MINISTRY OF EDUCATION AND TRAINING

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SITUATION AND ETIOLOGY OF VIRAL ENCEPHALITIS AND PATIENT DIRECT TREATMENT COSTS IN 3 NORTHWEST PROVINCES VIETNAM, 2017 – 2018

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ABBREVIATION OF THE PUBLIC HEALTH DOCTORAL THESIS

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LIST OF PUBLISHED REAEACHES RELATED TO THE THESIS

1. Vũ Vi Quốc, Vũ Trọng Dược, Trần Vũ Phong, Hoàng Minh Đức, Vũ Sinh Nam, Nguyễn Thị Yên, Trần Hải Sơn, Trần Công Tú, Trần Chí Cường, Nguyễn Tiến Dũng, Đoàn Ngọc Hùng, Nguyễn Văn Sửu, Trần Như Dương (2018), "Véc tơ truyền bệnh Viêm não Nhật Bản tại một số điểm thuộc khu vực Tây Bắc, 2018", *Tạp chí Y học dự phòng*, tập 28, số 7, tr. 96-103.
2. Vũ Vi Quốc, Ngũ Duy Nghĩa, Ngô Huy Tú, Trần Ngọc Thanh, Phạm Thị Cẩm Hà, Nguyễn Thị Thường, Lê Thị Hiền Thu, Trần Thị Nguyễn Hòa, Vũ Sinh Nam, Đặng Đức Anh, Trần Như Dương (2019), "Một số tác nhân phổ biến gây Viêm não vi rút tại 3 tỉnh khu vực Tây Bắc, 2017-2018", *Tạp chí Y học dự phòng*, Tập 29, số 12, tr. 57-62.
3. Vũ Vi Quốc, Phạm Thị Cẩm Hà, Ngũ Duy Nghĩa, Ngô Huy Tú, Lưu Nguyên Thắng, Trần Anh Tú, Trần Ngọc Thanh, Nguyễn Công Khanh, Vũ Sinh Nam, Nguyễn Tiến Dũng, Đoàn Ngọc Hùng, Nguyễn Văn Sửu, Trần Như Dương (2020), "Đặc điểm dịch tễ học của Viêm não vi rút tại một số tỉnh Tây Bắc năm 2017-2018", *Tạp chí Y học dự phòng*, tập 30, số 1, tr. 64-73.
4. Vũ Vi Quốc, Nguyễn Thị Thi Thơ, Ngô Huy Tú, Ngũ Duy Nghĩa, Trần Ngọc Thanh, Phạm Thị Cẩm Hà, Nguyễn Tiến Dũng, Đoàn Ngọc Hùng, Nguyễn Văn Sửu, Hoàng Minh Đức, Nguyễn Hồng Sơn, Vũ Sinh Nam, Trần Như Dương (2020), "Chi phí điều trị trực tiếp liên quan đến y tế của bệnh nhân Viêm não vi rút tại cơ sở y tế 3 tỉnh Tây Bắc: Sơn La, Điện Biên và lào Cai, 2017-2019", *Tạp chí Y học dự phòng*, tập 30, số 6, tr.42-52.

ABBREVIATIONS

ARN	Axist ribonucleic	
CI	Khoảng tin cậy	Confidence Interval
Cx	Culex	
CSMĐ	Chỉ số mật độ	
DCCN	Dụng cụ chứa nước	
EBV	Vi rút Epstein Barr (vi rút Herpes 4)	Epstein Barr Virus
ELISA	Kỹ thuật miễn dịch gắn men	Enzyme-linked Immunosorbent Assay
hCMV	Vi rút Cytomegalo	Human Cytomegalovirus
HCVNC	Hội chứng Viêm não cấp	
HSV	Vi rút Herpes Simplex	Herpes Simplex Virus
NPEV	Các vi rút đường ruột không phải polio	Non-Polio Enterovirus
PCR	Phản ứng khuyếch đại chuỗi polymerase	Polymerase Chain Reaction
PTN	Phòng thí nghiệm	
PV	Phỏng vấn	
SL	Số lượng	
RdRP	ARN polymease phụ thuộc ARN	RNR dependent RNR polymerase
TB	Trung bình	
TCM	Tay chân miệng	
TTYTDP	Trung tâm Y tế dự phòng	
VNNB	Viêm não Nhật Bản	Japanese Encephalitis
VNVR	Viral Encephalitis	
VRĐR	Vi rút đường ruột	
VSDTTƯ	Vệ sinh dịch tễ Trung ương	

BACKGROUND

Viral Encephalitis (VE) is a pathological condition due to an acute viral infection in brain parenchymal organization, caused by various viruses with neural cell affinity. VE has been and is being a large public health problem worldwide, due to its high fatality rate and permanent neurological sequelae. Globally annual viral encephalitis morbidity varied from 3.5 – 7.4 case per 100,000 inhabitants, of which small children occupied higher rates, varied from 15 - 22 cases per 100,000 small children [78].

So far, the most common factor of encephalitis had been identified as viruses, occupying about 70% total diagnosed factors [138]. In different regions, distribution of encephalitis viruses was different depending on the geographic and climate characteristics. In 2007, research done by Solomon et al had listed some viral encephalitis factors being characterized for continents, of which: Asian region - Japanese Encephalitis virus (JE), West Nile virus, Nipah virus; European and American regions – commonly encephalitis virus, tick borne virus, West Nile virus, Toscana virus, rabies virus, Dengue virus, St. Louis virus, Rocio virus. In Africa there were often West Nile virus, rabies virus, Rift Valley virus, Congo hemorrhagic fever virus, Dengue virus, Chikungunya virus, … [7] [121]. Certain rersearches also recorded encephalitis caused by Herpes virus, gastroenteritis virus (VGE) [138] [42] [97]. In the Asia, JE virus was the primary cause of VE with an estimated annual morbidity of 67,900 cases, of which, fatality rate was about 20 – 30%, and neurological sequelae presented in about 30 – 50% survivors [121].

In Vietnam, VE was an endemic disease in the infectious disease surveillance system regulated by the Ministry of Health. The disease was recorded in most provinces and cities nationwide, notably in the North. During the recent 10 years, VE morbidity varied from 1.000 – 2.000 cases per year, concentrated in certain northern mountainous provinces, especially in 3 of them: Son La, Dien Bien and Lao Cai [4]. This region had a population of about 2.5 million people living in a widespread surface and had frontier borders with Laos and China. Inhabitants were mainly ethnic minority groups including Thai, H'mong, Tay and Nung. During the year 2014, Son La had recorded a VE epidemic outbreak lasting from June until September with 164 cases infected, of which there was 21 death [10]. In Dien Bien and Lao Cai, during the last 5 years there were also hundreds cases with VE and tens deaths. Only in six first months of 2016, Dien Bien had recorded VE outbreaks with 54 cases in 10/10 districts/towns. Although it was a prominent epidemic in the region, so far there had bene no comprehensice research to answer questions on its epidemiologic

chareacteristics, etiology, transmission vectors, as well as its cost burden. Therefore, we had conducted the research: "Situation and etiology of Viral Encephalitis and patient direct treatment costs in 3 northwest provinces of Vietnam, 2017-2018" with the following objectives:

1. ***Situation of của Viral Encephalitis in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018 described.***
2. ***Some viral encephalitis factors and presence of mosquitoes transmitting Japanese Encephalitis in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018 identified.***
3. ***Viral Encephalitis patient direct treatment costs in health facilities of 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018 identified.***

New scientific points and practical value of the research

Provision of updated information on VE situation in 3 northwest provinces 2017 – 2018: high number of VE cases recorded; the diseases occured widely, with a seasonal characteristic; most cases and deaths were children under 15 years old (occupied 51.8 and 94,1), 23% deaths were positive with JE.

Identification of the diversity of viral encephalitis factors in 3 northwest provinces, including JE virus, VGE, HSV, Dengue virus, and hCMV, of which JE virus and VGE were 2 most common factors. 8.9% specimen detected as co-infected with 2 types - JE virus and VGE. 13 VGE serotype found. Most JE cases had not been vaccinated or fully vaccinated against JE (97.1%).

Identification of the presence of two mosquito species (and their larvae) - main vectors for JE transmission, *Cx. tritaeniorhynchus and Cx. vishnui* with predominant proportion (68,48%) in 3 northwest provinces. Mosquito density indices of *Cx. tritaeniorhynchus* and *Cx. vishnui* in animal sheds were 19.5 time (*Cx. trtaeniorhynchus*) and 11.8 time (*Cx. vishnui*) higher than indoor mosquito density index.

Identification of average medical service direct treatment costs of each VE patient in 3 northwest provinces, 2017-2019, at rather high level (8.010.875 dong). Of which patients had to pay 414.299 dong from their own pocket, equivalent to 5.2%, the rest was paid by the government through the health insurance. The two medical items occupied huge proportions in the treatment cost including medicines, blood, IV fluid and bed expenses. Medical service direct treatment costs had been associated with age group and duration of treatment.

Structure of the thesis

The thesis consists of 140 pages not counting references and annexes, with 25 tables, 45 figures and charts. Background: 2 pages; overview: 41 pages; research subjects and methodology: 26 pages; research findings: 39 pages; discussion: 29 pages; conclusion: 2 pages and recommendation: 1 page. 148 references, of which 41 in Vietnamese and 107 in foreign languages.

Chapter 1. OVERVIEW

1.1. Outlines of Viral Encephalitis

1.1.1. Concepts of Acute Encephalitis Syndrome (AES) and Viral Encephalitis (VE)

Acute Encephalitis Syndrome (AES) was an acute brain damage with clinical manifestation of perceptual disturbances, convulsions, possibly with focal or systemic neurological signs, increased mononuclear white blood cells in cerebrospinal fluid, abnormal cranial imaging and electroencephalogram diagnoses [1], [122].

VE was one of causes for AES. VE was a pathological condition due to an acute viral infection happened in brain parenchymal organizations, caused by various viruses with neural cell affinity. Clinical chareacteristics were diversified, but key manifestation was acute brain syndrome leading to perceptual disturbances at different levels.

1.1.2. Some common Viral Encephalitis

a. Mosquito-borne Viral Encephalitis

Mosquito-borne Viral Encephalitis was the most common encephalitis, consisted of the following groups: Japanese Encephalitis, Western Equine Encephalitis, Eastern Equine Encephalitis, St. Louis Encephalitis, Murray Valley Encephalitis, Lacrosse Encephalitis, California Encephalitis, Rocio Viral Encephalitis, Jamestown Canyon Encephalitis, Snowshoe Hare rabbit encephalitis.

b. Tick-borne Viral Encephalitis

Including the following groups: Far Eastern Tick-borne Encephalitis, Mid European Tick-borne Encephalitis, Louping ill, Powassan encephalitis. Tick-borne Viral Encephalitis had similar clinical chareacteristics as Mosquito-borne Viral Encephalitis.

c. Viral Encephalitis caused by other common viral factors

Besides Mosquito-borne and Tick-borne Viral Encephalitis, it was recorded hundreds other viral encephalitis factors, commonly: HSV, CMV, Dengue, VGEs, chickenpox virus.

1.2. Situation of Viral Encephalitis worldwide and in Vietnam

1.2.1. Situation of Acute Encephalitis Syndrome and Viral Encephalitis worldwide

AES used to cause severe clinical manifestations, with prolonged hospital time, requiring multiple diagnosis techniques and expensive treatment measures, however it left behinds a lot of severe sequelae, even fatal outcomes. Most AES cases had not been able for doing direct etiology identification from brain organisation, but etiological factor detection via seral, immunological or molecular biology tests... Among factors causing AES, only about 10% etiological factors had specific treatment medicines such as bacteria, fungi, parasites and certain encephalitis viruses like Herpes simplex, Varicella zoster; however majority of cases had no specific treatment [118, 144].

Jmor et al, 2008, combining 87 researches on AES worldwide revealed that morbidities in western countries during the recent years was 7.4 per 100,000 inhabitants, of which among children was 10.5 to 13.8 per 100,000 children; among adults was 2.2 per 100,000. In the Asia, AES was rather common; JE virus was the primary factor causing AES for children in Asia Pacific region and in South East Asian countries, of which children under 15 years old had higher risks of acquiring the disease [50], [72], [88], [133], [143].

1.2.2. Situation of Acute Encephalitis Syndrome and Viral Encephalitis in Vietnam

In Vietnam, AES had already been studied begining from the last century, of which JE had been recorded since 1952. During the last 10 years, VE morbidity had been commonly recorded higher in northern mountainous provinces such as Lao Cai, Son La and Dien Bien. Average morbidity during 3 years 2014 - 2016 in these 3 provinces occupied 46% total cases of the northern region. Research done by Nguyen Thi Thu Yen et al on HCNC in Vietnam revealed that cases had been extensively recorded during summer months, especially in June [109]. Since 1993, Vietnam had been able to produce JE vaccine, and in 1997 the vaccine had bene introduced to the Expanded Immunization Program for children 1–5 yeas of age in high risk districts. So far, JE morbidity had been reduced significantly. However, in the northern mountainous region, JE morbidity remained rather high.

1.3. Factors causing Viral Encephalitis

There were over 100 types of viral encephalitis factors, of which JE was one of the most important causes of encephalitis among children. JE virus was endemic mainly in the Asia, meanwhile, Tick-borne Viral Encephalitis was an important cause of encephalitis in East, Mid and North European countries, North China, Mongolia and Russi. Researches done in 2017 and 2019 in the United States revealed that gastroenteritis virus was the most common etiological factor, causing about 58% cases of meningitis/encephalitis among children and newborns and 52% cases among adults [51].

Table 1.1. Common factors causing Viral Encephalitis [121]

Groups of viral factors	
Arbovirus	JE, St. Louis Encephalitis, West Nile Encephalitis, Eastern Equine Encephalitis, Western Equine Encephalitis, Tick-borne Viral Encephalitis, …
Gastroenteritis virus	Coxsackie, Echo, Enterovirus 70 and 71, Parecho, and Poliovirus
Herpes virus	HSV types 1 and 2, chicken pox, Epstein Barr, Cytomegalovirus (hCMV), Human Herpes Virus types 6 and 7
Paramyxovirus	Mumps virus and measles virus
Other	Influenza virus, Adenovirus, Parvovirus, Lymphocytic Choriomeningitis virus, Rubella virus

Following were certain common groups of viruses causing encephalitis:

1.3.1. Arbovirus causing Viral Encephalitis

Arbovirus (Arthropod borne virus) carried by blood-sucking arthropods and transmitted within vertebrates including human beings. The virus replicated in arthropods however it could not cause them diseases. Nowadays it was detected more than 400 types of Arbovirus, of which about 150 types caused diseases to human beings and animals. The most dangerous were các encephalitis and hemorrhagic fever viruses, which could lead to a high fatality.

1.3.2. Gastroenteritis virus causing Viral Encephalitis

VGE was a branch of the family Picornaviridae, including 15 species. VGE A, B, C and D was potential to infest human beings, and each species had many

serotypes. Most VGE was transmitting via fecal-oral route. Certain VGE could infest directly from hands to eyes. Natural hosts of VGE species A-D were human beings [1].

1.3.3. Viral Encephalitis caused by Herpes virus

a. Herpes simplex virus (HSV)

HSV was classified into Herpesviridae family, Simplexvirus genre, including two species HSV-1 and HSV-2 or also HSV type-1 and type-2. In countries where JE was not endemic, HSV was the most important group of virus. However, depending on countries, infection rate varried from 1%-10% or higher (France: 14%; Netherlands: 11%; Japan: 20%; USA: 20%)[71], [98].

b. Cytomegalovirus

Cytomegalovirus (common name hCMV) or Herpes virus that infected human beings was coded as 5 (human herpes virus, briefly HHV-5), belonged to Herpesviridae family, Cytomegalovirus genre. hCMV infested bone marrow CD34 cells, monocytes-macrophages, and endothelial cells in hidden form. hCMV caused encephalitis via blood.

1.4. Mosquitoes transmitting Japanese Encephalitis

Many mosquito species had been found as vectors transmitting JE virus. Researches done in countries where JE was endemic identified *Cx. tritaeniorhynchus, Cx. vishnui, Cx. gelidus, Cx. pseudovishnui and Cx. fuscocephalus, Cx. pipiens* as JE transmitting species. Of which *Cx. tritaeniorhynchus and Cx. vishnui* were confirmed key vectors transmititng JE virus to human beings in the Asian region. Besides, at least 11 other mosquito species were infectged with experiemtal virus in laboratories.

Cx. tritaeniorhynchus and Cx. vishnui prefered animal blood – such as of pig and bird – than of human beings. Therefore, they often focused on fiding their hosts in animal sheds. JE transmitting mosquitoes often carried out blood sucking activities during the night, especially from 18 to 22 o'clock and digested outdoor [27].

1.5. Economic burden and treatment cost of Viral Encephalitis

1.5.1. Burden of Viral Encephalitis

Research by Khetsuriami et al on VE disease burden in USA, 1988-1997, revealed that average expenses for one treatment episode in 1997 were 28.151 USD, and total country annual expenses for VE were 650 millios USD [87]. During the period 2004 - 2013 in USA, average treatment time was 16 days; for children admitted to pediatric ICU, their treatment time was up to 25 days. Average treatment cost for acute patients was 64.604 USD, and 260.012 USD for those in pediatric ICU [46]. In the region, Tarantola et al revealed that direct and indirect expenses for JE treatment were equivalent to 10 month salary of a Cambodian [107].

In Vietnam, from 1998 until 2007, acute encephalitis had been recorded in all 64 provinces/cities, average morbidity in northern provinces was 3.0 cases per 100,000 inhabitants and in southern ones was 1.9 case per 100,000, etiological factor was mainly JE virus [146] [128]. In 2017, the whole country recorded 1.180 cases and 37 deaths due to VE, morbidity per 100,000 inhabitants was 1.18, mortality per 100,000 inhabitants 0.04 [8]. However, so far there had not been any research analyzing the VE disease burden.

1.5.2. Disease treatment cost

a. Classification of expenses

(*) Direct medical expenses: including 1) vaccine, medicines; 2) testing; 3) medical supplies; 4) use of diagnostic equipment; 5) personnel costs such as doctors, nurses, technicians; 6) wards, material cost, necessary equipment and relevant services [26], [34], [104].

(*) Direct non-medical costs: travel expenses, meals and drinks for patients and family members, indoor care services; insurance; expenses not paid by the third party [53], [104].

(*) Indirect costs: loss of income due to temporal or partial or permanent injuries; Non-paid support and loss of income by family members due to stop working to take care for patients [5],[41], [76], [111] .

Chapter 2. RESEARCH METHODOLOGY

2.1. Objective 1: Situation of Viral Encephalitis in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018 described

2.1.1. Research subjects

Patients diagnosed with VE admitted to treatment facilities following defined criteria (Decision No. 2322/QĐ-BYT dated 30/6/2006, Guidelines on diagnosis and treatment of acute viral encephalitis in children)

2.1.2. Research location and time

4 provincial general hospitals and 31 district general hospitals of three provinces Son La, Dien Bien and Lao Cai from January 2017 – December 2018.

Research design: **Description of case series study**.

2.1.3. Sample size:

All cases meeting case definition criteria had been included in the research. According to VE surveillance data in 3 provinces Son La, Dien Bien and Lao Cai for

the last 5 years, average VE morbidity of 3 provinces was about 150 cases per year. Estimated sample size was 150 cases x 2 years = 300 cases. In fact it were recorded 473 VE cases, 2017-2018.

2.1.4. Methods and tools for data colletion

For the patient meeting case definition criteria, the following steps should be carried out:

- Enrolling the patient, inviting him/her to take part in the research.
- Investigating with the designed case investigation form
- Collecting specimen: 1 cerebrospinal fluid specimen, 1 seral specimen and 1 stool specimen.

2.2. Objective 2: Some viral encephalitis factors and presence of mosquitoes transmitting Japanese Encephalitis in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018 identified

2.2.1. Identification of some viral encephalitis factors

2.2.1.1. Research subjects

Specimen collected from VE patients under Objective 1 included: cerebrospinal fluid, seral, and stool specimen

2.2.1.2 Research location and time

Tests had been done in 3 reference laboratories of NIHE, including: Laboratory for arbovirus, Laboratory for gastroenteritis virus and Laboratory for Herpes virus from January 2017 until June /2019.

2.2.1.3 ***Research design:*** Description in combination with analysis of laboratory findings.

2.2.1.4 ***Sample size:*** All specimen collected from the Objective 1.

2.2.1.5 Methods and tools for data colletion

Collecting 3 types of specimen: cerebrospinal fluid, seral and stool specimen. Concretly:

- Cerebrospinal fluid: 2 ml from a patient over 1 year old and 1 ml from an infant under 1 year old at the admission or within 5 days from the onset.
- Sera: 5 ml venous blood from a patient over 1 year old and 3 ml from an infant under 1 year old within 7 days after admission or before discharge.
- Stool: 1 tube, equivalent to 5 – 10 grams at the admission or within 5 days from the onset.

Specimen were transported to the National Institute of Hygiene and Epidemiology for testing.

b. Testing method

Using ELISA technique to detect IgM antibodies for: JE and Dengue; single-primer Realtime PCR technique with cerebrospinal fluid specimen to identify viruses: Dengue, JE, VGE (EV71, ECHO, Coxsackie A), HSV (HSV-1 and HSV-2), hCMV; Multiplex PCR technique with stool specimen to identify VGE factors such as EV71, and Coxsackie A6, A10, A16; snRT-PCR/Sequencing technique to identify viral factor ECHO.

2.2.2 Identification of the presence of mosquitoes transmitting Japanese Encephalitis

2.2.2.1 ***Research subjects:*** JE virus transmitting mosquito and larvae.

2.2.2.2 Research location and time:

a. **Location:** 12 communes of 3 provinces: Son La: Mai Son district (township Hat Lot, commune Co Noi), Son La city (ward Quyet Thang, commune Hua La); Dien Bien: Dien Bien district (communes Thanh Xuong, Nua Ngam, Thanh Luong and Thanh Hung); Lao Cai: Bao Thang district (communes Xuan Giao, Gia Phu and Phong Hai, township Pho Lu)

b. Time: investigation was conducted in June and July 2018, when Viral Encephalitis reached the highest level.

2.2.2.3 ***Research design:*** Cross-sectional descriptive study.

2.2.2.4 ***Sample size:*** In each commune, to collect mosquitos in 30 households and 30 animal sheds following routine mosquito surveillance guidelines of the National Institute of Hygiene and Epidemiology.

2.2.2.5 Methods and tools for data colletion

a. Mosquito collection

Time for collection: To collect mosquitoes resting in animal sheds and in house from 18 to 22 o'clock. To investigate larvae from 14 to 17 o'clock of the same day.

Mosquito collection technique: To use hand aspirator to catch mosquitoes. Each group had 2 people, one catched mosquitoes indoor and another in animal sheds. Each household was investigated for 15 minutes.

b. Larva collection:

To use plastic ladle with handle, diameter of 15 cm, deapth 10 cm, to collect larvae. To obtain from each water body 10 ladles (5 with slow and 5 with rapid speed). To use pipettes to attract larvae and put in a bottle. After collecting larvae, to observe and record the presence of aquatic plants.

2.2.3 Identification of mosquito and larvae:

To identifyy mosquitoes and larvae using the mosquito identification chart for Vietnam by Chester J. Stojanovich and Harold Georye Scott, 1965 [123].

2.3 Objective 3: Viral Encephalitis patients direct treatment costs in health facilities of 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018 identified

2.3.1 Research subjects

VE patients who were research subjects for Objective 1.

Patients meeting criteria for research subjects. Deaths caused by VE were not included because it was unable to count expenses for the whole treatment episode.

2.3.2 Research location and time

The research was carried out in health facilities where VE patients had been consulted and treated in 3 provinces of Son La, Dien Bien, and Lao Cai from January 2017 until December 2018.

2.3.3 Research design

Description in combination with analysis of treatment cost in health facilities, based on the retrospective study of available data, following point of view of service providers.

2.3.4 Sample size

There was a total of 473 VE patients. After removing deaths, 456 recovered patients were included in the research for direct treatment costs.

2.3.5 Methods and tools for data colletion

- To retrieve information from medical record files and hospital bill receipts of VE patients.

2.3.6 Content and method for cost analysis

In this research, we mentioned only direct medical expenses: spending on medical examination, spending on bed day, and spending on image analysis, testing, and treatment medicines.

2.4 Data processing and analysis

Data were entered and processed using Epi Data 3.1, and analysed using STATA. Univariate statistical algorithms were used to describe characteristics of research subjects. Data were presented in tables and charts.

2.6. Research ethics

This research had been approved by the Medical Ethics Council of National Institute of Hygiene and Epidemiology in Certificate IRB-VN 01057-47/2016 dated 30/12/2016 No. 47/2016.

Chapter 3. RESEARCH FINDINGS

3.1. Situation of Viral Encephalitis in Son La, Dien Bien, and Lao Cai, 2017-2018

3.1.1. Distribution of Viral Encephalitis by geography

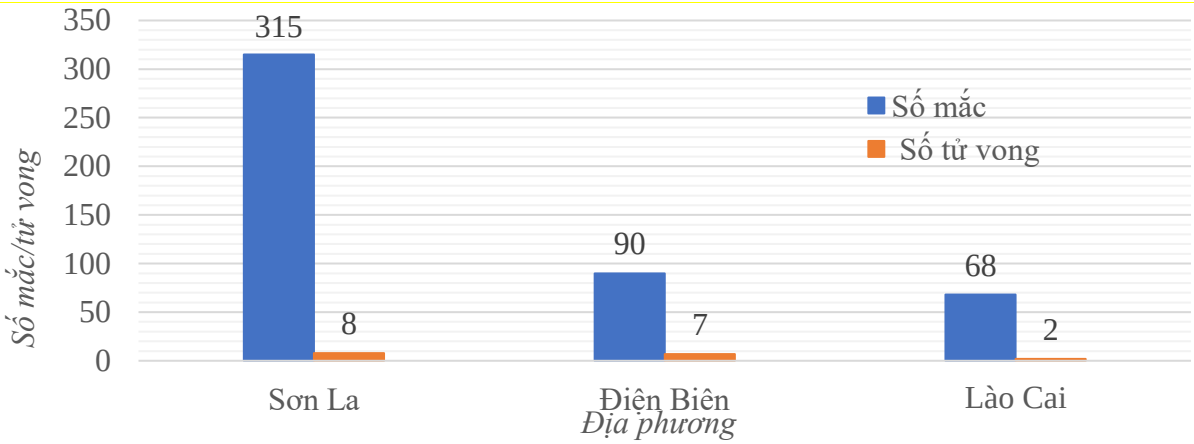

Figure 3.1. Distribution of norbidity and mortality caused by VE in 3 northwest provinces, 2017 – 2018 (n=473)

In 2 years 2017-2018 in 3 northwest provinces it was recorded 473 clinical VE cases, of which 17 deaths, fatality rate was 3.6%. Son La: 315 cases, 8 deaths; Dien Bien: 90 cases, 7 deaths; Lao Cai: 68 cases, 2 deaths. Average morbidity per 100,000 inhabitants of Son La was 13.1, Dien Bien 8.5; Lao Cai 5.1. Fatality rate was highest in Dien Bien (7.8%), then Lao Cai 2.9%, and Son La 2.5%. In Son La, cases were presented in 11/12 districts and the city. Son La city, Mai Son, Thuan Chau and Song Ma had higher morbidity. In Dien Bien, cases were recorded in 9/10 districts and town with higher morbidity in districts of Mường Chà, Dien Bien Dong and Nam Po. In Lao Cai cases found in 8/9 districts and town, with high morbidity in Sa Pa, Bao Yen, Bao Thang, and Van Ban.

3.1.2. Distribution of Viral Encephalitis by time

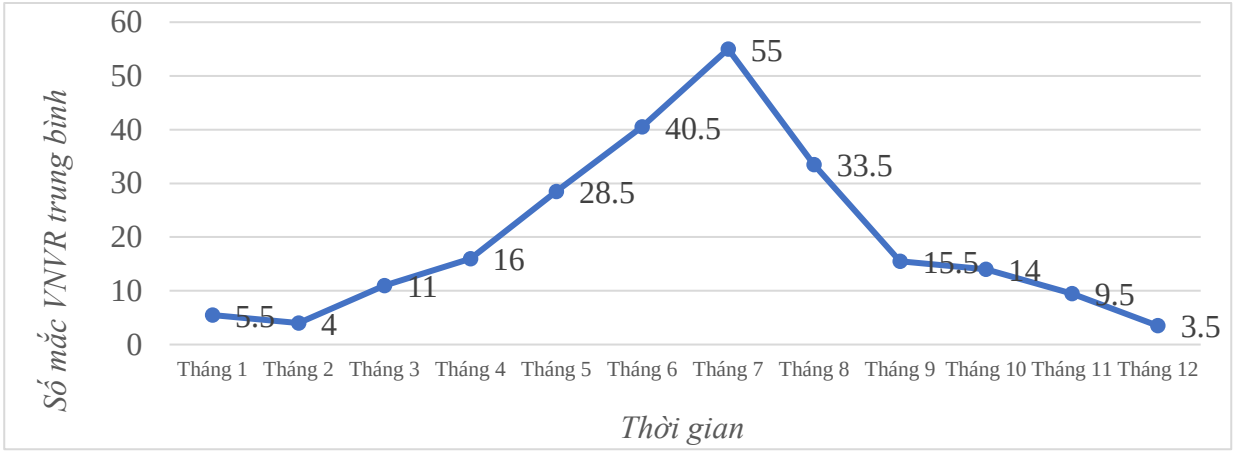

Figure 3.5. Distribution of VE cases by month in 3 northwest provinces, 2017 – 2018 (n=473)

Cases recorded in all months of year, however increased from April and reached their peaks in June and July with average morbidity from 40 – 55 cases per month. Only two months, June and July, had 40.4% total cases of the year. In December, January and February lower cases were recorded. Deaths also reached their peak in June and July.

3.1.3. Distribution of Viral Encephalitis by sex

Cases were presented in both sexes, males occupied 55% (260 cases) but were not significantly higher than among females. For individual province, in Son La there were 173 males (54.9%); in Dien Bien there were 55 males (61.1%). In Lao Cai, there were 32 males (47.1%), slightly lower than females.

3.1.4. Distribution of Viral Encephalitis by age group

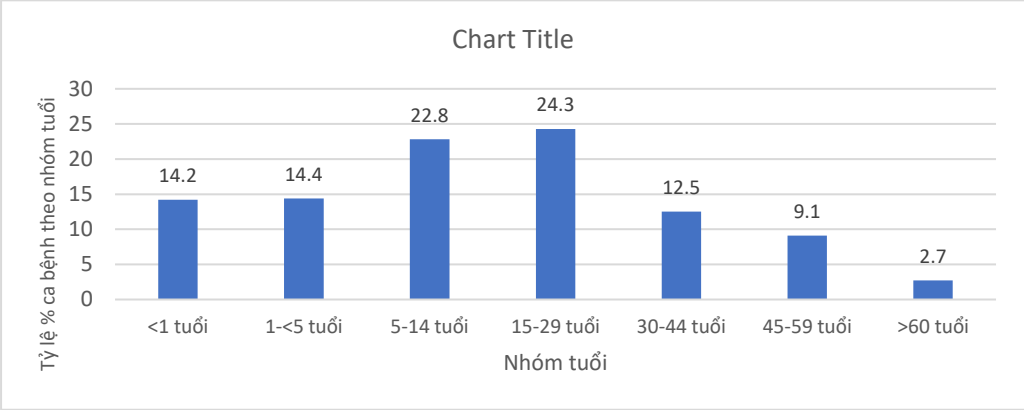

Figure 3.10. Distribution of VE cases, 3 provinces by age group, 2017–2018 (n=473)

VE cases presented in all age groups, mainly in the group of children under 5 years old, occupying 28.6%; then the group of 15 – 29 years (24.3%); and the group of 5 – 14 years (22.8%). Recorded 13 cases in the group of over 60 years (2.7%). In Son La, the highest proportion of cases wa in the group of 15–29 years (29%), then the group of 5–14 years (24.4%). In Dien Bien, children <15 years occupied 66.7%. In Lao Cai, the group of 1–<5 years had the highest proportion (35.3%). Overall, 70.6% of cases was <15 years old.

3.1.5. Distribution of Viral Encephalitis cases by occupation

Research findings revealed that 58.1% cases were small children, school children, then farmers that occupied 33.8%; other occupations recorded small proportion. In Son La, cases among farmers occupied 41%, and school children 30.2%. In Dien Bien, 48.9% cases were small, preschool children. In Lao Cai, 57.4% cases were preschool children and 22.1% were school children.

3.1.6. Distribution of Viral Encephalitis cases by ethinic group

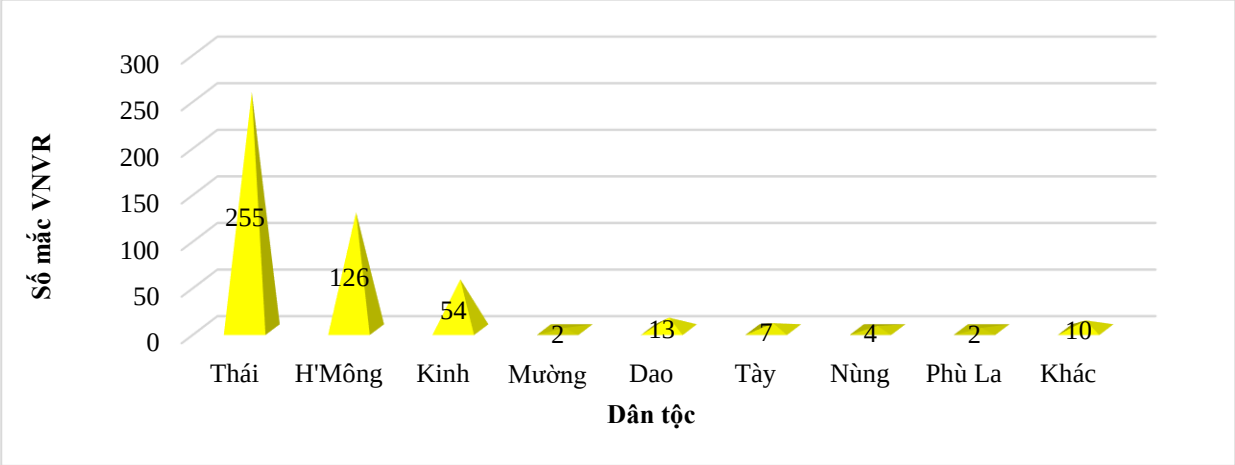

Figure 3.16. Distribution of VE cases in 3 northwest provinces by ethinic group, years 2017 – 2018 (n=473)

Cases in Thai ethnic group occupied the highest proportion (53.9%), then H'mong ethnic group (26.6%), and Kinh ethnic group (11.4%). Muong, Dao, Tay, Nung, Phu La and other ethnic minorities occupied small proportions. In Son La, Thai ethnic group occupied a high proportion of cases (72.7%), H'mong and Kinh had similar proportions of 12.7%. In Dien Bien, cases in H'mong ethnic group occupied the highest proportion (60%), then Thai ethnic group (28.9%). Similarly, in Lao Cai, cases in H'mong reached the highest proportion (47.1%), then in the ethinic groups of Dao (17.6%), Kinh, Tay, Nung, … which occupied smaller proportions.

3.1.8. Some chareacteristics of deaths due to VE

In 2 years of research, in 3 northwest provinces there were recorded 17 deaths out of total 473 VE cases, fatality rate was 3.6%. Son La recorded a fatality rate of 2.5%; in Dien Bien it was 7.8% and Lao Cai 2.9%.

3.2. Some viral encephalitis factors and the presence of mosquitoes transmitting Japanese Encephalitis in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018

3.2.1. Some viral encephalitis factors in 3 northwest provinces, 2017-2018

Of total 473 patients investigated, 393 blood specimen (83.1%); 396 cerebrospinal fluid specimen (84%) and 126 stool specimen (26.6%) had been collected.

3.2.1.1 Results of viral factor testing among patients investigated

Of total 473 patients, it was detected that 135 cases were positive to at least one viral factor. Overall positivity was 28.5%.

Table 3.5. Results of viral factor testing among VE patients (n = 473)

Factor	Cerebrospinal fluid		Sera		Stool		Total Positive /Total cases (%)
	No. specimen	Positive	No. specimen	Positive	No. specimen	Positive	
JE	396	79 (19.9%)	393	89 (22.6%)	-	-	105/468 (22.4%)
VGE	173	4 (2.3%)	-	-	126	34 (27.0%)	38/265 (14.3%)
Dengue	-		69	1 (1.4%)	-	-	1/69 (1.4%)
hCMV	377	2 (0.53%)	-	-	-	-	2/377 (0.53%)
HSV	377	1 (0.26%)	-	-	-	-	1/377 (0.26%)
Total							**135/473 (28.5%)**

Various viral encephalitis factors were detected, including JE virus, VGE, HSV, Dengue virus, hCMV. Positive rate of JE virus was highest (22.4%); then VGE (14.3%). Other viruses were: Dengue (1.4%), hCMV (0,53%) and HSV (0,27%). In Son La, 58/315 VE patients were positive with at least one viral factor (18.4%). In Dien Bien, positive rate was 42.2% (38/90 patients). In Lao Cai, positive rate was highest with 39/68 patients (57.4%).

3.2.1.2. Types of factors detected when testing specimens in each province

Positive rate of JE in Son La was 12.1%, in Dien Bien 38.9%, and it was highest in Lao Cai (49.2%). With gastroenteritis virus, positive rate was highest in Dien Bien (30.4%), then Lao Cai (19.6%), and lowest in Son La (12.3%). Dengue virus, hCMV and HSV were found only in Son La with corresponding proportions of 1.7%; 0.7% and 0,35%.

3.2.1.3. Distribution of types of factors detected among positive specimens

Of total 135 positive specimens, positive rate of JE virus was highest at 68.9%; then VGE 19.3%. 12 specimens recorded as co-infected with JE and VG viruses at a rate of 8.9%. Other viral factors were recorded at lower rates: hCMV (1.5%), HSV (0.7%) and Dengue virus (0.7%).

In Son La it was recorded the presence of all 5 factors: JE virus, VGE, HSV, hCMV and Dengue virus, of which JE virus occupied 58.6%, and VGE 27.6%; 4 specimens were co-infected with JE and VG viruses (6.9%). In Dien Bien it was recorded JE virus and VGE, of which JE was predominant (86.8%), and VGE

occupied 7.9%. Two specimens were co-infected with JE and VG viruses (5.3%). In Lao Cai there were 2 types - JE virus and VGE, of which JE occupied 66.7% and VGE 17.9%. Six specimens were recorded as co-infected with JE and VG viruses, occupied 15.4%.

3.2.1.4. Distribution of factor type by specimen type

Analysis of positive cerebrospinal fluid specimen revealed that JE virus occupied a majority with 91.9%. Other viruses including VGE, hCMV and Herpes virus were detected at lower rates, correspondingly 4.6%, 2.3% and 1.2%. Of 90 positive seral specimen, 89 were positive with JE virus (98.9%), and 1 with Dengue virus (1.1%). Among 34 positive stool specimen there were 22 successfully identified serotype VGE including 13 serotypes: EV-A71, Coxsackie A viruses (CV-A6, 10, 20, 24), ECHO viruses (E-6, 11, 18), CV-B5 virus, EV-B73, EV-B80, EV-C96 and PV-3. The most prominent VGE type was CV-A6 (11.8%), then E-6 and EV-A71 (both 8.8%) and 3 serotypes CV-A24, CV-B5 (each was 5.9%).

3.2.1.7. Immunization history of cases positive with JE

Of total 105 cases positive with JE virus, it was recorded 3 cases fully vaccinated with 3 shots (2.9%). The rest was not vaccinated or not to remember (79%), not fully vaccinated (4.8%) and was too young to get vaccinated (13.3%).

3.2.2. The presence of JE transmitting mosquitoes in the research areas

3.2.2.1. Findings on the composition of mosquito species in research sites

a. Mosquito species collected in research sites

Table 3.12. Mosquito species collected in research sites

No.	**Mosquito species**	**Province**							
		Son La *(n_1 investih=gated households = 120)*		**Dien Bien** *(n_2=120)*		**Lao Cai** *(n_3=120)*		**Total**	
		No. mosquiotoes	**%**	**No. mosquiotoes**	**%**	**No. mosquiotoes**	**%**	**No. mosquiotoes**	**%**
1	*Cx. tritaeniorhynchus*	167	29.67	995	63.83	676	46.59	1838	51.06

2	*Cx. vishnui*	5	0.9	239	15.3	383	25.9	627	17.42
3	*Cx. quinquefasciatus*	10	2.0	2	0.12	1	0	13	0.36
4	*Cx. fuscocephalus*	0	0	0	0	42	2.8	42	1.17
5	*Ar. kuchingensis*	68	11.73	11	0.7	16	1.0	95	2.64
6	*An. vagus*	312	55.4	310	19.8	349	23.6	971	26.97
7	*Ma. indiana*	1	0.3	3	0.19	7	0.04	11	0.31
8	*Ae. albopictus*	0	0	1	0.06	2	0.07	3	0.08
Total		**563**	**100**	**1,561**	**100**	**1,476**	**100**	**3600**	**100**

In research sites, 8 mosquito species of 5 benres were collected. The most recorded was *Culex* (Cx) with 1.838 *Cx. tritaeniorhynchus* (51.06%), 627 *Cx. vishnui* (17,42%), 42 *Cx. fuscocephalus* (1.17%), and 13 *Cx. quinquefasciatus* (0.36%).

b. The presence of JE transmitting mosquitoes (Culex) in research sites

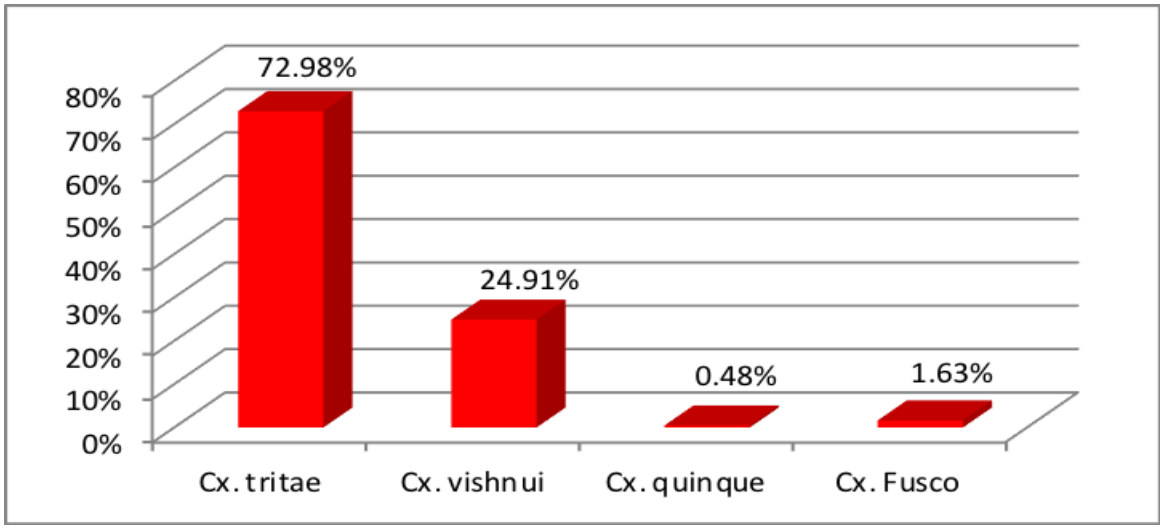

Figure 3.25. Proportions of Culex in 3 provinces Son La, Dien Bien and Lao Cai, 2018

Four *Culex* mosquitoes, of which 3 species could transmit JE - *Cx. tritaeniorhynchus*, *Cx. vishnui* and *Cx. fuscocephalus* – were found in research sites. *Cx. tritaeniorhynchus* occupied the highest proportion (72.98%), then *Cx. vishnui* (24.91%) (two key mosquito species transmitting JE).

3.2.2.2. Distribution of Culex mosquito species in research sites

Cx. tritaeniorhynchus was recorded with high amounts in rural areas, highest rate was in Dien Bien, then Lao Cai and the least was in Son La. Similarly, *Cx. vishnui* was recorded with high amounts in rural areas in Lao Cai, then Dien Bien and the least was in Son La.

3.2.2.3. Densities of Culex mosquito species and larvae in research sites

a. Densities of Culex mosquito species in research sites

Table 3.13. Density indices of Culex mosquito species

Province	Density Index *Cx. tritaeniorhynchus*		Density Index *Cx. vishnui*		Density Index *Cx. quinquefasciatus*		Density Index *Cx. fuscocephalus*	
	Indoor	**Animal sheds**	**Indoor**	**Animal sheds**	**Indoor**	**Animal sheds**	**Indoor**	**Animal sheds**
Son La	0.36	3.36	0.00	0.12	0.16	0.06	0.00	0.00
Dien Bien	0.82	21.28	0.16	5.16	0.00	0.04	0.08	0.66
Lao Cai	0.78	13.34	0.94	7.74	0.00	0.00	0.02	0.88
Average	0.65	12.68	0.36	4.28	0.05	0.03	0.03	0.52

Cx. tritaeniorhynchus and *Cx. vishnui* had high density indices in animal sheds. Average densities of *Cx. tritaeniorhynchus* and *Cx. vishnui* in animal sheds were higher than indoor correspondingly 19.5 and 11.8 time.

b. Culex larvae in water bodies in research sites

Total 2682 larvae were collected from 244 water bodies, including 110 wet rice fields; 36 aqueducts; 57 ponds and 31 water containers of households. Findings showed that there were larvae of 4 species: *Cx. tritaeniorhynchus; Cx. vishnui; Cx. quinquefasciatus* and *Cx. fuscocephalus. Cx. tritaeniorhynchus* larvae presented in all water bodies with high density, concentrated mainly in wet rice fields. Then *Cx. vishnui* larvae, which were mainly in rice fields, aqueducts and water containers.

3.2.2.4. Some factors affecting the presence of Culex mosquitoes and larvae

Proportion of mosquitoes caucht in buffalow/cow barns was very high, following by pigsties and poultry houses, and was less indoor ($p < 0,01$). Proportion of mosquitoes caucht in rural areas was higher than in urban ones ($p < 0,01$). Larvae collected from water bodies with water level of <10 cm and with aquatic plants were more than from water bodies with water level of >10cm and without aquatic plants ($p < 0,01$).

3.3. Medical service direct treatment costs of Viral Encephalitis patients in health facilities in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018

There was a total of 473 JE patients, after removing deaths, 456 patients were selected to take part in the research on direct treatment costs.

Table 3.17. Basic information of research subjects (n = 456)

13	Dien Bien		Lao Cai		Son La		Chung	
	No.	%	No.	%	No.	%	No.	%
Age group								
< 5 years	37	44.6	31	47.0	37	12.0	105	23.3
5- <15 years	17	20.5	18	27.3	89	29.0	124	27.2
15 - 45 years	21	25.3	12	18.2	146	47.6	179	39.2
>45 years	8	9.6	5	7.6	35	11.4	48	10.5
Sex								
Male	52	62.6	31	47.0	169	55.0	252	55.3
Female	31	37.4	35	53.0	138	45.0	203	44.7
Ethinic group								
Kinh	40	48.2	9	13.6	5	1.6	54	11.8
Other ethinic group	43	51.8	57	86.4	302	98.4	402	88.2
Academic level								
No schooling	8	19.0	12	20.0	4	1.3	24	5.9
Completed primary school	11	26.2	23	38.3	30	9.9	64	15.8
Completed junior high school	19	45.2	18	30.0	79	26.2	116	28.7
Completed high school	3	7.1	2	3.3	157	52.0	162	40.1
College/University	1	2.4	5	8.3	32	10.6	38	9.4
Postgraduation	0	0.0	0	0.0	0	0.0	0	0.0
Occupation								
Small children	38	45.8	38	57.6	59	19.2	135	29.6
School children/Student	0	0	6	9.1	129	42.0	135	29.6
Farmer	17	20.5	15	22.7	93	30.3	125	27.4
Other	28	33.7	7	10.6	26	8.5	61	13.4
Total	**83**	**100.0**	**66**	**100.0**	**307**	**100.0**	**456**	**100.0**

Group of children under 15 years of age occupied the highest proportion (50.5%) ; in Dien Bien it was 65.1%, in Lao Cai 74.3% and in Son La 41.0%. Group of 15-45 years occupied 39.2%. Group of patients over 45 years formed the lowest proportion (10.5%). Males were 55.3%, ethnic minorities were 88.2%; highest proportionn was in Son La (98.4%), then in Lao Cai (86.4%) and Dien Bien (51.8%). Preschool, pediatrict patients were 29.6 %. Farmer patients were 27.4 %.

In average each VE patient was treated for 9.7 day ; duration spent in provincial hospitals was longer thna in district hospitals (9.8 day and 8.4 day). Highest duration of treatment was 58 days in provincial hospitals and 17 days in district hospitals.

3.3.1. Direct costs for treatment of Viral Encephalitis

Table 3.20. Treatment cost by treatment level (*Unit: VND)*

Treatment cost	Average	SD	Median	Lowest	Highest
In District Hospital	5,203,333	2,349,986	4,131,977	2,777,265	10,546,786
In Provincial hospital	8,174,104	8,838,778	5,867,518	2,658,390	102,275,320
Whole episode	8,010,875	8,635,579	5,844,793	2,658,390	102,275,320
Exemption	*7,596,576*	8,601,578	5,491,865	0	102,275,320
Self-payment	*414,299*	1,069,683	0	0	9,304,963

Average treatment cost for a patient was 8,010,875 dong, highest treatment cost was 102,275,320 dong. Out of total cost, the patient had to pay 414,299 dong (equivalent to 5.2%), the rest was pupported by the government through the health insurance.

Table 3.21. VE direct treatment cost by medical item

Treatment cost	Average	SD	Median	Lowest	Highest
Hospital bed	2,349,215	2,030,586	1,949,000	99,550	25,607,400
Subclinical services	1,154,749	1,270,147	804,100	39,200	10,594,500
Medicines, blood, IV fluid	3,358,140	3,974,314	2,424,912	9,335	44,552,357
Consumable supplies	228,927	221,902	171,270	25,053	2,307,798

Operations	829,674	2,838,981	139,000	26,200	32,804,600
Transportation	77,274	493,190	0	0	4,797,000
Other	11,847	104,311	0	0	1,292,000
Whole episode	**8,010,875**	**8,635,579**	**0**	**0**	**102,275,320**

Figures from Table 3.21 revealed that expenses for medicines, blood and IV fluid was the highest (41.9%), then bed expenses (29.3%), subclinical services (14.4%), and operations (10.4%). Other expenses occupied low proportions. Patients treated at ICU and emergency unit required higher expenses (10,224,857 dong and 10,216,609 dong), then at infectious unit (7,438,035 dong) and other ones (7,047,294 dong).

3.3.2. Some factors affecting medical service direct treatment costs

Group of patients over 45 years old had an average treatment cost as highest (7.733.876 dong), followed by group of < 5 years old (5.992.298 dong) and group of 15-45 years old (5.912.022 dong), the lowest was group of 5-15 years old ($p<0.001$). Significant difference was not detected between treatment costs among male and female patients, and among groups of ethnics ($p>0,05$). Higher costs were paid for patients who required longer treatment. For patients who were treated for more than 14 days, average treatment cost was 11.764.325 dong, nearly two-fold of those who were treated from 7 to 14 days (6.166.919 dong) and triple of those treated less than 7 days. Treatment cost by etiological factor varied from 4.367.165 dong with HSV, Dengue, hCMV, … to 6.403.675 dong with JE virus. However significant difference was not detected ($p>0,05$).

Chapter 4. DISCUSSION

4.1. Situation of Viral Encephalitis in 3 northwest provinces, 2017-2018

4.1.1. Viral encephalitis morbidity in North West of Vietnam, 2017 - 2018

Research findings recorded 473 VE cases, of which 17 deaths in 3 provinces - Son La, Dien Bien and Lao Cai - 2017-2018, fatality rate was 3.6%. This rate was lower than findings by Gurav et al in India, 2014, which was 28.9% [64]. In Son La, 2017– 2018, VE cases distributed in 11/12 districts and the city. In Dien Bien, 9/10 districts and the city recorded cases. In Lao Cai, cases were recorded in 8/9 districts and the city. Our finding was similar to the ones of Duong Thi Hien in Bac Giang, 2004-2017 and Pham Khanh Tung in Tay Nguyen, 2005-2018 [21, 39].

Morbidity per 100,000 inhabitants in Son La was 13.1, in Dien Bien 8.5 and Lao Cai 5.1. This rate was higher than of other regions in the country (in the North, 2018, it was 1.4 case per 100,000 inhabitants) [3]. Research done in USA by Benjamin P. George et al, 2000 – 2010, showed that admitted encephalitis was 7.3 case per 100,000 inhabitants (95% CI: 7.1–7.6). In western countries, estimated morbidity was about 10.5 – 13.8 pediatrict case per 100,000 children, and 2.2 adult case per 100,000 inhabitants. Thus, viral encephalitis morbidity of three provinces in the northwest region of Vietnam, 2017 – 2018 was higher than of contry's other regions and of certain endemic regions worldwide.

4.1.2. VE progress in 3 northwest provinces, Vietnam, 2017 – 2018

Cases presented in all months of year, however concentrated mainly in June and July, which were summer months, when the population of JE transmitting mosquitoes developed rapidly – a favorable condition for the disease to spread. Research findings in Vietnam, 2012, revealed that it was a clear seasonal characteristic in admitted encephalitis cases, with the peak reached in June ($p<0.001$) [10]. Researches done in Son La, 2015, Bac Giang, 2004-2017, in Tay Nguyen, 2005-2018, in India, 2014, and in Taiwan showed similarly results [14, 87, 21, 39] [64] [126]. However, seasonal characteristic depended also on etiological factors. Research in USA for 11 years revealed that HSV, chickenpox virus and Herpes virus circulate during the whole year, meanwhile group of arbovirus, West Nile virus and VGE increased in July to September [60]. In 3 northwest provinces, VE was mainly caused by JE and VGE viruses, therefore it had clear seasonal characteristic and rapidely increased during the summer (June and July).

4.1.3. Distribution of VE cases by certain epidemiologic factors

Among VE cases in 3 northwest provinces, 2017 - 2018, male : female ratio was 1.22 : 1. This was appropriate to the ones obtained by Ho Dang Trung Nghia, 2007 – 2010 [142], by a research in Cambodia [133], by Duong Thi Hien, 2020 [21], and by Benjamin P. George, USA, 2000 – 2010 [60]. In our research, group of adults occupied a rather high proportion (24.3%). Many years ago, north western provinces often recorded low viral encephalitis morbidity, perhaps many adults had not been exposed to VE, making morbidity increased. However, morbidity among children under 5 years of age was highest (28.6%), followed by group of 15 – 29 years old (24.3%). Infants under 1 year (not reaching age for JE vaccination) also occupied a rather high proportion (14.2%.). Perhaps mountainous provinces had remoted districts/communes where coverage of the Expanded Immunization Program remained low, and access to immunization services was limited.

Worldwide, age distribution of VE cases was diversified. In USA, among 48,598 admitted encephalitis cases, group of 45–64 years old occupied 29%; group of 20–44 years old 28.2%, infants under 1 year old and 1–4 years old occupied very low proportions: 2.5% and 3.7% [60]. In the Indian outbreak, children under 10 years old occupied 16.8%, adolescents 12.3%, and the highest proportion belonged to group of > 20 years old (70.8%) [64]. In Finland, proportion of VE among children under 10 years old was highest (29.5%), followed by group of over 71 years old (12%). In Thailand, 68% JE cases was among group of <20 years old. Thus, distribution of VE cases by age was very much diversified according to geographic regions and countries, depending on the circulation of etiological factors and effectiveness of vaccination programs. VE cases in our North West during 2017–2018 involved many different ethnic groups. Son La recorded cases mainly among Thai ethnic group, because Thai people formed 53.2% population of the province. Similarly, in Dien Bien and Lao Cai, H'mong ethnic group occupied the highest proportion. Besides, Lao Cai recorded significant cases among Dao ethnic population.

4.2. Some viral encephalitis factors and JE transmitting mosquitoes in 3 northwest provinces

4.2.1. Some viral encephalitis factors in 3 northwest provinces, 2017-2018

According to results of specimen testing in 3 northwest provinces years 2017-2018, positive rate of viral factors was 28.5%. There was still 70% not being able to identify etiological factors. In each province, positive rate varied from 18.4% to 57.4%. This proportion was lower than of the northern region, 2015 (44.4%) [16] and of the central region, 2015-2017 (47.3%) [25]. In USA, 2000–2010, positive rate of encephalitis cases was 25.6% [60], in Finland it was 20.4% [97].

In our research, JE virus had positive rate of 22.4% (including JE and co-infection with JE–VGE), this was lower than the one of another research in Son La, 2015 (49.4%) [16]; however was higher than JE positive rate in the central region, 2015-2017 which was 12,68% [25]. Perhaps the difference was due to different circulation of JE virus between years, geographic regions, populations, and coverage of JE vaccination. Research findings also revealed that, although there was JE vaccine, JE still remained a common factor for VE in this region. Out of 105 positive specimens with JE, there were 3 cases fuly vaccinated with 3 JE vaccine doses, perhaps due to individual immune response, immunization techniques or due to vaccine transportation and preservation in remote areas – these should be reviewed and improved. In Vietnam, proportion of JE etiological factor among AES was 26%-49% [12], [31], [33], [115], [129]. In many Asian countries, JE virus was still a

primary etiological factor causing AES: India, Philippines, Malaysia, Thailand, and Taiwan [59], [70], [79], [108, [110].

Besides JE virus, positive rate of VGE was recorded as 14.3% (including specimen co-infected with JE – VGE). This was lower than of the other research in some northern provinces, and higher than of Bac Giang (13,13%) [19], and Son La, 2015 (2.3%) [16]; Factor EV71 could cause sever manifestation and dangerous compliction, therefore surveillance and research on clinical chareacteristics of VE cases due to VGE should be strengthened, in order to provide appropriate prevention recommendations. Our research had detected 13 seral types causing VGE, of which higher rates belonged to CA6 and EV-A71. There was no case positive with VGE simultaneously for both stool and cerebrospinal fluid specimens. Among 34 positive specimens, 22 stool and 2 cerebrospinal fluid specimens were successfully identified genotype (serotype) of VGE. Two cerebrospinal fluid specimens were identified as E-6 and E-11. 22 stool specimens were confirmed positive with EV-A71, Coxsackie A viruses CV-A6, 10, 20, 24, ECHO viruses E-6, 11, 18, and CV-B5, EV-B73, EV-B80, EV-C96 and PV-3 viruses. All 13 VGE types had been identified, of which the most prominent were CV-A6 and E-6 (16.67%), then EV-A71 (12.5%) and 3 serotypes CV-A24, CV-B5 and E-11 (each 8.33%).

Our rersearch had detected acute encephalitis factors such as Herpes (HSV) (0,27%), Dengue (1,45%) and hCMV (0,53%). Positive rate of Herpes virus was lower than finding from certain rersearches in the country. In a research on 624 admited cases in Vietnam, 2012, positive rate of Herpes virus was 2% [107]; in another research in Son La, positive rate of HSV was 2.8% [16], in the central region this was 10.7% [25]. There was no vaccine for Herpes virus, however it could be specifically treated by antiviral medicines (acyclorvir), therefore, early diagnosis of VE caused by HSV could make the treatment effective and reduce sequelae. With Dengue virus, although it was a common factor endemic in Vietnam and currently there was no vaccine for its prevention, only limited Dengue hemorrhagic cases had been recorded in the northern montainous areas [25]. In 3 northwest provinces, vector circulation and density index was low, unfavorable for transmission of Dengue hemorrhagic fever. During two years, only one case positive with Dengue virus detected. Besides, we also found 2 cases positive with hCMV. Our finding revealed that next to JE virus surveillance, it was necessary to perform surveillance on certain other factors to provide effective preventive measures.

Thus, in 3 northwest provinces it was able to identify viral factors causing VE from 28.5% specimen collected. More than 70% could not have etiological factors identified. Especially, of 17 deaths in 3 provinces, it was able to identify factors for 7

cases, the rest was not verified. A new method (peptidomic) for detecting peptid of etiological factors in VE patient blood was jointly studied between the National Institute of Hygiene and Epidemiology and Hadassah Hebrew University (Israel) in north western provinces, giving a hope to complement a list of new factors for VE that could help diagnosis and treatment.

4.2.2. The presence of JE transmitting mosquitoes in research areas

4.2.2.1. Distribution of JE transmission vectors

JE virus could not transmit directly from person to person but via mosquitoes. Many researches identified two mosquito species *Cx. tritaeniorhynchus and Cx. vishnui* as key vectors for transmitting JE virus. According to David W. Vaughn, there were more than 17 mosquito species transmitting JE [100].

Our research had collected 8 mosquito species of 5 genres. Individual mosquitoes of *Culex* (Cx) genre were the most numerous. 4 mosquito species of *Culex* genre, of which 3 could transmit JE - *Cx. tritaeniorhynchus, Cx. vishnui and Cx. fuscocephalus* – were present in research sites. Of which, *Cx. tritaeniorhynchus* occupied the highest proportion of 72.98%, then *Cx. vishnui* 24.91%. These two mosquito species (including adult mosquitoes and larvae) were present in all 3 research provinces. In Tay Nguyen, 2005-2018, it was also found 9 Culex mosquito species, of which *Culex tritaeniorhynchus* and *Culex vishnui* were predominant. There, 9 virus strains were isolated from mosquitoes, confirming Culex role in JE transmission [39]. JE transmitting mosquitoes were caught mainly in rural areas, with high density indices in animal sheds. Average densities of *Cx. tritaeniorhynchus* and *Cx. vishnui* in animal sheds were higher than indoor, correspondingly 19.5 and 11.8 time.

4.3. Direct medical expenses of Viral Encephalitis patients in health facilities in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018

4.3.1 Direct medical expenses of Viral Encephalitis patients

Results of medical service direct treatment costs analysis for 456 VE patients revealed that average cost for each patient was 8,010,875 dong. Direct medical expenses of each patient was equivalent to 2.7 time of average per capita income per month in rural areas in 2018 (2,990,000 dong); 3.3 time of average per capita income per month in the northern midland and montainous areas in the same year (2,455,000 dong), and varied from 3.4 to 5.4 time of average per capita income per month in provinces of Lao Cai (2,324,000 dong), Dien Bien (1,477,000 dong), and Lai Châu

(1,493,000 dong). Compared to spending limits, then expenses for eating, drinking, and direct medical expenses of VE patient were equivalent to 8.6 time in rural areas (933,000 dong) and 9.4 time in the northern midland and montainous areas [101]. In the research in USA, 2016, average treatment costs for acute patients were 64.604 USD and 260.012 USD for a pediatrict ICU patient [89]. Compared to researches in the USA, then VE treatment costs in north western provinces were much lower, however i twas due to differences in living standards and incomes. Similarly, direct medical expenses in our research were lower than in research done by Griffiths et al, 2013 in Nepal. There, expenses of families having children treated for acute encephalitis or severe or moderate JE were 1,151 USD (10 times average income per month of the whole household) and for mild cases were 524 USD (4.6 time average income per month of the whole household) [92].

Although, 3 research provinces were mountainous with large amounts of poor and near-poor population. These were also provinces that the Government had to support. Proportion of people owing health insurance cards was high. Therefore, out of total direct costs for the disease treatment, patients had to pay 414,299 dong from their own pocket, equivalent to 5.2% direct medical expenses. 94.8% of expenses was supported by the government through the health insurance. Expenses were exempted greatly, showing concerns of the Government to people living in mountainous areas regarding disease treatment.

4.3.2 Factors affecting medical service direct treatment costs of Viral Encephalitis patients

Analysis results revealed that group of patients over 45 years old had average treatment costs as highest (7.733.876 dong), followed by group of children under 5 years old (5.992.298 dong), group of 15-45 years old (5.912.022 dong) and the lowest was group of 5-15 years old (4.636.132 dong) ($p<0.001$). Patients who were treated longer had higher treatment costs. Concretly, those treated for more than 14 days had an average treatment cost as many as 11.764.325 dong, nearly twice compared to group of treatment duration from 7-14 days (6.166.919 dong) and nearly triple compared to group of duration less than 7 days (4.438.378 dong). Timely detection, diagnosis and treatment could help reduce treatment time, following by reducing treatment costs and at the same time minimize sequelae.

Among factors causing VE, JE virus led to the most severe clinical manifestations. Therefore, treatment costs for JE patients were highest. However, with limited sample size, our research could not reveal statistically significant differences between direct medical expenses for factors causing VE.

CONCLUSION

1. Situation of Viral Encephalitis in 3 provinces Son La, Dien Bien and Lao Cai, 2017-2018

During 2017 - 2018, in 3 northwest provinces including Son La, Dien Bien and Lao Cai it was recorded a lage number of 473 cases with 17 deaths due to VE. The disease occured widely, in 28/31 districts/towns of three provinces. Morbidity and mortality were highest in Son La (315 cases, 66.6%), then Dien Bien (90 cases, 19%) and Lao Cai (68 cases, 14.4%). Cases appeared sporadically from early months of year, increased, and reached their peaks in summer months, June and July, then regressed and became sporadical in late months of year. Most cases were children under 15 years old (51.8%), however it was also recorded a not small proportion of cases in group of 15 - 29 years old (24.3%). Males occupied 55% cases, not sifnificantly higher compared to females (45%). Deaths were mainly among children under 15 years old (94.1%); 23% deaths were positive with JE.

2. Some viral encephalitis factors and the presence of mosquitoes transmitting Japanese Encephalitis in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018

28.5% specimen was detected positive with viral factors among clinical VE patients in the North West. Common viral factors causing encephalitis were rather diversified, including JE, VGE, HSV, Dengue virus, and hCMV. JE and VGE viruses were 2 most common factors causing Viral Encephalitis in 3 northwest provinces in 2017-2018, their positive rates were correspondingly 68.9% and 19.3%. Besides, 8.9% specimen was recorded as co-infected with 2 types - JE virus and VGE. JE virus was the most common factor (91.9%) found in cerebrospinal fluid. Other viral factors occupied lower proportions, including HSV, Dengue virus and hCMV. For VGE, there were 13 serotypes with the most prominent as CV-A6 (11.8%), then E-6 and EV-A71 (8.8%) and serotypes CV-A24 and CV-B5 (5.9%). Most cases positive with JE had not been vaccinated for JE or not fully vaccinated (97.1%).

In 3 provinces - Son La, Dien Bien and Lao Cai - 8 mosquito species of 5 genres had been collected, of which two mosquito species were main vectors for Japanese Encephalitis transmission, *Cx. tritaeniorhynchus and Cx. Vishnui*, with predominant proportion (68.48%). Mosquito density indices of *Cx. tritaeniorhynchus* and *Cx. vishnui* were high in animal sheds (3.36 – 21.28 individual/shed for *Cx. tritaeniorhynchus*, and 0.12 – 7.74 individual/shed for *Cx. vishnui*), 19.5 time (*Cx. trtaeniorhynchus*) and 11.8 time (*Cx. vishnui*) higher than mosquito density indices indoor. The presence of JE transmitting larvae was recorded in water bodies: wet rice

fields, aqueducts, small ponds and water containers of households, of which wet rice fields were the main sources of JE transmitting larvae (81.8% for larvae *Cx. tritaeniorhynchus* and 98% for larvae *Cx. vishnui*).

3. Medical service direct treatment costs of VE patients treated in health facilities in 3 northwest provinces: Son La, Dien Bien and Lao Cai, 2017-2018

Average medical service direct treatment cost of each VE patient in 3 provinces Son La, Dien Bien and Lao Cai, 2017-2019, was rather high (8,010,875 dong). Of which the patient paid 414,299 dong himself/herself, equivalent to 5.2%, the rest was paid by the government through the health insurance. Median cost was 5,844,793 dong. The two medical items occupied huge proportions in the treatment cost were expenses for medicines, blood and IV fluid (3,358,140 dong, 41.9%) and bed time (2,349,215 dong, 29.3%). Medical service direct treatment costs had been associated with the age group and duration of treatment. Thus, the older the patient and the longer the duration of treatment, the direct cost was higher.

RECOMMENDATION

1. To accelerate JE vaccination for both children and adults in the Expanded Program for Immunization as well as outside of the Program.
2. To continue and expand researches on epidemiology (infectious sources, risk factors…), on new viral factors causing VE, and on VE disease related burden in order to have a full and comprehensice picture of the disease.
3. Conduct pilot rerearch on JE vector source reduction such as intensive farming, proper irrigation, mobilizing community to build proper, far from home concentrated animal sheds, reducing human - vector – host contacts.