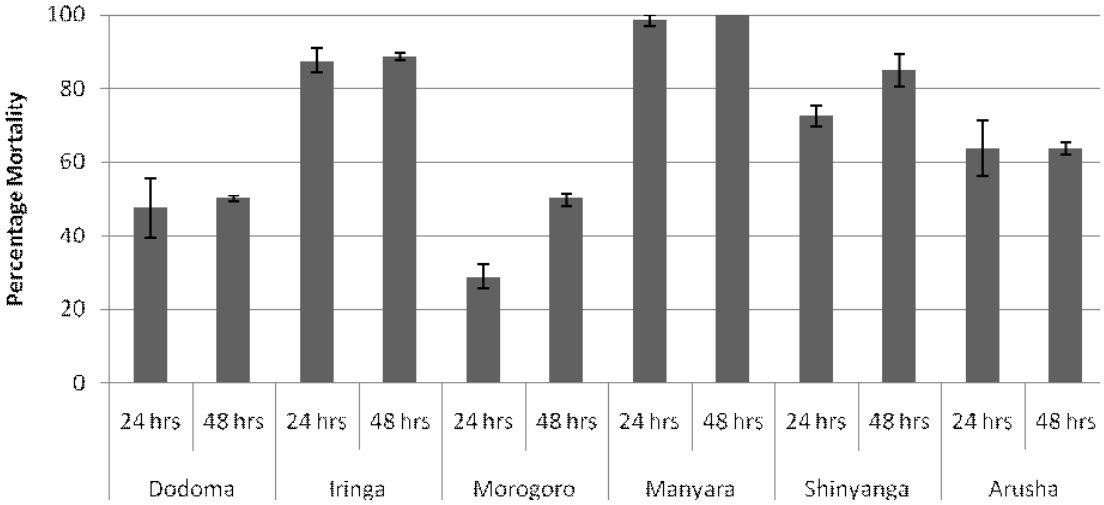

Figure 3: *O. moubata* mortality induced by Deltamethrin in 24 and 48 hours post exposure

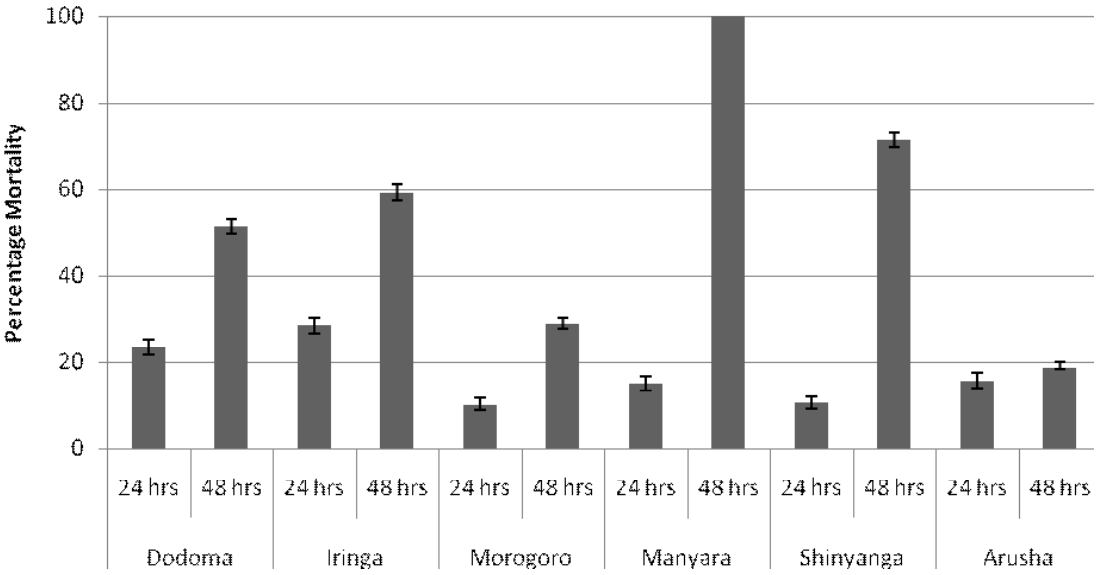

Figure 4: *O. moubata* mortality induced by Permethrin in 24 and 48 hours post exposure

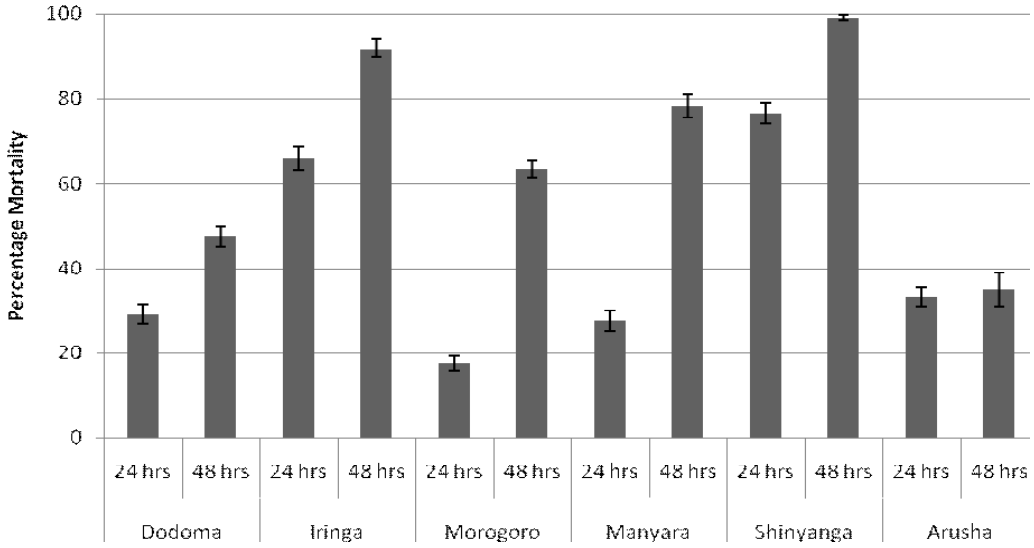

Figure 5: *O. moubata* mortality induced by Dieldrin in 24 and 48 hours post exposure

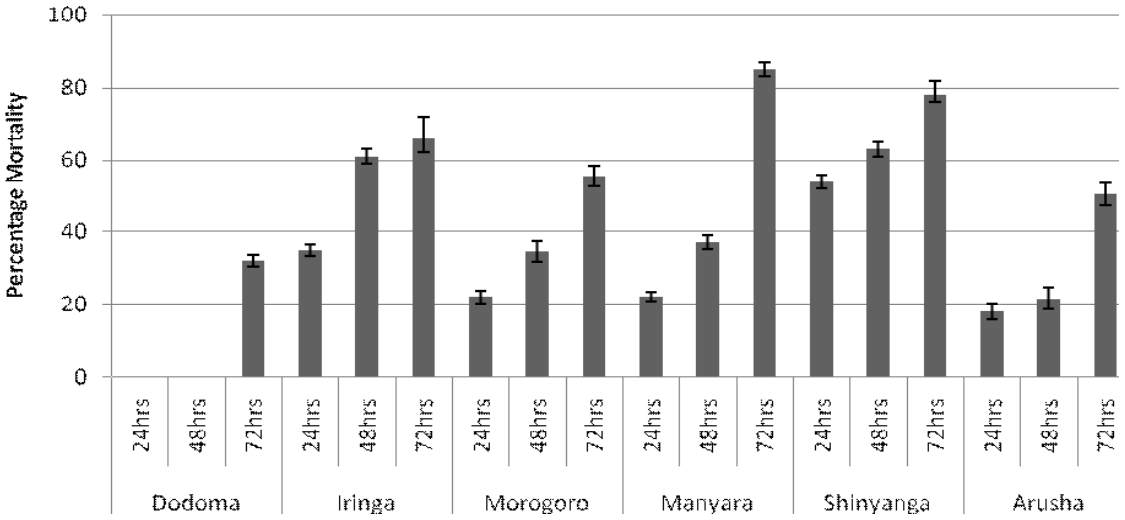

Figure 6: *O. moubata* mortality induced by DDT in 24 and 48 hours post exposure

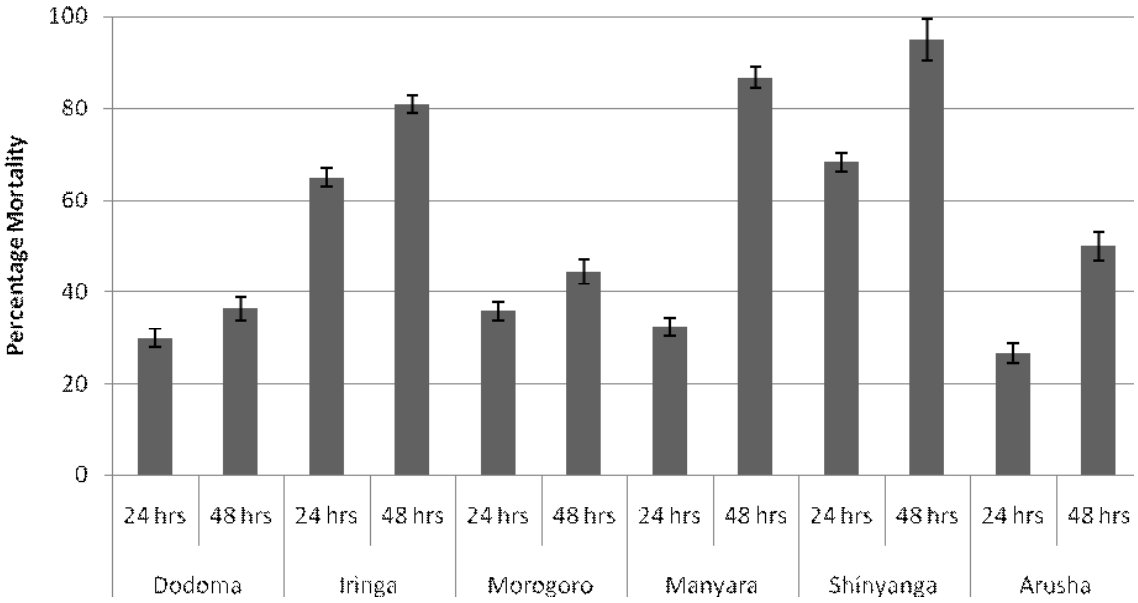

Figure 7: *O. moubata* mortality induced by Fenthion in 24 and 48 hours post exposure

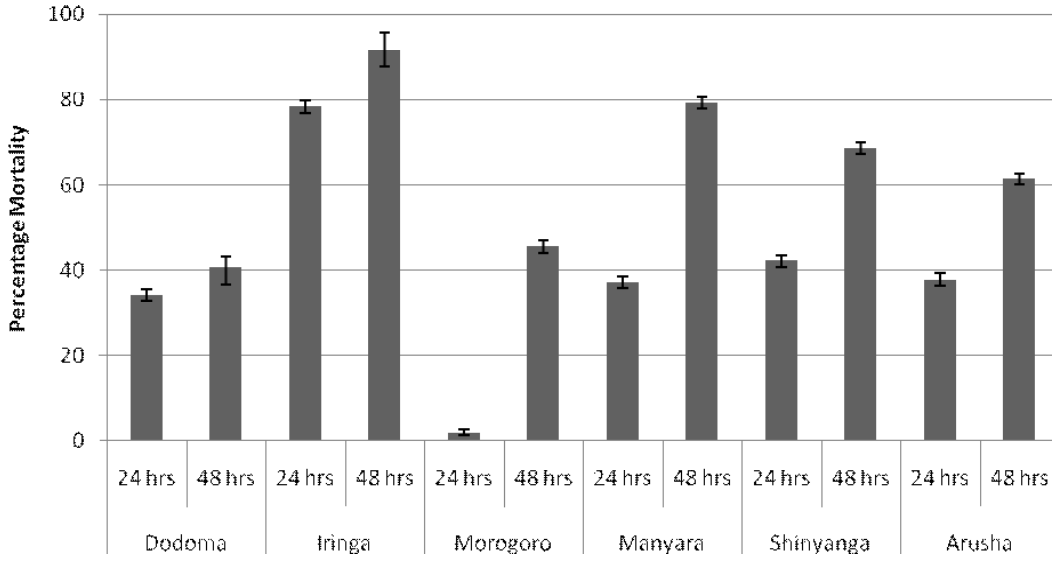

Figure 8: *O. moubata* mortality induced by Malathion in 24 and 48 hours post exposure

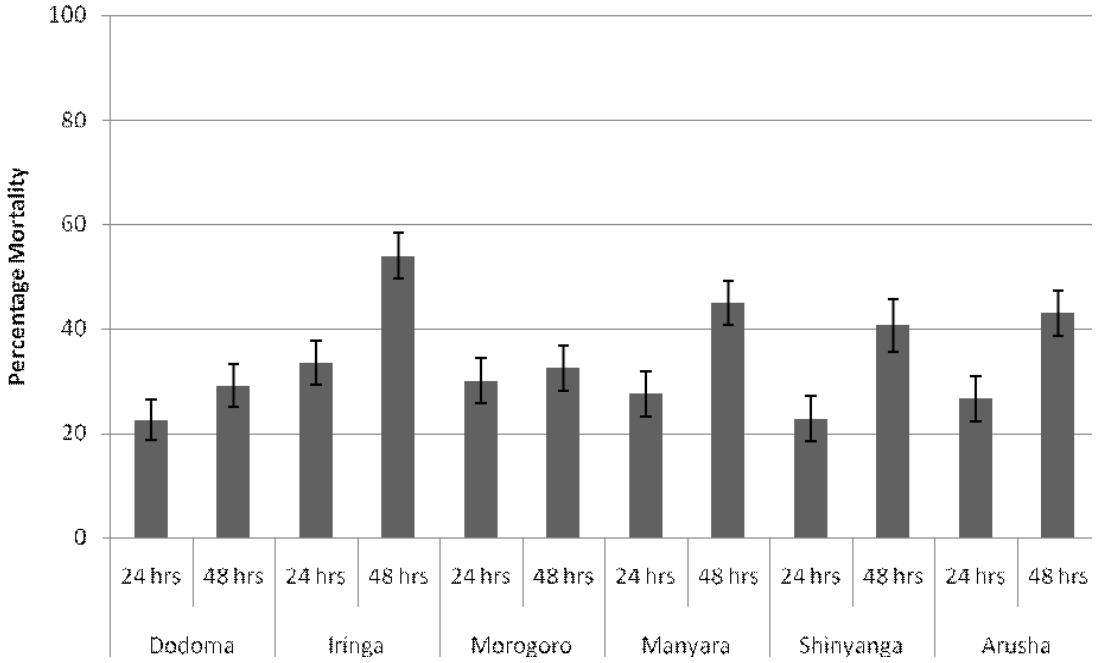

Figure 9: *O. moubata* mortality induced by Carbaryl in 24 and 48 hours post exposure

for maintenance of tick colonies and experimental animals while Mrs Katolina Ruhara is for typing some of the manuscript.

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Vector-Borne Diseases & Treatment

Chapter 4

Mosquito Borne Diseases: Current Status and Control Approach in India

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1. Introduction

Hematophagous arthropods pose a serious threat to human health because of their ability to transmit hundreds of disease carrying viruses, bacteria, protozoa and helminthes to vertebrate hosts, particularly humans [1]. Diseases transmitted to humans by an arthropod or another living organism (vector), is known as vector borne disease that accounts for 17% of the estimated global burden of all infectious diseases [2]. Annually, more than 1 billion vector borne infections take place and more than 1 billion people die from such diseases [3]. Historically vector borne diseases were responsible for more human deaths than all other causes combined [4]. Some of the greatest plagues that mankind has observed such as the 'Black Death' in Europe (14^{th} Century) and the epidemics of yellow fever were caused due to such diseases [5]. First discovered in 1877 by Sir Patrick Manson who demonstrated that *Wuchereria bancrofti* (a parasite of humans causing filariasis), was transmitted by a mosquito, *Culex pipiens fatigans*, since then many medically important disease pathogens have been found to be transmitted by blood sucking arthropod vectors [5].

Vector-borne diseases stand as a major public health problem, mainly in countries belonging to tropical or sub-tropical region, where proper sanitation, consumption of safe drinking water resources and regular surveillance is a huge challenge [2]. However, owing to the impact of globalisation and increased human mobility throughout the world due to air travel, these diseases no more remain problem of the tropics only rather they pose a major threat to the whole world [5]. Some of these diseases, if left untreated prove to be fatal, whereas some other leave patients disfigured or disabled [2].

Of all disease-transmitting insects, mosquito which has a slender body and long needle shaped mouth parts specialised for sucking blood from vertebrates, is the greatest menace. Mosquitoes are the vectors of several dreadful diseases which include tropical diseases like malaria, filaria and viral diseases like dengue, Japanese encephalitis, yellow fever, west nile fever, zika, chikungunya *etc* which together are responsible for several million deaths and hundreds of millions of cases every year [6]. There exist about 3000 species of mosquito of which around 100 are vector of medical significance [7]. Most of the mosquito borne viral infections cause typical manifestations like haemorrhagic disease, encephalitis, biphasic fever, flaccid paralysis and jaundice [8].

Many control strategies have been designed and followed since centuries ago but despite of such efforts and programmes, mosquito borne diseases are still prospering throughout the world [9]. Earlier mosquito fauna were limited to the low land areas only but as a result of immense climate change, their geographical distribution has expanded to higher altitudes and latitudes [10]. Due to failing efficacy of vector control programmes, there has been a dramatic emergence and resurgence of mosquito borne diseases [11].

India owing to its subtropical and tropical climatic parameters (high rainfall and relative humidity), lack of proper drainage system, water stagnation and vast vegetation cover provides the favourable ambience for mosquito growth and proliferation [12] and thus to the transmitted diseases. India is endemic to five of the mosquito borne diseases namely, malaria, dengue, chikungunya, filaria and Japanese encephalitis. Moreover three confirmed cases of zika has also been reported from India very recently [13]. This chapter focuses on the above mentioned mosquito borne diseases and the burden it has imposed on India.

2. Major Mosquito Vectors

In India, there are mainly four mosquito genera carrying disease causing pathogens namely, *Anopheles*, *Aedes*, *Culex* and *Mansonia* each causing different diseases.

Mosquitoes belonging to the genus *Anopheles* are responsible for transmission of malaria. About 380 species of *Anopheles* occur around the world of which 60 species act as vectors of malaria to humans [7]. In India, 58 anopheline mosquitoes exist, of which only six taxa act as malaria vectors namely, *An. culicifacies, An. fluviatilis , An. minimus, An. dirus, An. sundaicus and An. stephensi* [14]. *Anopheles culicifacies* also known as the rural malaria vector in the country and *An. fluviatilis*, found in the plains and foothills accounts for 60-70% and 15% of the annual malaria infections respectively [15]. Moreover, *An. minimus* breeding in streams of northeastern foothills, *An. dirus* found in forest areas of northeastern states of India, *An. sundaicus* found in brackish waters (their breeding sites) in Andaman - Nicobar islands and *An. stephensi* (known as the vector species of urban malaria) also contribute towards the total annual malaria infections [15]. Control of malaria in India is basically concerned with the

control of *An. culicifacies* [15].

Mosquitoes belonging to the genus *Aedes* house a number of pathogenic arboviruses causing dengue, dengue haemorrhagic fever, chikungunya, zika, yellow fever, west nile fever *etc*. They have also been shown to transmit filariasis [7]. Around the world there are approximately 950 species of *Aedes* of which two species *Aedes aegypti* and *Aedes albopictus* pose the greatest public health concern [7]. *Ae. aegypti* has its origin in Africa whereas *Ae. albopictus* originated in Asia and has now expanded its geographical distribution through different countries of world as a result of human activities [16]. *Ae. albopictus* has its distribution northern than its counterpart *Ae. aegypti*, owing to its ability to survive through the colder seasons by entering into dormancy [16]. Earlier *Ae. aegypti* was called as the primary vector of dengue virus (DENV), whereas *Ae. albopictus* was known as the secondary vector, however recent studies have shown that both the species contribute equally towards DENV infections. Both the species are distributed throughout Indian subcontinent and their breeding habitat mainly consist of artificial containers or water logged vessels such as bamboo stumps, tyres, cemented tanks *etc* [12]. The *Ae. aegypti* mosquito vector was found to be prevalent in the western, northern, Indo Gangetic and eastern plains, Assam valley and the coastal areas of Orissa state in India. The elevation, type of relief, terrain, density of population, water storage practices in drought-prone regions and high rainfall has direct relationship with the prevalence of the species [17]. Altitudes above 1000 metres have been reported to be unfavourable for *Ae. aegypti*. *Ae. albopictus* has been reported to be encountered in the peripheral areas of Indian towns where it has replaced the *Ae. aegypti* populations [17].

Another disease carrying mosquito genus is *Culex*, which consists of around 550 species [1]. Most of the *Culex* species inhabits tropical and subtropical countries. Species such as *Culex quinquefasciatus* is a vector of bancroftian filariasis where as others such as *C. vishnui and C. tritaenorhynchus Cx. Pseudovishnui, C. gelides and C. fuscocephala* transmits disease Japanese encephalitis (JE) [18]. Other species transmit arboviral diseases such as St Louis encephalitis virus and West Nile virus [19]. In India, main concern to *Culex* mosquitoes are due to bancroftian filariasis and Japanese encephalitis.

The genus *Mansonia* comprises of mosquitoes mostly found in marshy areas in tropical countries, some of which act as vectors of brugian filariasis. This disease is common in south India, Indonesia and Malaysia. In 1980, the virus for JE was isolated from *M. annulifera*, indicating its potency in transmission of JE also [20].

3. Major Mosquito Borne Diseases in India

Mosquitoes act as vector for numerous human diseases worldwide (**Table 1**). However in India they transmit five endemic diseases which are explained below. Also has been explained Zika, a disease that may have a serious outbreak in the upcoming season.

Table 1: Mosquito vectors and the disease transmitted by them worldwide

Mosquito vector	Disease	Continents at risk
Anopheles	Malaria	South America, Africa, Asia
Aedes	Dengue	South America, Africa, Asia, North America
	Chikungunya	North America, South America, Europe, Africa, Asia
	Yellow fever	South America, Africa
	Zika	Africa, Asia, South America
	La Crosse encephalitis	North America
Culex	Japanese encephalitis	Asia, Australia
	St. Louis encephalitis	North America
	West Nile fever	North America, Europe, Africa, Asia, Australia
Anopheles, Culex, Mansonia, Aedes	Lymphatic filariasis	South America, Africa, Asia, Australia
Aedes, Coquillettidia, Culex	Eastern equine encephalitis	North America, South America
Culex, Culiseta	Western equine encephalitis	North America, South America

3.1. Malaria

Among mosquito borne diseases, malaria poses one of the greatest threat to human health. Malaria is an illness caused by parasites of *Plasmodium* species transmitted exclusively by the bites of *Anopheles* mosquito. Malaria is endemic in 91 countries, putting approximately 40% of the world's total population at risk. Globally around 500 million cases of malaria infection occur causing up to 2.7 million deaths annually [6]. Southeast Asian region stands 2nd just after sub Saharan African region in total malaria cases throughout the world [2]. India contributes to 80% of the malaria cases occurring in Southeast Asia with around 24 million cases per year, this endemicity is attributable to the presence of multiple vector species and India's diverse ecology [3,21].

In 2016, around 1,090,724 malaria infections were reported in India, causing 331 deaths [22]. Malaria is endemic in most of the parts of India excluding elevations above 1800 metre and a few coastal areas [23]. About 90% of the Indian population reside in malaria endemic areas [24]. The Indian National Malaria Eradication Programme (NMEP) has reported that 2.5 to 3 million malaria cases causing 1,000 malaria deaths occur annually in States. The dominant causative agent in India is *Plasmodium vivax* (60-65%), whereas malignant malarial protozoa *i.e. P. falciparum* accounts for 30-35% of the infections [25]. Malaria was nearly eradicated from states in the early 1960s but the disease has re-emerged as a major public health problem [26]. Currently, the Eastern and Central states, *i.e.* Orissa, Jharkhand, West Bengal, North Eastern India, Chhattisgarh and Madhya Pradesh contribute to the bulk of malarial infections (>65%)[27,28]. Moreover, majority of the death attributable to malaria are from Orissa and other forested areas occupied by ethnic tribes in the country. The availability of diverse malar-

ia parasites and vector species, variable microenvironment favouring growth and proliferation of both the parasite and vector along with a highly susceptible human population have resulted in higher malarial infection rates in tribal areas [29].

The malarial incidence and deaths due to malaria have reduced significantly in recent years. During the period 2000 to 2015, malaria cases declined by 44% from 2.03 million to 1.13 million and deaths declined by 69% from 932 to 287. The Pf (*p.falciparum*) percentage remained around 50% from 2000 to 2013, but rose to 65.6% in 2014 and 67.1% in 2015 [30]. Encouraged by the success achieved in malaria control in recent years, the National Framework for malaria elimination in India 2016-2030 was launched in February 2016 with a goal to eliminate malaria throughout the country by 2030 and maintain malaria free status wherever malaria transmission has been disrupted. The strategies for achieving the above goals [30] have been pointed out as:

- Early diagnosis and radical treatment
- Case-based surveillance and rapid response
- Integrated vector management (IVM)
- Indoor residual spray (IRS)
- Long-lasting insecticidal nets (LLINs) / Insecticide treated bed nets (ITNs)
- Larval source management (LSM)
- Epidemic preparedness and early response
- Monitoring and evaluation
- Advocacy, coordination and partnerships
- Behaviour change communication and community mobilization
- Programme planning and managements

Though there is no vaccine available for malaria in India, chloroquine is the first line treatment for vivax malaria. For *P. falciparum* infection, chloroquine is only administered in low risk and chloroquine sensitive areas [31]. It has been reported that chloroquine has been found to result in treatment failure due to the development of drug resistance in *P. falciparum*, so as an alternative ACT (Artemesin combined therapies) has been introduced in the high burden states for the treatment of *P. falciparum* [31].

Malaria control strategies in India are either early detection and prompt treatment (EDPT) or vector control [22]. Under EDPT, early treatment of malaria is done so as to minimise transmission from the diseased. Drug Distribution Centres (DDCs) and Fever Treatment Depots (FTDs) have been established in the rural areas for providing easy access to anti-malarial drugs to the community [22]. For chloroquine resistant malaria, alternative drugs are recommended. Under vector control, many strategies are followed such as, chemical control (use of indoor residual spray, uise of larvicides, malathion fogging during intense disease outbreaks),

biological control (use of biological agents for vector control), personal prophylactic measures (use of mosquito repellent creams and coils, proper covering of exposed human parts, screening of house with wire meshes), community participation (spreading awareness within the community for detection of *Anopheles* breeding places and their elimination), environmental measures (source reduction of mosquito breeding habitats) and monitoring and evaluating the programme by state national program officers or different malaria research institutes [22].

Malaria not only causes significant rates of morbidity and mortality but it is also responsible for the downfall of the productivity, agriculture & economic status of a country if left uncontrolled [24]. Malaria decreases the economic growth of a country by more than one percent per year in endemic countries. Malaria transmission season (vector mosquito's flourishing season) coincides most of the time with the harvesting season and periods of illness during this productive time of the year proves very depressing on the world's poorest regions (UN millennium project 2005). Despite of the recent advancements in diagnostic and treatment facilities throughout the world, malaria still remains a public health concern in developing countries particularly in resource poor regions [3]. By undermining the health and working capacity of hundreds of millions, it ultimately results into poverty and halts social and economic development [6]. Unlike Africa, where most of the deaths (associated to malaria) are reported in infants and children, in India, malarial mortaility has been observed to occur maximally in the age groups of 15-44 years *i.e.* economically productive age group [27], thereby affecting the economy of the country drastically. It has been reported that the total economic burden imposed by malaria in India could be around US$ 1940 million, the major burden attributable to lost earnings (75%), while rest from costs of treatment [32]. In India, most affected areas remain the poverty stricken tribal, hilly and forest fringe ones [27]. So, to minimise the affect of malaria on the socioeconomic index of India, an efficient mosquito control strategy should be the prime concern of the involved authorities.

3.2. Dengue

Dengue is the world's most threatening and fastest growing mosquito-borne viral disease, with a 30 fold increase in disease incidence over the last 50 years putting 2.5 billion people (> 40% of the world's total population) at risk of infection worldwide and 20 million cases occurring every year in more than 100 countries [2,6]. Globally, 5,00,000 people with severe dengue require hospitalization, a huge proportion of whom are children and 2.5% of those die annually [2]. In 1953-54 a new syndrome associated with dengue appeared in the Philippines, which later spread throughout the world, unlike classical dengue, this disease affected young children causing severe illness with haemorrhage and shock, resulting in high mortality, it was termed as Dengue haemorrhagic fever (DHF) [17]. Before 1970, only nine Southeast Asian countries suffered severe dengue epidemics but in 1981 large numbers of dengue haemorrhagic fever cases began to appear in the Caribbean and Latin America. It has been predicted that dengue is

omnipresent throughout the tropics, with local differences in risk mainly attributable to degree of urbanisation and climatic parameters such as rainfall, temperature *etc* [33]. Today, dengue is endemic in more than 100 countries mainly in South-East Asia, Africa, Eastern Mediterranean, Western Pacific and America.

The history of dengue fever (DF) dates back to the Jin Dynasty (265–420 AD) in China, however, the first recognized epidemics occurred almost simultaneously in Asia, Africa and North America in the year 1780 [34]. Dengue virus infection in humans can lead to a range of medical manifestations, from mild fever to potentially lethal dengue shock syndrome [35]. The major challenge presented by dengue remains the presence of four serotypes of dengue virus (family Flaviviridae: DENV-1, DENV-2, DENV-3 and DENV-4) dengue. A person infected by a specific dengue serotype becomes immune to that serotype for lifetime but for other serotypes the immunity provided is for 3-4 months only, thereby enhancing the chances of secondary infection (more severe) in the same or upcoming season [33].

In India, dengue outbreaks have occurred since 1950s but the occurrence and severity of disease has raised in the last two decades [34]. In 2016, total 1,29,166 cases of dengue infection occurred causing 245 deaths [36]. Till July 2017, around 23,094 cases of dengue infection has already been registered taking 32 lives [36]. In India, the first outbreak of DHF was reported in Delhi in 1988 [37], prior to which, transmission of all four dengue serotypes had already been established [38]. The trend of dengue fever in the country has been very complex and has changed considerably over past six decades in terms of prevalent serotypes, disease severity and infected geographical locations [35]. Paediatric cases of dengue haemorrhagic fever in India have a considerably higher mortality than other age groups [34]. In India, the appearance of DHF were reported for the first time in Calcutta in 1963, during this outbreak both the dengue and Chikungunya, viruses were reported to circulate together [39]. Since then several dengue outbreaks have been reported throughout the different parts of country with manifestations of haemorrhagic symptoms in varying intensities [17]. In India, dengue is widespread and endemic in 15 states, namely, Andhra Pradesh, Goa, Gujarat, Haryana, Karnataka, Kerala, Madhya Pradesh, Maharashtra, Punjab, Rajasthan, Tamil Nadu, Uttar Pradesh, West Bengal, Chandigarh, Delhi and one union territory namely Puducherry [36]. Earlier, the presence of *Aedes* mosquito in southern India was very scarce and so was the incidence of dengue but with the introduction of piped water supply, dengue made its entry to rural areas of south India and disease outbreaks occurred [40].

There are currently no licensed vaccines or specific therapeutics for dengue and constant vector control efforts could not stop the increasing incidence of dengue fever epidemics and expansion in the geographical range of endemic transmission [41]. For dengue, the recommended treatment is replacement of plasma losses, correction of electrolyte and metabolic disturbances and blood transfusion. For vector control, following measures are followed in

India: i) personal prophylactic measures: use of mosquito repellent tools, use of bed nets *etc*, ii) Biological control: use of biocides and larvivorous fishes, iii) chemical control: use of larvicides and aerosol spray, iv) environmental management and source reduction: identification and management of mosquito breeding sources, v) Health education: imparting knowledge to common people regarding the disease and vector through various media sources, vi) community participation: involving the community for detection of *Aedes* breeding places and their elimination [36].

The high rates of mortality and morbidity associated with each dengue outbreak leads to great socio-economic impact. Dengue is an extremely expensive disease, estimated to cost the global economy over US$39 billion in 2011 only. Costs subjected in managing a group of dengue patients (serologically confirmed) at a tertiary-level private hospital in north India is quite high. The average cost of treatment per hospitalised dengue patient was estimated to be US$432.2 [42]. The mean total economic burden of dengue (loss of economic activities due to loss of workdays, the proportion requiring transfusion, deaths *etc*) was estimated to be US$27.4 million [42]. Moreover, Costs incurred in the private heath sector prove to be almost four fold higher than that of public sector expenditures. Significant economic losses are incurred by developing countries like India during each dengue epidemic [42].

The control and prevention of dengue outbreaks depend upon the proper survelliance of the disease (in order to ensure efficient and timely management of disease cases) and vector surveillance (for the effective and timely implementation of dengue vector control measures) [43]. For planning and implementation of effective public health prevention and control measures and targeting of future vaccination campaign, the knowledge on demographic differences in infection rates and severity of dengue may prove very important [44]. To minimise the illness duration and related complications, it is a must to devise effective diagnostic strategy for early diagnosis of the disease [43].

3.3. Chikungunya

Chikungunya, an arboviral disease is transmitted by culicine mosquitoes *i.e. Ae. aegypti, Ae. albopictus* and *Ae. polynesiensis*, although *Culex* has also been reported to transmit the virus in some cases [45]. This fever was first reported in Tanzania in 1952 [46,47] and the responsible pathogen, Chikungunya virus (CHIKV) belonging to the genus *Alphavirus* and the family Togaviridae was subsequently isolated in Tanzania in 1953 [47]. Epidemics were subsequently noted in the Philippines (1954, 1956 and 1968), Thailand, Cambodia, Vietnam, India, Myanmar and Sri Lanka [48]. This specifically tropical disease is characterised by fever, rash, and incapacitating arthralgia [49]. Chikungunya, affects all age groups but severe manifestations (Persisting arthralgia, neurological syndromes and non-neurological manifestations) are more often seen in children. Chikungunya is believed to have originated in Africa, in a cycle

involving wild mammals and forest dwelling mosquitoes [50], subsequently it was introduced in Asia where it is transmitted from human to human mainly by *Ae. aegypti* and secondarily by *Ae. albopictus*.

The start of Chikungunya outbreaks dates back to the 1960s and infection rates revolved around sporadic cases until a resurgence in 2006 [34]. Resurgence of chikungunya has been linked to various factors including globalization, increased growth of vector population, loss of herd immunity and the mutation increasing the CHIKV infectivity for *Ae. albopictus* [51]. Chikungunya occurs mainly in Africa and Asia, including the Indian sub-continent, since 2005, Southeast Asian countries, namely, India, Indonesia, Maldives, Myanmar, and Thailand have reported over 1.9 million chikungunya infections [2]. In 2016, 64,057 Chikungunya infection took place in India [52].

The entry of chikungunya virus in India is not clearly known, yet Calcutta sea and air roots may be the probable entry points in India [46]. Major Indian epidemics of chikungunya were reported firstly in Calcutta (presently Kolkata) in 1963, subsequently in Pondicherry, Tamil Nadu, Andhra Pradesh, Madhya Pradesh and Maharashtra in 1965 and again in Maharashtra in 1973 [53]. In the 1963-1964 outbreak of Calcutta and 1965 outbreak of Chennai more than 3,00,000 people were affected. After a gap of 32 years this disease again appeared affecting 13 states in 2005 causing 1,400,000 infections of chikungunya during 2006 and the responsible vector species was reported to be *Ae. aegypti* [49]. The reasons for the re-emergence of chikungunya on the Indian subcontinent, and its exceptional incidence rate may be explained by increased tourism, CHIKV inoculation in a naive population and viral mutation [49].

Chikungunya virus usually shows a periodicity with occurrence of disease in the community with an interval of 3-4 years [46].The intra-outbreak studies, towards the recent mutations/changes in the viral genome enhancing the pathogenecity and enabling rapid spread [46]. Transmission of chikungunya during birth can result in neurologic, hemorrhagic, and myocardial complications for the baby or even spontaneous abortions. Mosquito vectors of chikungunya have very recently spread to Europe and the Americas, thereby enhancing the chances of disease outbreaks in those areas. This disease has already been observed for the first time in Italy in 2007 and in Carribean in 2012.

The characterstic feature of chikungunya disease is a prolonged arthralgia, *i.e.* severe joint pain, the pain associated with CHIKV infection of the joints typically persists for weeks or months causing serious economic and social impact on both the individual and the affected communities [54].

3.4. Filariasis

Lymphatic filariasis, the second most common vector borne parasitic disease is caused by the nematode *Wuchereria bancrofti* (transmitted by *Culex* mosquitoes), *Brugia malayi and Brugia timori* (transmitted by *Mansonia* mosquitoes). Both the above mentioned parasites produce similar clinical manifestations of the disease, related to the lymphatic system [55]. In India, 99.4% cases are caused by *Wuchereria bancrofti* whereas only 0.6% is caused by *Brugia malayi* [56]. The worst symptom of this chronic disease appear in adults, *i.e.* damage to the lymphatic system, arms, legs or genitals with significant pain, loss of productivity *etc.* This disease is found in 81 countries belonging to tropical and subtropical areas [57]. An estimated 120 million people in 73 countries are currently infected with filariasis. Southeast Asia accounts for around 63% (876 million) of the total people living in filarial endemic areas (1.39 billion) [2] . Southeast Asia contributes around 57% of the total global burden of 5.1 million disability-adjusted life years (DALY) lost due to lymphatic filariasis [6]. Around 40 million people are reported to suffer from long term complications of the disease [58].

WHO has targeted this disease for elimination through mass drug administration (MDA). The effectiveness of which depends on the consumption of the drug by the population. This strategy (MDA) alone has been shown to suppress transmission of lymphatic filariasis quite efficiently but it is often accompanied by resurgence once there is residual infection in the population. So, ideal control of lymphatic filariasis can be achieved only through integration of different strategies of vector control along with MDA [59].

India is the largest filaria endemic country of the world. A National Filarial Control Programme (NFCP) was launched in 1955, which currently covers a population of 40 million people with a strategy of selective chemotherapy (mass diethylcarbamazine administration) [60]. In India, filariasis are endemic in 17 states and 6 union territories putting about 650 million people at the risk of infection [55]. The National Health policy (2002) envisaged elimination of lymphatic filariasis in India by 2015 through strategies mainly, i) Annual mass drug administration (MDA) of single dose of DEC (Diethylcarbamazine citrate) and albendazole, ii) home based control of lymphoedema cases and up-scaling of hydrocele operations [56]. To follow the above goals, the Government of India in 2004 launched nationwide MDA programme in endemic areas as well as home based morbidity management, scaling up hydrocelectomies. During 2004, only 202 districts could be covered with a coverage rate of 72.6%. In 2007, all the 255 known lymphatic filariasis endemic districts were brought under MDA. The population coverage during MDA improved from 72.6 % in 2004 to 89% in 2015, resulting in reduction of microfilaria rate from 1.2% in 2004 to 0.3% in 2015 [56]. As per WHO guidelines (2011), districts conducting minimum five rounds of MDA with more than 65% population coverage are subjected to Transmission Assessment Survey (TAS) for presence of circulating antigenemia in children born after initiation of MDA to unveil the current infec-

tion status, needed to take decision for MDA stoppage [56]. Till May 2016, 72 districts (each with approximately 164 million population) qualified for stoppage of MDA [56]. Since 2004, around 1,41,902 hydrocele operations have been reported form India [56]. Some states have started paying attention to home based foot hygiene practices for management of lymphodema cases [56].

Filariasis is a disease of poor and it is reported as a cause and effect of poverty [60]. Poor hygiene and sanitary facilities with low socioeconomic status of the community provide the ambience ideal for vector mosquito breeding and thus transmission of the causative pathogen [57]. It has been reported that the annual economic loss due to filariasis in India is US$ 1 billion and US$5.3 billion from blinding trachoma and substantial reductions in future wage earning capacity as a result of chronic hookworm infection in childhood [61]. Besides disability, this disease causes personal trauma to the affected persons and its long term suffering leads to social exclusion.

3.5. Japanese encephalitis

Japanese encephalitis (JE), one of the major public health disease was identified as a clinical issue in Japan in 1971 and in the past decades it has spread to many countries of Southeast Asia and parts of Western Pacific region [62]. JE is basically an infection of the brain and children are more vulnerable to this infection and inflammation of the brain. The infection with JE virus can range from non specific febrile illness to meningiencephalomyelitis illness [62]. While most JE virus infections are mild or asymptotic, approximately 1 in 250 infections results in severe disease [2]. Around 60 % of the world's population *i.e.* 3 billion people inhabit JE endemic regions [63]. JE is endemic mainly to rural areas with rice plantations, pig rearing, high temperature, rainfall and relative humidity (rainwater clogged rice fields serve as the the breeding sites for vector mosquitoes whereas pigs acts as the reservoir of virus), putting 1.9 billion people at risk of JE infection [64]. Japanese encephalitis is a principal cause of disability among the paediatric and rural people in Asia. In Asia, around 68,000 clinical cases of JE infections are reported to occur annually causing 5-35% deaths and 75% JE related disability rate [2].

In India, the first incidence of JE was reported in 1955 in Tamilnadu and neighbouring districts of Andhra Pradesh. Annually around 35,000-50,000 cases of JE infection are reported, of which 30-50 % individuals face neurological infection whereas 20-40% die [65]. Since 1972, JE has expanded its range and has spread to West Bengal, Uttar Pradesh, Assam, Manipur, Bihar, Andhra Pradesh, Pondicherry, Karnataka, Goa, Kerala and Maharashtra. This cycle consists of pigs (major reservoir / amplifying host), water birds (carriers) and mosquitoes (vectors). The *Culex vishnui* subgroup of mosquitoes had been established as major vectors of JE. India faced its first major JE outbreak in 1973 in districts of West Bengal causing

300 deaths [66]. In 2016, total 444 cases of JE were reported causing 60 deaths [67].

Though there is no specific antiviral medication available for treatment of JE infection, but the availability of JE vaccination (developed by Central research institute, Kasauli) [67] appears to be the best control measure in JE endemic areas. In JE endemic areas, the immunization of JE vaccine is included in the general immunization schedule. Also, immunization of pigs and locating piggeries away from human dwelling is also a preventive measure.

The prevalence of JE is higher in countries that have lower socioeconomic status, than more prosperous neighbouring countries, indicating the involvement of economic and social strength as an additional risk factor that affects the rate of JE transmission and prevalence in non-immune populations [64]. A principal part of India's economy depends on agriculture, and the presence of JE vectors breeding sites in agricultural land increases the chances of the poor farmer getting infected by JE virus, there by affecting both the economical and social indices of the country.

3.6. Zika

Zika virus (Zika virus genus Flavivirus, family Flaviviridae) is an emerging arbovirus of public health importance transmitted by *Aedes* mosquito. This virus is closely related to other flaviviruses of public health importance such as dengue fever, chikungunya and yellow fever [68]. Zika virus was first isolated in Uganda, in 1947 and for many years, the virus sustained on earth causing sporadic human infections in Africa and Asia [69]. Since 2013, cases and outbreaks of this disease have been reported from the Western Pacific, Africa, Asia and latin Americas and as of now, zika infection have been reported from 70 countries [70]. Most people infected with zika are mostly asymptomatic however clinical manifestations ranging from mild fever, skin rashes, joint pain, low-grade fever, conjunctivitis,- to severe neurological disorders, microcephaly, and Guillain-Barré syndrome may take place [71]. There are evidences relating ZIKV and severe neurological disorders during prenatal development [72]. The recent reports about the sexual transmission route of zika, changes in epidemiology, possible links with microcephaly cases and other neurological disorders have rapidly changed the risk profile of the disease pushing WHO to declare it as a 'Public Health Emergency of International concern' [70]. With three confirmed cases of zika in India and unavailability of either vaccination or treatment medications against zika, India stands at a very high risk of ZIKV infection and related socioeconomic disturbances in the near future.

4. Present Control Strategies for Mosquito Borne Diseases

The control strategies for mosquito borne diseases can be divided into two groups: 1. Diseases against which vaccination or therapeutic treatment is available, 2. diseases which have no available vaccine or medications. For the first group, both disease prevention by vac-

cination or early diagnosis followed by medication and control of vector population is sought. Whereas, for the second group the sole available approach remains minimising the infection rate through vector control.

4.1. Prevention by vaccination

This strategy is followed for Japanese encephalitis. In last few decades through vaccination JE has been eliminated from Japan, Taiwan, China and Korea [73]. Three types of vaccines are used throughout the world:

i) Formalin inactivated mouse brain derived vaccine,

ii) Inactivated primary hamster kidney cell derived vaccine,

iii) Cell culture derived attenuated vaccine.

Of the above only the first one is WHO approved. Three doses of this vaccine (produced by Centre for Research, Kasauli) provide immunity for few years [67]. JE vaccination was started in India in 2006. Large JE vaccination campaigns were carried out in 2006 (11 districts), 2007 (27 districts), 2008 (22 districts), 2009 (30 districts) [74]. In 2011, The JE vaccine was introduced in the routine immunization under Universal Immunization program in 181 JE endemic districts at a single dose at 16-18 months at the time of 1st booster of DTP vaccine. In 2013, another dose of the vaccine was added at 9 months age along with measles vaccine [74]. Till 2015, 155 JE endemic districts have been covered under JE campaign and approximately, 10.8 crore children have received the vaccination through campaigns [74]. Afterwards, JE vaccination campaigns for adults were conducted owing to outnumbering of pediatric JE infection by adult infection rates [74].

4.2. Anti pathogen measure

It is adopted for lymphatic filariasis and also for malaria caused by *P. vivax*. In case of Filaria, annual mass administration of single dose of DEC (Diethylcarbamzine, an anti filarial worm medication) and albendazole is done to interrupt the transmission of the disease [56]. For malaria, after early diagnosis, chloroquine is administered as an anti malarial drug. However due to increased chloroquine resistance often a combined drug therapy is followed.

However the above two strategies can suppress the disease, but strategies combined with Vector control is often adopted for efficient disease prevention and transmission.

4.3. Vector control

Majority of mosquito borne diseases *i.e.* malaria, dengue, chikungunya *etc* do not have available vaccine or safe medications, so the sole method to decrease their infection rate is to

cut down the number of vector population responsible for the transmission of disease causing pathogen, thereby obstructing the transmission cycle [75]. Since long time ago, vector control has been used throughout the world.

Adult vector control: The history of vector control in India can be divided into two phases: before and after the discovery of DDT. Before 1936, various control methods *i.e.* biological, mechanical and chemical had been employed for mosquito control such as the application of larvivorous fish (eg. Gambusia, Guppy) to the mosquito breeding habitats, use of oils and Paris green in breeding sites and the provision of a suitable drainage system [76]. A significant decrease in the malaria vector population was observed in Bombay city through the application of above mentioned measures along with implementation of legislative measures, where *An. stephensi* breeding was observed in water tanks, wells, cisterns *etc* [15]. Observing the success by spray of pyrethrum extract inside the houses to kill the adult mosquitoes in South Africa, mosquito control trials were undertaken in human dwellings and cattle sheds in some part of India [15].

DDT was discovered in the year 1939 by Paul Mueller who later became a Nobel laureate for the same [77]. On an experimental basis, it was introduced in the Assam-Burma front in the army camps of world war II as a residual insecticide in mosquito control programme with great results [78]. Afterwards, few more successful experiments, DDT was accepted as an indoor spray as the control measure against malaria [15]. In 1950, another insecticide Benzene hexachloride (BHC) was used in Assam [79]. In the year 1953, National Malaria Control Programme (NMCP) was launched which had a remarkable impact on the malaria situation in the country, also was noted a significant decrease in the malarometric indices [26]. During 1980s, insecticides belonging to synthetic pyrethroid group were introduced in the public health programmes. Deltamethrin was introduced in a trial and was found effective for vectors as residual insecticide [15]. Successively, synthetic pyrethroids such as cyfluthrin, lambda cyhalothrin were introduced into public health programmes; currently all three above mentioned synthetic pyethroids are in use both as indoor residual spray and as impregnated on mosquito nets along with some personal protective measures [15]. However, varying degree of insecticide resistance has been observed in different mosquito vectors throughout India [10,12,80-83].

Larval vector control: Destruction of larval habitats (sealing of water holding vessels), designing of a proper drainage system and spray of insecticide against larva include the major aspects of larval management in India. For mosquito larval control, temephos is the most preferred larvicide, also recommended by both WHO and National Vector Borne Disease Control Programme, India (NVBDCP).

5. Major Constraints in Mosquito Borne Disease Control

5.1. Drug resistance

With the use of drugs and medications for the treatment of infection, the pathogen subsequently develops resistance against the medication used, this is referred to as drug resistance. The *P. falciparum* resistance against chloroquine has resulted in increased malaria mortality and morbidity throughout the world [84]. Despite the worldwide spread of resistance, chloquine still remains the first line treatment for malaria [85]. Studies in African countries have reported a 2-3 fold increase in malaria death and approximately 6 fold higher malarial mortality in children attributable to emergence of chloroquine resistance [85]. *P. falciparum* has also developed resistance against artemisin derivatives [58]. Antimalarial drug resistance usually confers a fitness disadvantage upon the malaria parasites, but parasites in the Southeast Asian region have been exposed to several different selective forces which has created a genetic background that may predispose to the emergence of resistance [86]. WHO now recommends ACTs as the suitable treatment for uncomplicated *P. falciparum* malaria however, it will be terrible if artemisinin resistance reaches regions carrying the bulk of malaria, *i.e.* India and Africa [87]. Such drug resistance pose a huge challenge against malaria eradication worldwide.

Similar resistance has also been reported against anti filarial drug DEC and albendazole in *W.bancrofti* [88]. It has been noted that benzimidazole resistance is widespread in a number of nematodes of veterinary importance [89].

5.2. Insecticide resistance

Continuous use of synthetic insecticides under vector control programmes has given rise to a new phenomenon known as Insecticide resistance in many mosquito vector species [90]. This term refers to the selection of insecticide resistant populations of the vector mosquito under insecticide selection pressure. According to the World Health Organization (WHO), resistance is defined as the ability of an insect to withstand the effects of an insecticide by becoming resistant to its toxic effects by means of natural selection and mutations [91]. While Insecticide Resistance Action Committee (IRAC) defines resistance as a heritable change in the sensitivity of a pest population that is reflected in the repeated failure of a product to achieve the expected level of control when used according to the label recommendation for that pest species [92]. Appropriate tools (biological, biochemical and/or molecular) are needed to identify the mechanisms involved at individual or population levels [93]. Insecticide resistance is an increasing problem faced by those who need insecticides to efficiently control medical, veterinary, agricultural insect pest [93]. Resistance is a heritable character that relies on a genetic basis. Resistance results from the selection of a genetic modification in one or several genes occurring by migration or mutation [94].

The use of insecticides for agricultural purposes and more recently for public health has played pivotal step in the selection of resistance in mosquitoes [95]. Resistance involves

several physiological and behavioural changes. Changes in the insecticide target site that reduce its binding to insecticides (known as target site resistance) is the best understood type of resistance mechanism [96] whereas, enhanced insecticide metabolism that lowers the amount of insecticide reaching the target site (known as metabolic resistance) is more complex but recent advances have identified key enzymes responsible for insecticide detoxification [97]. Other physiological changes (e.g. reduced penetration through cuticle, *i.e.* cuticular resistance) and behavioural changes in the mosquito population have also been identified. The major mechanism that enables insects to grow resistance against insecticide can be divided into four categories: Behavioral avoidance, reduced penetration, metabolic resistance and target site insensitivity; the latter two being the major resistance mechanism occurring in insects. Metabolic resistance is caused due to the elevated activities of digestive/detoxification enzymes which help in the detoxification of foreign compounds [90]; enzyme groups mainly related to this task are Esterases, Monooxygenases and Glutathione-S-transferases [98]. While, target site insensitivity refers to the modification within the nervous system of a specific site where the insecticide binds [99].

Resistance Management(IVM) is therefore a major challenge for vector control programme in countries like India where there is a prevalence of vector borne diseases [80]. A detailed knowledge of the major factors behind insecticide resistance is the immediate need for implementation of safer and efficient vector control programmes [90].

6. Integrated Vector Management

Integrated Vector Management is defined (by WHO) as a rational decision-making process for the optimal use of resources for vector control [100]. The main driving force behind the IVM movement is the need to overcome the challenges or limitations associated with conventional single intervention approaches to vector control. Integrated vector management aims to improve the efficacy, cost-effectiveness, ecological soundness and sustainability of vector control [101]. IVM entails the use of a range of interventions, alone or in combination, in order to implement a more cost-effective control and reduce dependence on any single intervention. This strategy also serves to extend the useful life of insecticides and drugs by reducing the selection pressure for resistance development [101]. IVM has been shown to delay onset of behavioural resistance [102].

An IVM approach takes into account the available health infrastructure and resources and integrates all available and effective chemical, biological or environmental measures. It also encourages effective coordination of other important sectors that have an impact on vector borne diseases, such as, health, water, solid waste and sewage disposal, housing and agriculture [101]. An IVM approach is evidence-based and it has the capacity to generate local data on disease epidemiology and vector ecology. The key elements of IVM are [100]: i) Advocacy,

regulatory control and social mobilization, ii) Collaboration between the health sector and other sectors to make optimal use of resources, and improve planning and decision-making, iii)Integration of non-chemical with chemical vector control methods, and integration of vector control with other disease control measures which target the parasite or pathogen, iv) Evidence-based decision making which is guided by operational research and entomological and epidemiological surveillance and evaluation, v) Development of adequate human resources, training and career structures at national and local level to enhance capacity and management of IVM programmes.

IVM is guided by the following basic principles: 1) to effectively reduce adult vector populations and pathogen transmission; 2) that interventions should be ecologically, environmentally, socially, economically and politically acceptable; 3) that management strategies should not create adverse side effects such as environmental contamination or the development of resistance, nor should they have a negative impact on non-target organisms, including beneficial insects, humans, domestic animals and wildlife; 4) to understand the transmission cycle, the life history of the vector species, and the natural factors regulating vector survivorship are critical; 5) that the most effective programmes develop descriptive and predictive models for population dynamics and transmission potential; 6) to have flexibility in terms of changing strategies and tools in response to surveillance and biological data; and 7) that management strategies should be dynamic and able to respond to the results of an active and sensitive mosquito/pathogen surveillance programme [103].

The success of IVM programmes are the integrated control of malaria in the Zambian Copper Belt in the 1930s and 1940s, the initiative against Chagas disease vectors in Latin America, and the Onchocerciasis Control Programme in West Africa since the 1970s. These success stories demonstrate that strategically effective, well-coordinated and sustained initiatives can bring extraordinary benefits in health and socioeconomic development [101]. The above mentioned programme could achieve their target owing to the use of efficient systems for monitoring, evaluation and reporting and ii) procedures for the rapid identification and correction of problems [101]. The adoption of a strategy for IVM provides new opportunities for effective action against vector borne disease.

7. Conclusion

To overcome the burden disposed on India by mosquito borne diseases, the only available approach is implantation of effective vector control strategy. An efficient vector control depends on proper planning which in turn depends on investigation before the planning of strategy. For treatment of disease with the use of medication, the major challenge is to minimise drug resistance, similarly for vector control, it is to halt the development of insecticide resistance. For combating drug resistance, the prime concern should be taking medications

only under medical supervision, completion of course of medication and safe disposal of medicines. For insecticide resistance, the best way is to manage the level of insecticide resistance within the vector population; this can be done through insecticide resistance management (IRM) [94]. For IRM, the first approach should be to monitor the level of resistance developed within the target species at a local level, so that site specific effective insecticide dosage can be devised. The alteration in behaviour of the target species should be studied to keep a check of behavioural modification taking place (if any). Constant use of insecticides belonging to same chemical group should be avoided, instead a rotation of different insecticide group should be followed while spraying [94]. Also, insecticide use should be limited both in space and time dimension, *i.e.* only those sites where insecticide usage is needed/inevitable for public health security, should be brought under vector control programmes using insecticide. There should always be a time period gap between successive sprays. Low doses of insecticide should be used to maintain the population of of susceptible strains [104]. Insecticide that persist in the environment for a very small time should be used, thereby reducing the selection pressure [104]. The mechanisms behind insecticide resistance should be thoroughly studied and methods to block such mechanisms (through enzyme blockers, synergists *etc*) should be sought for. Also research assignments on formulation of novel insecticidal compounds with novel targets, search for compounds of botanical origin with such potentiality, sterile male mosquito technology, biological control of mosquito, etc should be devised for sustainable, environment friendly and effective disease control. Lastly, public awareness regarding mosquito breeding habitats and source reduction by public health educational campaigns to reduce backyard mosquito larval habitats (*i.e. Anopheles, Aedes, Culex*) should be conducted on a regular basis. Community participation can help reduce mosquito habitats, while developing long term, low cost sustainable programs. In the event of public health emergency, community peer educators can both help in the reduction of vector habitats and provide assurance to the community regarding mosquito control programs.

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Chapter 5

Global Climate Change and its Impact on Mosquito Borne Diseases: A Complex Scenario

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Abstract

Climate change is one of the most critical global challenge affecting all aspects of our life and is believed to be the result of increase in the emission of green house gases causing global warming. Recent events such as excessive rain fall, droughts, heat wave, cyclones and hurricanes emphatically demonstrated our vulnerability to climate change. The increase in temperature, melting glaciers, rising sea level, retreating ice caps, and abrupt weather pattern are the consequences of the changing climate, the impact of which may range from affecting agriculture, accelerated erosion of coastal zones, species extinction and the spread of infectious and vector borne diseases due to natural disasters to food scarcity and malnutrition. The impact may differ from one place to another and from developed countries to resource poor developing countries. As mosquitoes are highly sensitive to temperature, humidity and rainfall any shift in temperature may have profound effect on disease transmission in highland areas and variation in rainfall and drought conditions may affect the transmission potential in the low land areas. Countries with sound health care delivery and having an early warning system may be able to reduce the impact to significant level. However, it is believed that dynamics of vector borne diseases is highly complex and factors other than the climate such as land use change, drug and insecticide resistance and people behavior also plays an important role, hence a comprehensive approach with increased awareness is needed to overcome the onslaught of the climate change.

Key words: Climate; Green house gases; Global warming; Mosquitoes; Malaria; Dengue

1. Introduction

From devastating floods in many parts of the world to cloudbursts and landslides in Leh and Uttaranchal in India and massive heat waves in Europe and Russia to extended rain fall and downpour in north India the altered climatic conditions have become a regular phenomenon in recent past blamed to be the consequences of abrupt weather pattern due to global warming affecting all aspects of the life including health and socioeconomic conditions of the society. Last few decades have witnessed more severe catastrophic climatic events like tsunami in Indian ocean to cyclones and hurricanes like Katrina, Wilma, Nargis, Laila, Aila and Irma in US and south-east Asia and from heavy rainfall in cities like Mumbai, Gujarat and arid areas of Rajasthan in India to severe drought and heat waves and forest fires in others displacing many people and causing untold miseries. The rise in malaria in some areas to increasing incidence of dengue in others the nation has constantly been reeling under the impact of climate sensitive mosquito borne diseases likely to have some weather connection. The climate pattern is changing fast and furiously affecting our lives particularly our health. Global climate change is considered to be one of the most serious threats to the global environment and has been at the centre of scientific and political debate in recent years.

2. The Climate and its Impact of Global Warming

It is highly believed that man-made activities are altering the world's climate as we are increasing the atmospheric concentration of energy trapping gases thereby amplifying the natural greenhouse effect that makes the earth inhabitable. Green House Gases mainly comprise of carbon dioxide (mostly from fossil fuels combustion and forest burning), methane (from irrigated agriculture, animal husbandry and oil extraction), nitrous oxide and various human made hydrocarbons [1]. The level of these gases has increased considerably in recent past which is making our planet more warm and altering the weather pattern. The emission of CO_2 the main culprit in this complex scenario has increased 12 fold from 534 million to 6.59 billion metric tons in the 20th century [2]. The resultant meltdown of arctic snow caps, rise in sea level, changes in cloud formation and rain fall pattern etc are consequences of global warming. The adverse effects are also observed on natural resources, food supply, human health and national economy.

In 1896, the Swedish Scientist SavanteArrhenius suggested that human activity could substantially warm the earth by adding CO_2 to the atmosphere [3]. His predictions were subsequently independently confirmed by Thomos Chamberlin. The establishment of United Nations Intergovernmental Panel on Climate Change (IPCC) in 1988 was a pivotal move by the world community to address this issue. The IPCC predicts a 1.4 to 5.8^{0}C rise in temperature by 2100 and sea level rise is also expected in the range of 15-89 cm. IPCC posits that most climatic change since 1950 is human induced and will have far reaching environmental and

health effects [4] (**Figure 1 & Figure 2**).

3. Kyoto Protocol and Beyond

In an attempt to halt climate change, international efforts to reduce emission have already been put in place. Since 1990, international efforts have created the climate change regime, the centre piece of which is the UNFCCC and its instrument, the Kyoto protocol [l5]. The Kyoto protocol has now been ratified by 187 nations (not US) and went in to effect in 2005. The purpose of the meeting held in Copenhagen (COP15) in December, 2009 was to establish a framework for tackling climate change beyond 2012. However, in the end no binding solution was passed [6].

The Kyoto Protocol is an international agreement linked to the United Nations Framework Convention on Climate Change, which commits its Parties by setting internationally binding emission reduction targets. The Kyoto Protocol was adopted in Kyoto, Japan, on 11 December 1997 and entered into force on 16 February 2005. Its first commitment period started in 2008 and ended in 2012. In Doha, Qatar, on 8 December 2012, the "Doha Amendment to the Kyoto Protocol" was adopted. During the first commitment period, 37 industrialized countries and the European Community committed to reduce Green House Gas (GHG) emissions to an average of five percent against 1990 levels. During the second commitment period, parties committed to reduce GHG emissions by at least 18 percent below 1990 levels in the eight-year period from 2013 to 2020. Under the Protocol, countries must meet their targets primarily through national measures. The Kyoto Protocol, like the Convention, is also designed to assist countries in adapting to the adverse effects of climate change. It facilitates the development and deployment of technologies that can help increase resilience to the impacts of climate change. The Kyoto Protocol is seen as an important first step towards a truly global emission reduction regime that will stabilize GHG emissions, and can provide the architecture for the future international agreement on climate change. (*http://www.unfccc.int/kyoto_protocol/items/2830.php*).

4. Impact of Climate on Human Health

Climate is a key determinant of human health and climate constraints the range of infectious diseases while weather affects the timing and intensity of outbreaks. The concept that weather and climate are linked to incidence of infectious diseases in humans has been recognized since the time of Hippocrates. According to IPCC (2007) warming of the earth climate is unequivocal. Global changes already documented includes increased global surface temperature, rising sea level, decreased arctic and alpine snow & ice and evidence of plant and animal responding to these changes by moving to higher elevations or closer to the poles. Precipitation has increased in some parts of the world while decreasing in others. Climate change is predicted to have a variety of impact on human health, many of which have been extensively

reviewed [4].

Climate change will be the root cause of many public health nightmares. The World Health Organization (WHO) has documented more than 39 new and re-emerging diseases since 1960s that are linked to global warming. In addition there has been resurgence of old diseases like malaria and cholera in some areas. Though this change in some diseases may be due to deterioration of public health system but diseases that involve two or more species such as malaria reflect changing ecological and climatic conditions as well as social changes. Temperature increase over the past century have led to an estimated 5.5 million DALY (Disability Adjusted Life Years) and at least 1,50,000 lives annually [5,7]. According to the Centre for Disease Control & Prevention, there were 8015 heat related deaths in United States between 1979 & 1999. In addition, the heat wave that affected Europe during the summer of 2003 led to 22,000 to 45,000 excess deaths [8]. Mosquito populations are expanding across the globe and bringing nasty diseases like West Nile virus (WNV), malaria and yellow fever. Dengue and Chikungunya have also re-emerged as a significant public health problem. Hotter temperature also enhance smog formation and influence the disease conditions such as asthma and lung cancer. The impact of climate change on human health is likely to be two fold.

1. Direct Effects : Physiological effect of Heat and Cold

2. Indirect Effect : Spread of vector-borne pathogens in to areas where diseases does not exists currently or was eradicated and enhancement of transmission in others. However, in certain situations in countries having robust health infrastructure the impact may not be so prominent. Since the vector binomics is complex and local climatic and socio-econmic factors also play an important role, they will also need to be studied.

Climate change creates fertile conditions and alters the geographic range of disease vectors and carriers such as mosquitoes, ticks and rodents bringing them in to greater contact with human populations naïve to the diseases they carry. Malaria for example, is expected to move to higher altitude and dengue to move further north. A difference of 1^0C in the global mean average temperature increase could be the difference between a 10% and a 40% reduction in crop yields, between 16% and a 23% increase in malaria exposure in Africa or between 1 billion and 4 billion additional individual experiencing severe water shortage. Water quality and quantity are also likely to change in future as precipitation pattern change and warmer conditions adversely affect the potential levels of aquatic borne pathogens and water pollution [9,10] (**Table 1**).

Although the casual relationship between climate change and particular disaster is difficult to establish, the heat wave in Europe (2003), the flooding in Mumbai (2005), and Hurricane Katrina and Irma in the United States (2005, 2017) are indicative of events likely to occur more often in future [9].

5. Impact of Climate on Mosquitoes and Mosquito Borne Diseases

The existence of mosquitoes on this planet is known from time immemorial and they are found throughout the globe except in places that are permanently frozen. There are around 3500 species of mosquitoes of which nearly three quarters are native to humid tropics and subtropics and they transmit many dreaded diseases (**Figure 3**). The burden of major mosquito borne diseases in India is shown in **Table 2**. The temperature, humidity and rainfall are major detrimental factor for survival, proliferation and propagation of each and every species of mosquitoes. Hence climate and weather variability will have profound effect on mosquito immature as well as adult survival [11]. Vector mosquitoes are highly sensitive to weather conditions and their vectorial capacity is governed by the existing climatic conditions. Changing trend in average temperature and precipitation are anticipated to have an astounding impact on vector borne diseases and their distribution. It is expected that there is real risk of re-introduction of malaria in to non-malarial areas including parts of Australia, US and South Europe (IPCC estimates that potential malaria transmission area may increase to 60% as compared to 45% at present; *http://www.gcrio.org/ipcc/qa/10.html*).

Temperature and humidity are most important factors affecting mosquito development and longevity and consequently disease transmission. Extrinsic incubation period (EIP) of the parasite shorten dramatically at higher temperature, so mosquitoes becomes infectious sooner. It is also noticed that if water temperature rise, larvae take shorter time to mature, capacity to produce more off springs during transmission period. In warmer climate, adult female digest blood faster and feed more frequently thus increasing transmission intensity. With the increase in temperature epidemic potential is also increased. Climate change represents 1-3% increase in total population at risk (**Figure 4**).

6. Area Specific Impacts

Impact of global warming may be different in different areas for example in low land areas rain fall quantity and continuity will have important role in water logging, creation of more breeding places for mosquitoes or flushing of mosquitoes in severe rainy days. In riverine areas rivers may be subjected to flooding due to glacier melting or excessive rain fall and flush away the mosquito immature while in drought conditions subjected to formation of pools, provide breeding of mosquito vectors. As well as migration of population with their cattle to newer areas may enhance the man vector contact. Whereas, in highland areas temperature will play a crucial role as a slight increase in temperature may increase the survival of mosquitoes and extend the transmission period of the diseases they cause by creating more conducive environmental conditions.

6.1. Malaria

Malaria continues to remain the oldest scourge to humankind and a serious public health problem affecting around 40% of the world population in 100 endemic countries. According to the World Malaria Report 2017 around 216 million people around the world get crippled by this disease and more than 0.44 million lose their life with maximum damage occuring in Africa [12]. Malaria is highly sensitive to climate and excessive rain fall or drought may severely affect its transmission. Models of climate change indicate that increase in temperature will expand the geographic range of malaria to higher altitude and latitude and expand its area of prevalence from 40 to 60%. If global temperature increase by 2 to 3^0C as expected, it is estimated that population at risk for malaria will increase by 3 to 5%.Thermodynamic malaria development model clarifies that temperature fluctuation can substantially alter the incubation period of the parasite.

Although excessive heat kills mosquitoes but warmer average temperature within their survival limit increase their survival range, accelerate reproduction, biting and the rate that pathogens matures with in them including malaria parasite Plasmodium. P. *falciparum* and *P. vivax* require temperature of 18^0C and 15^0C for development respectively. At least 20^0C is needed to initiate a malaria epidemic. The IPCC predicted 1.4 to 5.8^0C in global temperature would increase the proportion of land areas experiencing temperature of 20^0C or higher. Warmer temperature will permit *P. falciparum* to mature faster and increase its epidemiological outcome [13,14].

The last few decades have seen a marked resurgence of malaria in the East African highlands. The reasons for this seasonal malaria are not fully resolved but factor that has been widely debated is the possible influence of regional warming due to climate change. Among the studies supporting a climate driven response, Pascual *et al* [15] used a temperature dependent population dynamics model to demonstrate that a small change in mean ambient air temperature of just 0.5^0C could translate in to 30-100% increase in mosquito abundance in other words biological amplification of temperature effect. In Africa and elsewhere such biological response may be especially significant in determining the risk of malaria. Predictions are common that in coming decades more cases will occur in regions where disease is already present and that vector and pathogens will move to higher latitudes and altitudes [16].

It is expected that due to rise in temperature there is every possibility of introduction of malaria in new areas or in areas from where it has already been eradicated. Rising temperature also pose problem for highland areas with the rising trend of malaria in the highlands of Kenya has already been discussed. In Kurseong, Drjeeling district in eastern part of India, Annual Parasite Incidence (API) rose from 2 to 7.8 between 2000 and 2004. Two foothill areas with forest and slow moving streams accounted for 88% of cases in 2004 [17]

Transmission windows for malaria in India are predicted to increase with climate change. For most vectors of malaria, the temperature range of 20^0C-30^0C is optimal for development and transmission. A relative humidity higher than 55% is optimal for vector longevity, enabling the successful completion of sporogony. Analysis of average temperature, humidity, precipitation and incidences indicate that maximum incidence occurs in the months of June, July and August, when the RH is in the range of >60 and <80 and temperature ranging between 25^0C to 30^0C. This window shift from state to state depending upon arrival of the monsoon. Study carried out by the National Institute of Malaria Research, New Delhi revealed that northern states such as Jammu and Kashmir, Himachal Pradesh, Panjab, Haryana, Uttarakhand and north-eastern states are more vulnerable to climate change and transmission windows are likely to extend temporarily by 2-3 months, while south eastern states such as Karnataka, Kerala and Andhra Pradesh are less vulnerable to climate change as the climatic conditions are already suitable for malaria transmission almost through out the year, however, there may be reduction in transmission windows in Orissa, and Tamil Nadu [18].

It has been reported that impact of climate change on malaria will vary in stable and unstable malaria situations. In stable malaria regions where the principal malaria vector is anthropophillic and in the situation of high survival rates the disease is hard to control because transmission is efficient and transmission rates are so high that most people experience many infective bites per year and climate change may not make large difference in already existing difficult situation but in unstable malaria situations where anophelines are zoophillic and their survival rates are low with epidemics separated by many years with low immunity in the populations the disease may appear suddenly. Thus behaviour and ecology of vector and host are the dominant factor in malaria transmission along with the climate [19].

6.2. Dengue

Dengue is another important arboviral disease occurring in tropical and sub-tropical regions particularly in urban settings and affecting about 100 million people worldwide with incidence increasing 30 fold in the past 50 years. Dengue fever has increased dramatically in Malaysia from less than 1000 cases in 1973 to about 46000 cases in 2007 [20]. In India since 1960 more than 50 outbreaks have been reported or investigated by National Institute of Communicable Diseases (renamed as National Centre for Disease Control). The 1996 epidemic in Delhi was the worst of its kind which affected 16,517 persons and killed 545 [21]. In much of south-east Asia region dengue is spreading not only geographically but in serious outbreaks. It has been reported in the mountainous countries of Bhutan and Nepal since 2002 [7]. WHO states that it is most rapidly spreading mosquito borne disease and experts estimates that 50 million dengue infections are occurring annually and 2.5 billion live in dengue endemic countries. In India dengue have shown rising trends from 5534 cases in 2007 to 1,29,166 cases in 2016 with 245 deaths [22].

Dengue fever is sensitive to climate. Studies have shown that an increase in 1-2^{0}C result in quicker and higher replication of viruses. Global warming resulting in drought may lead to increase of cases due to house hold storing of water particularly in urban/semi-urban areas which provide ideal habitats for *Ae. Aegpyti* the vector mosquito to breed, while in rural areas *Ae. albopictus* breed prolifically. The climate change is expected to increase the number of regions affected by arbovirus, such as Australia and New Zealand. Heavy rainfall and a rise in temperature increase the rate of infection. It is expected that by 2080, about 6 billion people will be at the risk contracting dengue fever as a consequence of climate change. Already, during 1988 heat wave in Mexicco, *Ae. aegypti* carried dengue fever from 1000 to 1700 m altitude [14]. Sometimes ENSO event affects dengue occurrence by causing changes in household water storage practices and surface water pooling. Between 1970 and 1995 the annual number of dengue epidemics in south Pacific was positively co-related with La-Nina conditions. In India it has been shown that immature of *Ae. aegypti* in Darjeeling are expanding geographical limits.

Along-with the impact of climate change on dengue prevalence the increase in population, rapid urbanization, escalation in construction activities also encourage the increase in the water storage containers such as Over Head Tanks, Cisterns, earthen pots, tyres, drums, Desert Coolers *etc* which support the breeding of *Ae. aegypti* and due to changed climatic conditions and extension of favourable period for mosquitoes to survive coupled with rapid travel and transport accelerate the problem of dengue.

6.3. Chikungunya

Chikungunya is another mosquito borne viral disease spread by the *Ae aegypti*, that is spreading fast in Asia region. In recent past outbreak of chikungunya has been witnessed in many parts of India and it has re-emerged as a serious public health challenge. It is expected that along with dengue it will also pose serious problem in climate change scenario. The emergence and resurgence of chikungunya fever and its association with global warming has been studied by Epstein [23].

6.4. Leishmaniasis

It is a climate sensitive disease affecting development of sand fly vectors in alluvial soil with high sub-soil water table. Temperature ranging from 7^{0}C to 37^{0}C and Relative Humidity (RH) more than 70% in India are suitable conditions for risk areas. The life cycle of sand flies is influenced by RH & temperature resulting in fluctuations in density. In north-eastern Colombia, it was found that during El-nino, cases of leishmaniasis increased whereas, during La-nina, leishmaniasis cases decreased [24].

The other mosquito borne diseases such as filariasis, Japanese encephalitis *etc* also needs

to be studied with reference to changing climate and it is expected that vector borne diseases of local distribution such as chagas disease, lyme disease, west nile virus, rift valley fever, eastern equine encephalitis, western equine encephalitis, St louis encephalitis, *etc* are also likely to be effected in climate change scenario.

7. **Abrupt weather, Ocean Circulation and El-Nino Southern Oscillation (ENSO): A Tool for Epidemic Forecasting**

Climatically important thermohaline circulation (THC) is a conveyer like circulation in the Atlantic ocean and transport heat throughout the planet where near surface current bring warm, saline water from the subtropics to higher northern latitude. This is important as it affect the weather. Rapid change in ocean circulation is associated with abrupt weather.

El-Nino Southern Oscillation (ENSO) is a climatic phenomenon and comprises changes in Pacific Ocean, which occurs every 2-7 years. The cycle of warming (El-Nino or warm water) and cooling (La-Nina or cold event) of sea surface temperature (SST) in the eastern pacific results from changes in the ocean circulation. ENSO creates rainfall and temperature fluctuations in certain geographic areas world wide, which on average has less rain fall (drought) during warm event (El-Nino) and more rain fall during cold phase (La-Nina). Malaria epidemics have been associated with excess rain fall in arid areas and drought in humid climate, where rivers can be transformed in to pools and becomes conducive for mosquito breeding. Climate change is expected to increase the intensity and frequency of ENSO events and thereby affecting mosquito borne diseases. The ENSO pattern has become more pronounced since 1970s.

El-Nino associated drought appears to affect malaria transmission in the following year. Reduction in transmission during a dry year is likely to reduce population immunity and hence increase the size of vulnerable population in the following season. ENSO has been suggested as predictive tool for vector borne diseases and in epidemic forecasting as well as targeting scarce resources. Major focus of research is the ability to predict El-Nino events several months in advance.

Bouma *et al* [25] have shown that rainfall in west Rajasthan in the year after El-Nino event was 40% higher than in the El-Nino year and 50% higher in the La-Nina year. Strong co-relation was seen between rainfall and malaria incidence and also with number of rainy days in Jodhpur district [26]. In Venezuela malaria morbidity and mortality increased by an average 36.5% in years following recognized El-Nino events [27]. Kilian *et al* [28] in Uganda attributed increased Pf infection to increased and prolonged rainfall caused by ENSO. Many malaria epidemics every 5-8 years have been associated with ENSO cycle e.g.Former British Panjab, Pakistan, Sri Lanka, Highlands of Uganda, Columbia, Peru, Bolivia, Ecuador, Rwanda etc. In Dehradun (Uttarakhand), India, higher co-relation between parasitic incidence and climatic variables was found, the highest being between rainfall and malaria incidence [29].

8. Other View Point

Chris Dye and Reiter [30] reported that a rise in temperature spreads the development of parasite but if there is no water for mosquito to breed and limited control with human, high temperature would not matter much. In an other study carried out by Hay *et al* [31] , no evidence was found with warming in highland locations in East Africa and it was suggested that the cause of resurgence of malaria was due to change in land use, human demography, resistance to anti-malarials, *etc*. Pattern of rainfall and malaria in MP was studied by Singh and Sharma [32] and no clear relationship was observed though it was stated that a major water resource might have masked any significant association. Lindsay *et al* [33] found more rain fall after strongest recorded El-Nino in Tanzania but strikingly less malaria was noticed in preceding years. Hence, in certain situation non-climatic factors may play an important role.

9. Early Warning System

Epidemics/outbreaks of mosquito borne diseases are serious public health emergencies. Typically they occur with little or no warning in areas where health system is unprepared to deal with the emerging problem. Early identification of an infectious diseases outbreak is an important first step towards implementing effective diseases intervention and reducing resulting mortality and morbidity. The impact of epidemics can be minimized by prediction and improved prevention through vector control and deployment of appropriate drugs. WHO advocates the development of integrated malaria early warning system based on vulnerability assessment, seasonal climate forecast, weather and environmental monitoring and case surveillance.

9.1. Historical Early Warning System

The use of climate data for predicting outbreak of infectious diseases dates back to work of Gill and others in India [34]. Gill (1923) [35] developed an Early Warning System (EWS) for malaria based on rainfall, prevalence of enlarged spleen, economic conditions and epidemic potential. Recently a study has been conducted on the development of Epidemic Early warning in Eritrea using the parameters of vulnerability assessment, surveillance data and seasonal climate forecast based on NDVI and SSTs [36] .

9.2. Climate Models

Most of the mosquito borne diseases including malaria are dependent on rain fall, temperature, humidity, wind, land cover-use, topography and other local conditions. Accurate seasonal prediction of rainfall, temperature and other hydro-meteorological variables and land cover-use are very useful for early warning of malaria risk, mapping disease distribution and decision making about prevention.

9.3. Predictor of Malaria Early Warning System (MEWS)

By combining information through satellites, weather statistics and health centre data, researchers have developed statistical models to help predict malaria transmission. MEWS use 4 main groups of indicators to predict the timing and severity of malaria epidemics:

1. Vulnerability indicators (e.g. immune status, drug resistance)

2. Transmission risk indicators (unusual increase in rain fall higher than the average seasonal rain fall, seasonal climate forecast, 1-6 month in advance, weather monitoing)

3. Early case detection indicator (case surveillance)

4. Monitoring vector population

Kenya Medical Research Institute (KEMRI), Kenya, Kenya Meteorological Department and International Centre for Insect Physiology and Ecology have launched a new tool that calculate data based on environmental factors (weather, geography) and mosquitoes mating schedule successfully(with 86-100%) and predict a malaria epidemic 90 days before [37]. The disease prediction tool should help policy makers and health officials prepare in time to deal looming outbreaks with regards to when and where to spray.

9.4. Disease Surveillance

Monitoring of malaria cases can be used for early case detection of an epidemic if collection and notification are timely (*i.e.*weekly). Disease surveillance for early detection of malaria epidemics has been used in Thailand [38], where deviation from seasonal averages were used to detect outbreaks (*i.e.* where monthly cases exceed the long term mean plus 2 SD). This approach detected 228 out of 237 epidemics in 114 district from 1973-1980. Parasitological data for the years 1973-81 were examined to determine the years of acceptable or normal transmission of malaria for every district of northern Thailand. The monthly mean number of cases plus 2 Standard Deviation (SD) were calculated for the selected years and plotted on log-linear graph paper and distributed to Malaria Sector Officers. If the observed incidence in their Sector was more than 2 SD greater than the normal mean for that month, the Zone and Regional Malaria Officers were informed. Retrospective analysis of data of the districts where outbreaks reported indicated that the method provided an effective warning of impending epidemics.

9.5. Land cover and vegetation index (NDVI)

Land cover and Land use has a significant impact on malaria transmission. A biological indication of rainfall *i.e*. the normalized difference vegetation index (NDVI) derived from satellite data is a measure of the amount of photo-synthetically active vegetation and is thus

proxy for land cover, it has been found useful in prediction of malaria incidence. Many studies have shown a positive correlation between NDVI and malaria incidence. Temporal changes in the vegetation index (NDVI) have been shown to be a good indicator of the malaria season in The Gambia, Niger [39] and Kenya [40].

9.6. Land use change and enhanced incidence of malaria

Agricultural and land use practices in developing and rapidly industrializing countries have been found to affect vector borne diseases [41]. Deforestation was found to affect the ecological succession of vector mosquitoes in Nainital District, in Uttarakhand, India. *An. minimus* was the principal vector in 1930s and deforestation resulted in the succession of *An. fluviatilis* and further colonization of terai and irrigation introduced *An. culicifacies* which is now the vector of malaria [42]. The indiscriminate digging of borrow pits, rice paddy cultivation, use of pesticides in agriculture resulting in evolution of resistance in disease vector, malaria diffusion through population movement and inaccessibility of villages in the hinterland are some of the factors that would maintain the transmission.

In many areas, major ecological changes have occurred and vectors were uprooted and eliminated but soon these niches were filled by new vectors. Classical examples as mentioned above is the succession of *An. minimus* by *An culicifacies* in UP terai and a similar succession of *An. sundaicus* by *An. culicifacies* in Chilka lake area in Orissa. In Orissa, *An. culicifacies* has established itself all over the state even in areas where it was not recorded previously and now it is playing the role of primary vector [43-44]. In Malnad foothill areas in Karnatka dams were built in the valley resulting to deforestation and elimination of streams, the breeding places of *An. fluviatilis* the major malaria vector in the area and thus eliminated the malaria from the area [45,46].

Agronomic practices have also contributed to technical obstacles in malaria control. Use of insecticides in agricultural crops *e.g.* in Andhra Pradesh and Orissa has precipitated malathion resistance in *An. culicifacies* [43]. Malaria began to appear at higher altitude of Kenya after clearance of forests for development of tea estates and importation of labour [19]. Construction of Roads and railways create innumerable flooded borrow pits due to depression left by excavation and contribute to mosquito breeding. In highland of Madagascar, following extensive development of rice irrigation, diseases became endemic [47].

Changes in land use might also be responsible for recent emergent foci of Crimean-congo hamorrhagic fever virus in many countries. Evidence is presented to show that an expansion of brackish water bodies in coastal zones can increase the densities of salinity tolerant mosquitoes like *An. sundaicus* and *Cx. sitiens* and lead to adoption of fresh water mosquito vector *An. culicifacies*, *An. stephensi*, *Ae aegypti* and *Ae. albopictus* [48].

10. Geographical Information System/Remote Sensing

Geographical Information System (GIS) and Remote Sensing (RS) technologies can be utilized properly for mapping of mosquito breeding places and planning better control strategies. GIS is an information technology to input, store, update, retrieve, analyze & output geo-referenced data. It has the potential to develop thematic maps of the input data with overlaying and integration of the maps and has a strong statistical component to visualize, interpret complex real situation to provide effective solutions. GIS analysis helps to identify factors which will indicate disease threats and would also help in planning rationale and suitable control strategies and early preparedness in preventing outbreaks/epidemics. Remote Sensing is the technology of collecting images of the earth surface from satellite platforms and transforming the images in to maps. Remote sensing can generate data on land use features, soil type, water bodies, vegetation, forest cover, human habitation etc, which can be used as databases in GIS for vector borne disease analysis. The combined use of GIS & RS in addition to stratifying areas, identify risk factors can also help in identifying the priority areas for control and in construction of spatial decision support system for planning disease control strategies. This may also be useful for rapid Geographical Reconnaissance at village level with coverage of large and inaccessible areas and may be useful for ecological change detection for micro stratification and help in early warning of malaria (short and long range).

11. Cold Cloud Duration

Clouds with the coldest top surface produce heaviest rainfall. It is possible to derive estimates of rainfall by measuring the cloud top temperature using half hourly infrared images obtained from Metostat channel (satellite).

12. ENSO and Sea Surface Temperature (SST)

As global warming increases, there is an expected rise in the frequency of irregular climate fluctuations, including phenomenon known as ENSO, which causes characteristic changes in atmospheric conditions. Mosquito borne diseases are sensitive to changes in temperature and precipitation. Any increase in frequency of ENSO event could bolster epidemic. SST is an early indicator of ENSO event in some parts of the world, where SST in the Pacific are important predictions of climate events. Significant co-relation between malaria incidence anomalies and SST has been observed. Both rainfall and annual malaria incidence anomalies were significantly related to SST in eastern Pacific suggesting that they may be predictable months in advance using seasonal climate forecasting methodologies [49]. Thomson *et al* [50] showed that in Botswana indices of El-Nino related climate variability can serve as the basis of malaria risk prediction and early warning.

13. Comprehensive plan may include:

- Development of an integrated early warning system
- Emergency response plan
- Refugee management plan
- Increase capacity to provide shelter, drinking water, sanitation and sustainable agricultural products to most vulnerable population
- Partnership with both Govt and non-Govt sector will also be necessary
- Regional climate models must be integrated with health data
- Satellite and geospatial technology may provide new insights regarding the geographic distribution of risk and diseases
- Integration of social, demographic and land cover data with health data will aid in describing a holistic health scenario
- Data on land use and land cover may provide additional information on relevant environmental factors that influence risk and vulnerability.

14. Conclusion

The epidemiology of vector borne diseases is highly complex and is the function of many abiotic and biotic factors including temperature, humidity, rainfall and insecticide and drug resistance to poor health care delivery systems to individual immunity. Deforestation, agronomic practices and land use changes are also detrimental factor in disease transmission. The understanding the role of climate is rather more complex. As certain situations favour or encourage the breeding of mosquito vectors but if proper health care management is there the impact of such climate catastrophes can be minimized. An early warning system can predict the genesis of epidemic in advance and help in making the better control and prevention strategies. Availability of key intervention tools for mosquito control, drugs and effective surveillance can also play a positive role. Though it is essential to cut down the emission of greenhouse gases and reduce the magnitude of the problem but on the other hand there is also need to equip yourself to face such challenges. Government of India is also taking positive steps in this direction and released its much awaited National Action Plan on Climate Change to mitigate and to adopt climate change on June 30, 2008.Awareness and strengthening of health care delivery system may produce positive results. This is the time to act and act in right direction with integrated approach.

15. Tables

Table 1: Impact of Climate Change on Human Health

Environmental Change	Climate Change	Ecological Change
Air Pollution	**Thermal Extremes**	**Food Availability**
Cough Asthma	Heat strokes	Malnutrition Growth Retardation Developmental Delay
UV Radiation Sunburn Malignant Melanoma Immunosuppression	**Weather Disasters** Drowning Dehydration Gastrointestinal illness Psychosocial Trauma	**Allergen/Mycotoxin** Allergies Cancer Birth defects
Sunburn		**Infectious Diseases Exposures**
		Malaria Dengue Encephalitis Lyme Diseases
		Emerging Infectious Diseases
		West Nile Virus Hantavirus Others

Source: based on Bunyavanich, Ambulatory Pediatrics, 2003; 3: 44-52

Table 2: Burden of Vector Borne Diseases in India

Sr No.	Diseases	Cases/annum	Death
1.	Malaria	1.09 million	331
2.	Filariasis	0.20% mf rate	Nil
3.	Kala-Azar	6245	Nil
4.	Dengue	1,29,166	245
5.	Chikungunya	64,057	Nil
6.	JE/AES	1676/11651	283/1301

Source: NVBDCP, Govt of India (nvbdcp.gov.in); cases in 2016

16. Figures

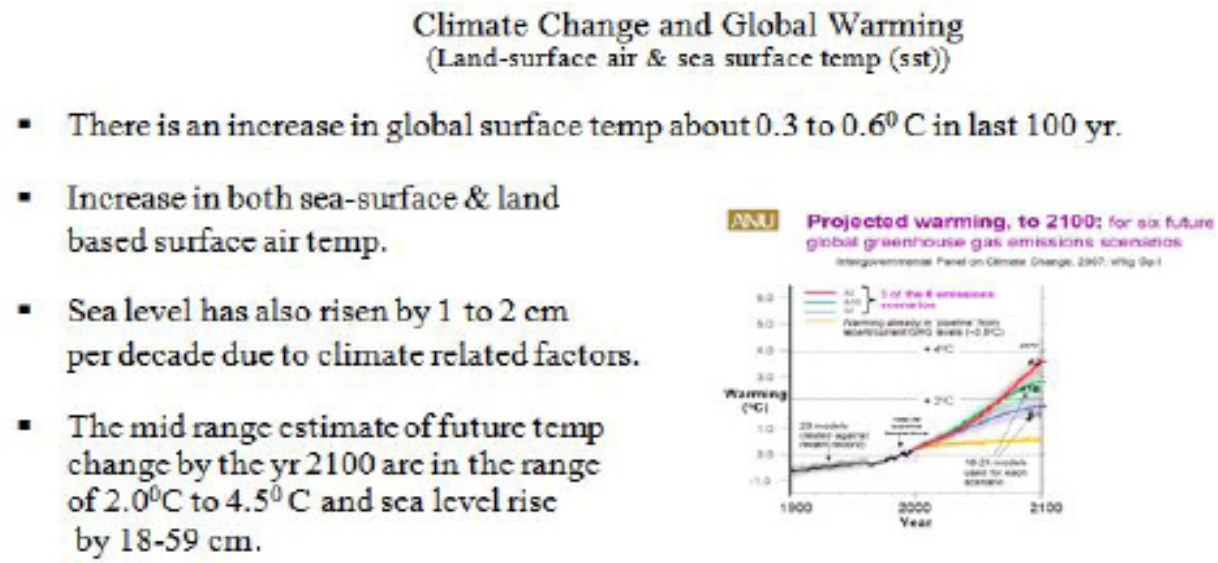

Figure 1: Global warming and its consequences on increase in temperature and sea level rise.

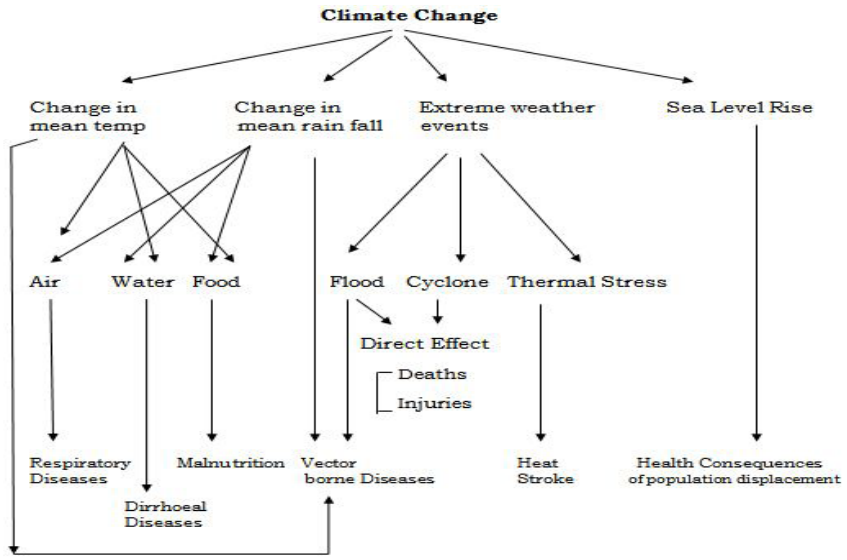

Figure 2: Impact of Climate Change on Human Health
(based on Climate Change and disease dynamics in India edited by Dogra N and Srivastava S, 2012, The Energy and Resource Institute: New Delhi.)

- Malaria
- Filariasis
- Dengue
- Yellow fever
- Japanese Encephalitis (JE)
- Eastern Equine Encephalitis
- St. Louis Encephalitis
- La-Crosse Encephalitis
- West Nile virus
- Chikungunya

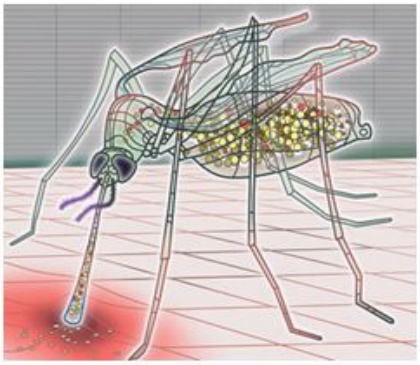

Figure 3: Major Mosquito-borne diseases

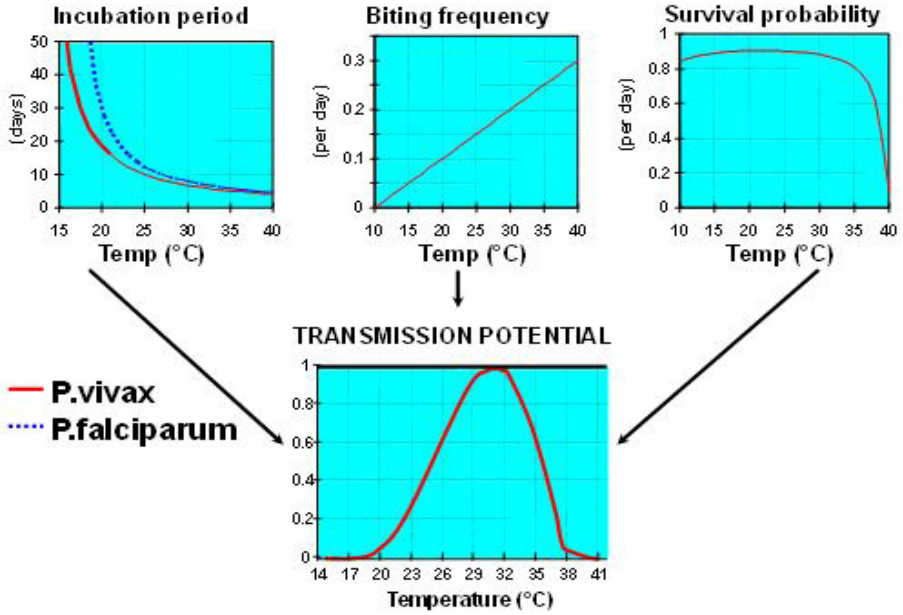

Figure 4: Impact of temperature on transmission potential of mosquito borne diseases

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Vector-Borne Diseases & Treatment

Chapter 6

Malaria Eradication: A War How To Win?

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Abstract

Since Nobel research of late 19th century by Laveran and Ross, now ample of data is available about malaria but no sign of its eradication. Today science is accelerating with an unforeseen pace resulting into a burst (an explosion) of data and analyses, still fall short to resolve the problem. What's the reason behind it? In our view the major issue behind failure is defining the problem. Here we discussed the various aspects of malaria required for malaria eradication.

Keywords: Plasmodium; Drugs; Vaccine; Malaria Eradication

1. Background

The relationship of human and plasmodium is supposed to be of 50000 years and this parasitic organism has learnt to survive during a long history of co-evolution with their hosts [1,2]. As a result there exists a fine balance between the survival tactics of parasites and immune response posed by the hosts. With the development of human race and inventions of drugs posed additional selection pressure on the parasite but not on the human host. This artificial selection led to more evolved parasites [3]. Therefore, it is must to ensure that the direction in which we are trying to move for malaria eradication is right or not because it is the right strategy which only will give the right outcome. Here we tried to discuss the available data and strategies in context to resolve and eradicate malaria.

2. Mosquito as Target

If we see the map of malaria spread out, it is the tropical countries which are predominantly affected whereas temperate zones successfully eradicated the malaria. The eradication from temperate zones is not only because of good economic ground but also the environmental conditions helped them [4]. The disease remained endemic in hotter countries; South America, Africa and South Asia and the burden is so high that claims death always more than a world war. This is only because tropics support the vector host Anopheles. In supportive environment vector control even become disastrous when they attain resistance against insecticides [5].

Keeping in mind the resistance developing nature of vectors, studies majorly focused insecticides development will be helpful in long run is a big question? Secondly no insecticides is specific to only one type insects and may also affect human friend insects that may lead to extinction of our friend without much effect on enemy.

In our view Mosquitos are not at all a problem and direct targeting them is not possible as they belongs to Arthropoda which have amazing powers of adaptations which made them unique and diverse [6,7]. Further they are not the host but vector. We should work on how to break parasite transmission from human the host to mosquito. Like all mosquitoes, anophelines go through four stages in their life cycle: egg, larva, pupa, and imago. The first three stages are aquatic and the adult stage is when the female Anopheles mosquito acts as malaria vector. The adult females can live up to a month but most probably do not live more than 1-2 weeks in nature. There is no parasite storage mechanism in them and human host is the only store house which time to time supply parasite to circulate. We should learn from chimp's behaviour of changing their habitat during monsoon to prevent mosquito bite. Such an educated mind and behaviour is expected to cope with malaria and vector borne diseases. This is the best way which could help in eradicating malaria as if we could be able to cut transmission for 1-3 year will lead to definite eradication of falciparum malaria.

3. Parasite as Target

In post Koch era of modern science, parasites become the prime focus of disease management and also lead to control and eradication of many diseases *viz* small pox, polio etc. But one of big questions 'malaria parasite' is still a big problem. Since the discovery of malaria parasite many milestones have been achieved but none led to its eradication which was the final objective. Where are we missing? What remain unnoticed? And what was over looked? Before aiming big we must look in to such issues.

The prime mode of tackling parasites is killing them. Being multifaceted life cycle of malaria parasite while attempting strategies we need to note how to kill it and in which way we should do it. This could only be achieved by thorough and serious review rather than just start-

ing by taking one aspect of its life cycle. Hence it is necessary to discuss the utility of target weather focusing on it is worthy or not and also in which context one should focus whether for drug or for vaccine.

Sporozoites and liver stages of malaria never remain prime focus even it is the first step of encounter between host and parasite [8]. Asymptotic nature of this stage made it highly unfavourable target for a drug and also if targeted for drugs, this stage may be useful only for a small class of people of non-tropics, travelling to epidemic zones. Getting drugs against hepatic stages could be much useful if these are against latent liver stage of malaria or if we establish relation with fresh infection through vector during already established septicity. In such cases they could be used in combinations otherwise it never will be of first line of choice for drug discovery.

Seeking vaccine against these stages have emerged with great potential [9] which invigorated researchers to work in this field and also provided hope to malaria victims. Vaccine against these stages also hold potential because of the blockage of door step and providing least chance to parasite to come in action for combating against human host. But in current scenario parasite entry to host liver is incessant and uninterrupted to blood to show its real macabre face.

If there are symptoms like shaking chills, high fever, profuse sweating and headache i.e. malaria with blood stage of parasite as their presence is also visible in blood smears and in true sense we call, disease. Most of studies and discoveries in field of malaria belong to this stage further most of drugs available belong to this stage.Whatever success being claimed in malaria control and decreasing death toll is because of targeting blood stage of parasite. But the major drawback in targeting this stage for combating is that it made parasite stronger and stronger [10] by insisting parasite to search alternate routes to bypass the encounter of drug bullets *viz* dormant stages and sexual stages.

When parasite feels its job in one host is over it reprogram itself and turn some of the blood-stage parasites to differentiate into male and female gametocytes as asexual stage parasite cannot be transmitted naturally from one human host to another. Targeting these stages could provide great help in malaria control as it could cut down source of transmittable parasite.

4. Rescue Mechanisms as Target

Keeping themselves alive and maintaining through generations is a unique phenomenon of living organisms and it had played a great role in evolution of life. Survival of fittest is always considered as major factor which substantiate the selection of favoured races in the struggle for existence. Parasitic organisms learnt to survive during a long history of co-

evolution with their hosts. As a result there exists a fine balance between the survival tactics of parasites and immune restrictions posed by the hosts. With the development of human race and inventions of drugs further posed additional selection pressure on the parasite but not on the human host. This artificial selection led to more evolved parasites. Therefore, it would be interesting to study pathways of parasites which the rescue it from host immunity, drug pressure and nutrition deficiency in a host-parasite relationship.

Malaria parasite undergoes complex life cycle which involve two host and about six transition states. The transitions are also accompanied by decision to switch to multiplication or to enter dormant stage or to transform into sexual stages or to give polymorphic expression. This decision of commitment may very well affect development of resistance under selection pressure.

It seems that it is quite important to study survival tactics of malaria parasite for that we need to understand features of death and signalling in malaria parasite. Death of malaria parasite occurs under the stress of nutrition or drug inhibitors. However, exact mechanism is still unclear. One school of thought believes that it occur in a programmed way i.e. it is apoptotic [11] where as, the other believes it is by dis-functioning of some pathways [12]. Apoptosis in malaria is highly debatable whether it exist or not and if it is there why a single cell organism would like to die by itself where unlike to multicellular organism death of a cell is death of an organism. However in malaria parasite semi-multi-cellularity seems to occur when it shows rosseting or cytoadherence [13]. If we consider the existence of apoptosis in plasmodium then it should definitely be a communication mechanism similar to the quorum sensing in bacteria [14] which regulate gene expression in response to fluctuations in cell population density and is mediated by signaling molecules released into the environment. However in plasmodium quorum sensing an under appreciated phenomenon and very little is known about it [15].

Both quorum sensing and apoptosis seems to be survival tactics to let other parasites escape to continue future life. Recently, some transcriptional switches [16,17] which seem to play critical role in commitment toward sexual developments were also reported. However, detailed signalling mechanism and factors that regulate these switches are unknown and need to be explored. It is well known that drug pressure leads to up and down regulation of transcription and expression. However it is not known that how they determine the fate for future. Recent studies reported that in plasmodium cell to cell communication occur via exosome like vesicle [18] but it is not known that how this communication is regulated and it meant for what?

It would be quite interesting to study how various death symptoms have some protective role under various stress or and how quorum sensing like signalling aware the parasite about the threat of survival via commitment towards rescue mechanism.

5. Human as Target

Human the true victim of malaria in true sense is missing from discussions those researchers made and making about malaria. They mention threat to human but empowerment is missing. What is the meaning of this empowerment here? If we ask, who is ill with malaria? Definitely answer will be human. But the malaria eradication strategies least bothers the human as prime target. In any combat one cannot remain just dependent on the weaknesses of other but also have to make himself strong so opponent dare to attack.

How can we make ourselves strong without giving a chance to parasite for evolving? Obviously first answer will be an effective vaccine but unfortunately even after long struggle we remained failed and are vaccine less. Then what we can have or what we should to do.

Slight modified approach of Behet *et al.* [19] can be used in broad perspective. Drawback of Behet`s CQ based approach is that here purified drug is being used and it also impractical to force infected mosquito bite.

Alternatively if we search a plant product which have antimalarial and immune booster properties and have ability to become the part of daily diet e.g. *Phyllanthus, Curcuma, Syzygium* etc. It will help by two ways (a) as we know that native sporozoites are best source for developing long lasting and sterile immune protection. If we maintain safe drug bullets always at a certain basal level in blood stream to tackle the parasite, it will help in peak season or in monsoon when mosquito will definitely bite but then they will be a native source of sporozoites for immune response not for disease as bullets are already present to tackle them. b) Secondly it has been established that these plant products have immune booster properties e.g. Chwanprash an ancient formulation that is being recommended during winter to take care of common flu and other associated disease.

6. Conclusions

With above discussion we would like to suggest that we need to rethink and reprogram ourselves to deign malaria eradication strategies. Further we alsowould like invite discussion for development of ideas to achieve our goal of malaria free world.

7. Declaration

Authors have no competing Interests and manuscript can be published as part of publisher's Data Support Services.

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