CHAPTER 1
INTRODUCTION

1.1 Rationale

Rabies is a zoonotic viral disease which is fatal to both animals and humans. Rabies infects both domestic and wild animals. It is transmitted to other animals and humans through close contacts with saliva from infected animals (i.e. bites, scratches, licks on broken skin and mucous membranes). Once symptoms of the disease develop, Death occurs during the first seven days of illness without intensive care. In both furious and dumb rabies, paralysis eventually progresses to complete paralysis followed by coma and death in all cases, usually due to respiratory failure [1].

Reliable data on rabies are scarce in many areas of the globe, making it difficult to assess its full impact on human and animal health. The annual number of deaths worldwide caused by rabies is estimated to be between 40,000 and as high as 70,000 if higher case estimates are used for densely populated countries in Africa and Asia where rabies is endemic. An estimated 10 million people receive post-exposure treatments each year after being exposed to rabies suspect animals [2].

Since 1990 rabies in wildlife has been eliminated in some Western European countries that have conducted oral vaccination campaigns (active campaign). With the help of this technique rabies could eventually be totally eliminated from its terrestrial reservoirs in Western Europe. Oral vaccination programs for dogs have been or are in the process of being evaluated in a few developing countries where canine rabies is endemic [1].

Dramatic decreases in human cases of rabies have also been reported during recent years in China, Thailand, Sri Lanka and Latin America following implementation of programs for improved post-exposure treatment of humans and the vaccination of dogs [2].

In Thailand, the number of Rabies infected cased had been dropped continuously from 185 cases in 1990 to 78 cases in 1994 and 50 in 2000 (See Table 1.1)[3]. Rabies was still in the first rank of Top-Ten case Fatality Rate (See Table 1.2)[3] with 100% rate. The incidence of Rabies fluctuates throughout the year. Most of the cases were found during January and May (See Table 1.3)[3]. Most cases were from Central Region of Thailand (See Table 1.4)[3]. The infected cases were usually aged 7 or up (See Table 1.5)[3].

Table 1.1: Reported Cases and Deaths of Rabies by Year, Thailand, 1990-2000

Year	Rabies Cases	Deaths
1990	185	185
1991	171	171
1992	113	113
1993	93	93
1994	78	78
1995	74	74
1996	77	77
1997	58	58
1998	57	57
1999	68	68
2000	50	50

Source: Annual Epidemiological Surveillance Report, 2000 Division of Epidemiology, Office of the Permanent Secretary for Public Health, Ministry of Public Health

Investigation of death case due to rabies in year 2000 [3]

In year 2000, there were 50 reported rabies cases. The incidence of rabies in that year was 0.08 per 100,000 population. Bangkok was the province with the highest incidence (6 cases) and followed with Patumthani (5 cases), Surin (4 cases), Burirum and Chonburi (3 cases) respectively. The provinces which had reported case for 3-year consecutively (1998-2000) were Bangkok, Prajuabkeeleekan, Chonburi and Samutprakan.

Table 1.2: Top-Ten case Fatality Rate (%) of Disease under Surveillance, Thailand, 2000

Rank	Disease	Rabies Cases	Deaths	Case Fatality Rate (%)
1	Rabies	50	50	100.00
2	Diptheria	15	6	25.00
3	Menigicoccal infection	74	27	19.61
4	Reye's syndrome	4	1	15.00
5	Menigico-encephalitis	4	1	14.79
6	Tetanus-total	234	28	11.52
7	Encephalitis-total	467	45	4.63
8	Suicide by liquid substance	6288	338	4.38
9	Leptospirosis	14285	362	2.87
10	Meningitis-total	3598	60	2.13

Source: Annual Epidemiological Surveillance Report, 2000 Division of Epidemiology, Office of the Permanent Secretary for Public Health, Ministry of Public Health

Table 1.3: Reported Deaths of Rabies by Month, Thailand, 2000

Month	Rabies Deaths
Jan.	8
Feb.	5
Mar.	5
Apr.	5
May	3
Jun.	4
Jul.	6
Aug.	4
Sep.	2
Oct.	2
Nov.	6
Dec.	0

Source: Annual Epidemiological Surveillance Report, 2000 Division of Epidemiology, Office of the Permanent Secretary for Public Health, Ministry of Public Health

The disease prevailed all over the year except in December. January was the month with highest incident rate (8 cases).

From 50 rabies cases, There were 32 males and 18 females. The female to male ratio was 1:1.8. Most of the cases were in the labor-force age group.

From 45 cats and dogs, there were 28 pets (62.2%) without owners and without history of immunization.17 pets (37.8%) were with owners. In 17 pets, there were 12 pets (70.6%) which received no immunization. And 2 pets (11.8%) had no reliability record. And 3 pets (17.6%) were received immunization. However, there was only 1 dog with history of regular immunization.

Table 1.4: Reported Cases and Deaths of Rabies by Zone, Thailand, 2000

Region	Rabies Cases and Deaths
Central Region	26
North-Eastern Region	11
North Region	7
South Region	6

Source: Annual Epidemiological Surveillance Report, 2000 Division of Epidemiology, Office of the Permanent Secretary for Public Health, Ministry of Public Health

With characteristic of the bite wound, we found that, there were 21 cases with deep wounds with bleeding (42%). There were 9 cases with scratch wounds with bleeding (18%) and 9 cases with scratch wounds without bleeding. No specified wounds were reported for 11 cases (22%).

Wound sites were found over the bodies. 19 cases were bitten at calves, shins, knees, legs, and waists. 11 cases were bitten at hands, 6 cases at Chest and body, 3 cases at faces. No located sites of wounds were reported in 11 cases.

Most of the cases were employees-11 cases (22%). 10 cases were farmers (20%). 6 cases were students (12%). 5 cases were housewives (10%). 3 cases were merchants (6 %) and 1 case was civil servant (2%). There were 14 cases without occupational record.

In 50 cases, 42 cases were bitten by dogs (84%) and 5 cases were bitten by cats (6%). There were 5 cases with unknown type of animal bite.

The longest incubation period was 1 year and the shortage incubation was 7 days. The mean of incubation period was 66 days. The shortest duration of clinical manifestation was 1 day and the longest was 11 days. The mean of duration was 3 days

And in these 50 rabies cases, 48 cases received no medical prophylaxis after expose to rabies and 2 cases received either rabies vaccine or rabies immunoglobulin.

Table 1.5: Reported Cases of Rabies by Age-Group, Thailand, 2000

Age-group (year)	Cases and Deaths
Less than 1	0
1 +	0
2 +	0
3 +	1
4 +	1
5 +	0
6 +	3
7-9	1
10-14	5
15-24	9
25-34	6
35-44	8
45-54	3
55-64	7
65+	6

Source: Annual Epidemiological Surveillance Report, 2000 Division of Epidemiology, Office of the Permanent Secretary for Public Health, Ministry of Public Health

There were 2 main factors that caused the patients missed the proper post-exposure treatment.

1. Patient factor
    - No awareness and ignore of rabies -34 cases
    - Intimacy with rabid animals (pets)- 5 cases

- Believes of traditional medicine -5 cases
- Misunderstanding that the baby pets can not transmit the disease - 3 cases
- Misunderstanding that the rabies prevails only in summer -2 cases
- Vaccine financial unaffordable 1 cases

2. Health care provider factor
    - There were 2 patients who were ignored and given no vaccine or RIG although they came to visit the health posts.
    - There were 2 cases of post-exposure patients who were given either vaccine or RIG. However, they developed the rabies after immunization.

Category 1: the patient received both rabies vaccine and RIG

The 11- year patient was bitten by dog with the bite mark at upper lip and neck. The patient received both vaccine and ERIG at the same day at the hospital (10^{th} Jan 2000). The patient was injected with 3 doses of vaccine intradermally regularly. The patient developed the symptom in 2^{nd} Feb 2000 and died in next day.

Category 2: the patient received only rabies vaccine

The 64-year patient was bitten by dog on 18^{th} Feb 2000 at left foot. The patient received the 2 doses of rabies vaccine. The patient developed the symptom on 25^{th} Feb 2000 and died on 27^{th} Feb 2000.

The information above instructed the situation of rabies in Thailand. It showed that vagabond dogs were the important rabies hosts and the lack of awareness and knowledge is still the problem among the people in rural area as well.

Situation of rabies in animal

From table 1.6, dogs were still the important reservoirs for rabies especially in vagabond dogs. Most of the reservoir dogs were from outside municipality. The problem of vaccine coverage in dogs is still existed. The champagne for dog population control should be done more effectively.

Table 1.6: Result of Laboratory Diagnosis of Rabies in Animals

Type of animal	Number of specimens	Number of positive specimen	Percent
Dog	3,296	1,052	31.92
Cat	516	54	10.47
Cattle	70	40	57.14
Buffalo	1	1	100.00
Pig	9	3	33.33
Horse	1	0	0.00
Monkey	3	1	33.33
Rat	36	1	2.78
Squirrel	33	0	0.00
Rabbit	10	0	0.00
Wild animal	8	3	37.50
Unknown	41	9	21.95
Total	**4,024**	**1,164**	**28.93**

Source: Ministry of Public Health, The Report of Development of Expanded Rabies Immunization Program in Thailand, 2001

Table 1.7: Prophylaxis Protocol for Rabies Vaccine and RIG

Category	Type of contact and characteristic of wound	Prophylaxis
1	Feeding	**No prophylaxis**
	Being licked (intact skin)	
2	Being Scratch	Rabies vaccine
	Being licked (not intact skin), being bitten (no bleeding)	
3	One deep bite or multiple bitten wound	Rabies vaccine
	Being licked at mucosa	and RIG

Source: Ministry of Public Health, The Report of Development of Expanded Rabies Immunization Program in Thailand 2001

Rabies prophylaxis

Rabies is one of the most fatal diseases. Nonetheless, it is preventable. In case of exposure to Rabies (post-exposure) e.g. dog bite, the first step of treatment is to clean the wound immediately with water and antiseptics. No suture except in case of large wound and heavy bleeding. Tetanus toxoid, antibiotics and other medication might be given as well. Then, Rabies vaccine and immunoglobulin will be given to the patient as soon as possible to lower the infection rate. Especially, in case of large wound and heavy contact with saliva of suspected rabid animal, the patient will be treated with Rabies Immunoglobulin (rabies antiserum). Rabies immunoglobulin provides immediate passive antibodies for a short period of time. This can protect the patients until they develop active antibody from the rabies vaccine [4,25]. There are two kinds of Immunoglobulin;

1. Human Immunoglobulin (HRIG) is a gamma globulin obtained form the plasma of hyperimmunized human donors. This kind of RIG is imported from Germany (Centeon) and Switzerland (Berna Swiss Serum and Vaccine Institute). National Blood Bank, TRCS is the

main supplier in Thailand right now. Complication of HRIG is rare and trivial. Dose of injection is 20 international units per kilogram.

2. Equine Immunoglobulin (ERIG) is a gamma globulin obtained from plasma of hyperimmunized horse. This kind of RIG is totally imported from France (Pasteur Merieux Connaught) and Switzerland (Berna Swiss Serum and Vaccine Institute). Purified of nowadays ERIG lowers the rate of allergy known as "serum sickness" to 1-6%. However, most of the complications are minor and occurs 7-10 days after injection. The serious complication such as anaphylaxis shock is rare. Dose of injection is 40 international units per kilogram.

Table 1.8: Reported of ERIG and HRIG Treated Cases by Queen Saovabha Memorial Institute-TRCS.

Year	ERIG treated cases	HRIG treated cases	Total case
1998	1,785	1,484	3,270
1999	1,594	1,783	3,377
2000	2,314	724	3,038
2001	1,930	454	2,500

Source: Annual Activity Report of Thai Red Cross Society, 2000

Demand for rabies immunoglobulin trends to increase every year [5] while there is a sign of shortage of both ERIG and HRIG from the producers according to the animal rights protest against the production and lack of human donors respectively. The shortage of rabies immunoglobulin therefore occurs in many areas of the world. ERIG that supply in Thailand right now is totally imported from aboard. Thailand, by Blood Bank-TRCS produces HRIG to supply in the country. However, HRIG cannot be substituted for the use of ERIG in this present setting because of the limitation of human donors [19,25], consequently, there is still shortage of HRIG in Thailand. Ministry of Public

Health (MOPH) is the biggest agency in Thailand that imports ERIG from aboard and distributes throughout the country. The report from MOPH shows the increasing trend of ERIG utilization.

Rabies immunoglobulin is indicated for post-exposure immunization against rabies infection in persons who have not been previously immunized against rabies with rabies vaccine.

The standard approach is to prescribe HRIG to post-exposure cases to avoid adverse drug reaction [1]. However, because of the inadequacy and high market price of HRIG, Thailand still prescribes ERIG to the post-exposure cases. Nonetheless, it is accepted that the effectiveness of ERIG and HRIG to prevent rabies is generally the same [13,25]. Hence, the patient will be treated initially with ERIG but if the patient develop allergy against ERIG, HRIG will be given in that situation (See Table 1.7,1.8)[8,25,26].

In 1999 MOPH distributed 16,438 vials of ERIG and increased to 35,430 vials in 2000 and 44,864 vials in 2001 (See Table 1.9) [5] The number of patients those need ERIG increases continuously. There were 17,654 patients treated with ERIG and 19,378 patients in 2001. (See Table 1.10) [5]

Table 1.9: Volume of ERIG distributed by MOPH, Thailand, 1999-2001

Year	Volume of Distributed ERIG (vial)
1999	16,438
2000	35,430
2001	44,864

Source: Annual Report of Rabies Vaccine and Immunoglobulin distribution by Department of Communicable Disease Control, MOPH, 2000

Table 1.10: Number of Patient Treated with ERIG, Thailand, 2000-2001

Year	Number of Patient
2000	17,645
2001	19,378

Source: Annual Report Rabies Surveillance by Department of Communicable Disease Control, MOPH, 2000

The previous information informs us about the situation of rabies and rabies immunoglobulin in Thailand. The fact that Thailand uses ERIG 5 times more than HRIG, this poses the question of proper type of rabies immunoglobulin should be used in Thailand- HRIG as standard recommendation or ERIG due to low market price and more available. This study tries to explore the cost of both products as one of the reasons to be decided with.

This study tends to think of economic evaluation as a basis because the implicit and explicit objectives of economic evaluation are to improve decision-making about the allocation of health care resources [9]. This study discussed only costs because the consequences of the treatment being considered are almost equivalent. The result of treating patient with ERIG and HRIG for individual case is the same in term of protective efficacy and effectiveness [13,19]. This effectiveness do not include the complication arise from each RIG. Therefore, focus of this study is on costs and the cost that can save (benefit) between 2 alternatives of rabies immunoglobulin (ERIG and HRIG).

The study uses the concept of CMA (cost-minimization analysis) which is a special form of CEA (cost-effectiveness analysis) [9]. Both CMA and CEA are technique of full economic evaluation [9,10]. It is clear that when undertaking a CEA of treatment interventions, it is not possible to specify the result of the interventions in advance. Furthermore, if a study has been specifically designed

to show the equivalent of treatments (in term of cost and effects), it would be appropriate to conduct CMA [10].

Normally, the market price of HRIG production is higher than that of ERIG. However, The market price may not reflect to the real cost. The study explores another aspect of cost rather than merely cost of production. The economic costs will be put into calculation to find out the total cost of HRIG and ERIG utilization. However, analyses using economic costs do not replace studies done with financial costs but supplement financial cost analysis with additional information useful for decision making. [20,21] This study defines costs into 2 categories

1. Direct cost (production cost) includes cost of all inputs in each process of production of both ERIG and HRIG. [20.21]
2. Indirect cost (non-production cost, the opportunity cost or economic cost) includes costs due to morbidity (cost of treatment), costs due to mortality (income foregone loss) and costs due to the complication.

In case of ERIG, Thailand by TRCS society has a plan to produce ERIG commercially in next several years. The new plant of production can magnify the potential of production to meet the demand in the country. There will no longer be shortage of ERIG in Thailand. If we use solely ERIG, the morbidity and mortality costs will be calculated from the costs those arise from the occurrence of disease. The costs of complication are calculated mainly from the cost of medication and treatment that incurs from the adverse effect of ERIG use. The complication cost in ERIG is usually higher than that of HRIG because ERIG is originated from horse, not from human donors, thus, it has a chance to occur more often and more severe.

For HRIG, with the current production plant of National Blood Bank, TRCS and with no import of HRIG from aboard, there will be shortage of HRIG in Thailand. Consequently, if we strictly use only HRIG, costs due to morbidity and mortality those incur from occurrence of the disease according to

lack of HRIG must be included. This kind of cost does not appear when we use ERIG. This large cost is another aspect to put into consideration.

At the end of this study, all of direct and indirect costs will be summed up together to get total cost of each RIG. Then, the study will compare the cost per unit of these 2 alternatives.

1.2 Hypothesis

With the mass production and no shortage of ERIG because of new production plant, the cost per unit of ERIG is cheaper than those of HRIG.

1.3 Research Question

What is the cost per unit of ERIG and HRIG?

1.4 Objectives

The objectives of this study are to:

1. Identify the total cost of ERIG and HRIG
2. Identify and compare the cost per unit of ERIG and HRIG

1.5 Research Methodology

This study uses the secondary data of TRCS and MOPH to determine cost. There are two kinds of costs which are direct or production cost and indirect cost (cost of mortality, cost of life loss, cost of complication). Then, these costs will be compared to each other in cost per unit.

1.6 Scopes of the Study

1. This study is conducted under the societal perspective.
2. The study analyzes the data that available in year 2000.
3. The investment in ERIG production is incorporate with the new plant site production and ERIG is the only product.
4. The cost per unit of HRIG is base on current production plant.
5. The cost per unit of HRIG does not include cost of plasma from human donors.
6. The environment and determinant factors of rabies is holding constant.

1.7 Benefit

The result of this study will be used as one criterion which provides the important information to decision-maker for the suggestion of initiating the commercially producing unit of ERIG in Thailand.