Chapter

History of Dengue Fever Prevalence and Management in a One Health Perspective in Hainan Island, China

Qingfeng Guan, Archana Upadhyay and Qian Han

Abstract

Dengue fever (DF), a mosquito-borne viral infection common in warm, tropical climates, is an acute infectious disease caused by the Dengue virus (DENV). Geographically, Hainan Island falls in the southern belt of China holding an approximate area of 33,920 km^2. Meteorologically, Hainan is characterized to have a tropical maritime monsoon climate, giving rise to favorable natural conditions for different mosquito species. However, the diversity of mosquitoes and their abundance has undoubtedly put the island at a higher risk of mosquito-borne viral disease outbreaks. In this chapter, we have discussed the prevalence, control, and management of DF in Hainan Island in China along with the different species of mosquitoes responsible for transmitting the virus. In addition, future prospective of some important DF management strategies, related research methods, and integrated control strategies for the effective control and management of DF with One Health perspective has been summarized.

Keywords: dengue fever, dengue virus, Hainan Island, mosquito monitoring and control, one health

1. Introduction

Since the first reported outbreak in 1779 in Jakarta, Indonesia, many such outbreaks have taken place globally in tropical and sub-tropical climates majorly in urban and semi-urban areas having a wide array of weather conditions [1]. In this major outbreak, DENV type 3 was the causative agent, which was believed to be imported from countries in southeast Asia. Since then, several other imported DF cases have led to major and minor outbreaks in provinces like Guangxi, Yunnan, Hainan, Fujian, etc., in China [1]. Two major outbreaks of DENV type 1 and DENV type 3 were recorded, during 2006–2007 and 2012–2015, respectively [2]. From 1978 to 1991, DF outbreaks in China were mainly concentrated and limited to the coastal areas such as Guangdong and Hainan Province [2]. Hainan experienced the highest incidence rate between the years 1978 and 1992. However, fewer cases have been reported since then.

2. History of DF prevalence in Hainan Island, China

Hainan occurs as the southernmost province and the second largest island in China, having Guangdong province across the Qiongzhou Strait to the northern part of China (**Figure 1**). It boasts of a tropical monsoon climate experiencing rainy season during the months of May till October. The overall climatic conditions are suitable for the breeding of *Aedes* mosquito larvae and for the optimal transmission of DF. Hainan province has experienced three DF epidemics in the past. DENV type 3 was the causative agent for the first outbreak caused in 1978, followed by another outbreak in 1985–1988, and a third one, a dengue hemorrhagic fever in 1991, both of which were caused by DENV type 2 [3, 4]. In October 1979, a large number of suspected dengue cases were found in the northern coastal areas of Dan County (Danzhou city), Hainan Island. Later, the disease spread rapidly along the coastline *via* the transportation lines to the neighboring ports. By 1980, a total of 18 counties/cities and 208 towns, mainly falling in the coastal areas around the island, were facing a major outbreak [3]. In this period, 437,469 DF cases occurred in Hainan Island, and the infection rate was found to be 74% [3, 4]. Its long epidemic period and high incidence rate were of great significance in the epidemiological history. However, the incidence rates decreased significantly in 1981 and almost declined in September 1982 [3].

In early September 1985, suspected dengue cases were reported in Ganchong district along the northern coast of Dan County. Yangpu Township in the county became the local epidemic epicenter in mid-October and reached its peak in late October, which led to further spread of the infection. Neighboring townships in the Ganchong area started experiencing the incidence rates leading to a peak in early November. In late October, most of the adjoining areas along the northern coast started reporting patients, which caused several local outbreaks. However, in late November, cases invaded Changjiang, Lingao counties, and Haikou city, and still outbreaks occurred in a few areas of Changjiang. The outbreak hit Dan, Changjiang, Lingao counties, Haikou city, and 25 towns, with 12,449 cases reported in 3 months having an incidence rate of 210.68/100,000 and 28 deaths. The mortality rate of this

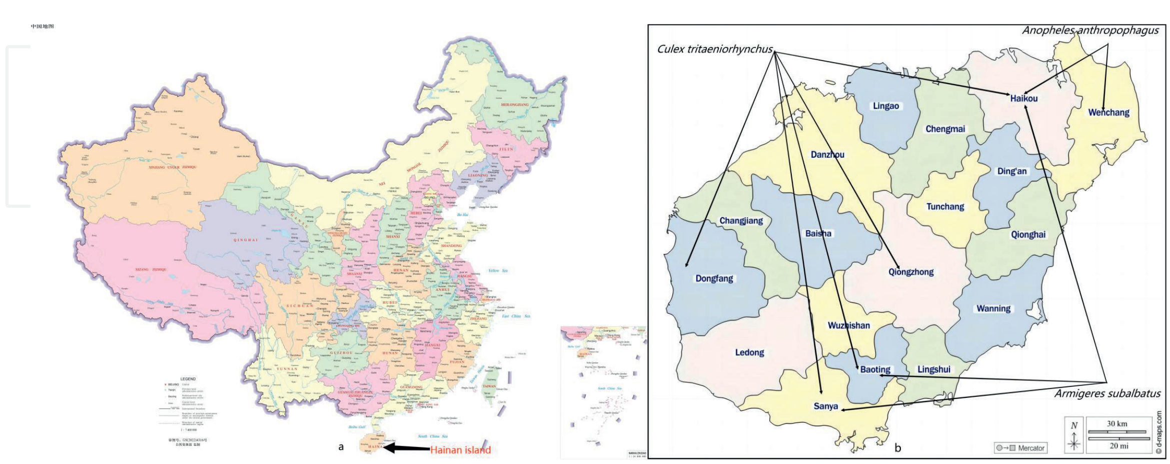

Figure 1.
Geographical representation of the map of Hainan, China, highlighting the prominent cities and counties of the province. A: Map of China, localizing and highlighting Hainan Island. b: Map of Hainan Island displaying different counties and cities harboring different species of mosquitoes due to its typical tropical climate. Three mosquito species were labeled on the map. Map of China was downloaded from the web of Ministry of Natural Resources of the People's republic of China (http://bzdt.ch.mnr.gov.cn/browse.html?picId=%224028b0625501ad13015501ad2bfc0690%22). Map of Hainan Island was downloaded from the web of d-maps (https://d-maps.com/carte.php?num_car=21235&lang=en).

prevalence was 0.47/100,000, and case fatality rate was 2.25 per thousand [5]. In the first half of 1986, the epidemic had gone down owing to the early diagnosis and appropriate control measures of the epidemic. Subsequently, the prevention and control measures failed to persist for a long time, and it gave rise to new waves of epidemic, and finally led to an island-wide pandemic in August and September 1986. In 1986, 113,589 cases were reported, and 289 people died, affecting 182 townships and 27 farms in 18 cities and counties [6]. By 1987, the epidemic had gradually declined, with 30,229 cases and 76 deaths. In 1988, 7379 cases were reported and 18 deaths were reported. By the end of 1988, the outbreak had ended. The 1985–1988 epidemic was due to the DENV type 2 [7].

From June to November 1991, the third epidemic broke out in five cities and counties, with 13 villages and 3 towns falling prey to the epidemic. 521 cases were reported, most of which were mild. 92.3% of the patients were uninfected during the 1985–1988 epidemic, and only 6.8% were reported to have dengue-like symptoms [4, 8, 9].

In 2019, a total of 291 dengue cases were reported in Haikou, with an incidence rate of 12.64/100,000, including 251 local cases (86.3%) and 40 imported cases (13.7%). Among the imported cases, 32 imported cases were reported from Cambodia and Thailand, and 8 imported cases were reported, mainly from Guangxi and Yunnan provinces. All locally confirmed cases were found to be type I, while in the imported cases, all types were reported [10].

3. DENV and its molecular and immunological characterization and identification

Diagnosis of typical cases during epidemics is easy, but the diagnosis depends on virus isolation and serological examination. However, due to lack of awareness, it is easy to miss diagnosis in early epidemics, and other grades of fever may be misdiagnosed as DF. Therefore, DF should be distinguished from influenza, leptospirosis, measles, scarlet fever, and epidemic hemorrhagic fever. In Hainan, malaria needs to be excluded first [11].

DENV is an RNA virus that can be classified in Flavivirus genus of the Flaviviridae family. Being an RNA virus, its genome is undoubtedly prone to mutations, which makes it widespread. DENV has five antigenically different but very closely related serotypes (DENV-type 1, DENV type 2, DENV type 3, DENV type 4, and DENV type 5). The genetic sequences of the DENV1, DENV 2, DENV 3, and DENV 4 are well defined. However, they have some differences in their antigenicity, which makes them graded as reference strains. DENV 1 strain was isolated from Hawaii (DENV-I, Hawaii strain), with DENV 2 from New Guinea (DENV-II, The New Guinea strain), DENV 3 (DENV-III, Philippine H87 strains), and DENV 4 (DENV-IV, Philippines strain H241 strain) from the Philippines. Since then, a large number of DENV strains have been isolated from all over the world. Although some scholars have advocated the classification of some emerging strains with special molecular and immunological characteristics categorizing them into class V serotypes, but the theory has yet to be validated and widely accepted. DF is a mosquito-borne viral infection that gives rise to a sudden onset of fever followed by symptoms such as headache, nausea, muscle and joint pain, and rashes on the skin. It can affect any person but leads to serious complications in immunocompromised people, which can turn out to be fatal. This type of infection can become more fatal and can be named dengue hemorrhagic fever. It can be a life-threatening condition, which may further give rise to the critical form of infection called dengue shock syndrome. Individuals who have been infected by one DENV serotype can usually have lifelong immunity to the same type of virus but have only partial or temporary protection against the other serotype viruses. Therefore, people living in dengue-endemic areas may develop infections with 4 DENV serotypes. Furthermore, there are common antigen-determination clusters between the 4 DENV serotypes and other members of the flavivirus family, with the presence of cross-reactive antibodies, and hence, the serological identification of different types of DENV becomes complex.

A wide range of laboratory diagnostic procedures have been developed and are in place for confirming DENV infection, which includes the classical method of isolation of the DENV, several molecular-based assays like PCR-based assays for testing the virus, serological assays like antigen or antibodies, or a combination of several assays. DENV can be isolated from the patient specimen or can be detected as the viral nucleic acid or as an antigen, IgM antibody in the blood. A blood specimen with a positive IgM or IgG antibody cannot confirm DENV infection, and can only be clinically diagnosed as suspected or possible cases as acute or convalescent serum samples.

3.1 DENV infection and the body's immune response

The incubation period of the virus ranges between 3 and 14 days, and it can be detected within 4 to 7 days of infection [12]. In many cases, even after collecting the biological specimens during the incubation period, it still at times fails to detect the virus or the corresponding body's immune response. After the onset, the presence of the virus in the blood (viremia period) is about 7 days, and the viral NS1 antigen exists in the blood for a slightly longer time. Within 4 to 5 days after the onset of the disease, the virus can be isolated from the patient's serum, plasma, white blood cells, cerebrospinal fluid, and autopsy tissue specimens, and the detection rate of viral nucleic acid and NS1 antigen is found to be higher during this period. Antibody levels in the patient's blood vary significantly depending on their individual immune status. If the patient has not been previously infected with DENV or other flaviviruses or has received flavivirus vaccine (e. g., Japanese encephalitis, yellow fever, etc.), the first infection slowly increases the levels of specific antibodies, and IgM antibodies appear the earliest, followed by IgA and IgG antibodies. The detection rate of IgM antibodies was about 50% in patients from 3 to 5 days after onset, about 80% in patients from day 5 after onset, and about 99% in patients from day 10 after onset. IgM antibody level reaches the peak 2 weeks after onset, then they gradually decrease followed by which they can be maintained for 2 to 3 months. The IgA antibody usually develops slightly later than the IgM antibody and persists for approximately 45 days [12]. One week after the onset, lower titer of IgG antibody can be detected in the blood specimen, after which the antibody titer persists for several months or even for lifetime. If a patient is reinfected with DENV (previously infected with, or sometimes possibly vaccinated against, or infected with other flavivirus vaccines), antibody titers can rise rapidly and react to a variety of flaviviruses. Mainly high levels of IgG antibodies can be detected in the acute phase of infection and persist for more than 10 months, even for lifetime. IgA antibodies can also be detected in the acute phase specimens. The IgM antibody titers in the early stages of the recovery period are significantly lower than the first infection, or can even be negligible. The application of IgA antibody detection system for detection of the antibodies is still in the evaluation stage.

3.2 Selection of appropriate detection methods

In the early stage of the disease (within 5 days of onset), virus isolation, nucleic acid detection, or antigen detection methods are the most commonly used techniques and methods for diagnosis. When the course of the infection enters the recovery period (after 5 days of onset), serological detection using virus-specific antibodies is generally used for diagnosis.

Virus isolation: Classical isolation of the virus by cell culture methods is the most opted method for the isolation of the virus. It requires a biosafety level (BSL-2) laboratory and related necessary equipment. It is very important to maintain a cold chain during specimen transportation (frozen or refrigerated) for virus isolation. Specimens are usually inoculated in mosquito-derived cells (C6/36) or mammalian cells (BHK21, Vero) for isolation and culture. After the lesions are seen, the virus can be identified by detecting antigens or nucleic acid. Isolation of DENV can be taken as a confirmatory test, however, it takes long time and, therefore, it cannot be suitable for rapid diagnosis.

Nucleic acid testing: A variety of molecular biology-based reverse transcriptional polymerase chain reaction (RT-PCR) methods can be used for DENV nucleic acid detection, including one-step RT-PCR, real-time fluorescent RT-PCR, LAMP (Loop-mediated isothermal amplification assay), RT-RPA (Reverse transcriptase Recombinase Polymerase Activation). Nucleic acid testing identifies viral RNA within 1 ~ 2 days. The detection of viral nucleic acid in patient specimens can be confirmed and subtyped and can be used for early diagnosis. However, it has its own set of drawbacks as it is easy to produce false positives due to number of inhibiting factors, which requires strict zoning operation.

Antigen testing: NS1 antigen detection is commonly done using ELISA method or rapid detection reagent, which can be completed in several minutes to several hours. It is suitable for field and point-of-care settings. It forms an important approach toward acute DF diagnosis, which can be detected within 1 day after the onset, and few other reports have also stated that it can still be detected in blood specimens after 18 days of the onset. Due to the specificity of the NS1 antigen detection method, it can also be used in the differential diagnosis of flavivirus infection.

IgM antibody detection: Capture method ELISA (MAC-ELISA) for IgM antibody detection is the most commonly used detection method, and there are many commercial fast test reagents available for IgM antibody detection, which, however, cannot be used for serotype detection. At present, the detection reagents mainly detect viral envelope protein-specific antibodies, and the major drawback of these tests is that it shows a cross-reaction with other flaviviruses. A positive IgM antibody in the specimen, suggesting that the patient may be newly infected with DENV, is suitable for early diagnosis of DF. However, it is not suitable for single specimen. Even after reinfection, the IgM antibody titer base in blood specimens can still not be detected at times, affecting the diagnostic accuracy for detection of IgM antibodies.

IgG antibody detection: DENV IgG antibodies cross-react with other flaviviruses. IgG antibody test can be used to identify the first; if the acute phase specimen IgG antibody is negative and the recovery phase is positive, it can be determined as the first infection. If the convalescent blood sample is IgG antibody titer than in the acute phase (the two specimens should not be less than 7 days apart). Collecting the second specimen for diagnosis is of great significance for dengue prevention and control, especially in non-endemic areas.

Detection of neutralizing antibodies: The plaque reduction neutralization test (PRNT) and neutralization experiments can be used to detect neutralizing antibodies in the serum, which are the most specific serological tests and have a scope of further typing. However, it requires a contained laboratory infrastructure and is time consuming, therefore, it is not deemed to be suitable for early and quick diagnosis. In this method, the levels of convalescent serum-neutralizing antibodies can be confirmed using this test.

4. Mosquito species and temporospatial distribution in Hainan Island

Hainan province, which is located in the southernmost part of China and is dominated by a tropical Marine monsoon climate, with an annual average temperature of 24.2°C, an average annual rainfall of 1684 mm, and an average relative humidity of 85%. It has the most optimum natural conditions, which are very suitable for mosquito breeding and reproduction. At the same time, under the background of the establishment of the international tourism island and the promotion of the Belt and Road policy, the tourism, trade, and personnel exchanges in Hainan province, which gives rise and provides favorable conditions for the infectious diseases mediated by mosquitoes, and further give rise to hidden dangers of disease transmission. Mosquitoes can act as the transmission mode of various viruses and can lead to the epidemics and outbreaks of various mosquito-borne infectious diseases. The mosquitoes in Hainan Province include *Ae. albopictus* (**Figure 2c, f**, & **i**), *Ae. aegypti* (**Figure 2b, e**, & **h**), *Culex tritaeniorhynchus*, *Cx. pipiens pallens*, *Cx. quinquefasciatus* (**Figure 2a, d** & **g**), *Armigeres subalbatus*, *Anopheles dirus*, *An. sinensis*, *An. tessellates*, *An. minimus*, *An. arbumbrosus*, *An. barbirostris*, *An. vagus*, *An. anthropophagus* [14–30] (some distributions were shown in **Figure 1b**).

Ae. albopictus belonging to the genus Aedes, is a small and medium-sized black mosquito species and is the vector of DENV and chikungunya virus. *Ae. albopictus* is widely distributed in Hainan Province, mainly in Sanya city [13, 14], Danzhou city [15], Qiongzhong County [14], Lingshui County [14], Lingao County [15], and Baoting County [16, 17].

Ae. aegypti also belonging to the genus Aedes, is a dark brown or black medium mosquito species and is an important vector of arboviruses such as Zika virus, DENV, yellow fever virus, and chikungunya virus. It is the dominant mosquito species of DF found in Hainan Province. *Ae. aegypti* is widely distributed in Hainan Province, mainly in Sanya city, Danzhou city, Qiongzhong County, and Lingshui County [18–20].

Although the following mosquitoes do not transmit DENF, we have listed them as a reference for any implication of other vector-borne diseases control. *Cx. tritaeniorhynchus* (**Figure 1b**) belonging to a small brown mosquito species, is an important vector of Japanese encephalitis virus in Hainan Province. They are widely distributed in Haikou city, Sanya city, Dongfang city, Qiongzhong County, and Baoting County and are dominantly found in Haikou city and Dongfang city [21, 22]. *Cx. pipiens pallens* belonging to the genus *Culex*, a hazel small and medium-sized mosquito species is the vector of epidemic Japanese encephalitis virus. It is mainly distributed in northern China and found scantly distributed in Hainan Province [15]. *Cx. quinquefasciatus* belonging to the genus of *Culex*, a medium-sized mosquito species of red brown or light brown, is a vector of various diseases such as Japanese encephalitis in Hainan Province. It is found well distributed in

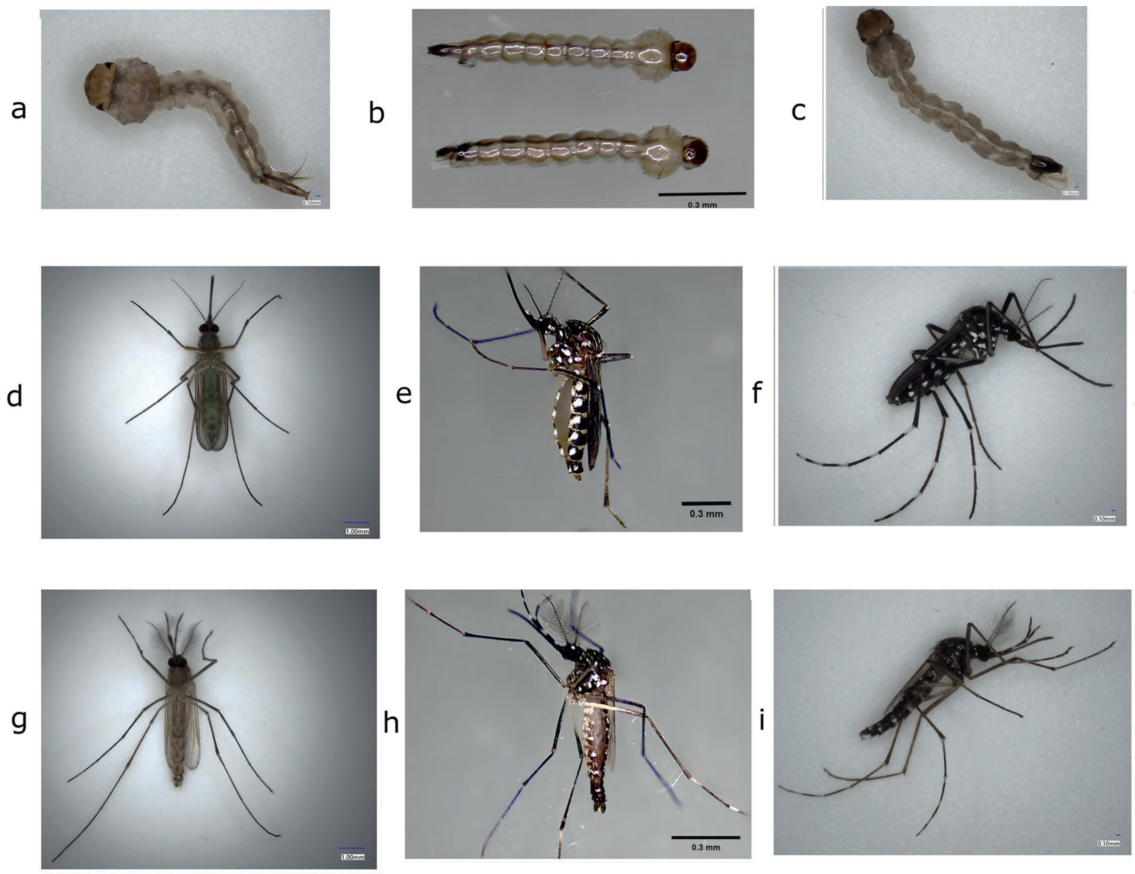

Figure 2.
Morphology of Culex quinquefasciatus*,* Aedes aegypti*, and* Aedes albopictus*. a, d, and g: fourth instar larva, female adult and male adult of* Cx. quinquefasciatus, respectively. *b, e and h: fourth instar larva, female adult and male adult of* Ae. aegypti, respectively. *c, f, and i: fourth instar larva, female adult and male adult of* Ae. albopictus, respectively. *Photos of* Cx. quinquefasciatus *and* Ae. albopictus *were kindly provided by professor Jinbao Gu from the Department of Pathogen Biology, School of Public Health, southern medical university, Guangzhou, China. Photos of* ae. Aegypti *were provided by Dr. lei Zhang, Laboratory of Tropical Veterinary Medicine and Vector Biology, School of Life Sciences, Hainan University, Haikou, China.*

Haikou city, Sanya city, Dongfang city, Qiongzhong County, and Baoting County, and is most dominantly found in Sanya city and Qiongzhong County. However, in the last few years, it has also started appearing dominantly in Haikou city [19]. *Ar. subalbatus* belonging to the subfamily Culicinae, is a large brown-black mosquito species that is the vector of epidemic B encephalitis, which is primarily distributed in Haikou, Sanya, and Baoting County [22]. *An. dirus*, belonging to the genus *Anopheles*, is a gray-brown medium-sized mosquito species that have lesser transmissibility, but can spread other diseases and can endanger health. Hainan province is the main place where *Anopheles* mosquitoes thrive, and are distributed in the areas rich in mountains, jungles, and water systems, such as Wuzhishan city, Qiongzhong County, and Baoting County in the Wuzhishan area, and Dongfang city and Danzhou city along the coastal coast, and hence they are all active areas of *Anopheles* mosquitoes [23–25]. *An. sinensis* is widely distributed in Hainan Province and is widespread in majority of the regions of the province. The areas where these mosquitoes are densely distributed include Haikou city, Sanya city, Changjiang County, Qiongzhong County, and Lingshui County [26–29]. *An. tessellates* belonging to the genus *Anopheles*, are widely distributed in Hainan Province, mainly in Haikou city, Sanya city, Wuzhishan city, Lingshui County, and Lingao County [28]. On the other hand, *An. minimus*, belonging to the genus *Anopheles*, is a tan small and medium-sized mosquito species. It mainly spreads nonviral diseases, causing serious harm. It is widely distributed in Hainan Province, mainly in Danzhou city, Qionghai city, and Tunchang County [30]. *An. arbumbrosus* belonging to the genus *Anopheles*, is found in Hainan Province, but has a small population, and is mainly found in Wenchang city, Qionghai city, Lingshui County, and Ding'an County [28]. In addition, *An. barbirostris* belonging to the genus *Anopheles*, is widely distributed in Hainan Province, mainly in Dongfang, Wenchang, Qionghai, Lingshui, and Chengmai counties [31]. However, *An. vagus* belongs to the genus *Anopheles* and is less distributed in Hainan Province [28]. *An. anthropophagus*, belonging to the genus *Anopheles*, is a gray-brown medium-sized mosquito species that have not been shown to transmit viral disease. *Anopheles* mosquito is only found in China and distributed in Haikou and Wenchang, Hainan Province [32].

5. Control and management of DF and mosquitoes with One Health perspectives

There is no effective vaccine to date to prevent DF, and most human population is susceptible to the disease. After recovery from infection caused by one serotype, individuals have lifelong immunity to that particular serotype of the virus but lack completely against the other three serotypes. Thus, people living in DF endemic areas may develop infections with DENV type 4 as well in future.

Since 1987, Hainan had spent three years comprehensively controlling the *Ae. aegypti* mosquitos. In 1987, it was in the stage of full implementation planning. Where *Ae. aegypti* mosquitoes exist, measures were carefully implemented according to local environmental and social conditions, and it was required that the Breteau index be controlled below 5 by the end of the year. In 1988, preventive measures and regular management continued to be implemented. By the end of the year, all villages (neighborhood committees, farms) having *Ae. aegypti* mosquitoes had the Breteau index below 5. In 1989, it was the stage of consolidation and validation of the mosquito management. By the end of the year, the Breteau index of *Ae. aegypti* in villages (neighborhood committees, farm companies) was kept below 1. In addition, from 1987 to 1989, two representative villages from each city and county were selected to monitor DF and *Ae. aegypti* mosquitoes annually. The main technical measures in this plan were to adhere to the comprehensive control of mosquitoes in both larval and adult stages, and the specific measures were as follows.

Mosquito larval control: Basic measures include pouring out water in the water tanks, changing the water once every 3 ~ 5 days, adding a lid to some water tanks, and removal of small stagnant water indoors and outdoors. Biological mosquito control includes that water tank was stocked with mosquito fish, *Macropodus opercularis (Syn. M. chinensis)* or *Silurus asotus*, with 1 ~ 2 fish in each tank. Tanks were checked frequently after stocking. For fish that escaped or died, it was necessary to replace them in time. *Bacillus thuringiensis* was placed in water tanks or wells and towers every 7 days.

Adult mosquito Control: Pesticides, such as dichlorvos, fenitrothion, and others, were chosen for spraying so as to kill adult mosquitoes. Villages with a Breteau index of more than 20 (neighborhood committees, farm companies) were subjected to spraying with pesticides twice in February ~ April 1987, each time with an interval of two weeks. The spraying dose was 40 ~ 60 mg of 80% dichlorvos emulsion or

50% chlorvos emulsion per cubic meter room. Doors and windows have to be closed when spraying. During the prevention and control period, once DF occurs, pesticides should be sprayed on the epidemic points or epidemic areas in time to kill poisonous mosquitoes.

In One Health perspective, the health and lifecycle of the zoonotic disease vectors should be explicitly considered alongside the human environment, demographics, and interaction with the zoonotic host vectors. In addition, continuous monitoring from epidemiological point of view has to be taken into consideration [33]. In addition to the increasing range of DENV infection and higher number of infected persons, the increasing frequency of international exchanges, elevation of the urban population, and the lack of effective control measures leading to the deterioration of urban environment and rise of mosquito growth, also needs to be further studied. And these factors along with geographical distribution of DENV make the presence of mosquito transmission vectors even wider.

6. Integrated control and management strategies of DF with One Health perspectives

Certain biological and synthetic control strategies can balance and manage the social, economic, ecological, and health benefits, which has to be carried out in a timely manner and help in combatting the disease in a better manner.

Additionally, carrying out timely and effective vector biological monitoring, practical risk assessment, control, planning, and preparation of vector biological and related diseases, orderly selection of environmentally friendly control technology and comprehensive measures would directly help in eradication. The following six main components of mosquito prevention and control in Hainan Island are as follows:

1. At the time of outbreak, epidemic sites are the core of prevention and control, hence both mosquitoes and their breeding sites have to be in control and managed accordingly.

2. Strengthening and creating awareness among the masses would also contribute to the prevention and elimination of mosquito-borne diseases. Educating the public on the effects of the diseases would create an awareness of the disease.

3. Improving environmental sanitation conditions, removing mosquito breeding sites, and reducing stationary water in the pool and logged water in containers can be useful. Furthermore, rational use of pesticides may be necessary.

4. Establishing and improving the *Aedes* mosquito monitoring network to improve the prevention and control capacity and training the technical personnel at all levels.

5. In addition to the above, special focus on special industries such as flower and bird markets, speeding up the construction of healthy cities, strengthening vector monitoring, and strengthening customs inspection and quarantine measures are a few important strategies to successfully prevent and control the spread of DF.

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Conflict of interest

The authors declare no conflict of interest.

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