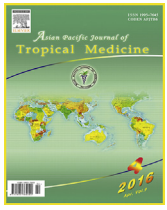
HOSTED BY
ELSEVIER

Contents lists available at ScienceDirect

Asian Pacific Journal of Tropical Medicine

journal homepage: http://ees.elsevier.com/apjtm



Review http://dx.doi.org/10.1016/j.apjtm.2016.03.004

Current perspectives on dengue episode in Malaysia

Ee Leen Pang[1], Hwei-San Loh[1,2*]

[1]School of Biosciences, Faculty of Science, The University of Nottingham Malaysia Campus, Jalan Broga, 43500 Semenyih, Selangor, Malaysia

[2]Biotechnology Research Centre, The University of Nottingham Malaysia Campus, Jalan Broga, 43500 Semenyih, Selangor, Malaysia

ARTICLE INFO

Article history:
Received 15 Jan 2016
Received in revised form 20 Feb 2016
Available online 8 Mar 2016

Keywords:
Dengue
Antibody-dependent enhancement
Pandemic
Vaccine
Malaysia

ABSTRACT

Prevalence of dengue transmission has been alarmed by an estimate of 390 million infections per annum. Urban encroachment, ecological disruption and poor sanitation are all contributory factors of increased epidemiology. Complication however arises from the fact that dengue virus inherently exists as four different serotypes. Secondary infection is often manifested in the more severe form, such that antibody-dependent enhancement (ADE) could aggravate ailment by allowing pre-existing antibodies to form complexes with infecting viruses as means of intrusion. Consequently, increased viraemic titter and suppression of antiviral response are observed. Deep concerns are thus expressed in regards to escalating trend of hospitalisation and mortality rates. In Malaysia, situation is exacerbated by improper clinical management and pending vector control operations. As a preparedness strategy against the potential deadly dengue pandemic, the call for development of a durable and cost-effective dengue vaccine against all infecting serotypes is intensified. Even though several vaccine candidates are currently being evaluated in clinical trials, uncertainties in regards to serotypes interference, incomplete protection and dose adequacy have been raised. Instead of sole reliance on outsourcing, production of local vaccine should be considered in coherent to government's efforts to combat against dengue.

1. Introduction

The alarming rise of dengue epidemiology has been highlighted to haunt 40% of world population; where disease severity varies from asymptomatic infection to undifferentiated dengue fever (DF) or possibly develop into life-threatening manifestations such as dengue haemorrhagic fever (DHF) and dengue shock syndrome (DSS) [1]. Classified under the Flaviviridae virus family, dengue virus (DENV) presents itself as a 500 Å single-stranded, positive-sense non-segmented RNA virus [2]. Size of the virus genome is approximately 10.6 kilo-base pairs (kbp) long; encoding a single polypeptide which will be processed by serine protease into structural proteins, namely capsid (C); envelope glycoprotein (E); precursor membrane (prM)) and non-structural biomolecules (NS1, 2A, 2B, 3, 4A, 4B and 5) [3]. During assembly, the highly-basic C protein will encapsidate the viral RNA to form nucleocapsid particles while prM assists the folding of surface-exposed E glycoprotein, with both integrated into the lipid bilayer [4].

Hitherto, transmission of the endemic virus has been reported in more than 100 countries. Incidence rate has expanded by 500-fold, spreading from South-east Asia to Americans and Western Pacific merely within a-half century [5]. Global distribution of dengue disease is strongly influenced by urbanisation, demographic and environmental factors. Cumulative concerns are also driven by increased travel of tourists and military personnel [6]. Based on the 50–100 million of cases reported annually, an average of 500000 patients are hospitalised with DHF and DSS where 22000 deaths are primarily among children [7,8]. Yet, recent study reported startling estimates of dengue burden that triples past predictions, where 390 million infections were mapped per annum [9]. The effect from global warming has also made it possible for *Aedes* mosquitoes to survive beyond its current distribution and further promotes the spread of virus. In fact it was projected that by 2080s, over 5–6 billion of world

*Corresponding author: Hwei-San Loh, Biotechnology Research Centre, The University of Nottingham Malaysia Campus, Jalan Broga, 43500 Semenyih, Selangor, Malaysia.
Tel: +60 389248215;
Fax: +60 389248018
E-mail: Sandy.Loh@nottingham.edu.my
Peer review under responsibility of Hainan Medical College.

population may be exposed to risk of infection due to climate change and population growth [10].

2. Pathogenesis

Humans are infected through the bite of *Aedes* mosquitoes that usually breed in domestic water containers. Abrupt fever accompanied by anorexia, headache, myalgia, retro-orbital pain and occasionally rashes are symptoms of classical DF within 4–7 days of febrile period [11]. Onset of critical DHF and DSS usually emerges during time of defervescence where increased propensity of capillary leakage is observed prior hypovolemic shock [12]. As infecting virus is being circulated in the peripheral blood of patients, a mosquito's bite during febrile viraemic stage would result in disease being transmitted to another host after an extrinsic incubation period [13]. DHF is commonly diagnosed with haemorrhagic bleeding, thrombocytopaenia and increased fluid effusion in addition to typical DF symptoms; while DSS is presented by weak pulse and pressure, where profound shock may set in and lead to death within 12–36 h [11].

Clathrin-mediated endocytosis is deployed as the cell entry mechanism during initial infection. Upon binding of the viral particle to the cellular receptor, clathrin-coated pit will capture the complex and then pinch off into cell cytoplasm [14]. During secondary infection, complexes are formed between replicating viruses and non-neutralising antibodies induced by previous infection or even derived from maternal IgG to usurp Fc-γ receptors as mode of entry [15]. This phenomenon is denoted as antibody-dependent enhancement (ADE). Upon entry, the vesicles move through the endosomes until conformational change is triggered by acidification which ultimately releases the uncoated single-stranded viral RNA into cytosol [16]. Translation of viral genetic material proceeds at rough endoplasmic reticulum (ER) before membrane is invaginated to form vesicles for RNA replication. Following virus budding into ER lumen, progeny virions are packed and transported to trans-Golgi complex for prM cleavage by cellular furin protease prior releasing mature virions through constitutive secretory pathway [17].

Feeding of disease carrier presumably introduces DENV into the bloodstream, where Langerhans cells are targeted followed by local replication of virus. Infected dendritic cells then undergo maturation and migrate towards the lymph nodes to target monocytes and macrophages [18]. Infection is amplified through the dissemination of virus in lymphatic system [11]. In the context of dengue pathogenesis, subversion of host immunity is achieved by hijacking host cellular machineries to promote infection. The virus adaption tricks are summarised as follow: (i) induction of autophagy via unfolded protein response to trigger production of double membrane vesicles as viral replication platform; (ii) mobilisation of triglyceride by lipophagy to produce energy for viral assembly; and (iii) sequestration of stress granules to prevent stalling of mRNA translation [19]. Albeit association of ailment aggravation to ADE still remains elusive, compiling evidences are now highlighting its cytotoxic outcome based on increased viraemic titre and/or modulation of immunosuppressive events to alter conduciveness of local milieu for viral replication [12]. In fact, it has been proven that ADE is the strongest risk factor of DHF/DSS development when severe illness is suffered by seropositive patients [20]. It was also emphasised that the risk of acquiring DHF in secondary infections was 40 times significantly higher than primary cases [19].

3. Prevalence and epidemiology

Transmission cycles of DENV are observed from two phenomena: (i) sylvatic cycle of canopy-dwelling *Aedes* mosquitoes that infect non-human primates in rain forest habitats of Asia and Africa; and (ii) infection of human hosts by *Aedes aegypti* (*A. aegypti*) (primary vector) and/or *A. albopictus* that circulate in urban and peri-urban environments of tropics [21]. Interestingly, DENV isolates in most urban centres are evolved from sylvatic progenitors approximately 100–1 500 years ago [22]. It is also believed that structural changes of the domain III of DENV E protein (EDIII) have prompted adaptation to new peridomestic vectors that led to resurgence of the arbovirus. Albeit the earliest record of epidemics could be traced back to 1780–1940, yet, it was the ecological disruption during World War II that intensified disease transmission in South-East Asia and Pacific [21]. In parts of Central and South American, the collapse of *A. aegypti* eradication campaign during early 1970s had set a scene of re-infestation and hyperendemicity followed due to increased circulation of viral serotypes into these areas [23]. Escalating movement of dengue virus into new territories had been mapped, where geographical spread of different subtypes was significantly noted in the last two decades, particularly in Asia and Latin America [24]. Contemporary understanding of the distribution pattern of DENV should be underlined in terms of providing insights to disease management and clinical research.

4. History of dengue in Malaysia

In Malaysia, onset of dengue infection was dated back in year 1901 following transmission from Singapore to Penang [25]. First epidemic outbreak was then alarmed in 1973, recording a total of 969 cases and 54 deaths [26]. The condition continued to worsen thereafter, with increasing disease infestation among urban dwellers throughout the nation [27]. Taxonomically, the causative agent is an icosahedral virus that manifests as four distinct subtypes (DENV1-4) with 65–70% sequence homology [28]. Not surprisingly, all serotypes were found to be co-circulating in Malaysia. For instance, DENV1, DENV2 and DENV3 were identified in Negeri Sembilan [29], multiple entries of DENV2 and DENV4 in Sarawak [30] while DENV4 dominated the populated regions of Kuala Lumpur and Selangor [31]. It was suggested that severity of disease outbreak could be predicted based on the predominant serotype at one point [32]. Such correlation was also proven by other findings, whereby intense illness was observed in patients suffering from primary infection of DENV1 or DENV3 whereas infestation by DENV2 in secondary case would further aggravate ailment with DHF [33,34]. Generally all gender and ethnic groups are equally vulnerable to dengue infection. In South-East Asia, severe DHF/DSS cases are predominant among paediatric patients aged between 2 and 15 years [35]. However, a shift of disease pattern inclining towards adult population has been highlighted recently. In Malaysia,