RECOMMENDATION STRATEGIES FOR THE PREVENTION AND CONTROL OF HIGH MORBIDITY OF DENGUE HEMORRHAGIC FEVER IN NORTH SUMATERA PROVINCE

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by

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LIST OF ABBREVIATIONS

WHO	:	World Health Organization
DHF	:	Dengue Hemorrhagic Fever
DSS	:	Dengue Shock Syndrome
DF	:	Dengue Fever
JD	:	Job Description
HIDs	:	High Incidence District
LIDs	:	Low Incidence District
KAP	:	Knowledge Attitude Practice
HF	:	Health Facility
H	:	Hospital
MOH	:	Ministry of Health
DHO	:	District Health Office
OHS	:	Other Health Sector
WB	:	Whole Blood
RNA	:	Ribonucleid Acid
IgG	:	Immunoglobulin G
IgM	:	Immunoglobulin M
HI	:	House index
CI	:	Container index
BI	:	Breteau index
AHI	:	Adult house index
RR	:	Resting rate
AD	:	Adult density

NCCLS	:	National Comitte for Clinical Laboratory Standard
SARIMA	:	Seasonal Autoregressive integrated Moving average
ADE	:	Antibody Dependent Enhancement
NAATs	:	Nucleid Acid Amplication Test
RT-PCR	:	Reverse Transcriptase Polimerase Chain Reaction
ELISA	:	Enzyme-linked Immunosorbent assay
NS1	:	Nonstructural protein
TNF-A	:	Tumor necrosis Factor Alpha
PAF	:	Platelet Activating Factor
IFN	:	Interferon
IL	:	Interleukin
NO	:	Nitric oxide
EIP	:	Extrinsic incubation period

REKOMENDASI STRATEGI UNTUK PENCEGAHAN DAN KAWALAN MORBIDITI TINGGI UNTUK DEMAM DENGGI BERDARAH DI PROPINSI SUMATERA UTARA

ABSTRAK

Latar Belakang : Insiden demam denggi berdarah (DHF) di Sumatera Utara kekal tinggi, meskipun pelbagai usaha dilakukan untuk mengawalnya.

Objektif: Kajian ini bertujuan untuk mendokumentasikan maklumat tentang kecukupan sistem surveilan semasa bagi DHF di Indonesia dan faktor-faktor yang yang menyumbang ke arah peningkatan kes DHF. Ia nya nanti akan digunakan untuk merekomen strategi pencegahan dan kawalan DHF di Sumatera Utara.

Bahan dan Kaedah: Lima reka bentuk kajian digunakan dalam kajian ini. Dalam kajian penerokaan, kesemua kaki tangan utama yang terlibat dalam sistem pengawasan bagi demam denggi berdarah di peringkat daerah dan fasiliti kesihatan di enam daerah telah ditemuramah untuk mengenalpasti fungsi dan prestasi sistem surveilan. Dalam kajian kes kohort, melibatkan 682 kes dan subkohort dengan nisbah 1: 1. Analisis *Simple dan Multiple regresi logistic* digunakan untuk menentukan faktor-faktor yang berkaitan dengan DHF. Untuk kajian keratan rentas perbandingan isi rumah di daerah dengan kes tinggi dan rendah telah dipilih melalui persampelan berbilang peringkat. Lagi sekali analisis *Simple dan Multiple regresi logistic* digunakan untuk menentukan faktor-faktor yang berkaitan dengan demam denggi berdarah di daerah dengan kejadian yang tinggi. Dalam kajian entomologi, *Independent T test* dan *Two Way Anova* digunakan untuk menentukan kesan bekas yang positif larvae ke atas DHF sementara bagi indeks larvae dan

Aedes dewasa analisis *Simple dan Multiple regresi logistic* digunakan. Kajian cuaca menggunapakai data cuaca bulanan selama 9 tahun (2003-2011). *Pearson correlati*on digunakan untuk menentukan hubungan cuaca dan DHF dan *Time series regression* digunakan untuk menentukan impak cuaca ke atas insiden DHF. Seasonal Autoregressive Moving Average (SARIMA) model dibina untuk meramal kejadian DHF.

Keputusan: Struktur sistem surveilan untuk DHF adalah bagus tetapi pelaksanaannya tidak optimum dengan kekurangan major yang termasuk ketiadaan garis panduan, kekurangan sumber, dan kelemahan ketara dalam fungsi utama dan sokongan. Faktor - faktor sosio-budaya dan alam sekitar dikaji melalui kajian kes kohort dan kajian keratan rentas perbandingan. Faktor yang signifikan dengan insiden DHF termasuk pengalaman dengan DHF dalam keluarga, sejarah perjalanan, tempoh penginapan, kekerapan bekas air pembersihan, kekerapan pembersihan pelupusan sampah, pendidikan, pengetahuan, amalan dalam langkah pencegahan, sumber air minuman, gaya rumah dan rumah dengan longkang. Indeks larva *Aedes* dan nyamuk dewasa diatas tahap kritikal terutamanya di daerah dengan insiden DHF yang tinggi dengan house indeks (indeks rumah) boleh digunakan untuk meramal jangkitan denggi. Faktor cuaca yang termasuk jumlah hujan, hari hujan, suhu dan kelembaban relatif adalah berikatan dengan insiden DHF. Model SARIMA $(0,1,1)(0,1,1)_{12}$ berupaya meramalkan kejadian DHF.

Kesimpulan: Fungsi dan keupayaan sistem surveilan bagi DHF perlu diperkuatkan dalam semua aspek. Faktor sosio-budaya dan persekitaran yang berkait dengan DHF perlu ditangani dan dikawal. Langkah perlu diambil untuk menghapuskan atau mengurangkan kepadatan vektor *Aedes*. Faktor cuaca patut diintegrasi didalam program kawalan dan pencegahan DHF nasional.

RECOMMENDATION STRATEGIES FOR THE PREVENTION AND CONTROL OF HIGH MORBIDITY OF DENGUE HEMORRHAGIC FEVER IN NORTH SUMATERA PROVINCE

ABSTRACT

Background: The incidence of dengue hemorrhagic fever (DHF) in North Sumatera Province remains high despite effort to control it.

Objectives : This study aimed to document information about the adequacy of the current Indonesia surveillance system for DHF and factors responsible for high DHF transmission. These will be used for recommending strategies for the prevention and control for DHF in North Sumatera Province.

Material and Methods: Five study designs were adopted in this study. In the exploratory study, all key personnels involved in the surveillance system for DHF at the district and health facility levels in the selected six districts were interviewed to determine the function and performance of the surveillance system. The case cohort study recruited a total of 682 respondents with case: subcohort ratio 1:1. S*imple and Multiple logistic reg*ression were applied to determine the factors associated with DHF. For the comparative cross sectional study, 688 households both in high and low incidence district were selected using multistage sampling. *Simple and Multiple logistic regression* were again applied to determine the factors associated with DHF among the households in districts with high incidence. In the entomology study, *Independent T test* and *Two Way Anova* were used to determine the effect of larvae positive containers on DHF transmission, whereas for larvae and adult indices *Simple and Multiple logistic regression* were applied. The climatic study utilises monthly a years climatic (2003-2011) secondary data. The relationship between climatic and dengue hemorrhagic fever incidence was determined by *Pearson correlation* and the impact of climates on DHF incidence by *Time series regression*. *Seasonal Autoregressive Integrated Moving Average* (SARIMA) model was then developed to predict the occurrence of DHF.

Results : The structure of DHF surveillance system was good but suboptimum with major deficiencies that include unavailability of guidelines, insufficient resources and poor core and supportive functions. Socio-cultural and environmental factors associated with DHF incidence were investigated through case–cohort and comparative cross sectional studies. Significant factors include experience with DHF in family, travelling history, length of stay, frequency of cleaning water container, frequency of cleaning garbage disposal, education, knowledge, practices in preventive measure, source of drinking water, house style and house with gutter. *Aedes* larvae and adult indices were above the critical level especially in the high incidence districts with house indices as the predictor for dengue transmission. Climatic factors that include rainfall, rainy days, temperature and relative humidity were significantly associated with DHF incidence. SARIMA model $(0,1,1)(0,1,1)^{12}$ was able to predict DHF occurrence.

Conclusion: The existing surveillance system for DHF need to be strengthened in every aspect. Socio-cultural and environmental factors associated with DHF should be addressed and controlled. Measures should be taken to eliminate or being down the density of *Aedes* vectors. Climatic factors should be integrated in the national prevention and control program for DHF.

CHAPTER 1

INTRODUCTION

1.1 Background

Dengue hemorrhagic fever (DHF) is considered to be the most important public health problem in many tropical and subtropical countries around the world. The disease has gained recognition in many countries and currently more than 100 countries are endemic with dengue virus infection (Guzman and Istúriz, 2010; Guzman *et al.*, 2010).

DHF becomes the leading cause of morbidity with 3.6 billion people living in areas of high risk for dengue infection (Wilder-Smith., *et al* 2012). Worldwide 50 to 100 million cases of dengue fever occur every year and 250,000 to 500,000 cases were DHF resulting in approximately 25,000 death (Guzman *et al.*, 2010). Recent studies suggested that there were about 230 million infections worldwide (Wilder-Smith *et al.*, 2012). However, the true incidence is still not known (Guzman *et al.*, 2010).

World health organization (WHO) reported that the annual average number of DHF cases had increased. For the period 2000-2004s, the number of DHF cases was 925,896 almost doubled compared that for 1990-1999s (Guzman *et al.*, 2010). While in 2010, there were 96 million dengue infections estimated worldwide with the Americas contributed 14 % and Africa 16 % of the infection (Bhatt *et al.*, 2013).

Asia ranked first in the number of patients with dengue fever each year and contributes as much as 70% of infections worldwide (Bhatt *et al.*, 2013). Dengue hemorrhagic fever is a leading cause of hospitalization among children with case fatality rate (CFR) exceeding 5% in some areas. The first case of dengue was reported in Penang, Malaysia in 1901 (Poovaneswari,1993). Then the disease spread to the Philippines (1953), Cambodia (1961), Calcuta (1963), Sri lanka (1966), Indonesia (1968), and Singapore. In Singapore dengue cases has been reported since the 1990s, with a peak in 2005 giving the incidence of dengue cases at 335 per 100,000 population (Carrasco *et al.*, 2011). From 1968 to 2009, WHO noted Indonesia as the country with the highest dengue cases in Southeast Asia and the second highest in the world after Brazil (Organization, 2012).

In Indonesia, DHF is one of the emerging diseases with an increased incidence throughout the year. The disease was first recognized in 1968 in Surabaya and Jakarta with a CFR of 41.3%. Since then, incidence of the disease has increased from 9 cases per 100.000 population in 1992 to 67 per 100.000 population in 2007, and 28 cases per 100.000 population in 2011. Meanwhile CFR had decreased from 2.9% in 1992 to 1.02% in 2007 and 0.73 % in 2011 (Ministry of Health Indonesia, 2012). The districts affected had also increased from 187 districts in 1992 to 337 districts in 2007, and 464 districts in 2010. This emerging disease posed an important public health problem in Indonesia because of its high rate morbidity and mortality mainly among children. Out of 34 provinces, one of the endemic areas is North Sumatera Province (Ministry of Health Indonesia,2010). The latest report by Ministry of Health, North Sumatera Province the third highest for DHF cases (Ministry of Health Indonesia, 2011).

In 2005, DHF incidence in North Sumatera Province ranked 19 with 31 cases per 100.000 population and a CFR of 0.9% (Ministry of Health Indonesia, 2007). DHF was recognized in North Sumatera Province in 1975. Within a 10 year period (2003-2012), incidence rate increased from 8 cases per 100.000 population in 2003 to 24 cases per 100.000 population in 2007 and 35.18 per 100.000 population in 2010 and 18.45 cases per 100.000 population in 2012. While CFR decreased from 2.45% in 2003 to 0.9% in 2007, to 1.0% in 2010 and 0.8% in 2012. However, spread of DHF extended from 24 districts in 2010 to 27 districts in 2011 and 31 districts in 2012 (Provincial Health Office of North Sumatera, 2012).

Out of 25 districts in North Sumatera Province, 16 were dengue endemic districts. They were classified into high and low endemic district based on the incidence data (2007). Medan, Pematang Siantar and Tebing Tinggi districts were classified as high endemic districts. While Langkat, Asahan and Deli Serdang were low endemic districts. Within a 5 year period (2007-2012), incidence rate fluctuated from 88.6 cases per 100.000 population in 2007 to 56.7 cases per 100.000 population in 2012 in Medan, from 291 cases per 100.000 population in 2007 to 260 cases per 100.000 population in 2012 in Pematang Siantar, from 295 cases per 100.000 population in 2007 to 106 cases per 100.000 population in 2012 in Tebing Tinggi, from 10.4 cases per 100.000 population in 2007 to 14.8 cases per 100.000 population in 2012 in Langkat, from 10.6 cases per 100.000 population in 2007 to 31.1 cases per 100.000 population in 2012 in Asahan, and in Deli serdang from 19.68 cases per 100.000 population in 2007 to 32.5 cases per 100.000 population in 2012. Overall the above data shows that the incidence rate of DHF in North Sumatera Province was still high.

Dengue hemorrhagic fever has a public health, social and economic impact. Public health impact is related to the burden of the disease including the number of clinical cases by severity, duration of illness period, quality of life during the illness period, and the number of deaths during the period (Suaya *et al.*, 2007). The public health impact of dengue fever is due to a poor surveillance system, where many cases are under detected and under reported. As a consequence, hospitalization of DHF cases resulted in overloading of DHF patients in hospitals and overworked medical staff. This would eventually lead to the increase in mortality (Kusriastuti and Sutomo, 2005).

The social impact includes the effects of the disease on patients and their family which is associated with the duration of the disease and financial cost. While loss of work productivity, absence from school, instability of family life due to risk of infection, reduction of life expectancy, and social disruptions are indirect social impacts (Kusriastuti and Sutomo, 2005; Carrasco *et al.*, 2011; Wettstein *et al.*, 2012). The economic impact includes expenses when seeking treatment for both hospitalized and out patients cases (Kusriastuti and Sutomo, 2005; Carrasco *et al.*, 2011; Halasa *et al.*, 2012).

Various efforts have been made to reduce morbidity due to dengue fever, but the results have not been as expected. Up to now there is no vaccine or spesific medication for dengue fever and many factors contributing to high incidence occurrence. The problem faced is the high incidence of DHF. Therefore, effective prevention and control measures are necessary in reducing the incidence of DHF and should be focused on the disease risk factors. It is closely linked to the effective surveillance system that provide accurate information to be used in planning and implementing health intervention for the control of DHF (Baker and Fidler, 2006) and monitoring the progress of interventions to reduce the disease, early detection and initiating investigation and control measures (John *et al*., 2004; Sahal *et al.*, 2009).

The Ministry of Health Indonesia had established DHF as one of the priorities in the prevention and control program of infectious diseases in Indonesia. Therefore, surveillance system was conducted since 1984. In order to understand the whole concept of surveillance system, the Ministry of Health created a guideline for the implementation of a surveillance system for DHF. In 2003, disease integrated surveillance system was introduced both to communicable and non communicable diseases with active and passive approach, and involved health services, hospitals, communities and laboratories (Ministry of Health Indonesia, 2004).

In Indonesia, DHF reporting is regulated by epidemic act (UU Wabah nr 4/1984) and Ministry of Health (regulation nr 560/1989), which states that every case of infectious disease occurs and which could potentially cause an outbreak, then should be reported to the district health authority within 24 hours (Ministry of Health Indonesia, 2005). Surveillance system relies on passive reporting by physician, healthcare provider, hospital, health facility that managed DHF cases. The system depends on the awareness and interest of the medical community. Although the system is relative insensitive, however it is useful in monitoring the trend in dengue transmission (Torres and Castro, 2007).

Health facility as primary health centre and important public health services in Indonesia, especially in the impelementation of surveillance system are bottom-up. Health facilities are expected to provide accurate information that describe the actual public health condition (Ministry of Health Indonesia, 2005). In the surveillance system for DHF, case ascertainment using standard case definition is based on clinical diagnosis and laboratory confirmation. However, not all health facilities have laboratory equipment to perform the test for identifying DHF. Therefore, adequate knowledge of the case definition among health personnels both in the health facilities and at the district health levels is necessary (Kusriastuti and Sutomo, 2005).

In addition to surveillance of cases, vector surveillance is essential in the implementation of dengue fever surveillance to monitor the density of vector mosquitoes. This information could determine outbreak risk and the need for specific vector control to break the chain of disease transmission. However, in North Sumatera Province the implementation of vector surveillance has not been conducted regularly. This certainly affects the accuracy of the information regarding high risk areas and factors associated resulting in less effective control measures for dengue hemorrhagic fever.

In North Sumatera Province, the surveillance system for DHF started in 1993 and was merely for data collection and data reporting. Currently, the implementation of surveillance system is mainly passive reporting. Based on the decision by the Ministry of Health (nr 1116/2003), the surveillance system implementation has been integrated, however the involvement of laboratory and private health sector is still low. It affects completeness and timeliness reporting from health facilities and hospitals and has impact on the actual number of cases of DHF. In addition, cases ascertainment of DHF based on WHO criteria and most of reported cases were not supported by laboratory confirmation due to the lack of laboratory facilities This also might have impact on the actual number of cases of DHF being reported and the performance of surveillance system.

Based on the North Sumatera Province surveillance report (2007), the completeness and timeliness of reporting from health facilities and hospital are still below of the Ministry of health standard. Completeness of reporting of health facilities and hospitals were 69,7% and 43,14%, while the timeliness in disease reporting was 62,69% and 38,37%, respectively. This result leads to misinterpretation in describing the magnitude of the problem and determining the prevention and control measures for dengue fever.

Effective prevention and control measures are essential in reducing mortality and morbidity of DHF, and they are closely linked to an effective surveillance system that provides accurate information that could be used for planning, implementing and evaluating health intervention. In addition, the effective prevention and control measures for DHF should be focused and based on the disease risk factor. Therefore, the factors associated with the incidence of DHF and deficiencies of surveillance system should be identified. These information is used as the recommendation for an effective surveillance system and successful control for DHF.

1.2 Problem statements

Dengue hemorrhagic fever is one of the major health problems in North Sumatera Province. The incidence of DHF increased annually and remains high. Geographically the district affected increased to 16 endemic areas in 2007.

Dengue hemorrhagic fever as a problem is complex. Many factors contribute to the incidence of DHF including socio-demographic and socio-cultural background, and environmental factors that create potential breeding sites. While geographical and climatic factors that promote vector proliferation, are also responsible. To achieve an effective control measure for dengue fever it requires accurate information both in the number of cases and the factors affecting. However, data on factors associated with the high incidence of dengue fever in North Sumatera Province have not been well known.

Various efforts had been made to reduce morbidity and mortality of DHF. However, the occurence of DHF could not be controlled and the incidence remains high. It was assumed that the prevention and control measure for DHF was not effective but the actual reasons are not known.

An effective prevention and control measures is closely linked to the surveillance system. However, the implementation of existing surveillance system does not seem optimum. The performance of the surveillance system that was reflected by completeness and timeliness of disease reporting was below the standard of Ministry of Health. In addition, most of the reported cases were based on WHO criteria and not supported by laboratory confirmation. Inadequate knowledge about case definition among health personnel and at the district health level may have impact on the accuracy of number of cases. Although vector surveillance is important to determine high risk area for DHF, vector surveillance has not been regularly conducted.

Since a surveillance system is essential in providing information that could be used in monitoring the disease, implementing health intervention and evaluating, the surveillance system must be effective. This is closely related to the structure, dynamics and attributes of the surveillance system, using the WHO standard as reference. Thus, it is necessary to identify deficiencies of the surveillance system implementation and areas for improvements. In addition, factors that have been associated with DHF incidence should be identified and used in preparing plan for reducing mortality and morbidity of DHF and to establishing priorities for surveillance purposes.

An effective surveillance system provides timely and accurate information that could be used in making decision and implementing health intervention for the control of DHF. This requires integrated surveillance data that include epidemiological, entomological, and environmental data. An optimum surveillance system could predict temporal and spatial risks of DHF.

To achieve an effective prevention and control measures to reduce mortality and morbidity of DHF and also successful control for DHF, an effective surveillance system for DHF is required, and the intervention should be focused and based on the disease risk factors.

1.3 Rationale of the study

The most appropriate approach to reduce the incidence of DHF is by conducting the effective prevention and control measures focusing on the disease risk factors. Risk and factors associated with DF and DHF in North Sumatera has not been officially reported and been made public. As such, it is not known what are the local factors responsible for sustaining high DHF cases in certain districts and area within the North Sumatera Province.

The surveillance system for DHF in North Sumatera Province is assumed to be not optimum but there has not been any report on the effectiveness of the system of DHF for North Sumatera. Thus, proper evaluation is needed to determine its effectiveness and optimize the current performance of the surveillance system. The system requires verification for all the parameters including accurate associated factors for DHF and identification of the structure and process of the surveillance system. This study aims to find, examine and document these information so that they can be used for an effective surveillance system and as a recommendation strategies for the prevention and control for dengue hemorrhagic fever in North Sumatera Province. The result of this study will definitely add information to the body of knowledge and refine the theoretical aspects of DHF surveillance, control and prevention.

1.4 Objectives of Study

1.4.1 General Objective

To study the adequacy of the current Indonesia surveillance system for DHF and to determine the factors responsible for high DHF transmission in North Sumatera Province and then document the information that can be used for recommendation strategies for the prevention and control of high morbidity of dengue hemorrhagic fever in North Sumatera Province.

1.4.2 Spesific Objective

i. To study and explore the current Indonesian surveillance system for DHF based on the attributes used by WHO as the reference standard.

ii. To determine the factors associated with DHF in North Sumatera Province according to respondents socio-demography, socio-cultural factor, knowledge, attitude and practice.

iii. To determine the association between environmental factors and DHF.

iv. To determine the association between entomological factors and DHF.

v. To determine the association between climatic factors and DHF.

1.5 Hypothesis

i. There is an association between socio-demography, socio-cultural, knowledge attitude, practice, and DHF .

ii. There is an association between environmental factors (breeding site, household characteristic) and DHF .
iii. There is an association between entomological factors (larvae density, adult density) and DHF .
iv. There is an associaton between climatic factors (temperature, humidity, rainfall, rainy days) and DHF .
v. Inefficient surveillance system influence the DHF incidence
vi. Effective surveillance prevention and control could reduce DHF incidence

1.6 Conceptual Framework

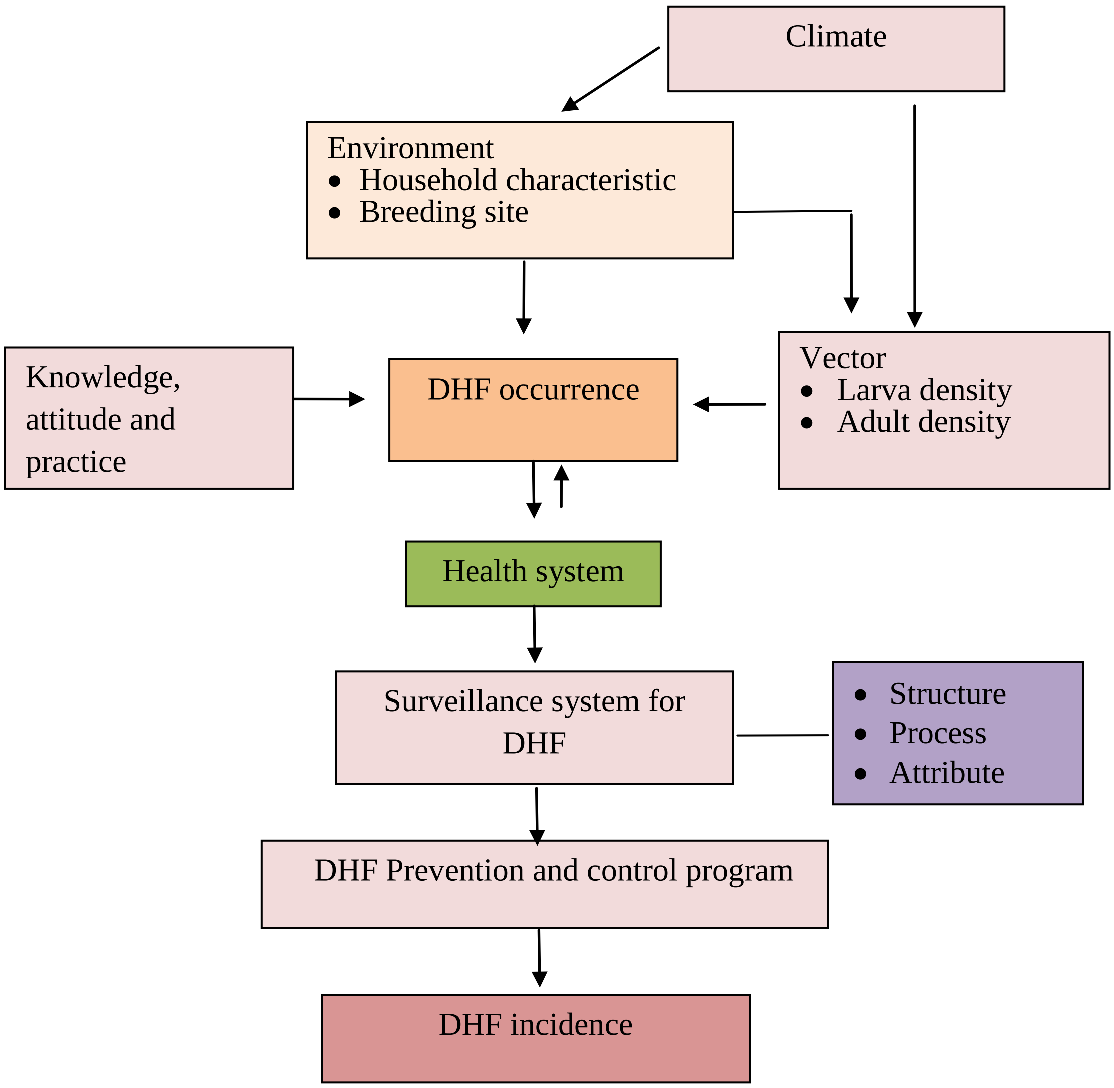

Figure 1.1. Factors associated with DHF occurrence and DHF control program

CHAPTER 2

LITERATURE REVIEW

2.1 The Epidemiology of Dengue Fever and Dengue Hemorrhagic Fever

2.1.1 Dengue Fever and Dengue Hemorrhagic Fever

Dengue infection is one the most important vector-borne disease of human that is caused by dengue virus and transmitted by *Aedes* mosquitoes. The disease becomes health problem around the world (Srikiatkhachorn, 2009; Guzman *et al*., 2010; Whitehorn and Simmons, 2011). The clinical manifestation of dengue infection varies from asymptomatic infection to mild manifestation and severe disease, dengue fever (DF) and dengue hemorrhagic fever (DHF)/dengue shock syndrome (DSS) (Lei *et al*., 2001; Guzman and Kouri, 2003; Noisakran and Perng,2008).

Dengue fever also known as breakbone fever is characterized by biphasic fever, severe headache, retro-orbital pain, myalgia, arthralgia, maculopapular rash, lymphadenopathy and leucopenia. DF is defined by the presence of fever and more than 2 of the following symptoms that include headache, retro-orbital pain, myalgia, arthralgia and maculopapular rash. Biphasic fever and maculopapular rash are the characteristics of dengue fever. Although DF is commonly benign and self limiting, a small percentage of dengue patients could develop progressively into DHF or dengue schok syndrome (Lei *et al.*, 2001; Guzman and Kouri, 2003; Noisakran and Perng, 2008).

DHF is characteristized by dengue fever that is accompanied with bleeding manifestation including skin hemorrhages, bleeding nose or gum, and possible internal bleeding. During the febrile phase, hemostasis disorder can occur. Increased vascular permeability causes bleeding manifestation ranging from petechiae to spontaneous bleeding from nose or gastrointestinal tract (Lei *et al.*, 2001; Guzman and Kouri, 2003; Srikiatkhachorn, 2009). DHF is defined by fever with thrombocytopenia (platelet count≤100,000 platelet/mm3), hemorrhagic manifestation and evidence of plasma leakage (≥ 20% increase in the hematocrit from the baseline value). According to WHO, DHF is classified into 4 gradings of severity as presented in Table 2.1.

Table 2.1. Grading of DHF according to WHO

Grade	Clinical Manifestation
1	no shock: only positive tourniquet test
2	no shock : has spontaneous bleeding other than a positive tourniquet test
3	shock
4	profound shock with unmeasurable blood pressure or and / pulse

Reference: Malavige *et al*, 2004

Dengue shock syndrome is the severe form that is characterized by changes in pulse rate and blood pressure with cold extremities and restless. Shock usually occur during or immediately between 3 and 7 days after the fever is down due to plasma leakage and abnormal hemostasis that could render patients unconscious (Guzman and Kouri, 2003).

2.1.2 Etiology of dengue infection

Dengue infection is caused by dengue virus which belongs to *Arthropod Borne Virus* (Arbovirus) of the flavivirus genus of Flaviviridae family. Dengue virus has four serotypes namely DEN1,DEN2, DEN3, and DEN4. The four dengue serotypes can be distinguished by serological methodologies. The structure of the serotypes antigens is similar to the others, but antibody against each serotype can not give cross protection (McBride and Ohmann, 2000; Shu and Huang, 2004; Noisakran and Perng,2008; Guzman *et al*, 2010). All dengue serotypes can be found in Indonesia whereby serotype DEN3 is dominan and causes severe clinical manifestation (Ministry of Health Indonesia,2005).

Dengue viruses have a ribonucleic acid (RNA) genome that is surrounded by a single chain of nucleotides icosahedral and is enveloped by lipid membrane. The virion has a length of approximately 11 Kb (Kilobases), and consists of a spherical particle, 40-50 nm in diameter, with a lipopolysaccharide envelope. The genome consists of three structural protein molecules that include C(core), prM (membrane), and E (envelope) that form the virus particles and seven nonstructural protein molecules NS1, NS2a, NS2b, NS3, NS4a, NS4b and NS5 (Figure 2.1). Viral protein and RNA synthesis commonly occur in the cytoplasmic of host cells. The NS protein is only found in infected host cells and is required for replication of the virus. The replication begins within 15 hours after infection and does not significantly affect the metabolic function of the host cells (Chuansumrit and Tangnararatchakit, 2006; Noisakran and Perng, 2008; Guzman *et al*., 2010; Whitehorn and Simmons, 2011).

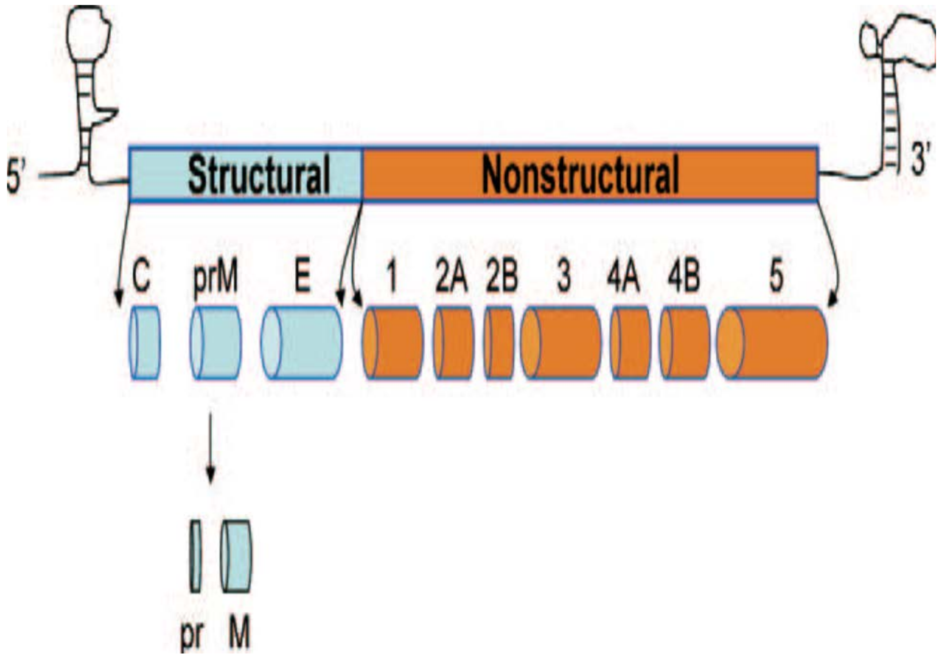

Figure 2.1. The dengue viral genome

A person can be infected with all four serotypes during his / her lifetime. Infection with one serotype of dengue virus produces a lifelong immunity against that specific serotype, but only partial protection is against other serotypes (Shu and Huang, 2004). An infection with a different type increases the risk of complication and the variety in severity depends on the level of virus virulence, viral load and host response (Chuansumrit and Tangnararatchakit, 2006; Wearing and Rohani, 2006; Noisakran and Perng, 2008). The virulence of dengue virus is related to the virus genotype and it plays a role in the pathogenesis of DHF. Dengue virus may infect and replicate in the endothelial and epithelial cells and the dengue virus antigen is detected in cells of the monocyte-macrophage lineage in the lymphoid organs, lung and liver of patients with dengue infection (Mc Bride & Ohmann, 2000).

2.1.3 Transmission

Dengue transmission is a complex phenomenon that involves dengue viruses, the mosquito vectors, human as reservoir and environment which favors the interaction between the mosquito vector and human host. The size, density and biological status of vector mosquito population are critical to the transmission of the dengue virus (Halstead, 2008).

The main vector involved in the spread of dengue fever is *Aedes aegypti*, while the others are *Aedes albopictus* and *Aedes scutellaris*. *Aedes aegypti* is a small, dark mosquito with white marking on its legs and a marking in the form of a lyre on the thorax (Figure 2.2). This mosquito originated in Africa, but now is widespread in tropical and subtropical region throughout the world. Female mosquitoes likes human blood (anthropophilic), while male mosquitoes prefer eating fruits and flowers. These mosquitoes commonly live around human dwelling in and around the house and in urban area (Halstead, 2008).

Figure 2.2. Aedes aegypti mosquito

Aedes aegypti experiences a complete metamorphosis of eggs, larvae, pupae and adult mosquito. During the stage of eggs, larvae and pupae *Aedes* mosquitos live in water. In general, the eggs will hatch into a larvae approximately 2 days after the eggs submerged in water. Larvae stage usually lasts 6-8 days and the pupae stage 2-4 days. Overall growth in eggs into adults mosquito lasts 9-10 days as presented in Figure 2.3 (Ministry of Health Indonesia, 2005).

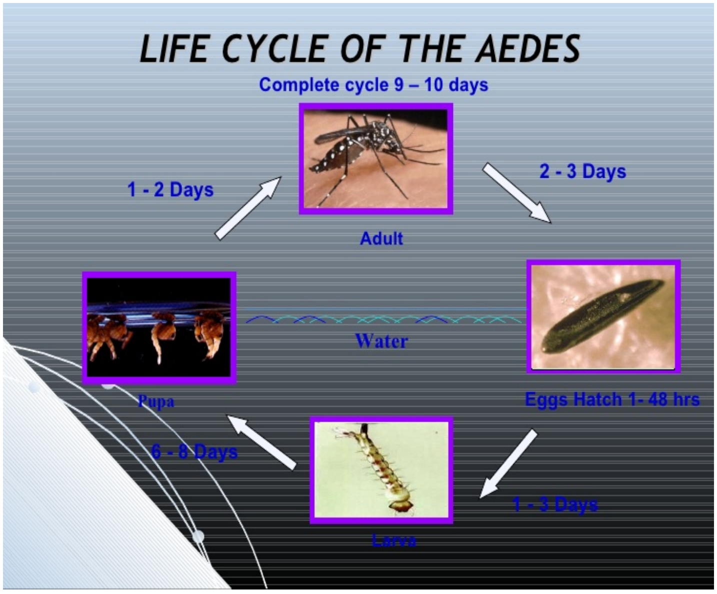

Figure 2.3. Metamorphosis of Aedes aegypti

Female *Aedes* mosquitoes transmit dengue viruses through its characteristics of biters day and preference for human blood. They feed in the morning (9.00 am until 10.am) and late afternoon (4.00 pm until 5.00 pm). *Aedes* mosquito have multiple biting to complete a blood meal so that they are enough for growth and development of eggs. Then the mosquito will rest in a place with optimum condition (humidity and dark place, and hanging clothes) while waiting for the mosquito eggs to mature (Suyasa *et al.*, 2008). After three days feeding on blood, the mosquito lay their eggs inside a container above the water line. Eggs can survive for six months or more. The breeding places of *Aedes* mosquitoes are dark colored artificial or natural water containers that are not directly related to the ground and commonly located in and around the house and protected from the sun. *Aedes* habitats in urban area vary. However, 90% are man made containers such as water storage container, bathtubs, drums, pails, jars, discarded tins, discarded bottles, flower pots, discarded tyres etc (Halstead, 2008).

Dengue hemorrhagic fever is transmitted by the mosquito *Aedes aegypti*. The female *Aedes aegypti* bite an infected person during the viraemic phase of the disease, and usually lasts 4 to 7 days (Figure 2.4). The virus passes from the mosquito intestinal tract to the salivary glands after an extrinsic incubation period, duration from when a mosquito bites an infected person until it becomes infectious, which takes approximately 8 to 12 days. Dengue virus is transmitted from mosquito to human by mosquito salivary proteins. After intrinsic incubation for 3-14 days (average for 4-6 days) the symptoms of the disease appear such as fever, head ache, myalgia, nausea, vomiting and rash (McBride & Ohmann, 2000; Ministry of Health, 2005; Clyde *et al.*,2006; Guzman *et al.*, 2010).

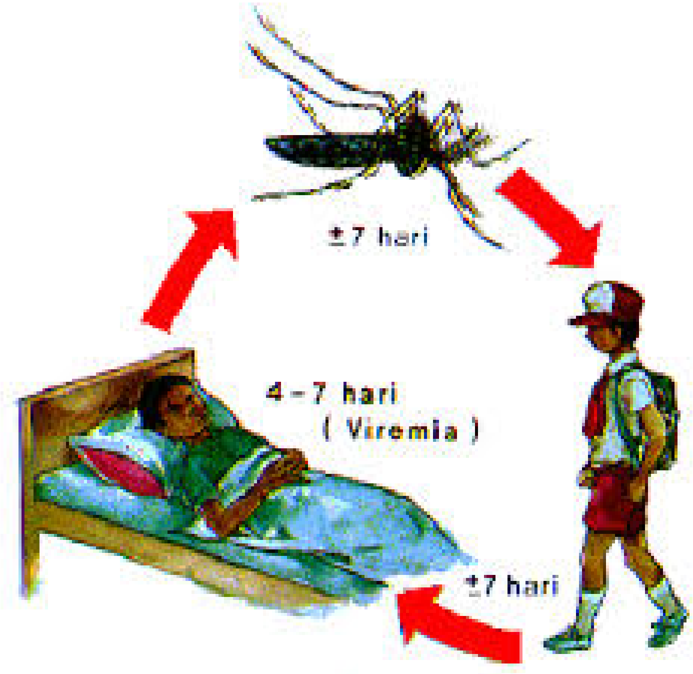

Figure 2.4. Chain of dengue infection

Vector density play a role in the transmission of dengue fever, particularly *Aedes aegypti*. Urbanization in tropical countries has resulted in both the proliferation of *Aedes egypti* and the increasing of susceptible human hosts number. Adult survey, larva survey and egg trap survey were carried out to determine the density of vector mosquitoes. A few indices were used as indicators to determine the abundance of vector mosquitoes such as house, container and breteau indices (Sanchez *et al.*, 2006; Abdalmagid and Alhusein Sh, 2008).

Climatic factors such as temperature and humidity that favor the survival of adult mosquito beyond the extrinsic incubation period, thereby increasing the viral transmission. However, increase transmission also occurs in the rainy season (Mc Bride & Ohmann, 2000).

2.1.4 Epidemiology of DHF

Dengue hemorrhagic fever, one of the most widespread vector borne disease of humans worldwide, initially occurred as epidemic in the tropical and subtropical countries. With increasing globalization and human movement, the geographic expansion of *Aedes aegypti* mosquito vector causes dengue virus infection to occurr worldwide. At the beginning of this new milleneum, approximately 50 to 100 million cases of dengue fever and 500,000 of cases of the DHF occurred annually, predominantly in children under 15 years of age (Gubler, 2002; Guzmán and Kouri, 2003; Guha-Sapir and Schimmer, 2005).

As many as 3.6 billion people are living in areas with high risk of dengue infection with approximately 230 million infection worldwide (Wilder-Smith *et al*, 2012). The majority of cases were in Southeast Asia and the Western Pacific (Guzman *et al*, 2010). World Health Organization (WHO) reported that the annual number of DHF cases for the period 2000-2004 had increased and almost doubled compared to 1990-1999 (Guzman and Kouri, 2003). Now, Dengue is endemic in many countries in Southeast Asia, and a public health problem in Indonesia, Myanmar, Sri Lanka and Thailand (Ministry of Health Indonesia, 2010). Likewise in Malaysia and Singapore (Carrasco *et al*, 2011).

In some tropical and subtropical regions the number of DHF cases are increasing and became a significant cause of death. In Indonesia dengue outbreak occur annually in several provinces with the largest occured in 1998 and 2004 with 79,480 cases and over 800 people died (Kusriastuti and Sutomo, 2005).

Although DHF may infect everyone, however children were more common to have DHF than elderly. It could be related to immunity and susceptibility to dengue fever. On the other hand, the risk of dengue infection in female is equal to male (Guha-Sapir and Schimmer, 2005).

2.1.5 Factors associated with DHF

Factors that are responsible for DHF incidence are complex and not fully understood. However some factors such as the increase in population density and unplanned urbanization, inadequate water supply and waste management system, the increase in air travel, the lack of effective vector control program , the climatic change and poor sosio-economic status have been identified as the key determinants (Guzman and Kouri, 2003; Torres and Castro, 2007).

Several studies had been conducted to look into factors that contributed to DHF incidence. A study conducted by Siquera *et al* (2004) found that older age, low education, and low income population were significantly associated with dengue fever. This was further supported by a study by de Maltos Almeida *et al* (2007) reported that the risks of contracting DHF were similar to the previous study and were associated with socioeconomic, demographic and infrastructure characteristics and higher household density.

A study conducted by Phuong *et al* (2008) found that the farming occupation, number of children less than 15 years old in household, inexperience with dengue fever in household, garden near the house and water containers having mosquito larvae were associated with a higher risk of dengue fever in Vietnam.

Other factors that contributed to increase DHF incidence were poor sanitation, housing pattern, poverty, illiteracy, cultural practices and climate (temperature, rainfall, humidity). All these factors were noted to promote vector proliferation (Chao *et al.*, 2000; Hossain *et al.*, 2000; de Mattos Almeida *et al.*, 2007).

Sosio-economic factors also play role in the incidence and prevalence of DHF. These factors are known to affect the abundance of *Aedes aegypti* mosquitoes and disease transmission related to housing with unhygienic condition and poor household design. Housing with the presence of solid waste around the house and prolonged storage of water for domestic use created potential breeding habitat for *Aedes aegypti*, therefore increasing the transmission of dengue infection (Nagao *et al.*, 2003; Mondini and Chiaravalloti Neto, 2007). A study by Heukelbach *et al* (2001) in Fortaleza found that there was no association between socioeconomic factors and dengue fever. The same was reported by Mondini *et al* (2007) in Southern Brazil where they found no association between risk occurence of dengue and socioeconomic factors. While Mobarak study *et al* (2008) in Dhaka city found dengue fever more commonly in middle and high sosioeconomic group.

A study conducted by Bohra and Andrianasolo (2001) in Rajasthan India investigated the association between risk of dengue and sosiocultural factor and they found housing pattern, limited use of mosquito protection measures, irregular water