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Advances in the understanding, management, and prevention of dengue

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ABSTRACT

Dengue causes more human morbidity globally than any other vector-borne viral disease. Recent research has led to improved epidemiological methods that predict disease burden and factors involved in transmission, a better understanding of immune responses in infection, and enhanced animal models. In addition, a number of control measures, including preventative vaccines, are in clinical trials. However, significant gaps remain, including the need for better surveillance in large parts of the world, methods to predict which individuals will develop severe disease, and immunologic correlates of protection against dengue illness. During the next decade, dengue will likely expand its geographic reach and become an increasing burden on health resources in affected areas. Licensed vaccines and antiviral agents are needed in order to effectively control dengue and limit disease.

1. Introduction

Dengue is a mosquito-borne disease caused by infection with four related, but antigenically distinct, dengue viruses (DENV1, DENV2, DENV3, DENV4). The main vector is *Aedes aegypti*. Globally, dengue causes more morbidity than any other vector-borne viral disease, with 55% of the world's population at risk throughout the tropics and subtropics [1,2]. Dengue is responsible for a large disease burden, with increasing incidence and explosive epidemics. Further expansion is likely because of rapidly growing urban centers which serve as epicenters for dengue outbreaks, increased worldwide travel, and generally ineffective vector control efforts [3,2,4–6]. The viruses cause a spectrum of illness ranging from dengue fever (DF), an acute self-limited febrile illness, to the more severe forms of dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS). The risk of DHF/DSS is increased with the second infection, and most dengue-associated deaths occur following DHF/DSS [7]. Because there are no available dengue vaccines or antiviral therapies, dengue represents an important unmet medical need. Research is ongoing to improve understanding of dengue transmission/burden, the host/virus/vector relationship, prevention, and treatment. This review will highlight recent advances and remaining challenges in these areas.

2. Advances in epidemiology

Dengue is endemic in over 140 countries in Africa, the Americas, the Eastern Mediterranean, and Asia. Approximately 4 billion people are at risk, with an estimated 390 million dengue infections each year, including 96 million clinically symptomatic cases, and approximately 20,000 deaths [8,1]. Globally, dengue cases have been reported in cyclic peaks, with epidemics and large outbreaks alternating with non-epidemic years [9–12]. Dengue typically occurs during rainy seasons [12,13].

The distribution of dengue has evolved over the past decades and simultaneous transmission of multiple dengue serotypes (hyperendemicity) is now documented throughout the tropics/subtropics [2]. Furthermore, the genotypes within each serotype are evolving, with clear evidence of subtype (clade) replacement [14]. The extent of hyperendemicity and time between serotype introductions are key determinants in a population's serotype-specific immunity and consequently, in the age distribution of clinically apparent dengue. Areas of long-standing hyperendemicity (e.g. Southeast Asia) typically show the highest

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disease burden in children, while areas where infection may be newly emerging often have more significant disease burden in adults (e.g. Latin America) [14,12]. When the incidence increases, the disease burden tends to shift over time from adolescents and adults to children [14,12]. However, other factors, including host comorbidities and strain virulence, influence these overall trends, resulting in complex and changing patterns for specific locations and countries [14].

Of the 96 million symptomatic infections that occur annually, an estimated 70% occur in Asia, 14% in the Americas, and 16% in Africa [12]. The largest disease burden occurs in India (34% of the global total). In the Americas, dengue is predominantly seen in Latin America with Brazil, Mexico and Colombia [8] having the highest recorded number of cases. In Brazil alone, over 1 million cases were reported during the 2010 epidemic, and the 2013 outbreak appears to have been of a similar magnitude (Coelho, personal communication [8,15]). In Africa, dengue epidemics have been reported in the last decade in all regions, although burden estimates are uncertain due to severe under-reporting [16,17,8,18]. In the last decade, local dengue transmission has also been documented in several new areas, including parts of the USA, Japan, France, Croatia, and Portugal [18–22].

As dengue has expanded in geographical range and intensity, there has been an increased focus on improved characterization of disease burden [2,5,23]. Updated models, using evidence-based consensus risk maps, spatio-temporal data (rainfall, temperature, and degree of urbanization), and known disease occurrence, have been developed. As knowledge of the mosquito vectors and transmission has grown, there has been a recognition of the importance of incorporating climatic variables (temperature, rainfall and humidity) into models to account for factors influencing mosquito density and feeding frequency [8,24–28]. Rising temperatures have been linked to a shorter extrinsic incubation period (the incubation period in the mosquito between the time of a viremic blood meal and when the mosquito becomes capable of spreading dengue), increased populations of more immature mosquitoes that need to feed more often, and expedited blood meal digestion leading to more frequent feeding [24,29]. In addition, recent studies have highlighted the importance of spatial measurements and patterns of the host and vector, including urban-population density and human house-to-house movement, in contributing to dengue incidence [30–32].

2.1. Challenges and implementation

Expanding surveillance of dengue incidence, hospitalization, and death will improve the accuracy of disease burden estimates [8,33]. Additional enhanced active surveillance and longitudinal-cohort studies, including application of improved models, are needed to document serotype and genotype prevalence over time, apparent vs. inapparent infection, and spatio-temporal factors influencing transmission.

3. Vector control

To date, vector control efforts to reduce mosquito breeding sites have been the mainstay of prevention. However, these efforts have not stopped disease transmission in countries where dengue is endemic. Alternative approaches being tested include the application of insecticides to novel targets (e.g. window curtains and school uniforms) [34,35], biological (e.g. bacterial or fungal) methods [36–39], and genetic modification of wild mosquito populations [40] (WHO, Vector Control, 2010). *Wolbachia*, a bacterial species that can infect *Aedes* mosquitoes and interferes with the ability of dengue virus to replicate in those mosquitoes, has also emerged as a potential candidate to control dengue transmission [40]. Transfection of mosquitoes with *Wolbachia* reduces adult mosquito lifespan, decreases reproduction, and interferes with dengue replication [41–44] and recently three field trials in Australia found artificially introduced *Wolbachia* established itself in wild *A. aegypti* populations [45,46,40]. Other recent developments include the use of a pathogenic fungus, *Beauvaria bassiana*, which has been associated with a decrease in mosquito survival in laboratory and field-like conditions [47]. Also, the release of mosquitoes carrying a mutation resulting in "genetic sterility" is being tested in field trials in Brazil and Malaysia [48,40].

In the last decade, the WHO has recommended integrated vector management, an evidence based approach which encourages optimal use of resources by examining local in-country evidence instead of "a one-size fits all approach". The goal is to develop more cost-effective, efficient, and ecologically sound vector-control programs [13].

3.1. Challenges and implementation

Challenges remain in the development and deployment of vector-control strategies that effectively minimize dengue replication and transmission [49]. Given the breadth and varying efficacies of vector-control methodologies, economic modeling and evidence-based assessments are needed to select the most cost-effective methods [50,51].

4. Advances in dengue immunology and virology

Several decades ago, the hypothesis of antibody-dependent enhancement was proposed to explain the observation that secondary dengue infections (different serotype) were associated with more severe disease [52]. Over the past decade there has been significant research aimed at trying to better understand the biology of dengue infection in humans, the immune response to the infection, and mechanisms leading to more severe disease in certain circumstances (e.g. secondary infections). This research has provided some clarity and led to new tools to help address remaining questions. Many key studies have focused on dissecting the innate, humoral, and cell-mediated immune responses following natural infection (e.g. [53–69]). These studies have provided insights related to key effectors (e.g. complement), as well as virus epitopes that may be involved in the protective immune response (e.g. epitopes presented in the context of the intact virion) [70–76]. Prominent immune responses to prM epitopes present in partially mature or immature virus particles have also been characterized, with the suggestion that such responses could contribute to increased viral replication in secondary infection [77–79]. Furthermore, structural studies have found the dengue envelope is dynamic, shifting and exposing epitopes previously thought to be cryptic, highlighting the complexity of dengue virus biology [80–82]. These studies have also informed the mechanisms for antibody-mediated neutralization and led to the development of updated hypotheses for the basis of protection and disease exacerbation [83,84].

The field has been hampered by lack of an animal model of disease and in particular a model that recapitulates DHF. The use of partially immunocompromised animals (e.g. AG129 mouse strain) has led to models that mimic dengue disease to some extent. These models can be useful for evaluating the potential efficacy of therapeutics, [85–87], however, their utility in evaluating dengue vaccine candidates is limited due to the fact that the animals are partially immunocompromised.

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