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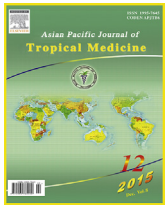

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Wolbachia pipientis: A potential candidate for combating and eradicating dengue epidemics in Pakistan

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ABSTRACT

Dengue virus syndrome is an emerging global health challenge which is endemic in tropical countries like Pakistan. In recent years dengue incidences have increased considerably in different areas of Pakistan with more sever impacts on urban and peri-urban populations. This review is an effort to highlight the changing epidemiology of dengue fever, role of Government of Pakistan in disease management and control using preventive and community based approaches in the region. Moreover, there is an emphasis on application of *Wolbachia* as novel, inexpensive and environmentally benign candidate for control and eradication of dengue transmitting vectors.

1. Introduction

Infectious diseases continue to plague the global community with high rates (26%) of morbidity and mortality. The main causes for transmittance of such emerging and reemerging disease outbreaks are unprecedented shifts in (a) environmental or climatic conditions either due to anthropogenic activities, (b) overlapping of geographical ranges, (c) change in land-use patterns or (d) emergence of drug and insecticidal resistances among vector populations [1,2]. Vector-borne diseases such as Congo hemorrhagic fever, Malaria, Dengue, Yellow fever, Chikungunya *etc*. account for a significant threat to human population in terms of health and economic losses all over the world. Such outbreaks lead to widespread epidemics which may result in deaths of many hundreds and millions of people annually [3,4]. These diseases have been reported to exert more devastating effects on developing or under transition countries. Because different variables *e.g*. water and sanitation facilities, population density, literacy rate *etc*. are the major players for spread of epidemics in such countries as compared to developed ones, where main contributors include ambient temperature, moisture or humidity along with rainfall patterns [1,2,5–7]. Most of these transmitted ailments are concentrated and prevalent with higher impacts in regions of South-East Asia, Southern Europe, Western Pacific and Eastern Mediterranean countries, Latin America, Australia and Sub-Saharan Africa [1,2,6,7]. As for instance, approximately 1.1 million deaths at global scale have been attributed to malaria alone [8]. Around 91% deaths involving 86% of children (<5 years of age) were recorded in Africa because of malaria [9].

Recently dengue fever (DF) has been recognized as one of emerging infectious diseases worldwide. It represents a considerable havoc to people living in urban and peri-urban localities of tropics and subtropics [10]. The viral epidemic has led to hospitalization of 20 million people with around 24 000 deaths as documented by Sulehri *et al* [7], which now has raised up to 50–100 million infected people with 2.5 billion at risk of contracting dengue [11,12]. Pakistan has experienced a number of dengue outbreaks with more server impacts in recent years. These outbreaks are affecting larger proportion of urban population and putting significant stress on health care facilities. Unfortunately the magnitude and severity index of the disease remains unreported due to deficiency and difficulty

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in data collection [6,11,13]. This review attempts to describe the prevalence of dengue virus infection and its associated serotypes in Pakistan with importance of potential biological control agents in eradication of the transmitting vector/s.

2. Dengue fever, signs and symptoms

Dengue globally affects 40% of world's population and occurs in repetitive cycles (3–5 years interval). The ailment presents high fever accompanied by frequent headaches, nausea, skin rashes, enlargement of lymph nodes, pain behind eyes, severe muscular, bone and joint pains, epitaxis along with leukocytopenia *i.e*. reduction in white blood cells count. Thus render individuals more prone to viral infection. DF is also characterized as bone break fever or bone crush fever due to severe pain in joints and bones [6,7,12,14–18].

3. Virology and serotypes

Being a member of a medically important viral family, Flaviviridae, the virus possesses single stranded positive sense RNA (+ve ssRNA). Albert Sabin in 1944 classified dengue virus into four antigenically related but immunologically distinct serotypes namely DENV-1, DENV-2, DENV-3 and DENV-4 [19–25]. All DENVs comprise of three structural [Capsid (C), membrane (prM/M) and envelope (E)] and seven nonstructural proteins (NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5). Each of these serotypes has been reported to exhibit extensive genetic variability due to distinct genotypes. Each of these genotypes is associated with severe dengue epidemics [17,22,23,26].

4. Principal transmission vector, breeding habitats and virus acquisition

The infection is usually transmitted through bite of infected *Aedes aegypti* (*Ae. aegypti*) (female mosquito). The mosquito is adapted to feed exclusively on human blood and is a day time feeder [6,11,15,17]. *Ae. aegypti* is well-known for being susceptible to all dengue viral serotypes and as an efficient vector with capability of transmitting dengue virus to many individuals in shorter time span [20,26,27]. This species of mosquito has spread extensively in tropical and subtropical regions of the world as a result of increased national and international trade, shipping and tourism [6,11,15,17,28]. *Aedes albopictus* (*Ae. albopictus*) has also been reported to transmit dengue viruses however to much lesser extent [29].

Ae. aegypti usually breeds in dark places, stagnant water kept in containers for (indoor and outdoor) storage, water coolers, drums, barrels, plant saucers, open buckets, in used tyres and places where rainwater collects. The mosquito unlike rural settings is specifically adapted to urban and peri-urban settings (*i.e*. cleaner environment). In such localities mosquito population density has been reported to be proportional to human population density. Moreover, breeding habitats of mosquitoes have strongly been associated with elevated temperatures, water supplies, sewage and sanitation facilities [6,15].

Virus is acquired by mosquito during blood meals of viremic (infected) patients. The acquisition is followed by incubation period (8–10 d) where viral genome is replicated within the mosquito, transferred to salivary glands via intestinal tract of mosquito. Mosquito then transmits virus to healthy persons upon subsequent biting [17,21,30,31] and also to offsprings via transovarian transmission during reproductive cycles [7,21]. Once inside the human host virus starts replicating within the target organs like white blood cells, lymphatic tissues *etc*. and gets released into blood following circulation [32].

5. Dengue viral syndromes

Depending upon age and immunological status dengue virus results in clinically different syndromes ranging from (a) classic DF characterized as a milder a typical flu-like form with high grade fever, head and body aches. It affects infants, young children and adults but is not fatal. Nonspecific febrile sickness with rashes has been reported in infants and young children. While mild febrile syndrome with high fever, head and joint-muscular pains along with skin rashes has been observed in older children and adults (b) dengue hemorrhagic fever (DHF) characterizes acute and continuous fever (40–41 °C) lasting for 2–7 d, accompanying hemorrhagic manifestations (ecchymosis and petechiae) with reduction in platelets. It may lead to liver enlargement and circulatory dysfunction in severe cases, and (c) dengue shock syndrome, a complicated and prolonged illness, in which DENV-1 viral infection is followed by DENV-2 and DENV-3. Thus exhibits symptoms of both DF and DHF. Such infections lead to hypervolemic shock (*i.e*. increased plasma leakage due to vascular permeability) and are associated with higher morbidity and mortality rates [6,7,14,31,33–37]. Furthermore, dengue infections have been reported to be life threatening upon coexistence in asthmatic and diabetic patients or in individuals with other chronic diseases [31]. According to Raza *et al* [12] and Mukhtar *et al* [38] approximately 250 000–500 000 people suffer from DHF and/or dengue shock syndrome and about 20 000–25 000 are succumbed to death every year.

6. Dengue in Pakistan

Pakistan being a developing urban and agricultural economy is more likely to be at risk of vector-borne epidemics. Mosquito-borne diseases such as dengue have now become a public health concern. This is due to exertion of considerable burdens of morbidity, mortality and economic distresses in many parts of the region. Over populated cities, lack of access to proper sanitation facilities, unavailability and shortage of clean drinking water, population influxes at massive scale and lack of awareness about possible health effects posed by vector transmitted pathogens are some of the leading causes of spread of mosquito-borne diseases [1,2,39]. Moreover, raised ambient temperature, huge population, overcrowded cities with poor resource settings and lack of health facilities (in terms of vaccination access and coverage) also serve as important prerequisites for reproduction of mosquitoes. This situation further exacerbates transmission of pathogens dwelling within these host vectors causing long-term illnesses [31,40].

Dengue viral infection killing 365 individuals with 21 597 positive cases is becoming endemic in Pakistan. The viral epidemic persists all the year round with greater intensity in months of October–December (post-monsoon period). Additionally, recent floods have enhanced the prevalence of dengue in entire country through provision of large number of breeding