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SITUATION OF DENGUE FEVER, CHIKUNGUNYA, ZIKA AND INTEGRATED SENTINEL SURVEILLANCE OF THE DISEASES IN VIETNAM

Luong Minh Tan
Vietnam

53rd Master of Public Health/ International Course in Health Development
19 September 2016 - 8 September 2017

KIT (ROYAL TROPICAL INSTITUTE)
Health Education/
Vrije Universiteit Amsterdam

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Signature:..

53rd Master of Public Health/ International Course in Health Development (MPH/ICHD)
19 September 2016 - 8 September 2017
KIT (Royal Tropical Institute)/ Vrije Universiteit Amsterdam
Amsterdam, The Netherlands
September 2017

Organised by:
KIT (Royal Tropical Institute) Health Unit
Amsterdam, The Netherlands

In co-operation with:
Vrije Universiteit Amsterdam/ Free University of Amsterdam (VU)
Amsterdam, The Netherlands

Acknowledgment

The thesis becomes a reality with the kind supports of helps of several individuals and organizations. I would like to express my sincere thanks to all of them.

At the first place, I want to thank The Royal Tropical Institute (KIT) and Hanoi University of Public Health for organizing the Master Of Public Health course where I have experienced the cultural exchange and develop professional understanding of public health and its application in my work.

I would like to express my special thanks and gratitude to my thesis supervisor and backstopper, Assoc. Prof. Tran Huu Bich and Dr. Lisanne Gerstel, for their great help and professional expertise in this study.

I highly appreciate the financial support of Greater Mekong Sub-region Capacity Building for HIV/AIDS Prevention Project for me to attend the Master course.

I would like to thank the National Institute of Hygiene and Epidemiology for dispatching me to join the course in the Netherland and giving me the access to some materials to complete this thesis.

I also extend the appreciation to my colleagues for their endeavor to fulfil the work when I was leaving for the study.

Thank you!

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List of abbreviations

Abbreviations	Explanation
Ae	Aedes
CHIKV	Chikungunya virus
DF	Dengue fever
DENV	Dengue virus
ELISA	Enzyme-linked immunosorbent assay
ISS	Integrated Sentinel Surveillance
RT-PCR	Reverse transcription – polymerase chain reaction
WHO	World Health Organization
ZIKV	Zika virus

Abstract

BACKGROUND: Vietnam has a high burden of dengue fever (DF) and recently face the emergence of zika. The Ministry of Health issued a national guideline for integrated sentinel surveillance (ISS) of DF, chikungunya and zika that is based on the current DF sentinel surveillance system. The thesis is to provide more evidence on characteristics of vectors, incidence and distribution of the diseases and the points for improvement of current DF surveillance for better implementation of the ISS of three diseases.

METHODS: Literature review was conducted with peer-reviewed articles, reports and gray literatures in English and Vietnamese were used to complete the thesis. The criteria for assessment of current DF surveillance system was develop by World Health Organization.

FINDINGS: *Aedes aegypti* is the primary vector of the three diseases while *Aedes albopictus* plays certain role in DF and chikungunya transmission. *Aedes malayensis* is a potential vector of DF and chikungunya but its distribution is unknown in Vietnam. The distribution of the vectors helps explain the pattern of the diseases. DF had the highest incidence of 248, 314 and 330 per 100.000 population in the north, central and the south, respectively. Chikungunya and zika remain little known with the various proportions between studies using different laboratory tests. The weaknesses of current DF surveillance were in timeliness and completeness of case notification.

CONCLUSIONS: The ISS of the three diseases should base on the distribution of the diseases and active vector surveillance should be added to enable the ability to predict the occurrence of outbreak in human. The weaknesses of current DF surveillance should be overcome to avoid missing cases and late response.

Key words: Dengue, chikungunya, zika, integrated surveillance, Vietnam

Full name: Luong Minh Tan

Country: Vietnam

Word count: 11,865

Introduction

I earned the bachelor of public health degree in Hanoi University of Public Health in 2010. Since then I have been working for the National Institute of Hygiene and Epidemiology in the Department of International Cooperation. I participated in several research on emerging and re-emerging infectious diseases.

It is a great opportunity for me to move one step further in my education by attending the Master of Public Health/International Course in Health Development at the Royal Tropical Institute in the Netherland. I have got deeper understanding in public health in many areas including communicable diseases prevention and control. I decided to pick dengue fever, chikungunya and zika as my thesis topic because it is relevant to my work and also the priority health problems in Vietnam.

The thesis includes 5 parts:

- The background information about Vietnam and relevant information for study
- Chapter 1: Study overview consists of problem statement, definitions, study questions, study objectives and methodology.
- Chapter 2: Study findings corresponding to three objectives.
- Chapter 3: Discussions
- Chapter 4: Conclusions and recommendations

BACKGROUND

The Socialist Republic of Vietnam is located in Southeast Asia that borders with China in the North, Lao People's Democratic Republic and Cambodia in the West, the Gulf of Thailand in the South and Pacific Sea in the East.

The country has 63 cities or provinces, which are divided into 4 main regions including the North with 25 provinces (Hanoi capital is located in this region), the Central with 14 provinces, the Central Highlands with 5 provinces and the South with 19 provinces. The preventive health system is also structured following the regions with 4 leading institutions responsible for disease prevention and control and the network of provincial, district medicine centers and commune health centers in the whole country.

Vietnam is located in tropical and temperate zone with high temperature and humidity [1]. It is one of the countries most affected by climate change that the average temperature in the last 50 years increased by 0.5°C nationwide and up to 1°C in northern region with wider range between minimum and maximum temperature [2]. Hot and sunny weather have increased dramatically [2]. This accelerates the development cycle of mosquitoes and lead to the emerging of mosquito-borne diseases.

Figure 1. Vietnam in Southeast Asia

Source: Internet

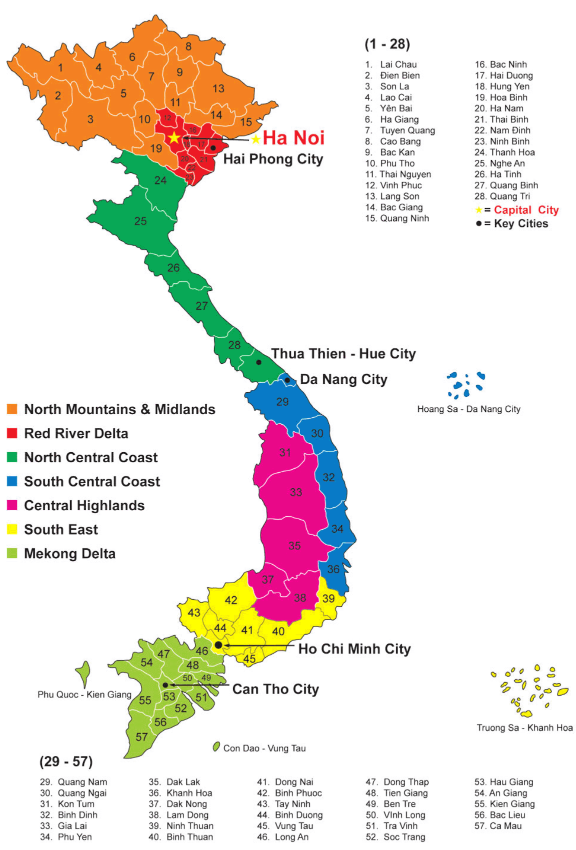

Figure 2. Map of Vietnam

Source: Internet

The population of Vietnam is about 94 million people, which is in "demographic window of opportunity" when nearly 70% of total population aged between 15-64 years old. It means that two or more people in working age are responsible for only one dependent person (children, elderly) [3]. This also facilitates the migration from rural to urban areas where migrant workers with low education face the difficulties in access to health care services while expose more to diseases like in a recent outbreak of dengue fever (DF) in Hanoi capital with more than 8000 cases in the first 6 months of 2017. The DF cases are more likely to occur in construction sites and on the migrant workers [4]. 84% of the hospitalized cases of DF included in another study in Hanoi were migrants from rural areas [5].

DF sentinel surveillance system was established in 1999 at the same time with the National guideline for DF and dengue hemorrhagic fever surveillance, prevention and control [6]. The surveillance was conducted in 7 provinces in Vietnam (1-2 provinces in each region). It was combination of hospital-based and community-based surveillance, 1 district hospital and 1 commune per province were selected as sentinel surveillance sites. The DF cases were notified by the hospitals or commune health centers to provincial preventive medicine centers and then to regional institute in charge of disease prevention and control. An emergency investigation team would be deployed to collect information, specimen and implement control measures if necessary [7].

Vietnam has become a lower middle-income country with the gross domestic product (GDP) per capita per year of about 2,200 US dollar in 2015, however, there is a remarkable disparity between urban and rural areas [8]. Due to the increase in the income, Vietnam is no longer eligible for low-interest funds that have contributed greatly for the activities to control infectious diseases leading to the interruption of some important national programs including dengue control program [6].

CHAPTER 1: STUDY OVERVIEW

1.1 Problem statement and justifications

There are a number of arboviral diseases spreading through *Aedes* mosquitoes like dengue fever (DF), chikungunya, Rift valley fever, yellow fever and zika [9]. However, only DF and yellow fever have been put in the list of communicable diseases with mandatory notification within 24 hours in the circular number 54/2015/TTBYT of Ministry of Health.

The MOH has issued a guideline for the integrated sentinel surveillance (ISS) of DF, chikungunya and zika, which bases on the existing surveillance system for DF due to the emergence of zika and the similarity in vector and clinical symptoms of the three diseases [10]. To be in line with the policy and to provide the evidence for the implementation of the guideline, this thesis will focus on the three diseases and *Aedes* mosquitoes.

1.1.1 Dengue fever

DF is mainly transmitted by *Ae. aegypti* and *Ae. albopictus*, which is the most common infection circulating in 128 countries and puts approximately 4 billion people at risk around the world [11, 12]. DF presents throughout the tropical areas and is spreading to other areas due to climate change and increasing adaptability and proliferation of the vectors in different climatic regions [13]. The Global burden of disease study in 2013 shows the sharp increase in the number of DF symptomatic cases worldwide from 8.3 million in 1990 to 58.4 million cases in 2013 [14]. Another study using geostatistical methods estimates higher number of apparent cases annually, 96 million [15]. The annual number of fatality cases ranged between 9000 and 22,000 [6, 14]. About 1.14 million DALYs per year were caused by premature mortality and disability due to moderate, severe and post-dengue chronic fatigue [14]. Another study shows that DF caused enormous global economic burden with the loss of 8.9 billion USD in 2013 [16]. The cost was computed with medical, non-medical cost and indirect costs related to time lost due to illness and time of caretakers. The most affected areas are Southeast Asia, Central Africa and South America in low and middle-income countries (figure 2) [14, 16]. Up to present, only one dengue vaccine has been licensed in some countries for people aged between 9-45 living in endemic regions [17].

Southeast Asia is the area with highest incidence rate of DF that is up to more than 3,000 per 100,000 person-years in 2013 [14]. An analysis of Shepard et al. based on data from countries in Southeast Asia from 2001 to 2010 shows that there were about 2.9 million cases of DF and nearly 6 thousand deaths due to the infection every year [18]. The report also reveals the enormous burden of DF that costs an annual average of 950 million USD for the 12 countries [18]. This might underestimate the economic burden of DF in Southeast Asia because the authors did not include the cost of prevention and vector control as well as long-term sequelaes of DF. At household level, the cost can cause catastrophe because of high cost treatment that is not affordable for many people living below poverty line as mentioned in a study in Cambodia [19].

Although Vietnamese government has put great effort to control DF by vector management, improvement in quality of care that help reduce the mortality rate to less than 1 per 1000 cases [20], the country still remains highest number of DF cases in Southeast Asia with about 76 thousand apparent cases per year [18]. DF also creates economic burden for the households that the treatment course costs about US$170 including direct and indirect costs. The amount of money is equivalent to 36% of annual personal income of people in the lowest economic quartile [21].

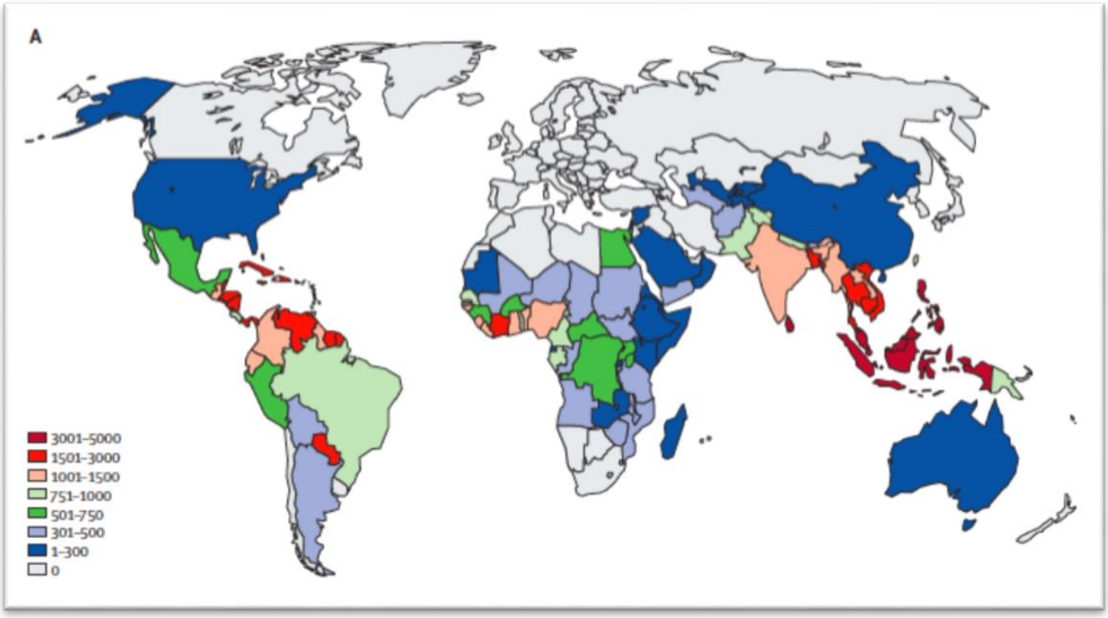

Figure 3. Dengue incidence rate per 100,000 person-years in 2013 [16]

1.1.2 Chikungunya

Chikungunya first occurred in Caribbean and caused nearly 350 thousand suspected cases in Western Hemisphere since 2013 [12]. Chikungunya is circulating in more than 60 countries in Americas, Europe, Africa and Asia [13]. Both *Ae. aegypti* and *Ae. albopictus* are responsible for the transmission of chikungunya but with different levels due to the ability to survive overwinter and biting habit of the mosquitoes [12, 13, 22].

The disease also shares some clinical symptoms and signs with dengue that chikungunya is usually misdiagnosed where dengue is emerging [22]. Chikungunya is not a fatal disease but the post-infection sequelaes may cause significant reduction in quality of life. A systematic review in 2017 shows the most common sequelaes of chikungunya infection including persisted arthralgia, alopecia and depression. The infection during pregnancy may lead to the dysfunction of neurocognition of the infants in early childhood [23]. Chikungunya presents in 94 countries where 1.3 billion people are living in areas at risk of chikungunya infection. Figure 4 shows that chikungunya mainly circulates in Africa and Asia with more intensive records since its first identification in Africa in 1952 [24]. There has been no commercial vaccine and specific treatment for chikungunya infection [12]

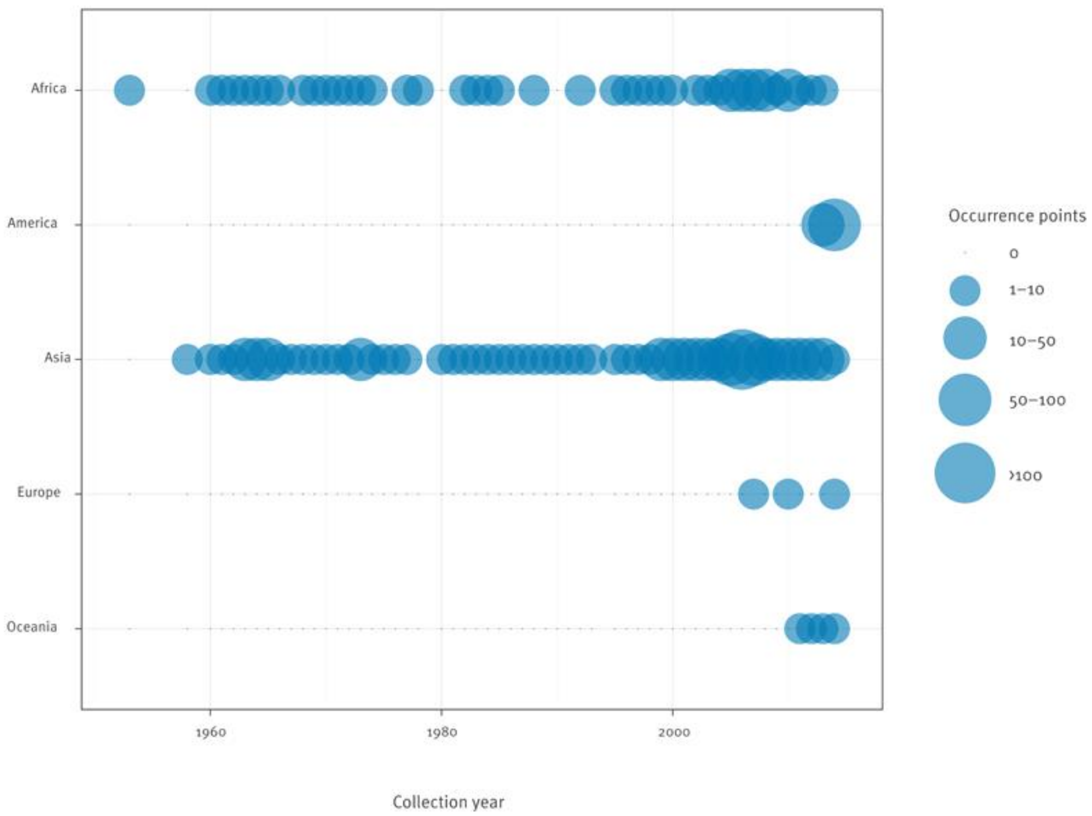

Figure 4. Chikungunya virus transmission occurrence points per continents, 1952-2015 [24]

80% of Asian countries reported the occurrence of chikungunya that is well documented for some countries in South and South-east Asia like in Singapore, Thailand, Myanmar, Philippines, India and Sri Lanka [24]. Although there has not been any systematic review to reveal the prevalence of chikungunya, some studies in different continents show high prevalence of the infection. In Tanzania, 12.9% fever patients were IgM-positive with chikungunya [25]. The figure is much higher in India where the prevalence of chikungunya-like in the community was 22.3% [26]. However, the criteria for identifying chikungunya cases in India were simple that all patients with fever and joint pain were included. This might explain the significant disparity between Tanzania and India. The evidence from La Reunion Island shows that in appropriate conditions like high density of human and mosquito population, chikungunya can cause outbreaks with hundred thousand people infected [26].

In South-east Asia, more than 1000 people in Singapore were infected in an outbreak in 2008 and nearly 46 thousand cases reported in Thailand in 2009 [27]. Chikungunya is also recorded in Cambodia with 2% of pediatric patients under 15 years old admitted to hospitals due to acute meningo-encephalitis [28]. However, there is little evidence about chikungunya in Vietnam.

1.1.2.1 Zika

Zika is mainly transmitted by *Ae. aegypti* [29]. The infection is more complicated and difficult to control because it is also possibly transmitted through sexual contact and only 20% of infected cases manifested with clear clinical symptoms [29, 30]. Zika was first identified in 1947 among monkeys in Uganda by surveillance system of yellow fever and among human in

1952 in Uganda and Tanzania [29]. Recently, Zika is spreading more rapidly across the world that WHO declared the Public Health Emergency of International Concern [29]. The current global epidemic started in 2015 in Brazil with nearly 1.5 million people infected in this country as cited by Wiwanitkit [31]. An analysis shows that 39 countries have been identified with imported cases of zika within only 44 weeks after the introduction of zika in Brazil [32]. Zika shares similar symptoms with dengue that are usually mild [29]. Because of the mild symptoms, many cases do not seek medical care in health facilities, so the reported cases may underestimate the real situation of zika. The literature review of WHO indicates that zika infection during pregnancy can cause abnormal development of brain of the fetus including microcephaly [29, 30]. It can also cause Guillain-Barré syndrome, an autoimmune syndrome that damages the nerve cells and leads to muscle weakness, paralysis or even death [12]. Since the knowledge about zika is limited, the panic of the disease can cause crisis in the community like the case in 2016 that 150 health experts made a call to postpone or move Rio Olympics to other location due to the fear that the international sport event can accelerate the spread of zika virus among visitors to other countries. There has been no specific treatment and zika commercial vaccine available [13].

Although there has not been major outbreak took place in Southeast Asia, zika cases were reported in Cambodia, Thailand, Indonesia, Philippines and Vietnam as cited by Enna et al. [30]. Thailand and Cambodia share the borderline and also the circulation of zika strains that some cases of travelers visited these countries were infected with zika strains of Cambodia [31]. In Indonesia, 3.1% of patients with fever admitted to hospitals were serologically positive with zika though there has been no outbreak recorded in this country [30].

In Vietnam, up to December 2016, the sentinel surveillance system reported 191 cumulative cases of zika confirmed by laboratory. All of the cases occurred in the South of Vietnam and mainly in Hochiminh city with 169 cases [33]. There is a big question about the possibility of large zika outbreak in the future in Vietnam where the vector exists and zika virus is circulating.

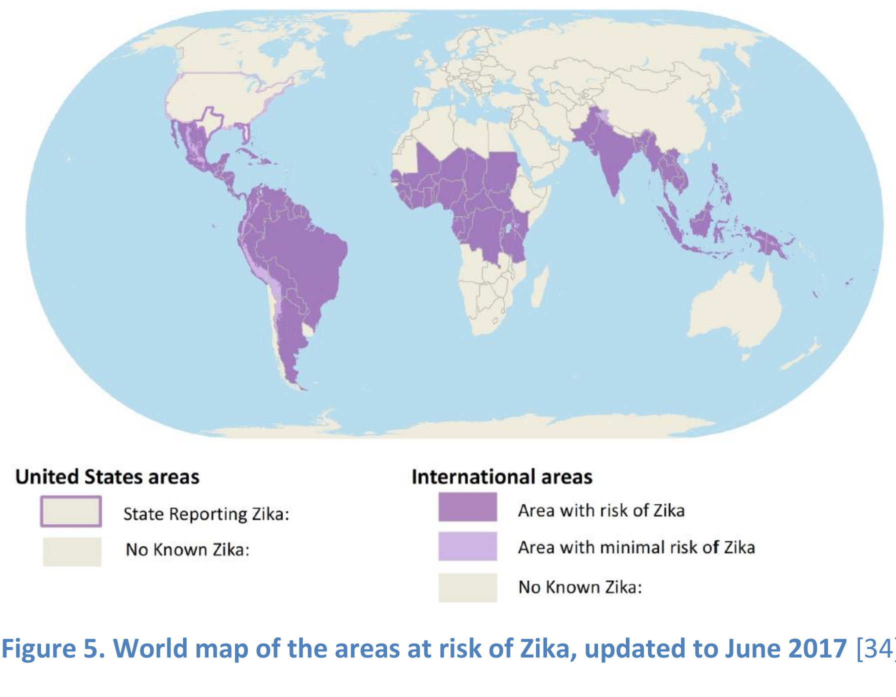

Figure 5. World map of the areas at risk of Zika, updated to June 2017 [34]

Many studies have been conducted to reveal the situation of DF in Vietnam including the incidence, sero-prevalence [35–38]. The studies also indicate the factors associated with DF outbreaks including individual factors like lack of awareness about DF; poor living conditions such as unhygienic housing, not good sewage management, high population density; high density of vectors; and some climatic factors such as high temperature, high humidity, high rainfall and short sunshine duration [39–42]. However, the evidence is insufficient for the implementation of the ISS of DF, chikungunya and zika due to the lack of evidence on the vectors (*Aedes* mosquitoes), the incidence and distribution of the latter two diseases and the evaluation of the weakness of the existing DF surveillance system. Therefore, this thesis will look at the evidence for those gaps.

1.2 Definitions and terminology

Dengue fever manifests the symptoms between 4-10 days after a bite of an infected mosquito. The symptoms include high fever, severe headache, muscle pain, joint pain, nausea, vomiting and rash [13]. It can progress to severe dengue (dengue hemorrhagic fever) or dengue shock syndrome that the symptoms may include temperature decrease, severe abdominal pain, rapid breathing, bleeding gums, blood in vomit etc. Critical medical cares are required since the symptoms occur to prevent complications and death [13].

Chikungunya causes the disease on human with primary symptom of severe joint pain accompanied with headache, nausea, fatigue and rash [12, 13]. Although the infection is often mild and may go unrecognized, it can cause persisted arthritic or death among elderly people [13]**.**

Zika is a flavivirus originated in central Africa [12]. There are three transmission modes of zika virus, the first and also predominant one is through mosquito bite; the next possible way is sexual transmission between uninfected and infected people and the last one is mother-to-child transmission [12]. The infection is normally mild with low fever, rash, conjunctivitis and joint pain that can last for several days to weeks or months [12].

Table 1. Summary of clinical features of DF, Chikungunya and Zika [43]

Features	Dengue fever	Chikungunya	Zika
Fever	+++	+++	++
Rash	+	++	+++
Conjunctivitis	-	-	++
Arthralgia	+	+++	++
Myalgia	++	+	+
Headache	++	++	+
Hemorrhage	++	-	-
Shock	+	-	-

***Aedes* mosquitoes transmitting DF, Chikungunya and Zika:**

There are a number of species of *Aedes* mosquito, but some play important role in transmission of DF, chikungunya and zika [13, 44]. The most medically important subgenus of *Aedes* mosquito is *Stegomyia* with 128 species, which includes two most significant vectors of many arboviral diseases (*Ae. aegypti* and *Ae. albopictus*)[45]. The other species of *Stegomyia* subgenus will be identified and described in the main content of this thesis if they exist in Vietnam.

Characteristics of mosquito species

The following characteristics will be examined: geographical and seasonal distribution, breeding sites, biting behaviors, disease transmission capacity and insecticide susceptibility. Other characteristics will be added if they are available in the literatures.

ISS of DF, Chikungunya and zika in Vietnam

Disease surveillance is defined by WHO as "the ongoing and systematic collection, analysis, and interpretation of health data in the process of describing and monitoring a health event"[46]. Sentinel surveillance is implemented in high risk groups or areas to monitor the trend of diseases and predict epidemic in the country.

The recently issued guideline (also called integrated sentinel surveillance - ISS) attached with decision number 3091/QD-BYT dated on 03/07/2017 of the MOH is to integrate chikungunya and zika into the existing DF sentinel surveillance system. All cases in sentinel surveillance sites that meet case definition will be notified, collected epidemiological information, specimen and tested for DF, chikungunya and zika. The data will be analysed and interpreted for decision making at all level of health system [10].

1.3 Study questions

1) What are the characteristics of *Aedes* mosquitoes of *Stegomyia* subgenus in Vietnam?
2) What is the incidence and distribution of DF, chikungunya and zika in Vietnam?
3) Could the current responses for DF would be sufficient the ISS of the three diseases?

1.4 Study objectives

1) To describe the characteristics of *Aedes* mosquitoes of *Stegomyia* subgenus in Vietnam
2) To describe the incidence and distribution including trend of DF, chikungunya and zika in Vietnam
3) To identify weaknesses of DF surveillance system and implication for the ISS of DF, chikungunya and zika

1.5 Methodology

The thesis was complete by literature review with steps from topic identification to writing a literature review developed by Helen Mongan-Rallis (2006) [47].

The literatures were identified by searching through the search engines including VU library, PubMed, Google, Google Scholar and database of Health Information Agency of Ministry of Health (where most of articles published in national medical journals in Vietnamese, PhD thesis, books are documented); websites of Ministry of Health and related departments for relevant policies. Main key words include Aedes mosquito, Stegomyia subgenus, dengue fever, chikungunya, zika, integrated surveillance and corresponding key words in Vietnamese (the list of key words and their combination in annex 1). Peer-reviewed articles, published/unpublished reports and gray literatures in the last 15 years were used to complete the thesis.

The Protocol of WHO for the Assessment of National Communicable Disease Surveillance and Response Systems will be used to assess the current surveillance system for the ISS of DF, chikungunya and zika based on the available literatures [48]. The assessment includes the following core components: priority diseases, structure, process and capacity for surveillance and response, output, integration/coordination/synergy, laboratories, health mapping, and communication.

CHAPTER 2: STUDY FINDINGS

Totally, 209 literatures were found from various sources of document including peer-reviewed papers, published and unpublished reports. Abstract scans help reduce the number of paper to be reviewed. Finally, 83 documents were used to provide the evidence for the three objectives in the next sub-sections.

2.1 The characteristics of *Aedes* mosquitoes of *Stegomyia* subgenus in Vietnam

2.1.1 Species of Aedes mosquito, Stegomyia subgenus in Vietnam

According to the review of the National Institute of Malariology, Parasitology and Entomology, there were 255 mosquito species of 21 genuses, 42 subgenuses. *Culicidae* family consists of 88 species of *Aedini* tribe, 43 species of *Culicini* tribe and 56 species of other tribes [49]. *Stegomyia* is a subgenus of *Aedini* tribe.

Up to 2015, among 128 species of *Stegomyia* subgenus, only 10 species have been reported in Vietnam including *Ae. aegypti*, *Ae. albopictus*, *Ae. annandalei, Ae. desmotes, Ae. gardnerii imitator, Ae. malayensis, Ae. mediopunctatus, Ae. patriciae, Ae. pseudalbopictus, Ae. w-albus* [49]. Other potential competent of DF, chikungunya and zika like *Ae. hensilli*, *Ae. albolateralis, Ae. africanus, Ae. scutellaris etc.* have not been reported in Vietnam [45, 50, 51]. Among those, *Ae. aegypti*, *Ae. albopictus* are well known as main vectors of the three diseases.

The following sections will focus on the characteristics (geographical and seasonal distribution, breeding sites, biting behaviors, disease transmission capacity, insecticide susceptibility) of the 10 mosquito species based on the available literatures.

2.1.2 Characteristics of Ae. aegypti

- ***Distribution of Ae. aegypti:***

Ae. aegypti (Yellow Fever Mosquito) is the most popular Aedes species around the world [44]. It is reported widely in tropical (Africa), subtropical regions (Southeast Asia, South America, the Middle East, the Pacific and Northern Australia) and recently reported in Europe [52].

Ae. aegypti has been imported into Vietnam since 1915 in the south and quickly replaced *Ae. albopictus* to become the major vector of DF in urban areas [53].

The evidence shows that *Ae. aegypti* is predominant in the south and central (figure 5) [54, 55]. The proportion of adult *Ae. aegypti* collected in the field of southern provinces was about 63%-67.5% (nearly doubled the number in 2003, 37.5% [56]) while it was lower in the north, particularly during winter [57, 58]. This is due to the difference in local climate that the temperature is low during the winter, *Ae. aegypti* is not able to overwinter and becomes less popular in comparison with *Ae. albopictus* in the north [59, 60]. This climatic barrier will be weakened due to the increasing adaptability of the mosquito and global warming that makes the winter warmer [2].

The mosquito used to lived mostly in urban areas, but now expands to rural areas [58, 61].

This species is less common in mountainous regions with higher altitude. A study in 11 northern mountainous provinces shows that *Ae. aegypti* is reported in only one surveillance site in rural area of Ha Giang province [62]. Another study in the Central also supports that *Ae.*

aegypti accounts for just 30% of mosquito in mountainous communes while it dominates the delta and coastal communes of the province [63].

Ae. aegypti also distributes differently between seasons. A study in 5 provinces in central and the south indicates that *Ae. aegypti* population boomed in dry-hot season from May when density index (DI) increased up to 25 larvae or 1.35 adult female mosquitoes per household due to the water storage habit of the local people, especially in areas with unstable water supply [64]. Although these studies were conducted in the central and the south, the result may reflect for the whole countries because of the similar climate pattern that is even more obvious in the north where it is much colder during wet-cool season causing more reduction in survival rate of mosquitoes.

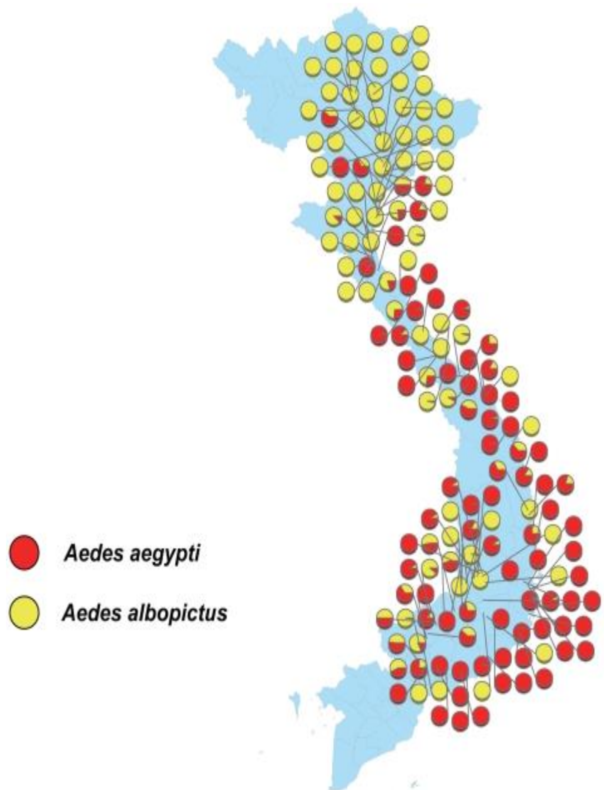

Figure 6. Larvae distribution of *Aedes aegypti* and *Aedes albopictus* [54]

- ***Breeding sites of Ae. aegypti***

Ae. aegypti lays eggs in artificial containers (e.g. used tires, water tank), which close to human and/or used by human in daily life that makes them more difficult to be controlled by standard spraying techniques [12, 58]. Besides, the mosquito is adapting to expand their dispersal to more temperate regions by looking for appropriate water containers, which partially help them survive through winter. *Ae. aegypti* prefers laying eggs in concrete tanks than other containers during winter because the tanks can keep the water 4^{o}C warmer than outside temperature [65]. Concrete tanks are very popular in rural and suburb areas (Figure 6) [65].

Figure 7. Underground and Semi-underground concrete water tanks in Vietnam [65]

- ***Biting behaviors of Ae. aegypti***

The mosquito has evolved domestic behaviors like feeding and resting indoor that make them more efficient to survive and transmit the diseases from human to human [66]. *Ae. aegypti* seeks for blood meals mostly during the day and more likely indoor (90.9%) [13]**.** *Ae. aegypti* remains its typical behaviors of feeding on human [58, 61]. A study in Binh Dinh province indicates that *Ae. aegypti* prefers resting on clothes and bed net in bedroom (78%) [58]. Thus, residual spraying on the wall would be ineffective to control the vector.

- ***Disease transmission capacity of Ae. aegypti***

Ae. aegypti is well known as the primary vector of DF and a common vector for other arboviral diseases including chikungunya, zika, yellow fever, West Nile fever [13, 44, 67].

- ***Insecticide susceptibility of Ae. aegypti***

The insecticides used to be very effective to control mosquito. But many pyrethroid insecticides were no longer effective with *Ae. aegypti* including alphacypermethrin, deltamethrin, lambdacyhalothrin, permethrin and DDT in 2012 [68]. *Ae. aegypti* was still susceptible to malathion [68, 69]. Other vector control measures should be in place when insecticides become ineffective on the mosquitoes.

- ***Other characteristic of of Ae. aegypti***

The survivorship of mosquitoes to the age when they are able to transmit diseases (12 days) is very important driver of disease epidemic [53]. There is a hypothesis that mosquito's life would be shortened by the virus infection. It has been disproved by a study in Vietnam that there was no difference in survival rate up to 12 days between dengue infected and non-infected *Ae. aegypti,* regardless the serotypes of the virus [70, 71]. The competence of the mosquito in disease transmission is not influenced by dengue virus infection in short term (12 days), however, there has not been evidence for the longer-term survivorship since the mosquitoes can live longer than 12 days [72].

Ae. aegypti is also seen to be more efficient to reproduce and live longer than it was 15 years ago that makes the vector more efficient to transmit the diseases. Under laboratory conditions (28^{o}C and 85% humidity), one female mosquito can lay 105 eggs per gornotrophic cycle (number of day the mosquito takes to lay eggs after having a blood meal) [72], which is much higher than in the past (78.6 eggs) [73]. Besides, 75%-98% *Ae. aegypti* larvae can develop to adult mosquito depending on the density of larvae [72], which is significantly higher than it was 15 years ago (59.7%) [73]. After turning to mosquito, more than 73% of adult female mosquito can live longer than 25 days (average of 33.84 days) [72]. The disease outbreaks are more likely to occur if the mosquitoes live longer, lay more eggs and survive with higher rate that make more chance for vectors to be infected with viruses and transmit the pathogens to the hosts (disease dynamic).

In conclusion, *Ae. aegypti* is more predominant in urban areas in the south and central of Vietnam during dry-hot season starting in May. It prefers breeding in artificial water containers close to human. The mosquito is more likely to feed on human during the day and indoor. Most of insecticide is no longer effective with this species except malathion. It tends to live longer and lay more eggs than it did in the past.

2.1.3 Characteristics of Ae. albopictus

- ***Distribution of Ae. albopictus***

Ae. albopictus (Asian Tiger Mosquito) is more predominant in temperate regions due to its ability to survive over the winter with the temperature tolerance of the eggs up to -10^{o}C [59]. It is currently of more concern because of its potential to expand beyond the climatic boundary to invade and import the diseases where *Ae. aegypti* is absent. The mosquito is found in some countries in Europe, Middle East, South Asia, North and Central America and Caribbean [44].

Ae. albopictus is living mostly in the north and north-central of Vietnam (figure 5) that can be explained by the recognized ability to overwinter of *Ae. albopictus* [59, 60]. A study in Hanoi shows that about 74% of mosquitoes collected from the field were *Ae. albopictus* [61].

Ae. albopictus is previously more common in rural areas and now expanding their habitats to urban areas. They were abundant in some urban and suburb districts of Hanoi where 63-85% of mosquito samples are *Ae. albopictus* [58, 61, 74]. The observation in Thua Thien Hue province shows that *Ae. albopictus* was absent in coastal regions of this province [63].

The surveillance in northern mountainous region shows that *Ae. albopictus* almost dominates this region where *Ae. aegypti* is nearly absent [62]. The larvae density index ranges from 6.0 to 44.2 larvaes per household [62].

- ***Breeding sites of Ae. albopictus***

This species prefers laying eggs in natural water containers like bamboo tree hole, coconut shells and sometimes artificial containers like used tires, bonsai container [64]. Thus, the number of mosquito increases quickly in rainy season when the containers are filled by rainwater [64]. The density index was 0.29 adult female mosquito per household during rainy season in 5 provinces [64]. This number was still much lower than *Ae. aegypti* (1.35 mosquitoes per household).

- ***Biting behaviors of Ae. albopictus***

The female mosquitoes are aggressive [44]. *Ae. albopictus* has a wider range of hosts rather than human and mostly feed outdoor during the day (93.9%) [58]. This may decrease human-to-human disease transmission but increase the risk of zoonotic diseases at the same time [75].

- ***Disease transmission capacity of Ae. albopictus***

Ae. albopictus is clearly known to be vector of DF, chikungunya, dirofilarial worms [75, 76]. In experimental conditions, the mosquito shows the ability to transmit yellow fever, Rift Valley fever, Japanese encephalitis, West Nile fever [77, 78]. Although *Ae. albopictus* is susceptible to zika virus, the ability to transmit zika is still limited because the virus cannot reach the saliva glands of the mosquito efficiently [44]. Thus, zika outbreak is less likely to occur in rural and mountainous areas where *Ae. albopictus* is predominant. It is the fact that recent zika cases are mostly reported in Ho Chi Minh city (76%), the biggest municipality in the south of Vietnam [79].

Ae. albopictus is considered as secondary vector of DF due to its weaker ability to transmit the virus, just about 70% of *Ae. albopictus* were found to have infectious saliva with virus [71]. Additionally, *Ae. albopictus* is more likely to have infectious saliva by the infection with DENV serotype 1 (DENV-1) and 3 (DENV-3) than serotype 2 (DENV-2) and 4 (DENV-4) [71]. This helps explain the co-circulation of all four serotypes where *Ae. aegypti* is predominant [80, 81] while the serotypes interchange to cause outbreaks where *Ae. albopictus* is more popular as cited by Do Thi Thanh Toan et al. in 2014 [82].

Besides, this species is less likely to transmit diseases from human-to-human because the infected mosquitoes can feed on other animals that interrupts the direct transmission cycle (human-vector-human) [58]. In the other words, *Ae. albopictus* does not play as important role as *Ae. aegypti* in disease transmission. A study in Hanoi reports significantly stronger correlation between the density of *Ae. aegypti* and number of patients recorded during the outbreaks while no correlation was found with *Ae. albopictus* [83].

- ***Insecticide susceptibility of Ae. albopictus***

Ae. albopictus was still susceptible but increased tolerance to pyrethroid insecticides (alphacypermethrin, deltamethrin, lambdacyhalothrin, permethrin), malathion and resisted to DDT in 2012 [68, 69]. The intensive use of pyrethroid in dengue and malaria control programs in Vietnam [54], the mosquito will soon increase their tolerance and ability to resist the insecticides.

In short, Ae. albopictus is more predominant in rural and mountainous areas in the north during rainy season. It prefers ovipositing in natural water containers that helps explain the difference seasonal distribution between *Ae. albopictus* and *Ae. aegypti*. This species likes feeding on multiple host and more likely outdoor that reduce the direct disease transmission from human to human of the mosquito but increase zoonotic disease transmission. It is able to transmit DENV and CHIKV but limited in transmitting ZIKV. Ae. albopictus is still susceptible to most of insecticides.

2.1.4 Characteristics of Ae. malayensis

- ***Distribution of Ae. malayensis***

Ae. malayensis was first recorded in Singapore in 1963 [84]. It was reported to appear in Vietnam, Cambodia, Thailand and Taiwan in 1972 and 1995 with the evidence of feeding on human and transmit filariasis [85, 86]. Since then, the species has been neglected and understudied until the recent study in 2017 in Singapore to take into consideration *Ae. malayensis* beside the primary species (*Ae. aegypti*) because of the re-emergence of the disease when vector control program was well implemented in this country[87]. In Singapore, this is a peridomestic species living in forested areas near human habitats like the parks [87].

The appearance of *Ae. malayensis* in Vietnam was reported by biologists in a national conference on ecology and biological resources in 2015 [49], but until now the distribution and behaviors of this species remain unknown. This may be because most recommendation and resources were to focus on *Ae. aegypti* as primary vector of many diseases leading to the neglect in studies on other mosquito species including *Ae. malayensis*. The other explanation is that *Ae. malayensis* could be misclassified with *Ae. albopictus* due to the similarity of these two species as illustrated in below figures [88], particularly when limited literature available for the differentiation of the species.

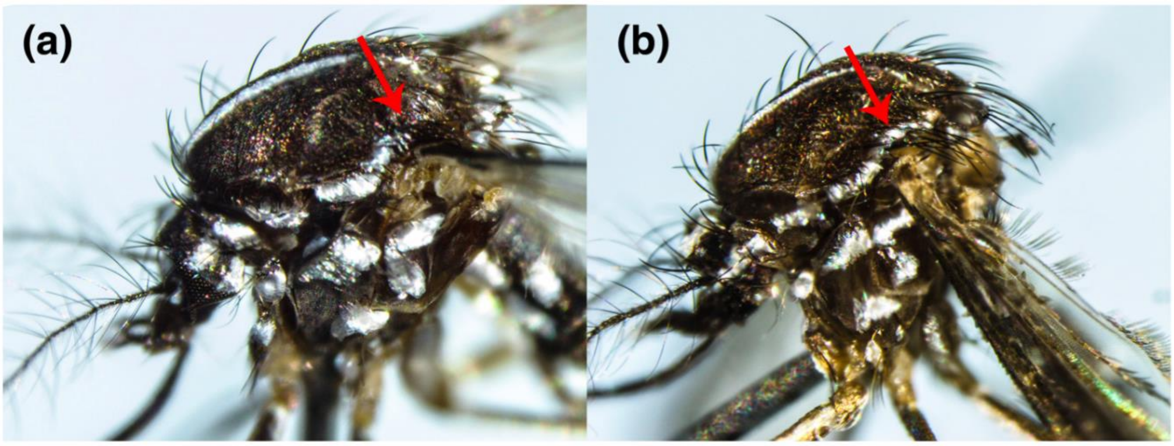

Figure 8. Morphological comparison between thorax of *Ae. albopictus (a)* and *Ae. malayensis (b)* [88]

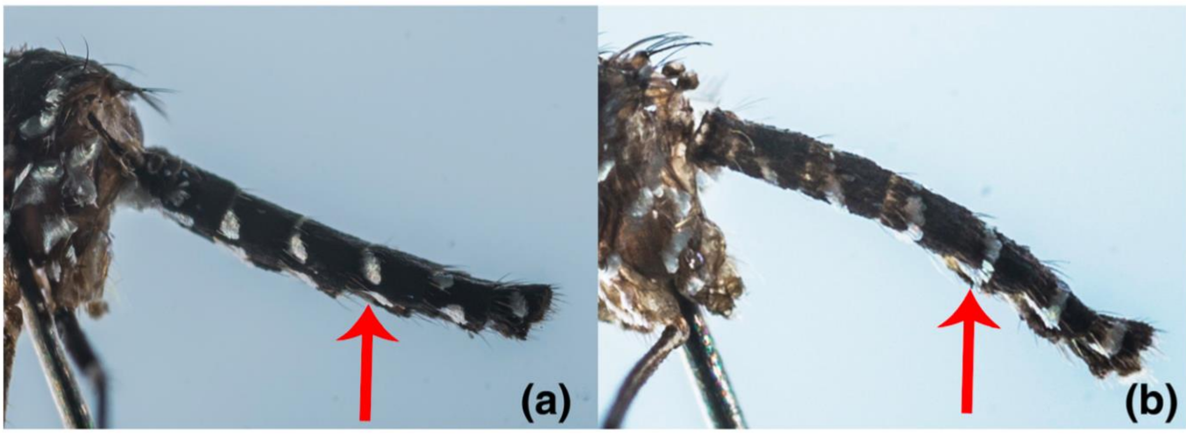

Figure 9. Morphological comparison between abdominal terga of *Ae. albopictus* (a) and *Ae. malayensis* (b) [88]

- ***Breeding sites of Ae. malayensis***

In Singapore, the larvae and pupae of this species were found in natural water containers like tree holes, bamboo stumps, coconut shells that are quite similar to breeding sites of Ae. albopictus [89].

- ***Disease transmission capacity of Ae. malayensis***

Although there has been little evidence for the arboviral infection and transmission capacity of *Ae. malayensis* in the field, a study in Singapore indicates that it is highly susceptible and able to transmit DENV-2 and CHIKV in laboratory conditions [87]. This species was even more susceptible to DENV-2 and CHIKV infection than *Ae. aegypti* and *Ae. albopictus* [87, 90]. The dissemination of the viruses from abdomen to thorax was more intensive as the viral genome copies collected in thorax parts of *Ae. malayensis* was significantly higher than the *Ae. aegypti* and *Ae. albopictus* [87]. This indicates the dissemination of virus from midgut to saliva glands and the ability to transmit the viruses.

Another laboratory study shows that *Ae. malayensis* has a quiescence period of about 1.2 days between the end of a gornotrophic cycle and the next blood meals to recover their physiological process before having blood meal and starting a new gornotrophic cycle. During quiescence period, the mosquitoes become non-responsive to human [91]. The period is much longer than that of *Ae. aegypti* (85% within 12 hours) [92] that it is not efficient for *Ae. malayensis* to reproduce and get abundant in comparison with *Ae. aegypti.*

However, the biting behaviors, host preference and insecticide susceptibility of *Ae. malayensis* have not been examined to reveal the involvement of this species in transmission cycle.

To sum up, *Ae. malayensis* is a possible vector of DENV and CHIKV that has been reported in neighboring countries but its distribution and other characteristics remains unclear in Vietnam though

2.1.5 Other species of Aedes mosquito, Stegomyia subgenus in Vietnam

Seven other species including *Ae. patriciae, Ae. pseudalbopictus, Ae. annandalei, Ae. gardnerii imitator, Ae. desmotes, Ae. mediopunctatus, Ae. w-albus* have been reported to occur in Vietnam by the entomologists [49]. However, according to the available literatures under this review, the involvement of those species in disease transmission, their distribution and behaviors (host preference, biting, resting, breeding sites) remain unknown in Vietnam. There are some information about the species in the world and in neighboring countries, but still cannot help reveal the unknown knowledge.

Ae. patriciae and *Ae. pseudalbopictus* were considered to have association with some arboviral infections including DENV and CHIKV as cited by Dev et al in 2014 when they conducted the research on dengue vectors in India [88]. Nonetheless, my literature search shows that there has been no evidence for disease transmission capacity of these species in Southeast Asia as well as in Vietnam.

Ae. w-albus was reported in 1960s in India and found to be abundant in this countries during the last decades [93, 94]. *Ae. w-albus* cell line is susceptible to infection with CHIKV, DENV-2 and some other arbovirus [95] but the natural infection of the mosquito with the viruses has not been reported. *Ae. w-albus* population reached the peaks during June-July or beginning of rainy season in India [94]. It had the breeding sites formed by trapped water between the rocks [94]. Under this literature review, no further evidence found in Vietnam for this species.

Ae. annandalei was identified to be abundant along with *Ae. albopictus* in Xishuangbanna district, Yunnan province of China that borders Lai Chau and Dien Bien province of Northwest Vietnam [96] but the appearance of the species and its role in disease transmission have not been reported in Vietnam so far.

Ae. mediopunctatus was recorded as a mosquito species in Vietnam in 1966 by the US Center for Disease Control [97]. *Ae. gardnerii imitator* occurred in Attapeu province of Laos that neighbors with Vietnam in a central province [98]. No further evidence associated with these species is recorded according to the available documents found.

Ae. desmotes was reported in Thailand as vector of filarial diseases and had no link with arboviral infections [99, 100].

Although being remained unknown, the neglected and understudied species may play some roles in maintaining and transmitting diseases, especially emerging diseases, that needs more attention of science community to conduct more research on those mosquito species.

2.2 The incidence and distribution of DF, chikungunya and zika in Vietnam

The following aspect will be take into consideration for this review: magnitude (incidence and/or prevalence and trend of disease) and distribution (geographical, seasonal); serotype distribution and some associated factors (age, sex).

2.2.1 Dengue fever

The literature search published international and national journals shows that not many studies on incidence of DF were published in the last 15 years.

Totally, sixteen studies have been found including 10 studies on cumulative incidence (based on surveillance data or cross-sectional studies) and 6 studies on incidence density (cohort studies) (table 2 and 3).

Most of the studies were conducted in the south of Vietnam with the main diagnosis technique based on the clinical symptoms according to the guideline of Ministry of Health for DF surveillance, prevention and control [7]. Some cohort studies used serological test (ELISA) to identify recent infection of DENV among the study participants.

2.2.1.1 Incidence, distribution of DF in each region

The studies show that DF distributed in the three regions with quite similar cumulative incidence and increasing trend of the disease.

- ***DF in the north***

DF outbreaks occurred in every 3-5 years in the north (in 2009, 2014, 2017). Studies in Ha Noi reveal that DF remained stable from 2002-2008 with the annual cumulative incidence of 69.2 per 100.000 population, and it had a peak in 2009 with the much higher cumulative incidence (384.0 per 100.000 population) [35, 101]. Then, the outbreak occurred again in 2014 with the high incidence of 248.0 per 100.000 inhabitants in the capital city [102]. In 2017, Hanoi is also experiencing a big outbreak of DF with more than 13,000 cases in the first six months but the incidence has not been calculated yet [4].

Cohort studies in rural areas of Ha Nam and Hai Phong province show the incidence density of about 1700 per 100.000 person-years [36, 103]. The incidence density would be significant higher in urban areas but there has not been any cohort study conducted in urban areas to generate this figure in the north. No data available for incidence in northern mountainous provinces.

DF season in the north seems to start later in July but end earlier in November at the end of rainy season [101].

The surveillance data from 1998 to 2009 in Ha Noi shows the increase in median and mean age of clinically notified cases of DF that 85% of cases were people aged older than 15 years old and the median age increases from 20 years in 1998 to 24 years in 2009 [102, 104], meaning that 50% of all cases were older than 24 years old.

More males than females were infected with DF in the north (54%) [104].

- ***DF in the central***

The results show the disparities in the burden of DF between urban and rural areas of the Central. The studies conducted in Khanh Hoa shows the increasing trend of DF in the central part of Vietnam that the cumulative incidence nearly trippled between 2009 and 2012 from 127.2 to 314.3 per 100.000 population [53, 105]. A study conducted in Binh Dinh province gives significantly lower cumulative incidence that is about 86.5 per 100.000 inhabitants in 2014 [106].

The explanation for the difference is that the study in Binh Dinh was carried out in two villages (Ham Kiem and Ham Hiep) in rural area where the population density and urbanization were much lower. In contrast, the studies Nha Trang were conducted in city that is more densely populated and urbanized. The association between urbanization, population density and DF outbreaks were demonstrated in study of Schmidt et al. in 2011 [42].

DF season in the central starts earlier in May but gets the same ending time as the south in December [106], less obvious seasonality of DF was reported in central highland where DF confirmed cases were recorded in all seasons [107].

Studies in central provinces show the increasing trend of DF in this region when the patients aged older than 15 years old accounted for nearly 72% - 89% of all DF cases [105–107].

Male patients were predominant among the DF cases that they accounted for about 53% of all cases in studies Vietnam [107, 108].

- ***DF in the south***

The south has been previously reported with the majority of the DF cases. However, the analysis based on 10-year data (2001-2010) collected in 19 provinces in surveillance system indicates the overall cumulative incidence of DF of 232 per 100.000 population [109], which was not much higher than in the north and central.

Other studies show the various cumulative incidences between provinces that were much lower in Can Tho (a province in the southwest) with about 130 per 100.000 population in 2011 and higher in Ho Chi Minh City (the capital city of Southern region) with 251 per 100.000 inhabitants in 2008 [110, 111].

The surveys in Ho Chi Minh City also indicate that children under 15 years old were more vulnerable to DF since this group had remarkably higher annual cumulative incidence of 712 and 518 per 100.000 population in 2008 and 2009, respectively [111].

The birth cohort studies among children under 1 year old in Ho Chi Minh City and among children aged 2-15 years old in Long Xuyen province gave a fairly similar incidence density to the figure in the north (1700 per 100.000 person-years) [112, 113]. The cohort study in Tien Giang in 2013 shows higher figure of 2700 per 100.000 person-years [114]. The hospital data in the south shows that DF still remains burdened in children under 15 years old with more severe illness, however, the median age of the patients is also increasing [111, 115, 116, 108].

The surveillance data in 19 provinces in the south from 2001-2010 indicates that 82% of all reported DF cases were recorded during rainy season starting in June and ending in December [109].

2.2.1.2 Serotype distribution of DF

The four serotypes of dengue virus are circulating in Vietnam but they distribute and cause the outbreaks differently between the regions, time periods.

- ***DENV serotypes in the north***

The statistics of the patients admitted to the National Hospital of Tropical Diseases also indicates the domination of DENV-1 and DENV-2 in the region (62% of confirmed cases) [117]. Surveillance data also supports that DENV-1 and DENV-2 were predominant in the north in the period of 2009-2014 [102]. DENV-3 was isolated in an outbreak on a floating village of Hai Phong province in 2013 but it was not concluded to cause the outbreak due to small number of isolates (3%) of all patients [36].

- ***DENV serotypes in the central***

All four serotypes were circulating but the serotypes were alternatively predominant to cause the outbreaks. The surveillance data in Khanh Hoa province shows that DENV-1 occurred to cause outbreaks in 2008-2009 whereas DENV-2 was dominant in 2011 and all four serotypes were identified in outbreak in 2012 [105]. During a large outbreak in 2013 in the central that caused more than 200.000 clinically notified cases, patients admitted to a national hospital were tested for dengue virus with real-time reverse transcription polymerase chain reaction (RT-PCR) technique, the results revealed that all four serotypes occurred in the outbreak but DENV-4 was the major serotype which accounted for 49% of all cases, then DENV-1 was the second dominant serotype with 28.1%, followed by DENV-3 with 12.6% and DENV-2 with 10.4% [118].

- ***DENV serotypes in the south***

DENV-1 and DENV-2 were the most common serotypes in the south but the other serotypes were also circulating in some provinces of this region [116, 119, 120]. For instance, DENV-1 and DENV-2 were predominant in Long Xuyen province in the period of 2004-2007 [113]. In Dong Thap province, DENV-2 and DENV-4 accounted for 71% of all dengue positive cases in a study in 2013 [108]. Although DENV-3 was isolated in the majority of southern provinces, it has been not sufficient to conclude that DENV-3 was responsible for the outbreaks in the region [119].

Table 2. Studies on DF cumulative incidence (per 100.000 population)

No	Study	Diagnosis technique	Site	Region	Year	Rural/urban	Eco-region	Subject (age)	Cummulative Incidence (per 100.000 pops)
1	Toan et al 2014 [101]	Clinical	Ha Noi	North	2002-2008	Urban	Delta	All	69.2
2	Cuong et al 2011 [35]	Clinical	Ha Noi	North	2009	Urban	Delta	All	384.0
3	Hanh et al 2016 [102]	Clinical	Ha Noi	North	2014	Urban	Delta	All	248.0
4	E. Hugo et al 2014 [53]	Clinical	Khanh Hoa	Central	2009	Urban	Coastal	All	127.2
5	Anh et al 2016 [105]	Clinical	Khanh Hoa	Central	2012	Urban	Coastal	All	314.3
6	Lan et al 2015 [106]	Clinical	Binh Dinh	Central	2014	Rural	Coastal	All	86.5
7	Anders et al 2011 [111]	Clinical	Ho Chi Minh	South	2008	Urban	Delta	All	251.0
	Anders et al 2011 [111]	Clinical	Ho Chi Minh	South	2009	Urban	Delta	All	199.0
	Anders et al 2011 [111]	Clinical	Ho Chi Minh	South	2008	Urban	Delta	Under 15	712.0
	Anders et al 2011 [111]	Clinical	Ho Chi Minh	South	2009	Urban	Delta	Under 15	518.0
8	Phuong et al 2008 [40]	Clinical	Binh Thuan	South	2001	Rural	Coastal	All	330.0
9	Dung et al 2015 [110]	Clinical	Can Tho	South	2011	Urban	Coastal	All	129.6
10	Cuong et al 2013 [109]	Clinical	19 provinces in the South	South	2001-2010	Both	Delta	All	232.0

Table 3. Studies on DF incidence density (per 100.000 person-years)

No	Study	Diagnosis technique	Site	Region	Year	Rural/urban	Eco-region	Subject (age)	Incidence density (100.000 person-years)
1	Fox et al 2014 [103]	ELISA	Ha Nam	North	2009	Rural	Delta	All	1700.0
2	Thanh et al 2015 [36]	Clinical	Hai Phong	North	2013	Rural	Coastal	All	1745.5
3	Chau et al 2009 [112]	ELISA	Ho Chi Minh	South	2007	Urban	Delta	Under 1	1700.0
4	Thai et al 2005 [121]	ELISA	Binh Thuan	South	2003	Rural	Coastal	7-14 years	1144.6
5	Tien et al 2010 [113]	Clinical	Long Xuyen	South	2005	Rural	Delta	2-15 years	1690.0
	Tien et al 2010 [113]	Clinical	Long Xuyen	South	2007	Rural	Delta	2-15 years	4040.0
6	Capeding et al 2013 [114]	ELISA	Tien Giang	South	2011	Urban	Delta	2-14 years	2700.0

2.2.2 Chikungunya

A multi-centre study conducted in five countries of Southeast Asia in 2010 and a retrospective study in South and Southeast Asia in 2016 retested samples of patients with febrile illness collected from 2001-2006 reveal that Vietnam was one of the countries with highest proportion of CHIKV infection among patients with febrile illness in the region [114, 122].

The study in 2010 indicates that CHIKV was the most common pathogen identified by serological test among samples collected from patients aged 2-14 years old with febrile illness in a southern province, which accounted for 59.4% of all dengue-negative samples [114]. The calculated incidence density for the infection is 18.5 per 100 person-years [114].

The retrospective study in 2016 in the south shows lower percentage of CHIKV infection among dengue-negative patients with febrile illness, which is about 25%, a little lower than Indonesia and Philippines with 27.4% and 26.8%, respectively but higher than Myanmar and Sri Lanka with less than 7% in the same study [122].

However, some studies using RT-PCR technique to find genetic materials of CHIKV in sera or plasma samples of dengue-negative patients indicate very low proportion of CHIKV positives. A study conducted in Dong Thap province found no evidence of CHIKV infection among patients admitted in a provincial hospital from 2015 to 2016 [108]. In another study in the south, more than 8000 plasma samples were collected from paediatric patients aged 1 to 15 years with fever of less than 72 hours and symptoms of suspected DF admitted to outpatient clinics of seven hospitals. More than 6000 DENV-negative samples were tested for CHIKV by RT-PCR that only 0.07% were positive with CHIKV [123].

The disparities between the studies may be explained by the difference in study site, patient inclusion criteria and laboratory techniques.

For instance, the study in 2010 recruited patients aged 2-14 years old from Vietnam with active surveillance in the community that participants were asked to present at health facilities if they had fever higher than 38^{o}C that helped increase the inclusion rate and reduce the missing cases of the infection. Then the patients received dengue diagnosis according to the guideline of WHO in 1997 to identify the suspected cases of dengue fever that helped increase specificity of the inclusion because DF, CHIK and zika share similar signs and symptoms [43]. The sera samples were collected within 5 days of fever onset and 7-14 days after the first collection. ELISA technique was used in this study as well as in the retrospective study in 2016 [114, 122].

Whereas the study in Dong Thap was conducted based on passive surveillance in provincial hospital with patients of all ages who got suspected arbovirus infection with fever and two of any following symptoms: headache, rash, myalgia, joint pain and arthralgia. The symptoms may not be specific enough to differentiate CHIKV infection from other febrile illness. The sera samples were collected within 7 days of fever onset and 10-14 days after the first sample collection. PCR was used to confirm CHIKV infection in this study [108].

Although there was evidence for the coinfection of CHIKV and DENV-2 and DENV-3 during a

DF outbreak in Lao PDR in 2013 [124], the coinfection has not been reported in Vietnam.

A study conducted in central highland and southern province on *Ae. aegypti* mosquitoes found that 0.2-0.4% of mosquitoes infected with CHIKV [55].

To conclude, chikungunya is circulating with more obvious evidence in the south and more likely to occur in children under 15 years old. However, the current information on the incidence of chikungunya cannot help conclude the trend of the disease in Vietnam.

2.2.3 Zika

The circulation of zika virus (ZIKV) in Vietnam remains little known though a survey in 1954 indicated the existence of neutralizing antibodies against ZIKV in sera samples (4%) collected from people living in the north of Vietnam as cited by Duong et al [125].

ZIKV infection was reported again in 2015 due to a case study of a traveler returning from Vietnam to Israel who had symptoms and was diagnosed with ZIKV infection [126], but since then no further case was notified by the surveillance system until February 2016.

It has been of greater concern of health sector and the community in Vietnam since it was proved to have the association with microcephaly [127].

In January 2017, the Ministry of Health (MOH) issued the national plan to response to the zika outbreak in Vietnam with the focus on pregnant women and women in reproductive age [33].

Figure 10. Distribution of reported cases of Zika in Vietnam (Updated to December 2016) [79]

A retrospective study conducted in 2016 on samples collected during a DF outbreak in Vietnam show that ZIKV was identified in only 2 samples (0.035%) of nearly 6000 DENV-negative samples [123].

The updated statistics show that 246 zika cases were reported in Vietnam up to June 2017, including 191 cases occurred between in 2016 and 55 additional cases recorded in the first six months of 2017 [10, 127]. The main symptoms of zika cases in Vietnam include fever, rash, conjunctivitis and headache [79].

The majority of zika cases were recorded in 15 provinces in the south, of which Ho Chi Minh City seemed to be the center of the outbreaks with nearly 76% of all cases reported in this municipality (figure 9) [10]. At the same time, one case of microcephaly was highly suspected to associate with ZIKV infection because the mother had been infected with ZIKV in second semester of pregnancy [127].

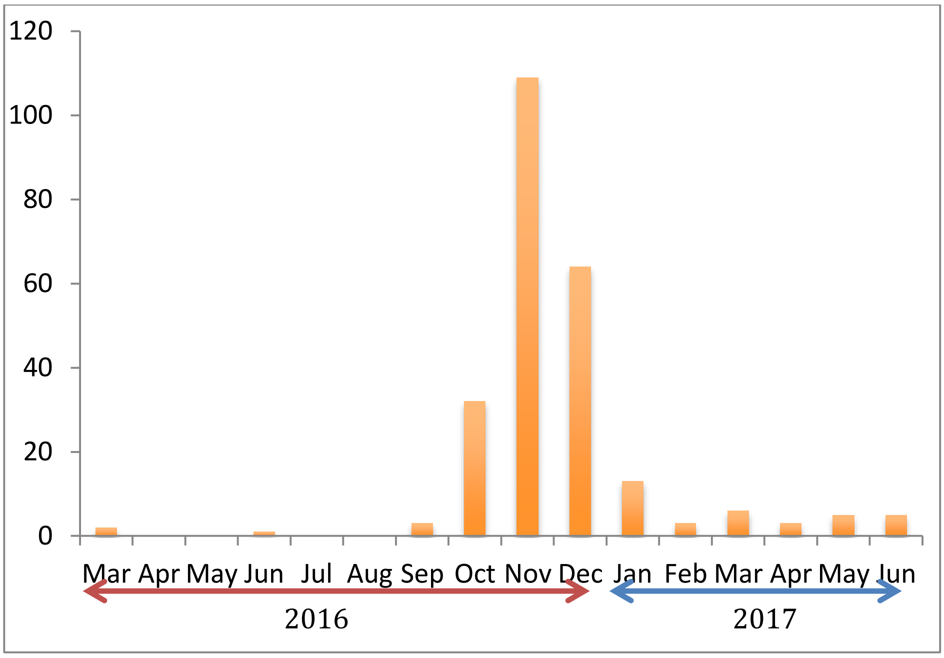

Figure 11. Monthly distribution of zika cases in Vietnam [128]

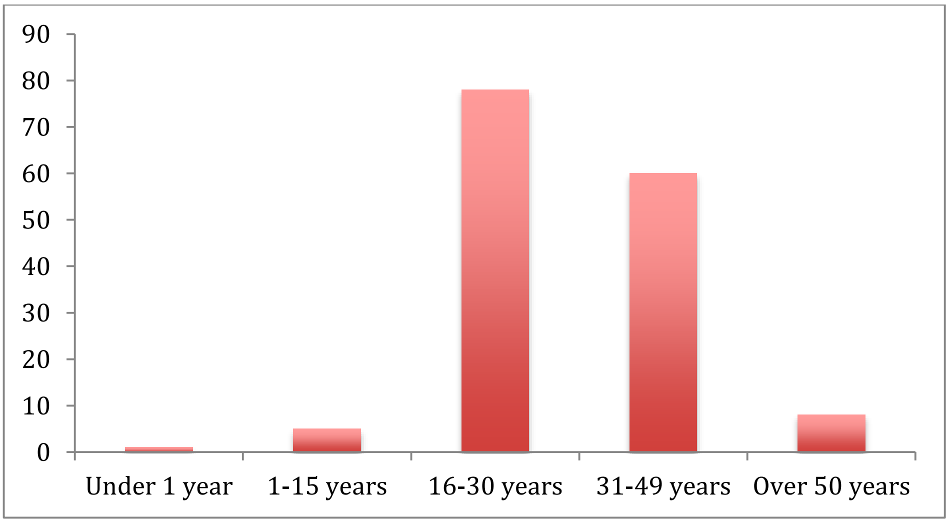

Figure 12. Age distribution of zika cases in Vietnam [128]

The statistics of National Institute of Hygiene and Epidemiology based on data of surveillance system shows that zika cases mainly occurred between September and December. The majority of the cases were older than 15 years of age [128]. The monthly and age distribution of zika are quite similar to DF that suggest the exposure to the same vector (*Ae. aegypti*).

An analysis of "Eliminate Dengue Project in Vietnam" on 23,682 *Ae. aegypti* female mosquitoes collected in the central shows that only 0.24% (56 mosquitoes) was positive with ZIKV [129]. The figure would be higher if the mosquitoes were collected in Ho Chi Minh City where most of the zika patients were notified to the surveillance system.

The increasing rise of zika cases in Vietnam in recent years shows the possibility of the occurrence of zika outbreak in the country that will soon expand to the north due to the advancement of the vector (*Ae. aegypti*) to survive in the temperate region.

2.3 The weaknesses of current surveillance system and implication for the ISS of the three diseases

2.3.1 The weaknesses of DF sentinel surveillance system

The efficiency and effectiveness of a disease surveillance system are measured by the ability to detect outbreak early that helps rational decision making process in timely implementation of disease prevention and control measures. However, if the system is less likely to notify the disease cases at the time of their occurrence (missing cases), it will fail to detect the outbreak.

A cohort study in the south indicates that the data of sentinel surveillance system just reflects 83.3% of dengue shock syndrome, 18.5% of dengue hemorrhagic fever and 6.4% of classical dengue cases in the community [21]. These figures may overestimate the difference between surveillance and cohort data, but they somehow reveals the fact that DF is underreported.

Besides, the report of DF sentinel surveillance from 2005-2014 indicates the disparity between weekly and monthly report of the disease that the number of reported cases in weekly reports was lower than in monthly reports. The difference between the reports is up to 21.8% in 2014 and the disparity is increasing. The difference in the reports show that many DF cases were not recorded at the time of their occurrence (adhoc and weekly reports) but recorded later in monthly reports [130].

The completeness and timeliness of case notification is very important in early detection of outbreak. However, a study conducted in 2013 shows that only 83.5% of adhoc notification of infectious diseases including DF at provincial and district hospitals were in time and just 20% of the notifications were completed according to the requirement of the MOH [131]. Another study in Dong Thap province shows that the completeness of weekly and monthly reports was about 34.3-66.5% and 30-50% respectively [132].

Because the ISS of DF, chikungunya and zika will be developed based on DF sentinel surveillance system, the ISS should overcome the above mentioned problems in terms of timeliness and completeness of the case notification.

2.3.2 The ISS of DF, chikungunya and Zika in Vietnam

The objectives of the ISS are to collect and analyze epidemiological data of DF, chikungunya and zika at some sentinel hospitals and to identify the circulation of the viruses in human and mosquito [10]. The assessment follows the Protocol of WHO for the Assessment of National Communicable Disease Surveillance and Response Systems [48].

2.3.2.1 Priority of the diseases

According to WHO, the diseases put in surveillance should be priority diseases in the country [48], particularly when Vietnam is facing many infectious diseases in the context of the international support is reduced in recent years. DF has been already one of diseases prioritized in the world as well as in Vietnam due to its magnitude and economic burden [11]. Since chikungunya and zika share the same clinical features, epidemiological characteristics and vectors with DF, it is more efficient to integrate the three diseases in one surveillance system.

2.3.2.2 Structure of the ISS

The ISS of DF-chikungunya- zika in Vietnam is based on the existing surveillance system of DF. The organization of the system is described for central, provincial and district level with responsibility of each level [10].

Central level includes General Department of Preventive Medicine based at Ministry of Health, 4 national/regional institutions in charge of disease prevention and control and central hospitals representing 4 regions of Vietnam. The implementing organizations remain the same as DF sentinel surveillance system [10].

At local level, 10 provincial or district hospitals (3 in the north, 2 in the central, 1 in the central highland and 4 in the south). There are some changes for local level that the provincial and district hospitals are not necessary to previously conduct the surveillance [10]. The provinces where the hospitals are located will be selected with the following criteria:

- Province/city with high incidence of DF/100.000 population
- Province/city with cases of suspected zika-related microcephaly or mosquitoes positive with ZIKV.
- Province/city with high vector index: Breteau index - BI>30 (or BI>20 in the north) and density index - DI>0.5 mosquito/household.

It will be better and clearer for the implementing organizations if the guideline is translated into SOPs indicating steps for detection, notification, investigation, confirmation/feedback, response, monitoring and evaluation, analysis and report as well as who will involve in the steps with clear time bound for each step.

2.3.2.3 Process and capacity for surveillance and response

WHO states that the surveillance system should indicate clearly the flow of information within the system and avoid the duplication of the information [48]. The DF surveillance in Vietnam has previously experience the disparities in information between reports as mentioned in section 2.3.1, possibly due to the lack of clear procedure for information flow.

In the guideline for ISS, the flow of information for case notification is not well described as a SOP from case detection to report [10]. It just mentions the responsibility of each level, for example, hospitals collect sera specimen of clinical cases but it does not indicate how the hospital notify the cases to relevant organizations (one of the four national/regional institutions in this case).

A web-based reporting system has been set up at all health facilities across the country for routine passive surveillance of 42 infectious diseases [128]. If the ISS of DF-chikungunya-zika can utilize of the online reporting system, it will be more efficient and effective than setting up a parallel system. However, computer training is required because less than 30% of people in charge of reporting infectious diseases in provincial and district hospitals had sufficient computer skills for entering the online report [131].

Human resource for the surveillance should be considered because only 71.8% of personnel in charge were solely trained and responsible for reporting the diseases regularly [131]. Furthermore, the sentinel sites should be piloted and expanded to as many provinces as possible with the limited budget.

2.3.2.4 Outputs of the ISS

The effectiveness and efficiency of the system will be assessed by the outputs of surveillance activities that are reflected by the simplicity, flexibility, completeness, sensitivity, timeliness and representativeness of surveillance system [48]. The timeliness and completeness of case notification were not well ensured as stated in section 2.3.1 that may be the same problem for the ISS of DF-chikungunya-zika. If the site selection (province/city) is just limited in 10 sites and not well conducted, it will not be representative. Other criteria including simplicity, flexibility, sensitivity have not been evaluated.

The case definition used in DF sentinel surveillance was too strict leading to missing cases because it included Tourniquet test as a criteria whereas Tourniquet test is lowly sensitive and specific (only 62% and 60% for dengue hemorrhagic fever) [133].

2.3.2.5 Integration/Coordination/Synergy

The integration of DF-chikungunya-zika should consider the coordination between implementing organizations because only 76.5% of provincial and district hospitals participated in a survey in 2013 indicate that they had good collaboration with preventive medicine center in disease notification and feedback of infectious diseases [131] that may reduce the timeliness and completeness of the specimen and data collection leading to the failure in early notification of the cases.

2.3.2.6 Laboratories

The laboratories should be evaluated for the testing capacity (equipment, reagent, human resource) because the laboratories have been familiar with serological test for DENV identification but the test used in new ISS is real-time RT-PCR [10, 134]. If laboratory trainings are well implemented, it will help enhance the capacity of the laboratory network, not only for surveillance of the three diseases but also for other diseases.

In DF surveillance system, only 16-27% of reported cases in Vietnam between 2001 and 2007 were confirmed by the laboratory as cited by Ha et al. in 2014 [104]. A little higher proportion of cases confirmed by serological test was reported in the south from 2004 to 2009 with 29.7% of all cases [111].

2.3.2.7 Health mapping

Geographic information system (GIS) has not been applied widely in Vietnam and it is not mentioned in the ISS. The mapping of disease cases is mainly conducted using a printed map and magnet node.

2.3.2.8 Communication

A good communication system can facilitate an efficient and effective surveillance system. The study in 2013 shows that 94.1% of provincial and district hospitals were equipped with landline and/or mobile phone and 97.6% with Internet connected computer for infectious disease notification [131]. The communication system is sufficient for the ISS of DF-chikungunya-zika.

CHAPTER 3: DISCUSSION

The literatures found and used in this review are skewed towards DF and its main vector (*Ae. aegypti and Ae. albopictus*) rather than chikungunya, zika and other mosquito species. The literatures are sometime contradicting each other about the abundance and distribution of the diseases. However, it is overall consistent among the findings of the literatures.

3.1 The characteristics of *Aedes* mosquitoes of *Stegomyia* subgenus in Vietnam

There are 10 species of Aedes mosquito, Stegomyia subgenus in Vietnam. Among those, 2 species are well demonstrated for the involvement in transmission cycle of DF, chikungunya and zika including *Ae. aegypti* and *Ae. albopictus*; 1 species (*Aedes malayensis*) was seen some evidence for the competence and transmission capacity of dengue virus serotype 2 and chikungunya virus in laboratory and filariasis in the field; 6 species remain little known about their distribution and involvement in disease transmission though some of them were susceptible to one of the viruses; 1 species has been identified to have no association with arboviral disease (*Ae. desmotes*). The shortage in evidence for the understudied mosquito species may be due to the priority in recommendations of international organization (WHO) that *Aedes aegypti* has been mentioned as the key in most of vector control program [13]. This leads to the neglecting and scarce of investment for studying the other mosquito species. It is necessary to do more research on other mosquito species to reveal their role and distribution. The other explanation is that the studies on the neglected mosquito species might not be published because of no significant association found (publication bias).

The distribution of the primary vector may help explain the occurrence and trend of the disease outbreak in Vietnam. The predominance of *Ae. aegypti* in the south and central is conducive to the occurrence of DF outbreaks in these areas more frequently than in the north where *Ae. albopictus*, a less competent vector, is more common. The recent zika outbreak in the south and central also supports the hypothesis since the main vector of zika is *Ae. aegypti* [29]. However, global warming and climate change will expand the distribution area of the mosquito suggesting the invasion of new disease (zika, chikungunya) and the seasonal expansion of DF to the north of Vietnam. *Ae. aegypti* is less common in mountainous area that the diseases are less likely to be reported in temperate mountainous provinces than in coastal and delta regions. *Ae. aegypti* is abundant in dry-hot season that lasts from May to August that is quite similar to the increase in human cases of DF and zika with the time lag of 1-2 months after the increase of mosquito in May [35]. *Ae. aegypti* and *Ae. albopictus* are expanding their habitats that the overlapping areas are more complicated in disease outbreak prevention and control because the mosquito species alternatively rise and continuously cause the outbreak.

Ae. aegypti and *Ae. albopictus*, *Ae. malayensis* have quite different preference of breeding sites. While Ae. aegypti prefer laying eggs in artificial water containers especially concrete water tanks during winter, *Ae. albopictus* and *Ae. malayensis* are more likely to oviposit in natural water containers (bamboo tree holes). This is important for the seasonal distribution of those species as the latter two species get abundant in rainy season when the natural containers are filled with water.

Ae. aegypti is also more efficient to live longer and lay more eggs in each gornotrophic cycle than it was 15 years ago [72], thus, the mosquito population becomes abundant more rapidly and cause the disease outbreak earlier at the beginning of season than in the past. The mosquito is developing the adaptability to domestic environment, particularly in urban areas where population density is high and the distance between water container and the host is closer than in rural areas, and resistance to insecticides that requires novel vector control measures since spraying techniques are becoming ineffective.

Ae. malayensis, a new species of Aedes mosquito *Stegomyia* subgenus has been considered as a novel mosquito species involving in disease transmission cycle of DF due to its high susceptibility to the virus infection and dissemination of virus to saliva glands indicating the transmission capacity of the mosquito. The mosquito is still neglected in Vietnam though it was studied in other Southeast Asian countries like Singapore. The species has morphological appearance quite similar to *Ae. albopictus* that *Ae. malayensis* could be existing and misclassified into *Ae. albopictus* species in vector surveillance [88]. There should be more research conducted to reveal the distribution and of this species in Vietnam.

3.2 The incidence and distribution of DF, chikungunya and zika in Vietnam

Among the three arboviral diseases, DF had longer history and more experience of research, prevention and control in Vietnam than chikungunya and zika because health sector paid more attention to DF due to its magnitude and economic burden. In previous literatures, DF was more predominant in the south where 85% of all DF cases were [20]. On the contrary, although the current literatures show the increase trend of DF incidence from the north to the south, the incidence was not much different between the regions, particularly in major outbreaks. The DF incidence in the north ranged from 69.2 to 248 per 100.000 population [35, 101, 102], while it was from 86.5 to 314.3 per 100.000 population in the central [53, 105, 106] and from 129.6 to 330.0 per 100.000 population in the south [40, 109–111]. All four serotypes of DENV are circulating in Vietnam but DENV-3 is less likely to cause large outbreaks. DENV-1 and DENV-2 are predominant across the country while DENV-3 is more common in the central and DENV-4 occurs more frequently in the central and the south.

Children under 15 years old were more vulnerable to DF infection as the incidence nearly doubled the figure for general population, which ranged between 518 to 712 per 100.000 population in the south [111]. However, the majority of DF cases are people older than 15 years old that are also increasing in recent years [102, 105–107, 104]. It suggests the infection occurs more outside the households because people older than 15 years of age are more likely to go to public places (school, office) rather than staying at home. The case will be more complicated to know the origin of infection to collect mosquito and implement control measures (spraying).

The circulation of chikungunya and zika remains little known due to few research on these diseases in Vietnam published though zika is emerging with the first case reported in 2016 in the south. Furthermore, the results vary between studies due to different study sites, patient inclusion criteria, specimen collections and testing techniques. Studies using serological test indicate the proportion of CHIKV ranged between 25-59.4% of DENV-negative sera samples (collected within 5 days of fever onset and 7-14 days after the first collection) [114, 122]. Whereas only 0.07% and 0.035% samples collected in a DF outbreak (within 7 days of fever onset and 10-14 days after the first collection) positive with CHIKV and ZIKV respectively by RT-PCR technique [123]. This result suggests that serological test (ELISA) should be used in combination with real-time RT-PCR in surveillance to confirm CHIKV and ZIKV infection.

3.3 The weaknesses of current surveillance system and implication for the ISS of the three diseases

The MOH issued a guideline for the integration of DF, chikungunya and zika into one surveillance system, which mainly base on the existing DF sentinel surveillance system.

The timeliness and completeness of case notification are a problems of DF surveillance system. The implementation of ISS of DF, chikungunya and zika using the same system can meet the same issues if proper training and SOPs are not well established. The utilization the existing web-based disease notification system can enhance the timeliness and completeness of the ISS.

The case definition used in DF sentinel surveillance was too strict leading to missing cases because it included Tourniquet test as a criteria, which is removed in new case definition used in the ISS. However, pilot phase should be implemented to test the sensitivity and specificity of case definition to avoid the missing of cases like it was in DF surveillance. Besides, the selection of surveillance sites should be performed carefully and expand more to the north to ensure the representativeness of the surveillance.

As mentioned above, RT-PCR was seen as less effective technique in detecting the infection status of chikungunya and zika that the serological test could be compliment to reduce the missing rate of case notification [117].

The ISS will collect mosquito and pupae in the household of patients after having laboratory confirmation of human cases. However, the literatures shows the association between the increase in mosquito population (*Ae. aegypti*) and the increase in human cases of the diseases, thus the active vector surveillance should be added in the surveillance to detect early the risk of outbreaks when mosquito population rises rapidly. The literatures also suggest the surveillance of virus infection in immature mosquitoes (pupae) because of the ability to transmit virus from mosquito to the eggs (transovarial infection) [90] that helps predict the occurrence in human case though the transovarial infection is not common (1.05-1.09%) [135, 136]. Transovarial infection should be studied more to have evidence for the surveillance.

CHAPTER 4: CONCLUSIONS AND RECOMMENDATIONS

4.1 Conclusions

Although the health sector in Vietnam has implemented many measures to reduce the burden of DF, it still remain one of the priority in Vietnam due to high and increasing incidence with geographical and seasonal expansion to the regions previously considered as low endemic areas. At the same time, the emergence of chikungunya and zika in Vietnam and neighboring countries put more burden to the health system that needs a novel approach to control the three diseases because they share the same clinical features and vectors. The establishment of integrated surveillance for the three diseases responds to the needs.

Vietnam Ministry of Health has issued a national guideline for the ISS of the three diseases in one system, which is based on the existing DF surveillance system. The weaknesses of current DF surveillance system should be overcome in the integrated system to make it more efficient effective in disease detection and response.

This thesis contributes some significant results on the characteristics of the vectors, the incidence and distribution including trend of the diseases, the weaknesses of current surveillance system and its implications for the new ISS of the three diseases in Vietnam.

Firstly, there are 10 species of *Aedes* mosquito, *Stegomyia* subgenus in Vietnam, but only 2 species (*Ae. aegypti* and *Ae. albopictus*) are considered as primary and secondary vector of the diseases and one new species (*Ae. malayensis*) is suspected as potential vector of dengue virus serotype 2 and chikungunya virus. The geographical and seasonal distribution of *Ae. aegypti* and *Ae. albopictus* can help explain the pattern and distribution of DF, chikungunya and zika in Vietnam that the vectors tend to expand to the low endemic regions. There is a need to conduct more research on the new mosquito species to reveal its distribution and involvement in disease transmission.

Secondly, the distribution of the diseases gives some implications for surveillance activities. The incidence of DF varied between the north, central and the south, however, the difference will be reduced due to the expansion of the vector across the country. Therefore, the sentinel surveillance sites should be selected accordingly to represent the three regions. The age of dengue patients are increasing that indicates the change in transmission mechanism of the disease and requires the change in case definition of the surveillance. It is also necessary to conduct study to identify the incidence and distribution of chikungunya and zika in Vietnam, the results will orientate the surveillance to the endemic regions of the diseases.

Thirdly, at the same time with the implementation of research on chikungunya and zika, the need assessment for surveillance of those diseases should be conducted to reveal the necessity of prioritizing the diseases in surveillance. Data quality, timeliness and completeness should be considered in the integrated system. It is essential to pilot the surveillance and case definition to avoid missing the case detection. Active vector surveillance should be also added in the surveillance to enable the prediction of the disease in the mosquito before the occurrence in human population. The tests used for surveillance should be the combination of serological test (ELISA) and real-time RT-PCR.

4.2 Recommendations

1. Conduct more research on the new mosquito species (*Ae. malayensis*) to reveal its distribution and role in disease transmission in the field.
2. Expand more ISS sites in the north due to the high incidence and increasing trend of DF in the north and the possibility of chikungunya and zika to invade this region following the expansion of the vectors.
3. Conduct research to indicate the burden and distribution of chikungunya and zika in Vietnam, especially in the north
4. Develop and pilot SOPs for case detection, notification, investigation, laboratory confirmation, feedback, report etc. in the ISS
5. Include active vector surveillance in the surveillance system to enable the ability to predict the occurrence of disease in human case by capturing the increase in mosquito population.
6. Combine serological test and real-time RT-PCR in case confirmation in the ISS of three diseases.

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Annex

Annex 1: List of key words and their combination for searching documents

Objectives	**English keywords**	**Vietnamese keywords**
To describe the characteristics of *Aedes* mosquitoes of *Stegomyia* subgenus in Vietnam	*Aedes* mosquito *Aedes Stegomyia* mosquito *Aedes aegypti* *Aedes albopictus* *Aedes malayensis* *Aedes annandalei* *Aedes desmotes* *Aedes gardnerii imitator* *Aedes mediopunctatus* *Aedes patriciae* *Aedes pseudalbopictus* *Aedes w-albus*	Muỗi vằn Muỗi truyền sốt xuất huyết Muỗi hổ châu Á Muỗi truyền bệnh sốt vàng
To describe the incidence and distribution including trend of DF, CHIK and zika in Vietnam	Incidence of dengue fever in Vietnam Dengue fever in Vietnam Dengue hemorrhagic fever in Vietnam Dengue shock syndrome in Vietnam Chikungunya in Vietnam Chikungunya in Cambodia Chikungunya in Lao Chikungunya in Indochina Chikungunya in Southeast Asia Zika in Vietnam Zika in Cambodia Zika in Lao Zika in Indochina Zika in Southeast Asia	Sốt xuất huyết Chikungunya Zika Tỷ lệ sốt xuất huyết tại Việt Nam Chikungunya tại Việt Nam Zika tại Việt Nam
To identify weaknesses of current surveillance system for the ISS of the three diseases	Dengue fever surveillance system in Vietnam Evaluation of infectious disease surveillance system in Vietnam Integrated surveillance of dengue fever, chikungunya and zika	Hệ thống giám sát sốt xuất huyết tại Việt Nam Đánh giá hệ thống giám sát bệnh truyền nhiễm tại Việt Nam Giám sát lồng ghép sốt xuất huyết, bệnh do vi rút chikungunya và zika