



## Research Article

Chew TL, et al. J Trop Med Health 3: 142.

DOI: 10.29011/JTMH-142. 000042

# Dengue Infection in Indonesia: Improved Clinical Profiling Is Needed to Better Inform Patient Management and Disease Outbreak Control

Tjhioe Lan Chew<sup>1</sup>, Trevino A Pakasi<sup>2,3</sup>, Andrew W Taylor-Robinson<sup>4\*</sup>

<sup>1</sup>School of Health, Medical & Applied Sciences, Central Queensland University, Australia

<sup>2</sup>Center for Research and Integrated Development of Tropical Health and Infectious Disease, University of Indonesia, Indonesia

<sup>3</sup>Department of Community Medicine, Faculty of Medicine, University of Indonesia, Indonesia

<sup>4</sup>Infectious Diseases Research Group, School of Health, Medical & Applied Sciences, Central Queensland University, Australia

\***Corresponding author:** Prof Andrew W Taylor-Robinson, Infectious Diseases Research Group, School of Health, Medical & Applied Sciences, Central Queensland University, Australia. Email: a.taylor-robinson@cqu.edu.au

**Citation:** Chew TL, Pakasi TA, Taylor-Robinson AW (2019) Dengue Infection in Indonesia: Improved Clinical Profiling Is Needed to Better Inform Patient Management and Disease Outbreak Control. J Trop Med Health 3: 142. DOI: 10.29011/JTMH-142. 000042

**Received Date:** 24 April, 2019; **Accepted Date:** 21 May, 2019; **Published Date:** 30 May, 2019

### Abstract

Dengue is the most frequent arthropod-borne viral disease of humans globally. The vectors of transmission are mosquito species of the genus *Aedes*, which are common in tropical and subtropical regions, especially metropolitan areas. Dengue imposes a significant economic burden, especially in low-income nations. Infection is often asymptomatic but mild to severe forms exist and the extent of clinical manifestations varies with gender and age. Symptoms of mild infection include fever, rash, muscle and joint pain, yet for a small proportion of individuals antibody-dependent enhancement of infection triggers severe dengue, which can be fatal. In many countries, including Indonesia, the incidence of dengue fever has increased dramatically in recent years but there is still no specific therapeutic treatment or widely accepted vaccine. In an Indonesian context, in order to reduce the escalating rates of morbidity and mortality there is a pressing need to understand in more detail the clinical profile of dengue outbreaks in tertiary hospitals in Jakarta, the capital and most populous city. Such research will enhance patient care and better inform future prevention and control strategies for this emerging public health threat, including improved vector management and effective vaccination programmes, in what is predicted to be within a decade the world's largest urban agglomeration.

**Keywords:** Clinical Profile; Control; Dengue; Incidence; Indonesia; Prevention; Vaccine; Virus

### Introduction

Dengue is the most rapidly spreading mosquito-borne arbovirus infection of humans in the world [1,2]. The aetiological agent is the dengue virus (DENV), a member of the *Flavivirus* genus of positively stranded RNA viruses [2], which is transmitted between persons by the bite of female *Aedes* spp. mosquitoes [3]. Worldwide, *Ae. aegypti* and *Ae. albopictus* are the most competent vectors to transmit DENV [4]. DENV has four formally recognised serotypes, DENV-1 to DENV-4 [1]. In Indonesia, dengue is transmitted mainly by *Ae. aegypti* [5-7] and all four serotypes are observed, with some case reports of mixed infection [7-11]. Most occurrences of dengue are asymptomatic and self-limiting, possibly three to four times higher than the number of symptomatic

infections [12,13]. While a minority of infections cause disease this still represents a huge number of cases, almost 100 million per annum globally [14], that vary from mild to severe and potentially fatal. Severity of infection is directly related to the causal dengue serotype [15]. Although the exact mechanism of pathogenesis of DENV is unclear, if secondary or subsequent infection is with a heterologous serotype to that which caused primary infection the immune pathological phenomenon of antibody-dependent enhancement (ADE) is thought to contribute [16].

As multiple serotypes of DENV circulate in Indonesia, more than half of all clinical cases are due to exposure to more than one serotype [17]. This means that subsequent infection will most likely lead to severe disease manifestations [8]. This may explain the high incidence and mortality rate of dengue in Indonesia and the difficulties in eradicating or controlling outbreaks.

## Global Public Health Threat

DENV is endemic in around 125 tropical and subtropical countries, placing at risk of infection more than 2.5 billion people, 40% of the world’s population [15,18,19]. Over the last 60 years the global incidence has escalated by 30-fold to affect many nations [15,18,20,21], including Indonesia [22]. The current global incidence of dengue is conservatively estimated at 400 million reported infections, both asymptomatic and symptomatic, annually [18,20,21]. Table 1 shows officially reported incidence rates of dengue for several countries around the world [23,24]. Cases in Asia account for 75% of the overall dengue disease burden, followed by those recorded in Latin America and Africa. The scale and impact of this major public health concern warrants considerable investment to improve health care systems in tropical developing countries, exemplified by Indonesia, where for many

decades’ dengue has been recognised as a so-called emerging infectious disease [24,25]. The World Health Organization (WHO) estimates that over 500,000 people with severe dengue are hospitalized annually and 2.5% of those patients die from severe symptoms and shock [26]. This equates to 1.1 million disability-adjusted life-years (DALYs) globally. The real number of dengue cases in the world is significantly higher than official statistics [3,27]. Worldwide, only 3.2 million symptomatic cases were reported to the WHO in 2015 [28], while the incidence of asymptomatic dengue is considered to be three to four times higher than the number of symptomatic infections [23,29]. This discrepancy is most likely due to a combination of factors: the often self-limiting nature of dengue as a disease [27]; its frequent misdiagnosis [30]; and delayed and inaccurate surveillance data in low-income countries [31].

Countries	Reported Incidence	Reported Mortality
World (current estimate) World, 2016	400 million cases per annum Data not available	20,000 deaths per annum 8,000
Delhi, India	129,166 cases in 2016	22,527
Vietnam, South East Asia	113,850 cases from 1 January to 30 November 2018	16
Malaysia, South East Asia	68,603 cases from 1 January to 30 November 2018	117
The Americas (Aruba, Panama, Peru)	2,177,118 cases in 2016 584,263 cases in 2017	Data not available
Brazil, South America	1,649,008 cases in 2015	863
Burkina Faso, Africa	9,029 cases from 1 January to 6 November 2017	18
Australia	990 cases from 1 January to 18 December 2017 731 cases from 1 January to 6 December 2018	Data not available
European Union	242 cases from 1 January 2012 to 31 December 2014	Data not available

**Table 1:** Dengue incidence in representative dengue-affected countries around the world. Latest available data [23,24].

## Disease and Treatment

In 1997 the WHO classified clinical cases of dengue into three different subgroups based on the disease symptoms: dengue fever (DF); dengue haemorrhagic fever (DHF); and dengue shock syndrome (DSS) [20,32]. Since overlap between these manifestations had been observed in 2009 this definition was revised as dengue with or without warning sign and severe dengue [20]. It is acknowledged by clinicians that the illness presents as a spectrum of disease instead of distinct phases. While the revised scheme is more sensitive to the diagnosis of severe dengue, and facilitates triage and case management, issues remain with its applicability, some experts considering that a more specific definition of warning signs is required. This calls for research into

the diagnostic value of these warning signs on patient outcomes and the cost-effectiveness of the new classification system to ascertain if the updated classification requires yet further modification, perhaps to include elements of both systems [33]. Currently, there are no antiviral medications to target DENV so treatment of each patient is supportive, i.e. provided to alleviate their disease symptoms only [34]. The main goal of clinical management is to restrict or reverse increased vascular permeability, a hallmark of severe dengue, that leads to leakage of plasma into pleural and peritoneal cavities and shock [34]. In the absence of a cure, therefore, effective prevention, control and early management strategies are important to combat the disease and to reduce both the incidence and mortality rate arising from dengue. Implementation of effective mosquito control

and surveillance strategies are critically required for more accurate early prediction and better preparation for outbreaks, as well as to directly reduce local transmission of DENV [2,3,10,32,35-37]. An efficacious vaccine is not currently available, but under development, and would also be beneficial as a prophylactic means to curb dengue incidence and mortality rate [1,21,38,39].

### An Emerging Infectious Disease

Just over 4 billion people of the current world population of 7.7 billion live in an urban area. According to a recent WHO prediction, the urban share will grow to 68% (6.4 billion) by 2050 [40]. Rapid urbanization has a profound impact on global health, including being a major predisposing factor for the spread of mosquito-transmitted infectious diseases [25]. The rapid urbanization rate in the capital city of Jakarta, located on the northwest coast of the world’s most populous island, Java, contributes to the noted dengue epidemics [10,41-43]. For a little more than 50 years Indonesia has faced the challenge of dengue. In addition to the public health threat, this has caused an enormous national economic burden.

The situation is becoming increasingly problematic as the expanding and more urbanized population, particularly focused on Jakarta, is put in a position of heightened vulnerability due to socioeconomic deprivation and cohabiting with *Ae. aegypti* mosquitoes. Therefore, vector control strategies, effective infection surveillance and early disease management programmes are key weapons in the armoury to reduce dengue incidence and mortality rates in Jakarta and its environs [24,25].

### Incidence in Indonesia

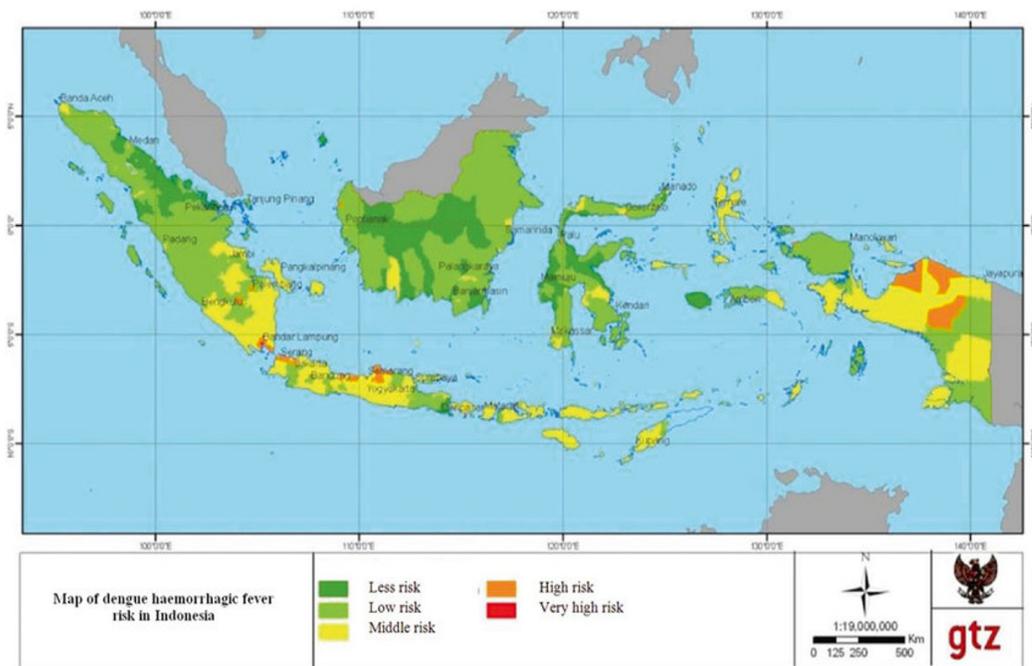
The significant morbidity and mortality that dengue causes contribute a huge economic burden in endemic regions, which is magnified in low-income countries [44-46]. This is a profound problem for Indonesia and poses a serious threat to its 270 million inhabitants [46]. The country is one of the largest dengue hyper-endemic territories in South East Asia and globally [9,47]. The first Indonesian case of dengue was reported in 1968, but by today over 50% of the population is affected by dengue, with over 750,000 new clinical cases confirmed annually [8]. Despite vector control campaigns, the incidence rate of dengue in this, an archipelagic country of 17,000 geographically dispersed islands, remains very high [24]. Thus, it is a matter of some urgency to gain a better appreciation of the considerable public health problem that dengue presents to the people of Indonesia. In part, this may be achieved through detailed clinical profiling of dengue patients, especially those hospitalized in the sprawling megacity of Jakarta. Although the officially recognised incidence of dengue in Indonesia is very high, as for elsewhere there may be significant under-reporting [9,24]. Table 2 shows national dengue incidence and mortality rates from 1968 to 2017. In many years, the only available data were from Jakarta, thus highlighting the overall inaccuracy of reporting of dengue cases nationwide. Some data were reported as incidence rate, others as case numbers [24,48], thereby making epidemiological analysis a difficult task. As a silent infection that does not manifest clinically in the majority of individuals, the country’s rate of infection, if not disease, might be expected to be extremely high [13,49].

Year	Incidence Rate (per 100,000 population)		Case Fatality Rate (% of incidence)	
	Absolute number of cases where data available		Absolute number of cases where data available	
1968	0.05	58	41	23
1970	0.2			
1972	0.2			
1974	13			
1976	18			
1978	23			
1980	19			
1982	23			
1984	28			
1986	29			
1988	37			
1990	42			

1992	32			
1994	36			
1996	39			
1998	54			
2000	41			
2002	57			
2004	49			
2005	43.31			
2006		~ 180,000		
2007		~ 220,000		
2008	60.06	1,170		
2009	317.09			
2010	85.7			
2011		~ 320,000		
2012	65	90,245	0.90	816
2013	41.3	~ 580,000	0.73	871
2014	77	100,347		907
2015		~ 620,000		1,229
2016	77.96	201,885		1,585
2017	22.55	59,047	0.75	444

**Table 2:** Annual rates of incidence and case fatality from dengue in Indonesia, 1968-2017 [24,48].

Figure 1 shows the dengue risk by region of Indonesia [50]. While the incidence rate varies between provinces [51], the average rate across the country as a whole is 78 per 100,000 population [24]. The Indonesian Government aims to reduce this to < 49 per 100,000 population over the next decade [24]. Clearly, to achieve this ambitious target more effective prevention and control strategies need to be developed [52].



**Figure 1:** Dengue risk by geographical region of Indonesia [50].

While the dengue incidence rate in Indonesia is increasing [46], the case fatality rate (CFR) has dropped significantly from 41% in 1968 to 0.75% in 2017 [24,53]. However, as the number of reported cases has escalated alarmingly, in fact the absolute number of fatalities from dengue has risen sharply over the same 50-year period, from 23 to 444 cases [54]. According to the WHO, from 2004 to 2010 Indonesia was the country reported to have the highest incidence of dengue in Asia [5,55], and the second highest in the world [47]. As recently as January 2019 there was sudden outbreak of dengue (13,683 confirmed cases and 132 deaths) in Indonesia [56]. An outbreak is declared by the Indonesian authorities when a minimum of 115 dengue-related fatalities is reached [57]. It is probable that this incident exemplified under-reporting, since by this time eight regions had already declared a state of emergency [56]. Between 2008 and 2017, more than 200,000 dengue cases were hospitalized in Jakarta. This represents an incidence rate of 207 per 100,000 population per year [9]. The densely populated capital city of 10.6 million inhabitants, and the surrounding metropolitan area of Jabodetabek with a population that exceeds 30 million people, are collectively a major global hot spot of dengue outbreak. Only very recently have dengue incidence and mortality rates been reported with any regularity from regions outside Jakarta [24]. The Indonesian Government issues alerts to residents of the greater Jakarta agglomeration of the potential

threat of dengue infection when an outbreak is predicted, most recently in February and March 2019 [57].

### Educational and Economic Burden

Globally, the gender and age distribution of people infected with dengue is heterogeneous [58,59]. In this regard, Indonesia is noteworthy in that dengue occurs mostly in juveniles. By the age of 5-9 years more than 80% of children have experienced infection, as demonstrated by seropositivity for at least one DENV serotype, if not overtly by diagnosed clinical manifestations [55]. At a societal level this scale of childhood illness will reduce attendance at school and thereby have a major negative impact on the education of Indonesia's young people. While the age of infected individuals ranges from under 12 months to 75-80 years old since 1980 the incidence rate among the urban-dwelling population has been increasing in teenagers aged 15 years and older, at a crucial time in their secondary education [55]. That dengue places a severe economic burden on endemic countries is undoubted, yet the real global cost is uncertain as the expense of vector surveillance and control, and of campaigns to prevent disease spread were often not included in previous cost analyses. Hence, the real economic impact is acknowledged to be grossly underestimated by authorized figures [60]. These show that in Indonesia, US\$ 381 million was spent on the combined prevention, control, detection and patient management of dengue in 2015 [47].

For the following year, the latest for which figures are available, in direct response to escalating incidence in immediately previous years the budget ballooned to US\$ 2 billion, approximately 22% of the global budget allocated to combat dengue in 2016 [47]. From the perspective of the burden placed on medical laboratory provision, this equates to the screening of over 750,000 cases, mostly in and around Jakarta, followed by the treatment of all those patients diagnosed with clinical symptoms of disease [8].

### **Classification and Reporting of Dengue Cases**

The WHO 1997 dengue classification system requires four essential criteria to be met for consideration as severe disease. Without any one of the four criteria, dengue patients will be classified as DF, although they might have already developed shock. This means that this classification system was not sensitive enough to include some cases of severe dengue [20]. Hence, not only did this result in inaccurate reporting but led to an avoidable potentially life-threatening situation for each misdiagnosed patient. This prompted the WHO within 12 years to revise its dengue classification system [20]. This was an apparent attempt to achieve better case management and to reduce mortality. However, in the decade since its introduction there is no evidence that switching to the 2009 classification system has had an effect in reduce mortality from dengue [20]. In part as a consequence, the mortality rate is unacceptably high in many developing countries, including Indonesia. Ignoring the update of the system, the 1997 classification is still used to report dengue in this country, where only DHF and DSS are diagnosed [9]. Reporting dengue in Indonesia is mandatory within 72 hours after diagnosis [8]. Severe secondary infection could explain the increase in CFR [20]. A possible reason is that nowadays, with different serotypes co-circulating in the population, DENV has become more pathogenic [61]. If the virulence of DENV remains stable, the CFR should be constant over time [61].

### **Signs and Symptoms of Clinical Infection**

Further to a person being bitten by an infectious mosquito the incubation period of dengue prior to onset of illness is around 3-7 days [62]. There are a variety of common symptoms of dengue infection, including fever, headache, rash and myalgia [41,63]. Most clinical symptoms of severe dengue only manifest at late stage infection [35]. Severe plasma leakage is determined by shock (DSS) or fluid accumulation with respiratory distress and ascites. Severe bleeding and significant damage to major organs are often involved [20], affecting the liver (aspartate transaminase (AST) or alanine transaminase (ALT) >1000 U/L detected), heart and central nervous system [64]. In Indonesia, predictors of severity are neither standardized nor used consistently. Clinicians assess for warning signs and symptoms for clinical case management, including spontaneous bleeding, plasma leakage (presence of ascites and pleural effusion), hepatomegaly, abdominal pain,

haemoconcentration, thrombocytopenia, and sharp increase of AST or ALT levels [63].

### **Diagnostic Tests**

Diagnosis of dengue infection in the acute phase is important primarily for clinical care, but also facilitates the timely implementation of control measures and outbreak surveillance. Currently, two types of detection method are used to diagnose dengue if infection is suspected, namely direct and indirect tests [65]. Direct testing includes virus isolation [61] and real-time RT-PCR assay [66-68] of different DENV serotypes, and so can provide a differential diagnosis. This type of method is limited in its use due to the short duration and low titre of the viraemia in the peripheral blood of an infected person, up to 7 days after the onset of symptoms [69]. Indirect (serological) testing can be used to attain a rapid diagnosis, as early as the first day of fever, and involves detection in patient serum of developing immunoglobulin (Ig)M and IgG antibodies to DENV non-structural protein-1 (NS-1) [32]. These methods include ELISA, for which there is now a commercially available kit, and immune chromatography [69,70]. Except for a few private institutions public and private hospitals in Indonesia do not yet perform dengue serotype surveillance [8]. Therefore, the great majority of dengue diagnoses are made purely by evaluation of clinical criteria using the outdated WHO 1997 classification system and supported by a basic haematological screen [9], including thrombocyte, leukocyte and haematocrit counts [71]. Not all Indonesian health services can utilize IgM/IgG and NS-1 rapid tests as diagnostic tools due to the relative expense of the immunological reagents and a lack of medical laboratory expertise that is required to run each of these methods [8].

### **Vector Locations, Behaviours and Breeding**

A recent detailed longitudinal study found that the most common mosquito species trapped in Indonesia from which DENV could be isolated was *Ae. aegypti* (90.9%), while *Ae. albopictus* contributed only 9.1% of virus-positive samples [7]. *Ae. aegypti* inhabits urban communities, living in close proximity to humans and resulting in more frequent bites [72] compared to *Ae. albopictus* which prefers more peri-urban and rural environments, which are thus less populated [73]. Both *Ae. aegypti* and *Ae. albopictus* may breed in water-holding vessels, including tyres, pots, tins and glass containers [72,74]. Dengue is particularly common in densely populated urban regions of Indonesia [54], where the co-existence of people and *Ae. aegypti* provides conditions that are conducive to a high rate of transmission. This is a significant problem in a country where more than half the inhabitants reside in metropolitan areas, notably Jakarta [10]. Rapid urbanization, as has occurred in the capital city in recent years, is associated with poor housing quality, limited safe water supply and restricted access to waste management. These encourage mosquito breeding and are significant contributing factors to the rising dengue incidence

rate in Indonesia and other tropical low-income countries that are similarly experiencing accelerated population growth [75]. Moreover, a tropical climate and humid environment are conditions conducive to *Aedes* mosquito transmission of DENV [24,72].

### **Mosquito Prevention and Control**

Estimates of mosquito abundance, including measurable correlates such as egg production and numbers of adults caught in baited traps, are valuable indicators of the adequacy of disease prevention and control in any given location [1]. There are also several ways to eliminate places where the peri-domestic *Ae. aegypti* prefers to lay eggs in and surrounding homes [76-78]. In low-income tropical countries where dengue is a public health threat mosquito control is an ongoing necessity, especially in urban areas of high endemicity such as Jakarta [14], in order to reduce the presence of the *Aedes* vector and thereby to lower the rate of DENV transmission. This can be achieved by effective environmental management, including draining mosquito-breeding containers [76]. Larvicide treatment of pooled water is important to suppress the growth of mosquito populations and thus to reduce the risk of a sudden dengue outbreak [79]. Fogging, the technique of spraying a fine aerosol of fast-acting insecticide, is also used but is only effective for killing adult mosquitoes in enclosed spaces such as household rooms and basements [80]. The limitations to control of *Aedes* mosquito populations include financial constraints, insecticide resistance and insufficient community involvement [81,82]. The prolonged use of chemicals insecticides has led to widespread development of mosquito resistance [83,84], while its indirect effects on community health and the environment are for debate [80]. Likewise, larvicides, including the commonly used organophosphate temephos (marketed by BASF as Abate®), are toxic to marine wildlife in which they accumulate, and at high doses can cause nausea and dizziness in people. Moreover, it was reported that temephos did not reduce mosquitoes long-term [80].

In Indonesia, ongoing control efforts are focused on removal of mosquito breeding sites, including the Government-funded Mosquito Nest Eradication Program [24,85]. This involves draining water and recycling waste that are potential sites for mosquito breeding, combined with periodic spraying of chemical larvicides and insecticides to eradicate larvae and winged adults, respectively [9,85]. Chemical fogging of domestic dwellings is widely supported. However, of considerable concern is the recent study reporting that chemical insecticide treatment is no longer an effective way to combat *Ae. aegypti* in some parts of the country [82]. The Indonesian Government also encourages its citizens to take simple steps towards personal responsibility, such as growing lemon grass in gardens, since the odour of the leave is believed to repel mosquitoes, and stocking ponds with insectivorous fish to consume mosquito larvae [56]. At an individual level there are several ways a person may protect themselves from being fed on

by a potentially infectious day-biting *Aedes* mosquito, including applying repellents [86], wearing trousers and long-sleeved shirts, and sleeping under a mosquito meshed curtain bed net [77]. While these personal measures might appear to be common sense, in dengue endemic areas outreach programmes are sometimes required to increase community awareness. Dengue is particularly prevalent during the Indonesian monsoon season (in Java, from October to March) due to the presence of many puddles of water in which *Aedes* may breed [87]. However, dengue cases are also reported in the so-called dry season (April to September), when the tropical equatorial climate remains very hot and humid, due to limited implementation of waste management measures [83,88], including routine disposal or emptying of water-holding containers [57]. It is evident that vector control alone cannot effectively reduce dengue incidence and mortality rate in Indonesia and other developing countries. Therefore, for future prevention of dengue there is a compelling need to focus more on the hitherto untapped potential of vaccination [21,38].

### **Vaccine Progress and Setback**

Large-scale vaccination of the public is another common strategy to combat tropical infectious diseases. A prime example of successful immunization against an arbovirus is provided by the closely related flavivirus yellow fever, for which a single vaccine dose is sufficient to induce protection that is potentially life-long [89]. Ideally, a vaccine for dengue should produce a balance of protection against all four serotypes, otherwise the vaccine may prime patients for more severe disease manifestations upon secondary exposure to a serotype different to that which caused primary infection [90]. However, the existence of multiple serotypes, combined with a lack of clear understanding of dengue disease pathogenesis, makes the construction of a vaccine a difficult, slow and very costly process [91,92]. Moreover, cross-reactivity by neutralising antibodies to different DENV serotypes risks activating ADE [93-95]. Therefore, the neutralising ability of antibodies to DENV serotypes is extremely important to vaccine design [96]. For a dengue vaccine ADE poses a significant problem as it may induce or enhance DENV antibodies and thereby increase the risk of severe dengue manifestations in vaccinated persons [95,96].

Despite these development hurdles that are unique to dengue in late 2016 a live recombinant tetravalent vaccine, CYD-TDV (marketed by Sanofi-Pasteur as Dengvaxia) [21,38] received commercial licensing by the WHO for a limited release in some endemic countries, including Indonesia [97,98]. However, following equivocal findings of probable ADE in seropositive individuals, notably in Filipino school children, its roll-out in mass immunization programmes is now blocked [99,100]. A further five vaccine candidates are under evaluation in various stages of clinical trial, including other live-attenuated vaccines, as well

as subunit, DNA and purified inactivated candidates. Additional technological approaches, such as virus-vectored and virus-like particle-based preparations, are under evaluation in pre-clinical studies [101,102]. The growing proportion of Indonesian people who live in Jakarta and other urban areas would be set to benefit from receiving an efficacious dengue vaccine [12,24]. However, the vaccination programme using Dengvaxia, currently suspended, has been too limited to date to prove effective [103]. Thus, while an advancement is awaited still the best strategy to both prevent and control the spread of dengue in Indonesia remains the low-technology approach of vector management [57,104].

## Conclusion

The global incidence of dengue has increased dramatically since the second half of the twentieth century. This emerging infectious disease has a significant impact on health care systems and is an economy burden to many developing countries in the tropics, including Indonesia. Current reporting systems in Indonesia are inadequate and very probably do not describe with any accuracy the actual situation. The need to ensure proper treatment for dengue, considering the various clinical and immunopathological subtypes of the disease, requires clear profiling or characterization of the individual patient, definition of clinical criteria for diagnosis and/or treatment and collection of real-world data in dengue patient care. Improved clinical profiling of dengue in Jakarta might inform better early case management, implementation of effective prevention and control programmes, and enhanced therapeutic vaccine development.

## Acknowledgements

The authors' preparation of this manuscript and their research discussed herein received no specific financial support.

## Conflicts of Interest

The authors declare that they have no competing issues of interest.

## Authors' Contributions

AWTR conceptualized the paper, which was developed further in discussion with TLC and TAP. TLC and AWTR collated articles for review, wrote and critically reviewed various drafts. All authors contributed to preparation of the final version and provided consent for submission.

## References

1. Betanzos-Reyes ÁF, Rodríguez MH, Romero-Martínez M, Sesma-Medrano E, Rangel-Flores H, et al. (2018) Association of dengue fever with *Aedes* spp. abundance and climatological effects. *Salud Pública de México* 60: 12-20.
2. Quinn EJ, Cheong AH-C, Calvert JK, Higgins G, Haahesly T, et al. (2018) Clinical features and laboratory findings of travelers returning to South Australia with dengue virus infection. *Tropical Medicine and Infectious Disease* 3: 6.
3. Lippi CA, Stewart-Ibarra AM, Muñoz ÁG, Borbor-Cordova MJ, Mejía R, et al. (2018) The social and spatial ecology of dengue presence and burden during an outbreak in Guayaquil, Ecuador, 2012. *International Journal of Environmental Research and Public Health* 15: 827.
4. Ding F, Fu J, Jiang D, Hao M, Lin G (2018) Mapping the spatial distribution of *Aedes aegypti* and *Aedes albopictus*. *Acta Tropica* 178: 155-162.
5. Siregar FA, Makmur T (2018) Survey on *Aedes* mosquito density and pattern distribution of *Aedes aegypti* and *Aedes albopictus* in high and low incidence districts in North Sumatera province. *IOP Conference Series: Earth and Environmental Science* 130: 012018.
6. Hamid PH, Prastowo J, Ghiffari A, Taubert A, Hermosilla C (2017) *Aedes aegypti* resistance development to commonly used insecticides in Jakarta, Indonesia. *PLoS One* 12: e0189680.
7. Mulyatno KC, Kotaki T, Yotopranoto S, Rohmah EA, Churotin S, et al. (2018) Detection and serotyping of dengue viruses in *Aedes aegypti* and *Aedes albopictus* (Diptera: Culicidae) collected in Surabaya, Indonesia from 2008 to 2015. *Japanese Journal of Infectious Diseases* 71: 58-61.
8. Sasmono RT, Taurel AF, Prayitno A, Sitompul H, Yohan B, et al. (2018) Dengue virus serotype distribution based on serological evidence in pediatric urban population in Indonesia. *PLoS Neglected Tropical Diseases* 12: e0006616.
9. O'Driscoll M, Imai N, Ferguson NM, Hadinegoro SR, Satari H, et al. (2018) Spatiotemporal variability in dengue transmission intensity in Jakarta, Indonesia. *bioRxiv*. doi.org/10.1101/496448.
10. Tam CC, O'Driscoll M, Taurel AF, Nealon J, Hadinegoro SR (2018) Geographic variation in dengue seroprevalence and force of infection in the urban paediatric population of Indonesia. *PLoS Neglected Tropical Diseases* 12: e0006932.
11. Anggriani N, Tasman H, Ndii MZ, Supriatna AK, Soewono E, et al. (2019) The effect of reinfection with the same serotype on dengue transmission dynamics. *Applied Mathematics and Computation* 349: 62-80.
12. Islam R, Salahuddin M, Ayubi MS, Hossain T, Majumder A, et al. (2015) Dengue epidemiology and pathogenesis: images of the future viewed through a mirror of the past. *Virologica Sinica* 30: 326-343.
13. ten Bosch QA, Clapham HE, Lambrechts L, Duong V, Buchy P, et al. (2018) Contributions from the silent majority dominate dengue virus transmission. *PLoS Pathogens* 14: e1006965.
14. Gyawali N, Bradbury RS, Taylor-Robinson AW (2016) The epidemiology of dengue infection: harnessing past experience and current knowledge to support implementation of future control strategies. *Journal of Vector Borne Diseases* 53: 293-304.
15. Hashem AM, Abujamel T, Alhabbab R, Almazroui M, Azhar EI (2018) Dengue infection in patients with febrile illness and its relationship to climate factors: a case study in the city of Jeddah, Saudi Arabia, for the period 2010-2014. *Acta Tropica* 181: 105-111.
16. Pang X, Zhang R, Cheng G (2017) Progress towards understanding the pathogenesis of dengue hemorrhagic fever. *Virologica Sinica* 32: 16-22.

17. Masyeni S, Yohan B, Somia IK, Myint KS, Sasmono RT (2018) Dengue infection in international travellers visiting Bali, Indonesia. *Journal of Travel Medicine* 25. doi: 10.1093/jtm/tay061.
18. Cheng KJG, Lam HY, Rivera AS, Tumanan-Mendoza BA, Alejandria MM, et al. (2018) Estimating the burden of dengue in the Philippines using a dynamic transmission model. *Acta Medica Philippina* 52: 153-159.
19. Imrie A (2018) Dengue introduced by travellers, Australia. *Microbiology Australia* 39: 67-71.
20. Low GK-K, Ogston SA, Yong M-H, Gan S-C, Chee H-Y (2018) Global dengue death before and after the new World Health Organization 2009 case classification: a systematic review and meta-regression analysis. *Acta Tropica* 182: 237-245.
21. Mishra AC, Arankalle VA, Gadhawe SA, Mahadik PH, Shrivastava S, et al. (2018) Stratified sero-prevalence revealed overall high disease burden of dengue but suboptimal immunity in younger age groups in Pune, India. *PLoS Neglected Tropical Diseases* 12: e0006657.
22. Wahyono TYM, Nealon J, Beucher S, Prayitno A, Moureau A, et al. (2017) Indonesian dengue burden estimates: review of evidence by an expert panel. *Epidemiology and Infection* 145: 2324-2329.
23. Liebig J, Jansen C, Pains D, Gardner L, Jurdak R (2018) A global model for predicting the arrival of imported dengue infections. arXiv:1808.10591v2 [q-bio.PE].
24. Haryanto B (2018) Indonesia dengue fever: status, vulnerability, and challenges. In: *Current Topics in Tropical Emerging Diseases and Travel Medicine*. IntechOpen, London, 81-92.
25. Neiderud CJ (2015) How urbanization affects the epidemiology of emerging infectious diseases. *Infection Ecology & Epidemiology* 5: 27060.
26. World Health Organization (2019) Dengue and severe dengue. <https://www.who.int/news-room/fact-sheets/detail/dengue-and-severe-dengue>.
27. Akter R, Naish S, Hu W, Tong S (2017) Socio-demographic, ecological factors and dengue infection trends in Australia. *PLoS One* 12: e0185551.
28. Maula AW, Fuad A, Utarini A (2018) Ten-years trend of dengue research in Indonesia and South-east Asian countries: a bibliometric analysis. *Global Health Action* 11: 1504398.
29. Woon YL, Hor CP, Lee KY, Mohd Anuar SFZ, Mudin RN, et al. (2018) Estimating dengue incidence and hospitalization in Malaysia, 2001 to 2013. *BMC Public Health* 18: 946.
30. World Health Organization (2018) A toolkit for national dengue burden estimation. <https://apps.who.int/iris/handle/10665/277257>.
31. Villanes A, Griffiths E, Rappa M, Healey CG (2018) Dengue fever surveillance in India using text mining in public media. *American Journal of Tropical Medicine and Hygiene* 98: 181-191.
32. Pan American Health Organization (2016) Dengue guidelines for patient care in the region of the Americas, 2nd ed. <http://iris.paho.org/xmlui/handle/123456789/31207>.
33. Hadinegoro SRS (2012) The revised WHO dengue case classification: does the system need to be modified? *Paediatrics and International Child Health* 32: 33-38.
34. Tate M, Saini G (2018) A review on dengue and current status of its treatment. *World Journal of Pharmacy and Pharmaceutical Sciences* 7: 570-582.
35. Suppiah J, Ching S-M, Amin-Nordin S, Mat-Nor L-A, Ahmad-Najimudin N-A, et al. (2018) Clinical manifestations of dengue in relation to dengue serotype and genotype in Malaysia: a retrospective observational study. *PLoS Neglected Tropical Diseases* 12: e0006817.
36. Shukla R, Ramasamy V, Rajpoot RK, Arora U, Poddar A, et al. (2019) Next generation designer virus-like particle vaccines for dengue. *Expert Review of Vaccines* 18: 105-117.
37. Madzlan F, Dom NC, Zakaria N, Hasnan SNA, Tiong CS, et al. (2017) Profiling of dengue vectors breeding habitat at urban residential areas in Shah Alam, Malaysia. *Serangga* 22: 185-216.
38. Vu T, Clapham H, Huynh V, Vo L, Le D, et al. (2019) A human *ex vivo* dengue virus neutralization assay identifies priority antibodies and epitopes for vaccines and therapeutics. *bioRxiv* doi: org/10.1101/516195.
39. Barde PV, Mishra N, Singh N (2018) Timely diagnosis, use of information technology and mosquito control prevents dengue outbreaks: experience from central India. *Journal of Infection and Public Health* 11: 739-741.
40. United Nations Department of Economic and Social Affairs (2018) 68% of the world population projected to live in urban areas by 2050, says UN. <https://www.un.org/development/desa/en/news/population/2018-revision-of-worldurbanization-prospects.html>.
41. Mehta SR, Bafna TA, Pokale AB (2018) Demographic and clinical spectrum of dengue patients admitted in a tertiary care hospital. *Medical Journal of Dr. DY Patil Vidyapeeth* 11: 128-131.
42. Modi A, Vaishnav KG, Pandya RC, Sahu GC, Naik A (2018) Urban dengue surveillance over sixteen years: integration, trend analysis and participation of private medical sector. *Journal of Communicable Diseases* 50: 52-59.
43. Akanda AS, Johnson K (2018) Growing water insecurity and dengue burden in the Americas. *Lancet Planetary Health* 2: e190-e191.
44. Tran BX, Thu Vu G, Hoang Nguyen L, Tuan Le Nguyen A, Thanh Tran T, et al. (2018) Cost-of-illness and the health-related quality of life of patients in the dengue fever outbreak in Hanoi in 2017. *International Journal of Environmental Research and Public Health* 15: 1174.
45. Bangert M, Latheef AT, Dev Pant S, Nishan Ahmed I, Saleem S, et al. (2018) Economic analysis of dengue prevention and case management in the Maldives. *PLoS Neglected Tropical Diseases* 12: e0006796.
46. Harapan H, Rajamoorthy Y, Anwar S, Bustamam A, Radiansyah A, et al. (2018) Knowledge, attitude, and practice regarding dengue virus infection among inhabitants of Aceh, Indonesia: a cross-sectional study. *BMC Infectious Diseases* 18: 96.
47. Nadjib M, Setiawan E, Putri S, Nealon J, Beucher S, et al. (2019) Economic burden of dengue in Indonesia. *PLoS Neglected Tropical Diseases* 13: e0007038.
48. Adrizain R, Setiabudi D, Chairulfatah A (2018) Hospital-based surveillance: accuracy, adequacy, and timeliness of dengue case report in Bandung, West Java, Indonesia of 2015. *Journal of Global Infectious Diseases* 10: 201-205.

49. Grange L, Simon-Loriere E, Sakuntabhai A, Gresh L, Paul R, et al. (2014) Epidemiological risk factors associated with high global frequency of inapparent dengue virus infections. *Frontiers in Immunology* 5: 280.
50. Indonesia Climate Change Sectoral Roadmap (ICCSR) Synthesis Report (2010) Government of Indonesia, Jakarta. [https://www.adaptationundp.org/sites/default/files/downloads/indonesia\\_climate\\_change\\_sectoral\\_roadmap\\_ic\\_csr.pdf](https://www.adaptationundp.org/sites/default/files/downloads/indonesia_climate_change_sectoral_roadmap_ic_csr.pdf).
51. Mariana, Diara A, Ismah Z, Irpani TH, Cahyo RD, et al. (2018) Correlational spatiotemporal analysis dengue haemorrhagic fever (DHF) with settlement condition in Palembang city, Indonesia. *LIFE: International Journal of Health and Life-Sciences* 3: 147-157.
52. Bisnis.com (2018) Kemenkes klaim kasus DBD di Indonesia Sudah Terkendali [Ministry of Health claims DHF cases in Indonesia are under control]. <https://lifestyle.bisnis.com/read/20180717/106/817431/kemenkes-klaim-kasus-dbd-di-indonesia-sudah-terkendali>.
53. Imai N, Ferguson NM (2018) Targeting vaccinations for the licensed dengue vaccine: considerations for serosurvey design. *PLoS One* 13: e0199450.
54. Ayuningtyas KD, Rahardjo SS, Murti B (2019) Risk factors of dengue fever: application of PRECEDE – PROCEED model. *Journal of Epidemiology and Public Health* 4: 37-46.
55. Prayitno A, Taurel A-F, Nealon J, Satari HI, Karyanti MR, et al. (2017) Dengue seroprevalence and force of primary infection in a representative population of urban dwelling Indonesian children. *PLoS Neglected Tropical Diseases* 11: e0005621.
56. The Jakarta Post (2019) Dengue death toll climbs to 132, eight regions declare emergency. <https://www.thejakartapost.com/news/2019/01/31/denguedeath-toll-climbs-to-132-eight-regions-declare-emergency.html>.
57. BBC News Indonesia (2019) Dengue fever mewabah: Pencegahan dengan jaga kebersihan dan tanam serai [Dengue fever is endemic: Prevention by maintaining cleanliness and planting lemongrass]. <https://www.bbc.com/indonesia/indonesia-47039921>.
58. Nagaram PP, Piduru P, Munagala VK, Matli VV (2017) Clinical and laboratory profile and outcome of dengue cases among children attending a tertiary care hospital of South India. *International Journal of Contemporary Pediatrics* 4: 1074-1080.
59. Tomashek KM, Lorenzi OD, Andújar-Pérez DA, Torres-Velásquez BC, Hunsperger EA, et al. (2017) Clinical and epidemiologic characteristics of dengue and other etiologic agents among patients with acute febrile illness, Puerto Rico, 2012–2015. *PLoS Neglected Tropical Diseases* 11: e0005859.
60. Luh D-L, Liu C-C, Luo Y-R, Chen S-C (2018) Economic cost and burden of dengue during epidemics and non-epidemic years in Taiwan. *Journal of Infection and Public Health* 11: 215-223.
61. Soo K-M, Khalid B, Ching S-M, Chee H-Y (2016) Meta-analysis of dengue severity during infection by different dengue virus serotypes in primary and secondary infections. *PLoS One* 11: e0154760.
62. Kusmintarsih ES, Hayati RF, Turnip ON, Yohan B, Suryaningsih S, et al. (2018) Molecular characterization of dengue viruses isolated from patients in Central Java, Indonesia. *Journal of Infection and Public Health* 11: 617-625.
63. Adam A, Schüttoff T, Reiche S, Jassoy C (2018) High seroprevalence of dengue virus indicates that dengue virus infections are frequent in Central and Eastern Sudan. *Tropical Medicine & International Health* 23: 960-967.
64. Ajlan BA, Alafif MM, Alawi MM, Akbar NA, Aldigs EK, et al. (2019) Assessment of the new World Health Organization's dengue classification for predicting severity of illness and level of healthcare required. *bioRxiv*. doi.org/10.1101/516229.
65. Gyawali N, Taylor-Robinson AW (2017) Diagnosis of dengue: strengths and limitations of current techniques and prospects for future improvements. In: *Dengue: Immunopathology and Control Strategies*. IntechOpen, London, 55-74.
66. Nair KR, Oommen S, Jagan OA, Pai V (2019) Detection of circulating dengue virus serotypes in a tertiary care centre in central Kerala, 2016. *International Journal of Current Microbiology and Applied Sciences* 8: 2669-2678.
67. Wang TT, Sewatanon J, Memoli MJ, Wrarmert J, Bourmazos S, et al. (2017) IgG antibodies to dengue enhanced for FcγRIIIA binding determine disease severity. *Science* 355: 395-398.
68. Ambrose JH, Sekaran SD, Azizan A (2017) Dengue virus NS1 protein as a diagnostic marker: commercially available ELISA and comparison to qRT-PCR and serological diagnostic assays currently used by the state of Florida. *Journal of Tropical Medicine* 2017: 8072491.
69. Banerjee A, Paul UK, Bandyopadhyay A (2018) Diagnosis of dengue fever: roles of different laboratory test methods. *International Journal of Advances in Medicine* 5: 395-399.
70. Rockstroh A, Barzon L, Kumbukgolla W, Su HX, Lizarazo E, et al. (2019) Dengue virus IgM serotyping by ELISA with recombinant mutant envelope proteins. *Emerging Infectious Diseases* 25: 1111-1115.
71. Pangestu WH (2019) Perbedaan profil hematologi rutin pada penderita demam berdarah dengue anak dan dewasa di RSUD Dr. Harjono Ponorogo. <http://eprints.ums.ac.id/69760/10/NASKAH%20PUBLIKASI%2827%29.pdf>.
72. Trewin BJ, Darbro JM, Zalucki MP, Jansen CC, Schellhorn NA, et al. (2019) Life on the margin: rainwater tanks facilitate overwintering of the dengue vector, *Aedes aegypti*, in a sub-tropical climate. *bioRxiv* 14: e0211167.
73. Cotchakaew N, Soonwera M (2019) Toxicity of several botanical essential oils and their combinations against females of *Aedes albopictus* (Skuse) and *Anopheles minimus* (Theobald): oviposition deterrent, ovicidal and adulticidal efficacies. *Asian Pacific Journal of Tropical Biomedicine* 9: 29-39.
74. Tuladhar R, Singh A, Banjara MR, Gautam I, Dhimal M, et al. (2019) Effect of meteorological factors on the seasonal prevalence of dengue vectors in upland hilly and lowland Terai regions of Nepal. *Parasites & Vectors* 12: 42.
75. Nagpal BN, Knox TB, Risintha P, Yadav RS, Ghosh SK, et al. (2018) Strengthening of vector control in South-East Asia: outcomes from a WHO regional workshop. *Journal of Vector Borne Diseases* 55: 247-257.
76. Singh A, Taylor-Robinson AW (2017) Vector control interventions to prevent dengue: current situation and strategies for future improvements to management of *Aedes* in India. *Journal of Infectious Disease and Pathology* 2: 1000123.

77. Mood BS, Mardani M (2017) Dengue: a re-emerging disease. *Archives of Clinical Infectious Diseases* 12: e27970.
78. Strugarek M, Bossin H, Dumont Y (2019) On the use of the sterile insect release technique to reduce or eliminate mosquito populations. *Applied Mathematical Modelling* 68: 443-470.
79. Guzzetta G, Trentini F, Poletti P, Baldacchino FA, Montarsi F, et al. (2017) Effectiveness and economic assessment of routine larviciding for prevention of chikungunya and dengue in temperate urban settings in Europe. *PLoS Neglected Tropical Diseases* 11: e0005918.
80. ten Bosch QA, Wagman JM, Castro-Llanos F, Achee NL, Grieco JP, et al. (2019) Community-level impacts of spatial repellents for control of diseases vectored by *Aedes aegypti* mosquitoes. *bioRxiv*. doi. org/10.1101/501700.
81. Neumayr A, Muñoz J, Schunk M, Bottieau E, Cramer J, et al. (2017) Sentinel surveillance of imported dengue via travellers to Europe 2012 to 2014: TropNet data from the DengueTools Research Initiative. *Eurosurveillance* 22: 30433.
82. Haziqah-Rashid A, Chen CD, Lau KW, Low VL, Sofian-Azirun M, et al. (2019) Monitoring insecticide resistance profiles of *Aedes aegypti* (Diptera: Culicidae) in the Sunda Islands of Indonesia based on diagnostic doses of larvicides. *Journal of Medical Entomology* 56: 514-518.
83. Faiz M, Nazri CD, Chua ST (2017) Spatial and temporal distribution of *Aedes* (Diptera: Culicidae) mosquitoes in Shah Alam. *Tropical Biomedicine* 34: 118-126.
84. Marcombe S, Chonephetsarath S, Thammavong P, Brey PT (2018) Alternative insecticides for larval control of the dengue vector *Aedes aegypti* in Lao PDR: insecticide resistance and semi-field trial study. *Parasites & Vectors* 11: 616.
85. Ministry of Health Republic of Indonesia (2019) Kemenkes imbau seluruh daerah siaga DBD [Ministry of Health calls for dengue alert of the entire area]. <http://www.depkes.go.id/article/view/19011800001/kemenkes-imbau-seluruh-daerah-siaga-dbd.html>.
86. Orsborne J, DeRaedt Banks S, Hendy A, Gezan SA, Kaur H, et al. (2016) Personal protection of permethrin-treated clothing against *Aedes aegypti*, the vector of dengue and Zika virus, in the laboratory. *PLoS One* 11: e0152805.
87. The Jakarta Post (2019) Health Ministry warns of dengue fever during rainy season. <https://www.thejakartapost.com/news/2019/01/21/healthministry-warns-of-dengue-fever-during-rainy-season.html>.
88. Mayer SV, Tesh RB, Vasilakis N (2017) The emergence of arthropod-borne viral diseases: a global prospective on dengue, chikungunya and zika fevers. *Acta Tropica* 166: 155-163.
89. Gotuzzo E, Yactayo S, Córdova E (2013) Efficacy and duration of immunity after yellow fever vaccination: systematic review on the need for a booster every 10 years. *American Journal of Tropical Medicine and Hygiene* 89: 434-444.
90. Gromowski GD, Henein S, Kannadka CB, Barvir DA, Thomas SJ, et al. (2018) Delineating the serotype-specific neutralizing antibody response to a live attenuated tetravalent dengue vaccine. *Vaccine* 36: 2403-2410.
91. Subedi D, Taylor-Robinson AW (2015) Development of a dengue vaccine in humans: so near, yet so far. *International Journal of Vaccine Research* 1: 1-7.
92. Screaton G, Mongkolsapaya J (2017) Which dengue vaccine approach is the most promising, and should we be concerned about enhanced disease after vaccination? The challenges of a dengue vaccine. *Cold Spring Harbor Perspectives in Biology* 10: a029520.
93. Yamanaka A, Moi ML, Takasaki T, Kurane I, Konishi E (2017) Neutralizing and enhancing antibody responses to five genotypes of dengue virus type 1 (DENV-1) in DENV-1 patients. *Journal of General Virology* 98: 166-172.
94. Taylor-Robinson AW (2017) Cross-reactivity of non-neutralizing antibodies to dengue and Zika viruses: implications for vaccination. *Archives of Preventive Medicine* 2: 10-14.
95. Taylor-Robinson AW (2017) Enhancement of infection by pre-existing non-neutralizing antibodies to cross-reactive flaviviruses: ramifications for vaccination against dengue and Zika. *Journal of Vaccines & Clinical Trials* 1:1000101.
96. Katzelnick LC, Gresh L, Halloran ME, Mercado JC, Kuan G, et al. (2017) Antibody-dependent enhancement of severe dengue disease in humans. *Science* 358: 929-932.
97. Reuters Health News (2016) Sanofi's dengue vaccine approved in 11 countries. <https://www.reuters.com/article/us-sanofi-vaccine/sanofidengue-vaccine-approved-in-11-countries-idUSKCN1240C5>.
98. Chen Y-C, Cheng H-F, Yang Y-C, Yeh M-K (2017) The regulation requirement of dengue vaccines. In: *Dengue: Immunopathology and Control Strategies*. IntechOpen, London, 109-123.
99. Dyer O (2017) Philippines halts dengue immunisation campaign owing to safety risk. *British Medical Journal* 359: j5759.
100. Rappler.com (2019) FDA permanently revokes Dengvaxia's certificate of product registration. <https://www.rappler.com/nation/223848fda-permanently-revokes-certificate-product-registration-dengvaxia>.
101. Ansari S, Taylor-Robinson AW (2014) Strategic approaches to multi-valent vaccine development against dengue virus infection. *Annals of Vaccines & Immunization* 1: 1005.
102. World Health Organization (2017) Dengue vaccine research. [https://www.who.int/immunization/research/development/dengue\\_vaccines/en/](https://www.who.int/immunization/research/development/dengue_vaccines/en/).
103. Aguiar M, Stollenwerk N, Halstead SB (2016) The impact of the newly licensed dengue vaccine in endemic countries. *PLoS Neglected Tropical Diseases* 10: e0005179.
104. Wilder-Smith A, Ooi EE, Horstick O, Wills B (2019) Dengue. *Lancet* 393: 350-363.