A Comparison of Canine Rabies Control Programs in Thailand and the Guangdong Province in China: A Case Study Approach

Submitted by:

Adrienne S. Dale

A Case Study submitted to the faculty at Tufts University – Cummings School of Veterinary Medicine in partial fulfillment of the requirements for the degree of:

Master of Science in Conservation Medicine

Tufts University – Cummings School of Veterinary Medicine

North Grafton, Massachusetts

August 12, 2013

Project Statement: *This narrative literature review evaluates rabies prevention programs in Thailand and the Guangdong Province in China through a comparative case study approach. I use the United States as a model of a country with a successful rabies control and prevention program, and compare to the current rabies control programs in Thailand and the Guangdong Province of China. In this review I compare the risk of canine rabies, rabies control protocols, and associated economic costs for each location. Finally, I explore possible technological advances that may be more cost-effective in decreasing the overall risk in these areas.*

A. Acknowledgements

This case study would not have been possible without the help and remarkable communication of my advisor, Dr. Mary Davis, of Tufts University. Thank you for your patience and continual support throughout this past year and these last few months, I cannot express how much I appreciate your comments, changes, and edits on this review.

I would also like to thank the Tufts Cummings School of Veterinary Medicine Faculty, and my director, Dr. Alison Robbins, all of whom gave me encouragement along the way.

I would like to acknowledge the support of my mentors, Dr. Charles Rupprecht and Dr. Emily Lankau, who have given me meaningful support and direction through this experience.

I would finally like to thank my classmates in the 2013 MCM class as well as my friends and family. You all know who you are. And to my classmates, thank you for continuously editing and working out the structure of my paper until the last days before it was due. I cannot express how much I appreciate these gestures and your continued support through this program and our many experiences together.

Table of Contents

B. List of Figures and Tables

Figures:

Tables:

C. Abbreviations

Abbreviation	**Description**
ACIP	Advisory Committee on Immunization Practices
CDC	Centers for Disease Control
CNS	Central Nervous System
DALY	Disability Adjusted Life Years
DCD	Department of Communicable Diseases
DFA	Direct fluorescent antibody
dRIT	Direct rapid immunohistochemical test
EPA	Environmental Protection Agency
ERIG	Equine rabies immunoglobulin
FDA	Food and Drug Administration
GARC	Global Alliance for Rabies Control
HDCV	Human diploid cell vaccine
HRIG	Human rabies immunoglobulin
ID	Intradermal approach
IFA	Indirect fluorescence assay
MMR	Measles Mumps Rubella
MMWR	Morbidity and Mortality Weekly Report
NTV	Nervous tissue vaccine
ORV	Oral Rabies Vaccination
PCEC/PCECV	Purified chick embryo vaccine
PCH	Primary Health Care Program
PDEV	Purified duck embryo vaccine
PEP	Post Exposure Prophylaxis
PHKCV	Primary hamster kidney cell vaccine
PrEP	Pre-exposure prophylaxis
PVRV	Purified vero cell rabies vaccine
QSMI	Queen Soavapa Memorial Institute
RABV	Rabies Virus Variant
RFFIT	Rapid fluorescent focus inhibition test
RIG	Rabies Immunoglobulin
RT-PCR	Reverse transcription polymerase chain reaction
TCV	Tissue culture rabies vaccines
USDA	United States Department of Agriculture
WHO	World Health Organization

A Comparison of Canine Rabies Control Programs in Thailand and the Guangdong Province in China: A Case Study Approach

1 Abstract

Rabies is an infectious zoonotic disease that kills an estimated 55,000-70,000 people worldwide each year, with over 95% of these human deaths occurring in Asia and Africa. Many countries have achieved elimination of dog rabies; however considerable work needs to be accomplished in rabies endemic countries to decrease the negative impact of rabies. This evaluation will apply a literature review and case study approach to comparing the rabies control programs of Thailand and the Guangdong Province in China, two locations endemic for canine rabies. First, I will review how and why rabies is a global conservation medicine concern. Secondly, I will explain the ecology of rabies transmission. Finally, I will address some of the economic differences of rabies burdens in Thailand, China, and the Guangdong Province within China.

The United States will be used as a model for successful canine rabies elimination program. Thailand represents a "success story," decreasing its deaths due to rabies every year, though there are still notable gaps in the program. The Guangdong Province is still in the beginning stages of creating a successful rabies elimination program; however it is on the right track with research and initiating a basic understanding of the importance of education and awareness for preventing human illness. This study will explore and assess economic costs of prevention and control for both countries, including the strategies that have enabled the US to achieve complete canine rabies elimination.

This case study explores the process needed to achieve similar successes in rabies prevention and control in the Guangdong Province and determines why programs are working better in Thailand, despite difficulties with dog population control in that country. Recommendations will be made to decrease human rabies cases yearly and provide assistance for rural and urban communities.

2 Introduction

2.1 Rabies Virus Overview

Rabies is a zoonotic disease transmitted through saliva and other bodily fluids among mammals, caused by an RNA virus within the genus *Lyssavirus* (Rupprecht et al. 2002). The virus enters the body through a bite, and travels along the nerves to the brain where it replicates, leading to severe central nervous system (CNS) damage. This damage results in an acute, progressive viral encephalomyelitis, or swelling of the brain and spinal cord. The damage from a rabies infection leads to physical and behavioral changes, and consequently death. The virus also replicates in the salivary glands of infected animals. These behavioral changes allow the virus to be transmitted to a new animal through close contact with infectious saliva, typically from a bite or scratch. Rabies is a fatal disease and a significant public health threat across the globe (Rupprecht, 2004).

2.2 Rabies: A Public Health Threat and a Conservation Medicine Problem

Rabies has the highest case fatality rate of any conventional infectious agent, at almost 100% (Rupprecht et al., 2002). Neglected and poorly controlled in many parts of the world (Coleman et al, 2004), rabies is responsible for an estimated 55,000 to 70,000 deaths globally each year (WHO, 2013, Knobel et al., 2005; Tenzin et al., 2012). Rabies deaths are believed to be significantly underreported such that the actual global impact of this disease may be closer 100,000 human deaths annually worldwide (Fooks, 2007). Ninety-five percent of these human deaths are in Asia and Africa and approximately 97% of all rabies deaths are a result of domestic dog bites (Meltzer and Rupprecht, 1998).

At a global estimated annual cost of $4 billion USD, (GARC, 2011) rabies is also a very expensive disease. This death toll confirms rabies as one of the most lethal zoonotic, or animal-transmitted diseases, causing more human deaths annually than SARS, H5N1 and Dengue fever (GARC, 2011). Despite the high economic and human health costs of rabies, preventing this disease has not received the attention it deserves. Rabies is not even mentioned in the Global Disease Burden 2004 update (WHO, 2004), and is only briefly mentioned in the Global Disease Burden 2010 update. The Global

Disease Burden 2010 update states it as one of the infectious diseases with the largest declines in cases, even though is severely underreported worldwide (Murray et al., 2012).

Rabies is a nearly 100% preventable disease through administration of safe, effective and extensively available vaccines for humans and animals (Coleman et al, 2004). However, the majority of humans who have possibly been exposed to the virus are either unaware of the danger of rabies or are not able to access post exposure prophylaxis (PEP). PEP, which includes both vaccination and delivery of passive immunity through rabies immunoglobulin (RIG) in persons not previously vaccinated, is effective for preventing rabies in humans if given early enough after exposure (Peterson and Rupprecht, 2011). In people who have been infected with the rabies virus but do not receive PEP, the virus will eventually overtake a victim's central nervous system (CNS). After onset of clinical symptoms, with no established treatment for rabies, the disease will typically progress to death.

Rabies threatens over three billion people in Asia and Africa, with over 31,000 people dying every year in Asia (WHO, 2013). This results in a substantial public health concern regarding rabies, with an estimated total annual cost of over $563 million USD in Asia alone (Gongal and Wright, 2011). I selected two locations in this region that have contrasting circumstances for canine rabies control and prevention for my case study: Thailand and the Guangdong Province in China.

Thailand and the Guangdong Province each have a very high poverty rates and large populations living in rural areas that are at particularly high risk because they have the least access to affordable health and medical care (Hampson et al., 2011). Rabies also represents a large conservation medicine concern as a threat to humans and wildlife. The virus is highly pathogenic, and can spread to other wildlife and domestic reservoirs without the proper protocols in control programs. Spillover is a current concern in many areas globally regarding endangered species such as the Ethiopian Wolf whose numbers are critically suffering due to rabies (Randall et al., 2004).

2.3 Social Problems Regarding Rabies

Worldwide, exposures from dogs lead to over 90% of the total rabies virus exposures, and over 99% of the total human deaths due to rabies (WHO, 2013; Cleaveland et al., 2006). There are many negative attitudes regarding canines and the threats and fears of rabies, and because of this social problems related to accessing proper health care evolve. Through public awareness and education, inexpensive vaccination, sterilization, and registration programs, canine rabies can be controlled and significantly decreased in these regions.

One controversial method used to control stray dogs as a vector for rabies is culling, or the elimination of a large portion of the population (usually feral and some free-ranging), often through shooting or poisoning (Knobel et al., 2007; Cleaveland et al., 2006). This method has been unsuccessful as a long-term solution (Briggs, 2012), yet it continues to be used as a short-term solution to the problem. In countries such as China, Sri Lanka and Ecuador, elimination campaigns have killed large percentages of the dog populations (Jackman and Rowan, 2007; Knobel et al., 2007). In Thailand, Buddhist religious beliefs and cultural influences cause controversy when rabies control programs involve the discussion of stray dog control through large-scale population elimination. Euthanasia and other forms of large-scale elimination will also cause problems for some programs in other countries that have similar religious beliefs.

In countries that do use these techniques, there may be controversy as well within the populations, even if there isn't a religious issue concerning the action. Large-scale elimination strategies are a tenuous topic and are proven to be ineffective and considered inhumane and cruel, and often will lose public support and trust (Jackman and Rowan, 2007; Zhang et al., 2011). It is common for these campaigns to mistakenly remove a large percentage of vaccinated canines, which will diminish the number of immunized animals in the population, potentially increasing the risk for rabies outbreak (Knobel et al., 2007). This method also has increased hostility of locals towards rabies elimination programs and mass vaccination campaigns, which can lead to owned dogs not receiving vaccinations.

2.4 Locations of Focus: United States, Thailand, and the Guangdong Province in China

The United States, Thailand and the Guangdong Province in China are all locations that are suffering in different ways from the rabies virus. The United States has successfully eliminated canine rabies, while Thailand and the Guangdong Province are still creating the systems and building the structure necessary for them to effectively eliminate the public health impacts and significantly reduce human deaths.

The United States has successfully eliminated canine rabies, and continues to spend millions of dollars on public health measures each year to prevent canine rabies from reestablishing in the country. This money is also used to continue to fight wildlife rabies, which is still a large problem in the US (CDC, 2011).

Thailand was chosen because its rabies prevention program has successfully reduced overall human deaths due to rabies in recent years, and is close to eliminating canine rabies (Burki, 2008). Canine rabies presents a unique obstacle that could be overcome in Thailand through decreasing stray dog populations, in combination with vaccination. With continued governmental support, a progressively successful rabies control program and increased research has occurred, and will lead to more accurate rabies statistics and economic data in Thailand. In 1980, 370 deaths were reported in Thailand (Mitmoonpitak et al., 1998), and this number has significantly dropped in recent years.

The Guangdong Province of China was selected because of the high prevalence of rabies in this region of China. Leading China in GDP for the past 24 consecutive years (Lin, 2013), the Guangdong Province has the resources to create a rabies program to reduce rabies burden in this country. The Guangdong Province has a similar demographic structure to Thailand, and through this case study, I analyze the gaps and barriers to success in Guandong’s rabies control program in order to improve rabies control efforts in similar regions. Major obstacles to tackling canine rabies in China are increased research on the rabies virus and its ecology, dog population control, lack of surveillance, and diagnostic capabilities (Davlin and VonVille, 2012, Tang et al., 2005).

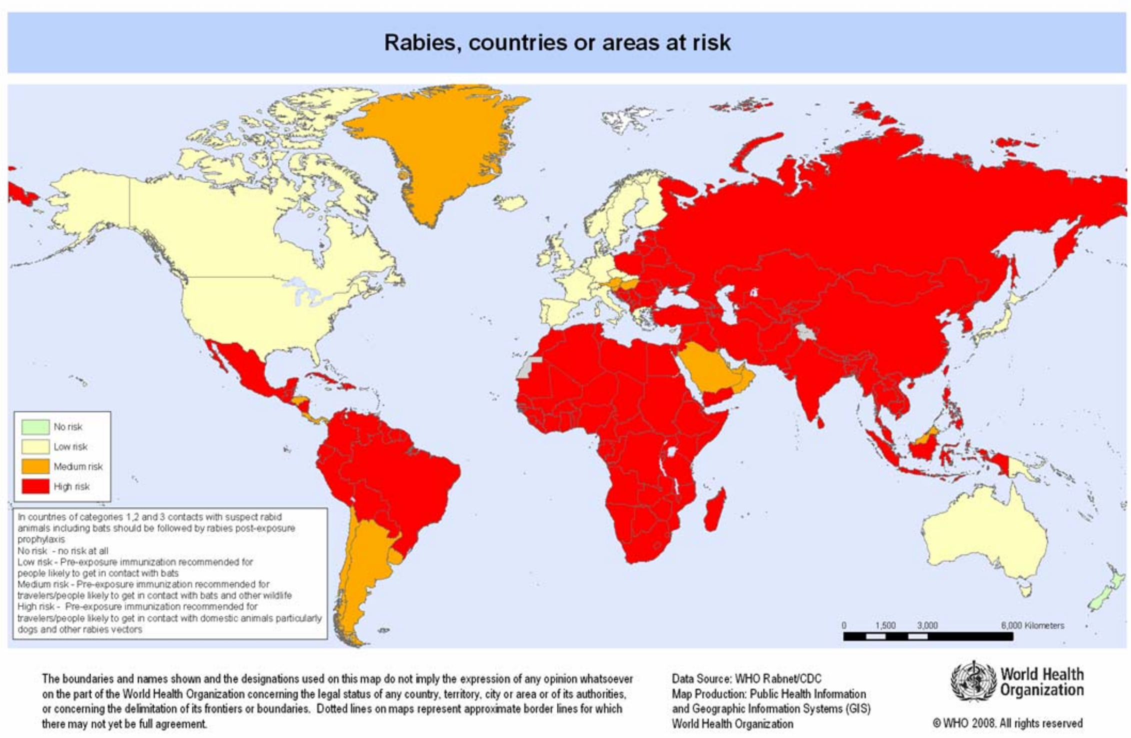
2.5 Geographic and Ecological Context of Rabies

2.5.1 Global

Rabies is a leading viral zoonosis with a very large public health influence globally, with various strains distributed on all continents except for Antarctica. Rabies is a larger problem in places where it is endemic, such as China and Thailand. It is difficult to assess the global impact of deaths due to rabies because the majority of the cases are in Africa and Asia, and it is known that many of these cases in developing countries are inconsistently or underreported yearly (Coleman et. al, 2004; Cleaveland et al., 2006). The majority of the deaths caused by rabies are due to lack of awareness, political support, and access to this vaccine, mainly in developing world rural areas (Knobel et al., 2005).

Developing nations are also usually lacking in surveillance and diagnostic institutions and equipment. These deficiencies hinder proper rabies diagnostic identification and treatment capabilities (CDC, 2011; Lembo et al., 2010), and it is critical that surveillance systems are created in these areas (Briggs, 2012). The largest percentage of deaths in a single country from rabies is in India, with approximately 30,000 human deaths annually (Dodet et al., 2001). As previously mentioned, Africa and Asia are two continents with countries and locations severely in need of this type of modernized care and equipment. One estimate expresses without the existence of PEP, Asia and Africa would lose approximately 327,000 people annually to rabies (Prakash et al., 2013).

Figure 1 - Rabies: Global Risk Map



(WHO, 2008).

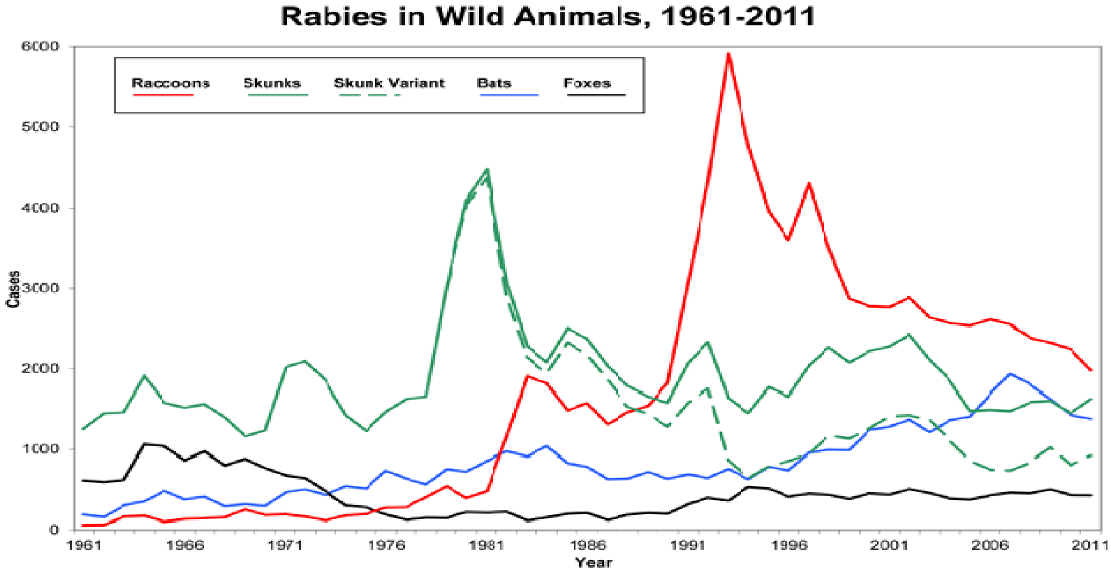
The WHO global map of rabies risk (Figure 1), evaluates countries from no and low-risk (colored green and tan, respectively), to medium and high-risk (colored orange and red, respectively). This map informs travelers regarding specific countries and areas and helps them determine if they need pre-exposure prophylaxis (PrEP). The WHO presents the United States as low-risk and all of China and Thailand as high-risk countries. The only country with no risk of rabies infection was New Zealand, though there is no data available for Western Sahara. New Zealand has never had rabies, and it is assumed to be because the lengths of average sea expeditions were much longer than the incubation period of rabies in animals (Crump et al., 2001). This map shows that there are billions of people at risk for rabies across the globe, but with the proper prevention and access to care, thousands of lives can be saved annually.

2.5.2 The United States

The United States has successfully eliminated the canine rabies variant from the country, and through increased effort, many countries and regions have achieved this, and more are in the process of eliminating canine rabies as well. The last human rabies case of canine rabies virus from within the United States was in 1994, and the last canine rabies virus variant in a domestic dog in the United States was detected in 2004 (CDC, 1995; Blanton et al., 2011). Human rabies cases do occur in the United States, though because of surveillance and proper PEP care, they are rare, and have been significantly reduced since the 1970's (Blanton et al., 2012). Six human rabies cases were reported to the CDC in 2011 (from New York, New Jersey, South Carolina, California, and Massachusetts), three of which were acquired while out of the country (Blanton et. al, 2012).

Thousands of animal cases reported every year and sent in for sampling. Ten states (Arkansas, Georgia, Idaho, Massachusetts, Michigan, North Dakota, Ohio, South Dakota, Vermont, and West Virginia) continuously send animal rabies data to CDC diagnostics laboratories in Atlanta, GA through the public health laboratory information system. Other states and the USDA Wildlife Services send animal rabies data on a monthly or annual basis directly to the CDC Poxvirus and Rabies Branch (Blanton et. al 2012). These actions allow the rabies databases to remain updated and the statistics to remain current. A total of 99,890 possible positive animal rabies samples were considered and sent in to the CDC for further testing in 2011. That was a 4.5% decrease in the number of animals tested than the previous year (Blanton et. al, 2012). More than 90% of the animal rabies cases in the US and Puerto Rico in 2011 were in wildlife species, and this has been the case since 1980 (Blanton et. al, 2012).

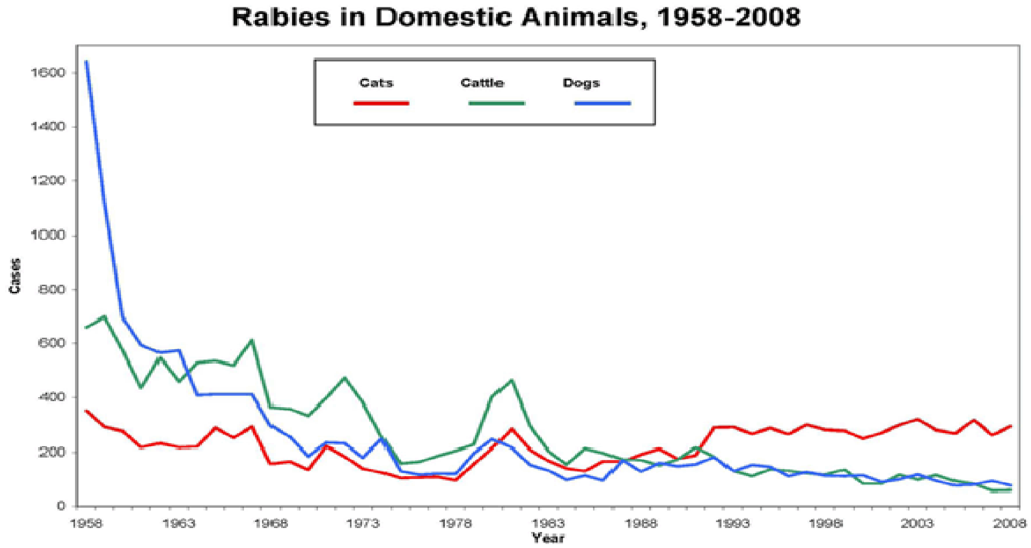
Figure 2 - Rabies in Wild Animals



(CDC, 2012).

Wildlife rabies virus variants are present in many mammal species in the United States, but due to awareness and oral rabies vaccine (ORV) programs, wildlife rabies has drastically decreased in the 1990's and has remained stable over the last decade (Figure 2).

Figure 3 - Rabies in Domestic Animals



(CDC, 2010).

Rabies in domestic animals is uncommon in the United States, however the largest domestic reservoir is the domestic cat, with dogs and cattle (respectively) following (Figure 3). Feral populations of cats are difficult to estimate and control through vaccination. Spay/neuter-vaccinate-release programs are in effect to overcome problems of overpopulated feline populations and vaccinations are given in many cases as well to decrease the spread of rabies (Roebling et al., 2013).

Domestic canines are required to get a rabies vaccine annually in the US. There are usually annual rabies vaccine clinics at pet shops where licensed veterinarians will provide vaccinations for animals for only the vaccination fee, rather than paying for the office visit as well. Though these vaccinations may last longer, the US has made a strict policy to keep canine rabies out of the country and to continue to keep immunity in the population as high as possible.

2.6 Identifying & Calculating Economic Problems with Rabies

Though canine rabies has been successfully eliminated in the United States, there is still a fight against rabies in wildlife carriers of the disease. Over 12 million RABORAL V-RG, or edible recombinant vaccinia rabies vaccines focused on protecting raccoons and coyotes from rabies, are distributed into wildlife habitats each year in order to keep rabies from spreading into domestic animal and human populations (RABORAL, 2013). The US spends millions dollars every year on prevention of rabies (wild and domestic) strains to prevent unnecessary deaths (CDC, 2012; Sterner and Smith, 2006).

To understand the financial impact of rabies, it is important to analyze the social costs, which include the value of a human life. Actuarial analyses measure the value of a human life based on life expectancy, productivity, and other factors. Disability-adjusted life years (DALYs) is a standardized measure to compare and determine the basic impact of different diseases across diverse locations (Coleman et al, 2004). Many studies rely on this method to economically estimate the impacts of rabies in Africa and Asia, which is estimated to cost 1.7 million DALYs annually (Grace et al., 2012). In 2004, rabies was responsible for an estimated 35,000 global deaths a year (Coleman et al., 2004). Using current estimates of rabies deaths at 55,000-70,000 per year (Knobel et al., 2005; Tenzin et al., 2012; WHO, 2013) rabies has rapidly increased to an even larger global public health impact.

Worldwide, over 15 million patients receive human rabies post exposure prophylaxis (PEP) every year (WHO, 2013), and in the United States, unnecessary administration and treatment of PEP has been described as a major issue in regards to overall cost spent in the prevention of rabies (Rupprecht et al, 1996). In the United States, the average cost of a rabies pre-exposure prophylaxis (PrEP) series of three shots totals around $700. The rabies PEP series of four shots averages around $1500 in the United States (Meltzer and Rupprecht, 1998). If RIG is needed (required in addition to PEP in a previously unvaccinated person) costs will increase significantly, and this is true across China and in Thailand as well (Song et al., 2009).

Direct and indirect factors for the patient are looked at in various ways in relation to rabies and its effects. Direct costs are considered the costs for the PEP, HRIG, and physician charges. Indirect costs are related to lost wages, travel and boarding costs, and possible effects of treatment (Shwiff et al., 2007). Direct costs of rabies treatments are lower in developing nations due to drug companies attempting to increase overall health in those locations (Fang et al., 2010). However, with countries that have much lower incomes, this cost is still very high, especially for those living in rural areas (Fang et al., 2010). Most versions of PEP are cell-cultured vaccines, which have been extensively tested and proven safe and effective (Knobel et al., 2007). In Asia, many people who cannot afford cell-cultured vaccines will chose clinics that use nerve-tissue based vaccines, which are cheaper in cost and lower quality (Knobel et al., 2007). Taking these vaccines has been shown to result in detrimental neurological side effects and many countries are trying to eliminate them from use (Knobel et al., 2007; Jentes et al., 2013).

3 Background of the Rabies Virus

3.1 History, Characteristics and Epidemiology of the Rabies Virus

According to the World Health Organization (WHO), rabies is one of the oldest known viruses on record, dating back nearly 4000 years, and having an immense impact on history (WHO, 2013). In 1885, Louis Pasteur of France used the first documented successful rabies vaccine on a patient that had been bitten 2 days prior to treatment (Jackson, 2013).

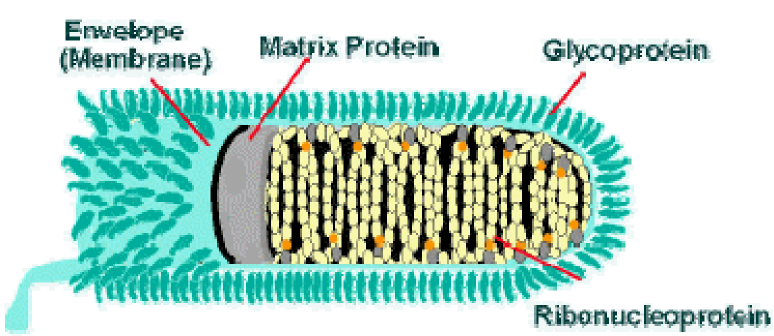
Rabies is caused by an RNA virus and is a progressive acute illness that is almost always fatal to humans and animals once symptoms develop (WHO, 2013). There have only been a handful of documented cases worldwide where the patient has survived through experimental treatment (ACIP, 2008).

It has been shown that rabies will increase in areas where there have been changes in demographics, environmental habitats, or animal movement or translocations (Rupprecht et al, 1996). The rabies virus has the ability to affect any mammal; however the primary reservoirs of the virus are typically in the genus Carnivora (primarily domestic dogs, canids, raccoons, skunks, and cats) and the genus Chiroptera (bats) (Cleaveland et al., 2006). Rabies virus is in the Order Mononegavirales, the Rhabdoviridae family and the genus Lyssavirus. This genus is responsible for all of the strains, or serotypes, of the rabies virus. These rabies virus variants differ in their most common reservoir hosts but all lead to development of clinical disease and death of the host and are infectious to humans.

Viruses in the Rhabdoviridae family are typically 180nm long and 75 nm wide and the rabies virus consists of about 12 kilobases (kb). There are five proteins included in the rabies virus (and all other Lyssaviruses): nucleoprotein, phosphoprotein, matrix protein, glycoprotein, and polymerase. The rabies virus is a non-segmented, negative-sense, single-stranded RNA genome (Ferguson, 1991). The virus has a characteristic bullet-shape, with a spiked-glycoprotein coating, with each spike approximately 10 nm long (CDC, 2011; Ferguson, 1991; see Figure 4). Rhabdoviruses have a distinguishing helical ribonucleoprotein core and a surrounding envelope, which is what fuses to the host cell membrane to originate the infection process (CDC, 2011). The ribonucleoprotein is composed of RNA encased in nucleoprotein, phosphorylated or phosphoprotein.

The rabies virus is fragile and not capable of existing outside of the host in the environment for long periods of time. Outside of the host, the rabies virus will not remain viable, and will die with exposure to UV light, alcohol, bleach, soap and detergents (GA Dept of Public Health, 2012). This virus is dependent on its host for survival and to reproduction to another host, and is not infectious if the saliva dries or is damaged by any of the above factors (GA Dept of Public Health, 2012).

Figure 4 - Rabies Cell



(CDC, 2011).

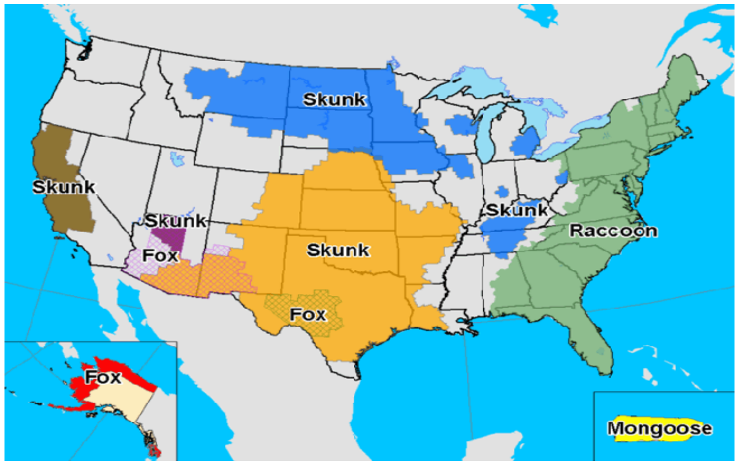
3.2 Rabies Virus Reservoirs in the United States

Though canine rabies virus variant was eliminated from the United States, there are multiple wildlife rabies virus variants across the US. Skunks, raccoons, foxes, bats and mongoose (only present in Puerto Rico) all have specific rabies viral variants that affect the United States and Puerto Rico (Figure 5). In the United States, the bat variants of rabies are the most common wildlife variant cases detected each year (and were probably responsible for the deaths in the United States last year not associated with travelers returning to the US). Globally, the most common reservoir of the rabies virus is the domestic dog, responsible for over 98% of all human rabies deaths annually (WHO, 2013).

3.3 Possible Routes of Transmission

The most common route of rabies virus transmission is through direct transmission of infectious saliva via a bite or lick from an infected animal. The rabies virus cannot infect an individual through intact skin, however other than a direct bite, rabies virus can be transmitted by contact with infectious saliva on broken skin or mucous membranes. Though rare in circumstance, transplantation of corneas and solid organs from rabies-infected donors has also resulted in transmission (CDC, 2011). There are other ways that the rabies virus can be transmitted from one host to another. Ingestion through oral exposure, infection through airborne particles, un-pasteurized-milk-borne transmission, and environmental transmission through fomites have also all been documented, but are not nearly as common and with proper awareness and protocols, the risk of transmission through these routes can be mitigated (CDC, 2011).

Figure 5 - United States Rabies Terrestrial Reservoirs, 2009



(CDC, 2010).

3.4 Pathogenesis/Pathophysiology of the Virus

Rabies infections spread through a bite or broken skin via the saliva of an infected mammal (WHO, 2013). Once an infection occurs from exposure, there is an incubation period, ranging from 5 days to 2 years. Within the next zero to ten days after the incubation period, the prodromal period, or the onset of the first symptoms will occur. After this stage, the acute neurologic period will ensue, lasting approximately two to seven days. This is the stage at which the central nervous system will become affected. After this neurologic period, the virus has replicated in the muscles and has traveled through the spinal cord to infect the brain and other tissues through nerves and will move to affect the kidneys and salivary glands (CDC, 2011).

The virus spreads to the salivary glands, and will continue towards the brain. The brain infection leads to virus-induced aggressive behavior in the host animal. This aggressive behavior increases the host's desire to bite and through the infected salivary glands, will spread the infection to susceptible individuals. Because rabies spreads so quickly, uninfected populations of animals are at an increased risk if located near infected individuals or groups. The rabies virus has exploited this change in the host's behavior, increasing its chances of spreading the infection to a new susceptible host (CDC, 2011). For patients who have been infected with the rabies virus, once symptoms appear, the patient rarely recovers (WHO, 2013). After this acute neurologic period, most cases result in a 5 to 14 day coma, which ultimately will result in death (CDC, 2011). There are very rare instances, reported in 5 documented cases worldwide, where individuals have survived (ACIP, 2008; Rupprecht and Gibbons, 2012).

3.5 Clinical Signs and Symptoms of the Rabies Virus

The rabies virus can present in two clinical forms: the furious type (also known as the classical form) and the paralytic, or dumb type. Well-known signs and symptoms recognized with rabies include hydrophobia (fear of water), aerophobia (fear of drafts or airborne matter), paresthesia (burning, tickling, numbing, tingling feelings), localized pain or weakness, priapism (continuously erect penis) or spontaneous ejaculation, dysphagia (difficulty in swallowing), fever, muscle spasms, hyper-salivation, increased anxiety and aggressiveness, hallucinations, autonomic instability, nausea, ataxia, anorexia, insomnia, seizures, malaise, fatigue, headache, and confusion or delirium (Peterson and Rupprecht, 2011; Gong et al., 2012).

The furious type is the more common form of the disease, experienced in over two-thirds of patients (Hemachudha et. al, 2001). Symptoms relating to the furious form of rabies in humans relate to an increase in agitation and aggression with an overall change in behavior most commonly due to internal stimuli such as anxiety or thirst, or external stimuli such as light or noise. Symptoms such as fever and behavioral changes due to stimuli are commonly the first neurological irregularities seen in rabies cases experiencing the furious form (Hemachudha et. al, 2001).

This classical form (furious) of rabies has five stages: an incubation period, the prodromal period (early symptoms before true developed symptoms appear), an acute neurological phase, coma, and death or recovery (in very exceptional cases). The incubation period can be anywhere from days to years (ACIP, 2008). After the incubation period, beginning symptoms in the prodromal phase are similar to those of the flu or a common cold and if they occur, may last only a few days, and then go away. These signs would include general aches and pains, discomfort, fever, weakness or headache. It is also not uncommon for feelings of discomfort or a tingling and itching to occur at the site of the bite (Hemachudha et. al, 2001).

The next phase of symptoms in the furious type would be the acute neurological phase. These symptoms would usually occur shortly (within days to weeks, depending on the location and severity of the bite/exposure) after the prodromal phase in most patients leading to symptoms including anxiety, confusion, “cerebral dysfunction” and agitation. Two of the most recognizable symptoms presented for rabies are aerophobia and hydrophobia. As these symptoms present themselves, and as the disease progresses through the body and the central nervous system, individuals may experience delirium, hallucinations, insomnia, and further abnormal and increasingly aggressive behavior.

The paralytic form, even though uncommon, occurs in approximately 20% of cases (Kureishi et al., 1992), and has symptoms more relating to paralysis and loss of motor function. General symptoms include fever, muscle and joint weakness, and a loss of proper urinary function. Weakness will begin at the site of the bite and progress through the body to the other limbs and muscles, including those in the throat, face and respiratory system (Hemachudha et. al, 2001). This form doesn’t have presentation of aggressive outbursts and behavior change symptoms are usually milder (Hemachudha et. al, 2001). Symptoms of this form will present themselves later in the progression of the disease (Hemachudha et. al, 2001).

There is no effective treatment for rabies once symptoms present themselves. There is only prevention and immediate PEP that can be taken for the rabies virus before the disease arises. Once clinical signs of rabies appear in the individual, rabies is nearly always fatal, and patient care is typically palliative.

3.6 Diagnosis and Confirmation of Rabies

In the United States, rabies is diagnosed through standard diagnostic techniques and laboratory tests that are performed by a state laboratory or the CDC, and positive tests are sent to the CDC headquarters in Atlanta, GA for confirmation. Antemortem, rabies is very difficult to diagnose due to rabies variable incubation time (Wu et al., 2009). Various tests using saliva, serum, skin biopsies from the neck, and spinal fluid can be performed to test for possible rabies antibodies and antigens (CDC, 2011). After death, rabies virus (RABV) variant can be determined through antigenic or molecular typing of brain tissue. Genetic testing can be done previous to death, however medical professionals need to have an idea of what they are looking for in order to diagnose a suspected rabies case, which is difficult due to the various symptoms and that rabies is often misdiagnosed (Wu et al., 2009). These tests use a database of other rabies variants genetic sequence to match the variant based on a nucleotide sequence that is obtained through using specific sequence-targeting primers and performing reverse transcription polymerase chain reaction (RT-PCR). This large database was created by collecting sequences from known reservoirs from the US and across the globe (Peterson and Rupprecht, 2011).

Determining the possible source or reservoir of an exposure is useful in case the exposure is not memorable to the patient (Peterson and Rupprecht, 2011). Rabies virus antigens are usually detected through the use of the direct fluorescent antibody (DFA) test, using skin biopsy samples, corneal impressions, or fresh brain tissue (CDC, 2011). Other tests that are commonly used for rabies detection are the indirect fluorescence assay (IFA) and the rapid fluorescent focus inhibition test (RFFIT) (Peterson and Rupprecht, 2011). If antibodies are discovered in the tested serum or spinal fluid, they are considered indicative of rabies even if there was no previous rabies immunization history (Peterson and Rupprecht, 2011).

Antemortem tests from nuchal skin biopsy, corneal impressions, and brain tissue samples all are different techniques used to positively test for rabies (Peterson and Rupprecht, 2011). The true diagnosis and confirmation of rabies is not completely positive until signs, symptoms, and history are satisfactorily diagnosed by the clinician involved, and when proper antemortem samples are collected from the patient or the source of the bite are confirmed to be positive.

3.7 Prevention and Post-exposure Prophylaxis of Humans

3.7.1 Pre-Exposure Prophylaxis (PrEP) and Post exposure Prophylaxis (PEP)

There are various methods for management options for rabies control in the US and globally. There is no cure for the disease of rabies, but an effective vaccine has been available since 1885 for the rabies virus. Once symptoms show, rabies is nearly 100%

fatal. There is only prevention through pre and post exposure prophylaxis for rabies-exposure patients.

Pre-exposure prophylaxis (PrEP) is any treatment that is given to a patient to prevent a reaction or infection before an exposure to a pathogen occurs. Post exposure prophylaxis (PEP) is any medical treatment that is given to prevent an infection in a patient after exposure to a pathogen. Rabies PEP is a series of injections that are comprised of rabies vaccine and immunoglobulin, which is injected into the wound itself. More than 15 million rabies PEP treatments are distributed worldwide every year (WHO, 2013). Rabies PEP is the most cost effective and common and ensures rabies protection to those who can access the vaccine (WHO, 2013). PEP for persons without previous inoculation against rabies is a combination of rabies immunoglobulin and the vaccination (CDC, 2011) and will effectively prevent progression to disease in a person if given soon after a rabies exposure. Rabies PEP will not be effective in preventing future rabies exposure; another round will have to be administered if a person is bitten again (Zinsstag et al., 2009).

3.7.2 PEP Procedure

The only prevention strategies for rabies that currently exist are pre and post exposure prophylaxis, which has to be given previous to any symptoms presenting themselves. Rabies PrEP is three doses of rabies vaccine, with an injection on day 0, 7, and 21 or 28.

Rabies PEP will prevent the development of the rabies viral infection in the body if given correctly and early after exposure and previous to the presentation of symptoms. PEP, if given properly and within five days after the exposure, ensures close to a 100% protection against the progression and development of the disease (ACIP 2008; WHO 2013).

Recommendations for rabies PEP protocol for a patient who is previously unvaccinated, suggest that the wound should be thoroughly cleaned, human rabies immunoglobulin should be permeated throughout the exposure site, and four doses of a cell-based-culture vaccine should be given to the patient, the first as soon as possible. In the US, PEP is usually given on days 0, 3, 7, and 14 for previously unvaccinated patients (Christian et al, 2009).

This dose number, however, is dependent on the vaccine schedule used and the amount in each dose. The 8-site intradermal method (also called the Oxford schedule), has the most injections, however they are very low doses of the vaccine. Eight injections are given at various sites on day 0 (2 injections), day 7 (4 injections), and on days 28 (1 injection) and 90 (1 injection). This method uses much less of the vaccine overall on each patient (Wilde et al, 2005).

Rabies virus exposed patients that have received PrEP will receive a condensed version of the PEP series: two shots given on days 0 and 3, and no RIG is necessary (CDC 2011; Christian et al, 2009). This approach has advantages because it removes the need for rabies immunoglobulin (RIG), which is usually limited in supply throughout the developing world and is a very expensive biological component of the procedure (Rupprecht and Gibbons, 2012; Malerczyk, 2012; Jentes et al. 2013).

3.7.3 Types of Post Exposure Prophylaxis Available

There are four rabies vaccines that have met the WHO standards for immunogenicity (Warrell, 2012). These vaccines are the human diploid cell vaccine (HDCV), the purified chick embryo cell vaccine (PCEC), the purified vero cell rabies vaccine (PVRV), and the purified duck embryo vaccine (PDEV). These all are given intramuscularly with a 1 ml dose, except for the PVRV, which is given with a 0.5 ml dose (Warrell, 2012).

3.7.4 Regulations, Vaccination and Traveler Information

The United States uses the recommendations of the Advisory Committee on Immunization Practices (ACIP) when there is a change in human rabies prevention practices and regulations (CDC, 2011). Each US state has its own requirements regarding regular yearly licensing and rabies vaccination of pets. By continued regulations for vaccination of susceptible pets, like dogs and cats, as well as oral vaccination strategies for wildlife, the US has obtained some degree of regional control of wildlife rabies and completely eliminated canine rabies.

In the United States, and in many other countries, dogs that are not up to date on their vaccinations and have been involved in a known possible rabies exposure should be given a booster, confined and observed for up to 10 days after biting a human (WHO, 2013; Mitmoonpitak et al., 1998). This is an important factor because an infected dog can shed the rabies virus for a few days before showing any signs of illness, possibly infecting other people and animals in that time period (Rupprecht, 2004). This shows that dogs can spread rabies before signs are visible, making education, surveillance and diagnostics all the more important in hard to reach communities in poverty without access to public health information and rabies awareness. If the domestic dog is healthy at the end of the 10 days, it was not a true rabies exposure and the human can cease finishing rabies prophylaxis (Mitmoonpitak et al., 1998). If the dog that bit a person was tested and confirmed rabid, then the dog will receive shots and will stay in confinement until there is confirmation that the animal is safe to let out in public, or if it is necessary be euthanized.

The CDC has recommendations for rabies vaccinations before international travelers visit specific countries that are usually based on what the profession and degree of contact to certain high-risk species is or whether rabies is endemic and prominent. In every bite event or possible exposure, wound cleansing should occur. In high-risk cases (severe wounds or bites to the head, face and neck) or bites where animal control cannot detain the animal for confinement, PEP is suggested (Rupprecht and Shlim, 2013).

3.7.5 Barriers to the Human Rabies Vaccine

One of the largest concerns regarding the rabies vaccines is that they require refrigeration during transportation and storage to maintain immunogenicity. Rabies vaccines are heat sensitive and the proteins will denature, or break apart, if outside the set temperature boundaries. Manufacturers recommend that the vaccines should remain stored for only 8 hours once they have been opened (Kamoltham et. al, 2003).

Denaturation is a problem in developing countries that are attempting to use the intradermal approach. This approach to rabies vaccination uses significantly less volume of the vaccine than intramuscular regimens, and many clinics aren't able to use the vaccines fast enough for them to remain viable (Hampson et al., 2011). The intradermal approach to rabies prophylaxis has the ability to increase vaccine availability and distribution and decrease overall costs (Hampson et al., 2011).

Research in Thailand has reported that tissue culture human rabies vaccines (TCV) are viable up to 7 days in 4-8°C after they are opened and remain sterile throughout the process. Two of the brands used in the US, RabAvert (PCEC), and Imovax (HDCV) explain that the vaccine should not be frozen and should be refrigerated in 2-8°C and in a dark space to prevent early denaturation. Because this is a sterile freeze-dried vaccine, it comes as lyophilized powder that must be added to a separate liquid diluent (RabAvert, 2012; Imovax, 2012). Once reconstituted, this vaccine (or any that must be combined in this way) must be used immediately. The vaccine should not be used past the posted expiration date on the package or vial (RabAvert, 2012).

3.7.6 Restrictions and Side Effects of the Vaccine

The only restrictions to this vaccine in the US are that a licensed doctor or veterinarian must order the shipment and should be responsible for giving the injection. Licensed physicians or veterinarians are always recommended to perform the injection series (WHO, 2013, CDC, 2011). Because of the high demand for prophylaxis, there are shortages some years, putting pressure on diagnosis in order to not waste supply. Currently, there are no shortages or restrictions on the rabies vaccine (as of May 2009) (CDC, 2011).

Significant adverse events related to use of rabies vaccine in humans are rare. (CDC, 2013). These side effects and symptoms are comparable to Guillain-Barré Syndrome (a rare disorder in which an individual's own immune system damages their nerve cells- leading to muscle weakness and sometimes paralysis) (CDC, 2013; Wu et al., 2009). These symptoms are so rare that it is not a proven fact that they are connected to the vaccine (CDC, 2013). Mild to moderate side effects of vaccine delivery are also not common, but could occur as a result of the vaccine. These range from a soreness, redness or itchiness at the injection site, headaches, nausea, dizziness, muscle aches, or abdominal pain, to hives, joint pain, or fever (CDC, 2013).

3.8 Vaccination of Domestic Animals, Specifically Canines, in Developing Countries

When vaccinating a population of animals, especially dogs, the ideal percentage of the population to be vaccinated is 70% or greater (WHO, 2013). This percentage is appropriate for canines and wildlife through vaccinations and oral rabies vaccines (ORV). Reaching a 70% vaccination rate provides strong herd immunity in the population to prevent a large-scale epidemic. In cases of high vaccination rates, rabies spread from unvaccinated dogs or wildlife will lack sufficient numbers of susceptible individuals, and will die out quickly in a community.

In contrast to wildlife rabies, domestic canine rabies surveillance is severely lacking worldwide (Hampson et al., 2007). A specific canine vaccination rate is a difficult task to accomplish in developing nations because laws do not always require vaccinations and dog registrations. This results in an inaccurate census of the dogs in the region and a lower number of dogs vaccinated than necessary. When this occurs, rabies will often quickly increase in those areas, endangering both the human and animal populations (Cleaveland et al., 2006).

Studies have shown that at a population vaccination of 60-70%, bite incidence will decrease 51% after the first canine rabies control campaign and up to a 92% decrease after the third campaign (Cleaveland et al., 2003). In rural areas and villages, increased use of implemented surveillance also has led to a decrease in canine rabies cases. This increased canine vaccination and decreased overall number of canine rabies cases in these areas also led to a reduced demand for PEP (Cleaveland et al., 2003), which if continued, leads to lower overall economic costs to control rabies annually.

A rapid decrease of canine rabies in a study in Tanzania shows that vaccination coverage at a lower percentage (65% in this case) may also be effective if the dog population estimate is accurate (Cleaveland et al., 2001; Cleaveland et al., 2003). To look at this issue another way, if there is not a decrease in rabies cases in an area with a recorded vaccination rate over 70%, this proves that the canine population was not properly accounted for. This shows how crucial an accurate canine census is in order to properly vaccinate an adequate percentage of the population. With these dogs having such quick turnover rates, too many unvaccinated animals will increase the possibility for rabies to spread rapidly.

In developing countries, the heat sensitivity of the rabies vaccine is a much larger concern. If trips need to be made out to rural areas, early preparation will occur for vaccine transport in order for it to stay chilled, and for longer trips, different modes of transportation made need to be used in order for the vaccine to remain viable. These areas also may not have the availability of the vaccine because it is only kept in limited supply to assure vaccine viability and drug effectiveness.

4 Developing World Case Studies: Case Study Analysis of Thailand and the Guangdong Province in China

4.1 Thailand

4.1.1 Country Statistics and Governmental Structure

In 2011, Thailand had a population of 69.52 million people (World Bank, 2013). Thailand's gross domestic product (GDP) for 2011 was $345.7 billion USD, increasing over 26 billion USD just since 2010 (World Bank, 2013). Thailand is a middle-income country that has shown immense development in the last two decades. The percentage of those impoverished decreased from 27% in 1992 to 9.8% in 2002, and malnourished children has decreased by half (United Nations, 2008).

Thailand covers an area of 514,000 km^2 and is located in the center of the Southeast Asia. It has many geographical assets including a coastline in the south, heavy forests and mountains in the North, country hillsides in the southeast regions, rubber farms in the south, and rice farms in the central region (United Nations, 2008). Nearly a third of the population is located in the Northeast, although there is a large concentration in Bangkok, the capital city in a more centralized location in the country.

Thailand has existed since the 13^{th} century and has been a constitutional monarchy under a parliamentary democracy since 1932. The country is ruled in combination by a king (head of state) and a prime minister and through the legislative branch of the Senate, the National Assembly, and the House of Representatives (United

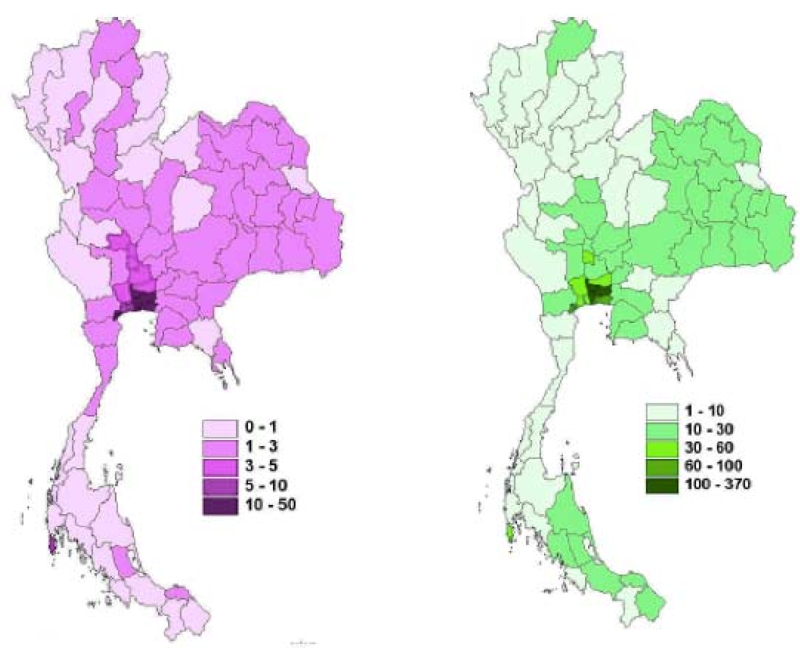
Nations, 2008).

Thailand implemented their universal "30 baht" health care program in 2001, which now covers over 70% of the population (United Nations, 2008; Damrongplasit and Melnick, 2009). Their goal for this system was to provide equivalent healthcare to all, and for no one to pay more than 30 baht (equivalent to $0.84 USD) per visit, including pharmaceuticals and rabies PEP. This was created to give universal coverage and to halt the use of under-the-table payments to health care providers in order to get special treatment (United Nations, 2008; Damrongplasit and Melnick, 2009).

4.1.2 Basic Rabies in Thailand

Rabies is a reportable disease in Thailand (Puanghat and Hunsoowan, 2005; Chuxnum et al., 2011) and is still considered a prominent public health concern nationally (Puanghat, 2001). The majority of both canine and human populations are concentrated in central Thailand (Figure 6). Highly endemic for canine rabies across the country (Chuxnum et al., 2011), Thailand's rabies burden was responsible for killing approximately 200 humans every year through the 1990's (Thiptara et al, 2011).

Figure 6 - Dog and Human Population Densities



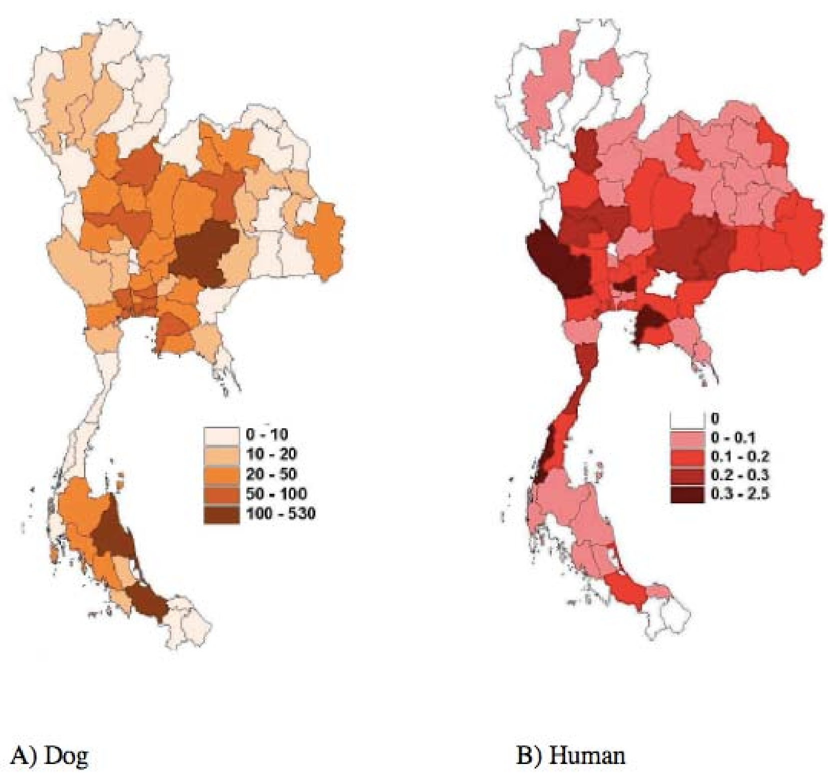
(A) Dog (B) Human

Average dog (A) and human (B) population densities shown in numbers per km^2 from 1993-1999 in Thailand (Panichabhongse, 2001).

Rabies cases decreased significantly in the late 1990's and throughout the last decade (Mitmoonpitak et al. 1998; Chuxnum et al., 2011). Through vaccination programs and increased public awareness about receiving proper rabies PEP, in 2008 there were only 8 human deaths due to canine rabies (Thiptara et al, 2011).

Incidence of animal bites and the need for PEP has substantially increased since the early 2000's, especially in major cities such as Bangkok and in central and coastal Thailand (Figure 7). Thailand was chosen as a case study here to illuminate a country that is reducing rabies deaths at a steady rate, yet still faces challenges to maintaining this success due to pressing issues to address regarding rabies virus circulation in the ever-growing stray dog populations across the country.

Figure 7 - Rabies Incidence for Dogs and Humans



Annual total incidence of rabies in dogs (A) and humans (B) per 100,000 people annually by province from 1993-1999 in Thailand (Panichabhongse, 2001).

Unvaccinated dogs are not addressed as well as they could be. Along with many licensed pet dogs, there are many “community dogs” in the areas of northern Thailand. These dogs are kept and fed by the local families, but with no particular owners.

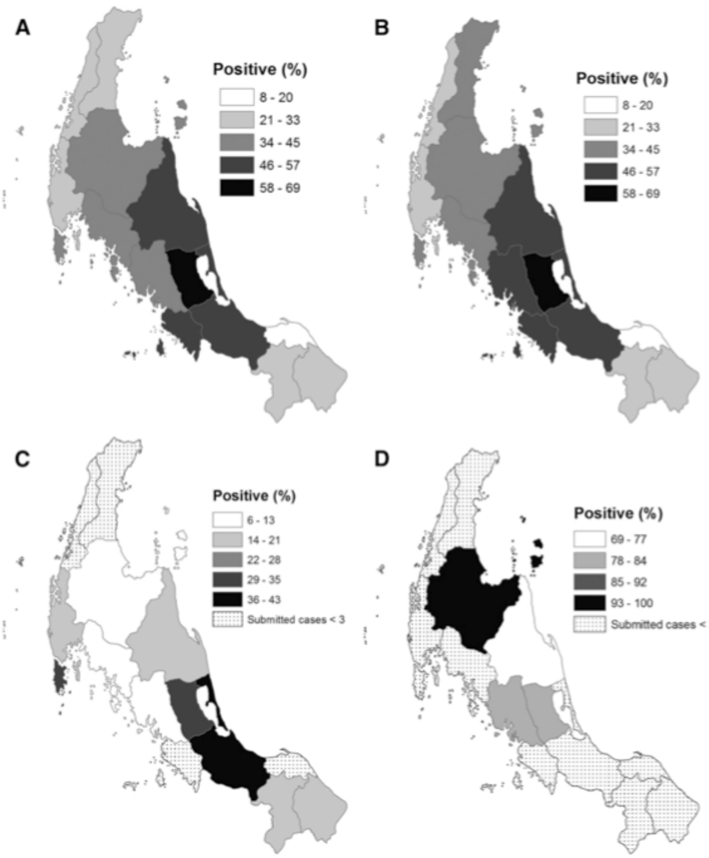
Culling, though ineffective for rabies control, is executed as a rabies control technique in many locations. However the religious (Buddhist) principles and influences for much of Bangkok and Thailand are against the elimination of strays and rabid dogs through euthanasia and there is support community dogs (Kasempimolporn et al., 1996; Mitmoonpitak et al., 1998; Rupprecht, 2004; Sriaroon et al., 2005).

Veterinarians and professionals who practice euthanasia are at risk for losing disapproving patients, and may provoke an issue in the community. In these situations, it is recommended that awareness and public education of rabies is increased and provided for (Rupprecht, 2004). For these many cultural reasons, and the recommendation not to use it via WHO guidelines, culling is not used for canine control in Thailand (WHO, 2013).

Instead of eliminating the dogs through culling the population, Thailand is in the process of finding ways to ensure vaccination of all canines, including community dogs and strays. Mandatory vaccinations of owned dogs, encouraging people to foster or adopt strays, and possibly increasing vaccination programs into rural areas are all ways that Thailand can improve the vaccination rate of the dogs, and decrease the number of strays in their communities (Zhang et al., 2011).

With the increase in community education, public awareness of the dangers of rabies has significantly increased, and PEP is sought by more people and at an earlier time after exposure than previously (Kasempimolporn et al., 2007). This is proof that Thailand has made significant progress, and with education, a measurable difference can be made to prevent unnecessary deaths. Rabies in Thailand can be looked at as a winnable battle, however controlling the dog populations will be difficult, lengthy, and expensive, and the best, most economically feasible option will be through canine vaccination.

Figure 8 – Southern Thailand Rabies Distribution



All positive rabies cases (A), dog rabies (B), cat rabies (C), and cattle rabies (D). [Figure used with permission from (Thiptara et al, 2011).]

The maps (Figure 8: A-D) above portray the distribution of all positive rabies cases in southern Thailand during 1994-2008 (Thiptara et al, 2011). As shown in the maps above, the majority of dog populations are throughout the central portion of southern Thailand (shown in map B). This is also the case for the largest density of rabies cases in this region.

4.1.3 Canine Rabies Control Program Structure in Thailand and Specific Case Study Results

The current rabies program structure in Thailand is controlled and regulated by the Department of Communicable Diseases (DCD) and the Ministry of Public Health

(Panichabhongse, 2001; Tenzin and Ward, 2012). The national rabies control program was established in 1995, and the goal was to have Thailand be rabies free by 2000 (Knobel et al., 2007) though this goal has been postponed to obtaining rabies-free status by 2020 (Tenzin and Ward, 2012). In 1996, a combined method of mass canine vaccination, education to increase public awareness of rabies, and increased access to low-cost and reduced dosage-intradermal vaccinations for PEP began in Thailand. This increased vaccination and PEP access decreased human rabies deaths to zero between 1999 and 2001 (Kamoltham et al., 2003; Knobel et al., 2007)

The Primary Health Care (PHC) Program and the ministry of health have integrated human rabies control as well (Panichabhongse, 2001; Knobel et al., 2007). These medical organizations and programs focusing on the increase of rabies education and community participation and involvement will help the overall knowledge in more remote areas of the country to continue to develop and increase (Panichabhongse, 2001).

Through the Department of Communicable Diseases, all possible cases of direct or indirect rabies exposures are required to begin PEP against rabies. In Thailand, prophylaxis for the patient will continue until the animal is caught and tested negative, or if the animal is not caught, the entire round of PEP will be given to the patient.

The Rabies Prevention and Control in Domestic Animals Act of 1992, a Thai law, states that all pet dogs and cats are required to receive their first rabies vaccinations between ages two and four months old and receive a booster annually after that. It is recommended for puppies not to receive their first rabies vaccination before the age of three months, even when puppies should have passive antibodies from their mothers at this point because they will not have a proper immune response to the vaccination (Panichabhongse, 2001; Knobel et al., 2007). One study found that only 15% of puppies younger than 3 months old that were tested had antibodies against rabies (Kasempimolporn et al., 1996; Knobel et al., 2007). A study also showed that 57% of the human rabies cases resulted from being bitten by puppies less than 3 months (Chuxnum, 2006).

From various reports it is also clear that rabies in Thailand is severely underreported (Lumlertdacha et al, 2005). From this researchers can assess that the damage done by rabies to public health in Thailand, and even globally, is much higher than recorded. This would also mean that the numbers of cases each year, if all were reported, would be much higher and significantly increase costs to the government and its people regarding increased control and PEP.

4.1.3.1 Case Example: Canine Rabies Control Program in Phetchabun, Thailand

In March 1993, a specific canine rabies program was implemented in the northern province of Phetchabun, Thailand, with a complementary canine vaccination program following shortly in 1996 (Kamoltham et al., 2003). This province is approximately 350 km north of Bangkok, with a population of over 1 million people. Using the beginning stages of mass vaccination, the program vaccinated 64-78% of the 100,000 dogs in the province of Petachabun, which was canine-rabies endemic (Kamoltham et al., 2003; Knobel et al., 2007).

The specific canine rabies program ended with marginally successful results, and has continued since the study ended. The program developed in this study used a multidisciplinary program to decrease human deaths due to rabies between 1997 and 2001. PEP use, accessibility and affordability increased (use of intradermal methods increased and the intramuscular Essen technique was also made more available), as well as awareness (through schools, TV, and news), dog population monitoring through vaccination and sterilization programs, and interagency collaboration of the Ministry of Education, the Ministry of Public Health, and the Ministry of Agriculture.

The canine population was monitored in this province through the Livestock Department in the Ministry of Agriculture. There was a census of the dogs in this province, collected by volunteers each year in the study. This canine vaccination program provided free animal vaccines and educational seminars, which were performed by public health volunteers and the staff. Communities surrounding schools and temples and individual dogs were the focus for contraception and sterilization in this program (Kamoltham et al., 2003).

The dog population in this area was not able to decrease overall at the end of this program, even with the vaccination and contraception methods, which led to exposures remaining high. The overall population of dogs in the province increased from 91,000 to 105,000 from 1996 to 2001. During this same time period, 417,147 (71%) dogs received one or more rabies vaccinations (Kamoltham et al., 2003).

Finally, the success of this program for public health was assessed through mandatory PEP forms (to determine number of vaccination series provided) and extensive patient follow up visits (Kamoltham et al., 2003). It was determined that there was an increased number of PEP distributed between 1997 and 2000, but there was less volume of vaccine used because of the increased spread of the use of the ID vaccination regimen (88% overall use by the end of 2001) (Kamoltham et al., 2003).

4.1.4 Canine Rabies Prevention in Thailand

Canine rabies related deaths in Thailand decreased significantly in the 1990's (Mitmoonpitak et al. 1998), but is still considered a prominent public health concern. The number of human deaths due to canine rabies has steadily decreased through the years in Thailand, from 200-300 or greater annually in the 1980's (Mitmoonpitak et al., 1998; Wilde et al., 1999; Garden, 2009) to 74 in 1995 (Wasi et al., 1997) and 48 in 2000 (Puanghat, 2001). This huge achievement in canine rabies control is mainly due to an increase in public education and awareness of PEP.

In Thailand, dogs 2 months or older are required by law to be vaccinated for rabies annually (Kongkaew et al., 2004). Canine vaccinations in Thailand will provide protection for 1-3 years, though laws request they be given annually if possible in order to keep a high immunity within the population (Kongkaew et al., 2004).

Location, health, and density of dog populations are usually associated with the socioeconomic level of the society they live among (Kasempimolporn et al., 2007, Hampson et al., 2008). There has been an intensive rabies control program in place in Thailand's capital, Bangkok, since the end of 2002. This program mainly focuses on canine vaccination and sterilization, in comparison to preventing wild strains of rabies, which would increase the possible risks, and thus increase the necessary resources, costs, and public education.

With an estimated 6-10 million dogs in Thailand there is no reliable estimate to determine their populations, locations, and health status (Chantapong et al., 1997; Wasi et al., 1997). In 2005, there were an estimated 630,000 dogs living in Bangkok, with only 520,000 of them registered with owners. That may seem like a large percentage, but that leaves 110,000 stray dogs that are unvaccinated and unaccounted for **(**Lumlertdacha et al., 2005). In another 2007 study, researchers determined that at least 30-46% of the known dog population is not vaccinated against rabies in Bangkok (Kasempimolporn et al., 2007). These 600,000 dogs are all living in an area of approximately 1565 km^2, a little larger than the area of the city of Houston, Texas (1552.9 km^2). This percentage of stray dogs (from the estimated dog census) has continuously increased from around 11.1% in 1992 to around 17.5% in 1999. The population number has gone from 40,000 to 110,000 in this 8-year period, and doesn't appear to be slowing down (Lumlertdacha et al., 2005).

Even with the canine population increase, Thailand is still making strides in reducing rabies deaths, however many strays and community dogs are not brought in to be vaccinated or only able to be brought in once (Kasempimolporn et al., 2007), leaving a large percentage of the population free to contract and continue the spread of rabies. In Thailand, there have been many attempts to use sterilization and vaccination programs, with most of the effort focused on Bangkok, with a capture-neuter-vaccinate-return-program introduced in 2002 (Kasempimolporn et al., 2007; Jackman and Rowan, 2007). There is public disapproval of the programs done in Bangkok because due to a lack of funding, there are shortages in staff and resources and they cannot introduce these programs nationwide (Jackman and Rowan, 2007). An important aspect is that elimination of canine rabies in Bangkok (or in any major central city in a country without extensive borders) will not happen without addressing the outer cities and neighboring regions in Thailand (Kasempimolporn et al., 2007).

Genetically diverse canine rabies viruses in Thailand will be reintroduced when unvaccinated canine and human movement changes or relocates from rural to industrialized areas (Lumlertdacha, 2005). A tactic that was used to prevent new dogs from entering Thai neighborhoods and areas was to sterilize and vaccinate dogs and release them back at the location they were picked up from (Lumlertdacha et al., 2005).

Translocation of dogs from one city or region to another is a controversial theory of how canine rabies could be regularly spread around the regions and districts in Thailand (Kasempimolporn et al., 2007). Rabies spreads very rapidly in areas that have not been infected and translocation of animals (especially across borders) emphasizes this problem (Briggs, 2010). Understanding canine population movement, demographics and ecology will also be an important milestone to canine population management and rabies control in Thailand and will assist in concerns of translocation as well (Zhang et al., 2012).

4.1.5 Availability of Prophylaxis in Thailand

Rabies vaccinations are supplied by the Thai Ministry of Health and the Thai Red Cross, and are free to those who cannot afford it (Kamoltham et al., 2003). Medical professionals realized the issues regarding nervous tissue vaccines, (used earlier in rabies vaccine history) including side effects and effectiveness, and decided to replace them with safer alternatives. In 1993, the Ministry of Public Health introduced highly purified tissue culture rabies vaccines (TCV). This introduction led into the use of intramuscular vaccination (5 doses of the series, each 1 ml of vaccine), known as the "Essen method," which was commonly used in Thailand (Kamoltham et al., 2003; Cleaveland et al., 2006).

There are four different forms of rabies PEP now available in Thailand. Purified Vero cell rabies vaccine (PCRV) and the purified chick embryo cell vaccine (PCEC) are both used by the government and distributed nationally in Thailand (Kamoltham et al, 2003; Panichabhongse, 2001). In the late 1990's, the PCEC vaccine, provided by the Ministry of Public Health Government and Pharmaceutical Organizations and companies, was used by most hospitals in the country (C. Wasi et al, 1997). HDCV is another rabies vaccine that is commonly used and produced by Sanofi (Panichabhongse, 2001). Because of the higher cost, human rabies immunoglobulin (HRIG) is usually used in private sectors more often than by public hospitals and clinics. The Thai Red Cross, however, is one of the larger organizations that use HRIG as a major source of rabies PEP. If HRIG isn't available, equine rabies immunoglobulin, or ERIG may be available. ERIG is only produced in the Queen Soavapa Memorial Institute (QSMI), and it is estimated that only about 10% of exposures in Thailand are treated with ERIG (Panichabhongse, 2001).

Post exposure treatment availability has increased throughout the years, however, so has the demand for it. PEP demand has increased ten to fifteen percent on a yearly basis. For example, an unpublished report from the Ministry of Public Health stated in 1991 there were 93,641 cases, in 1996 there were 183,815 cases, and in 2001 there were 350,535 cases requiring PEP treatments (Lumlertdacha et al, 2005).

4.2 The Guangdong Province

4.2.1 Country Statistics and Governmental Structure

The Guangdong Province borders the Guangxi, Hunan, Jiangxi, and the Fujian Provinces, with Hong Kong to the south. It has a total 4,300 km of coastline, a few mountain ranges bordering the north, and possesses a subtropical climate.

With a population of over 1.34 billion people and an area spanning across greater than 3.75 million square miles, China is too large of a country to analyze on its own. However with a population of 105 million (National Bureau of Statistics of the People's Republic of China, 2011), an area around 68,700 square miles (177,900 km^2), and located in the south of China, the Guangdong Province is a much more manageable geographic location to compare to Thailand.

Endemic throughout China, rabies is the most concerning in the southern and southwestern provinces of China (Meng et al., 2010; Si et al., 2008), and has only recently spread further north. The three most heavily affected provinces in China are Hunan, Guangxi, and the Guangdong Province, all located in the southern region of Mainland China (Hou et al., 2012).

The governmental structure is the same as the rest of China, including a socialist and communist state. However, Guangdong has been one of the few provinces to push for more democracy and additional control in the financial sector, and increased governmental transparency. Politics may be a hindrance to rabies control in this province and throughout China.

China's current gross domestic product (GDP) is $7.318 trillion US dollars. The Guangdong Province, one of the wealthiest provinces in China, had an $816 billion USD GDP in 2011. The Guangdong Province is the most populated province, and has the fourth highest gross domestic product per capita in Mainland China (The China Perspective, 2013). The Guangdong Province appears to have the financial means necessary to successfully maintain a canine rabies control program, if one is properly structured. There is evidence of governmental support to improve public health programs protecting their citizens from rabies with new medical coverage that includes PEP treatments (Yin et al, 2012).

4.2.2 Basic Rabies in China

Figure 9 - Annual Rabies Cases in China from 1950-2004

(Zhang et al., 2005).

Rabies cases in China were at a record high in 1981, with 7037 human rabies cases and the total annual cases remained high in the 1980's, averaging 5000 annual cases (Zhang et al., 2005; Hu et al., 2009; Figure 10). Overall, rabies cases in China decreased in the late 1980's and early 1990's. This was a possibly a result of increased awareness and knowledge of PEP, regulations regarding registration and licensing of owned dogs (Hu et al., 2009).

Another possible factor that contributed to this rapid decrease was the continued destruction of thousands of stray dogs a year to decrease the overall canine population and control rabies epidemics (Yang and Dong, 2012; Tenzin and Ward, 2012). A combination of these factors decreased the population of stray dogs for short periods of time and temporarily increased the strength of the records of owned canines in the country. Culling dogs, however, is not publically popular, nor is it a proper tactic currently supported as a cost efficient or viable rabies control solution by the WHO (Briggs, 2012).

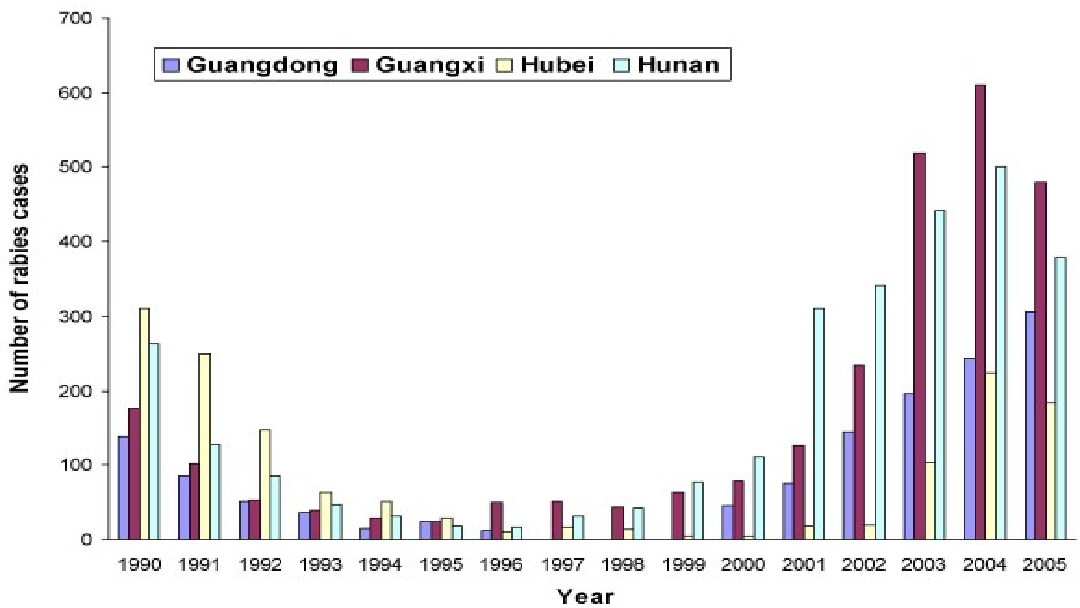
With a visible decline in rabies deaths[the programs, regulations, and improvements in reporting of cases reverted to previous levels, as individuals in China perceived the problem of rabies had been addressed (Hu et al., 2009). With this reduction in structure and surveillance, rabies prevalence and human deaths quickly began to rise again in the late 1990's, and has remained high since then (Hu et al., 2009). From 2003-2006 cullings occurred again throughout China to combat rising human rabies deaths (Jackman and Rowan, 2007). One southwest province in 2006 had 50,000 dogs culled in 5 days to end a rabies outbreak. Any dog that was found, even if it was owned and vaccinated, was put to death (Jackman and Rowan, 2007).

Over 120,000 human rabies deaths have burdened China from 1950 to 2010 (Hou et al., 2009; Zhang et al., 2011), with 22,527 of them occurring from January 1990 to July 2007 (Si et al., 2008). With an average of 2000 or more deaths yearly, rabies is a significant public health problem in China (Zhang et al., 2011). From 1990 to 1996 data has shown that rabies was controlled fairly well, however, in 2001 there was a jump in cases (Si et al., 2008). Guizhou, Hunan, Guangxi, Guangdong, and Sichuan were the five provinces with the highest amount of human rabies cases during 1996-2010, comprising almost 60% of all of the rabies cases in China (Zhang et al., 2011).

Farmers, young students, and children are the groups highest at risk for contracting rabies within the Guangdong Province (Song et al., 2009; Yin et al., 2012), and make up a total of 89% of all reported cases, with over 92% of the cases in China (including 88% of students and 89% of children) residing in rural areas and farming families (Hu et al., 2009). In the Guangdong Province, and much of China, rabies is still viewed with many myths and suspicions. Many victims in rural areas have continued to believe that death due to rabies is the result of misfortune and poor luck, and in some cases deaths occurred because of vaccine refusal (Hu et al., 2009).

Rabies dynamics have been studied in the Guangdong Province and there is current interest in discovering whether progress has been made in this region. Though data was not available from 1997-1999, it is visible that rabies incidents have increased steadily into the year 2005 in the Guangdong Province (Figure 11). There are many possibilities of significantly improving the rabies control program and the surveillance of rabies in this area.

Figure 10 - Comparison of Rabies Cases Across Chinese Provinces



(Si et al., 2008).

4.2.3 Canine Rabies Control Program Structure in the Guangdong Province of China

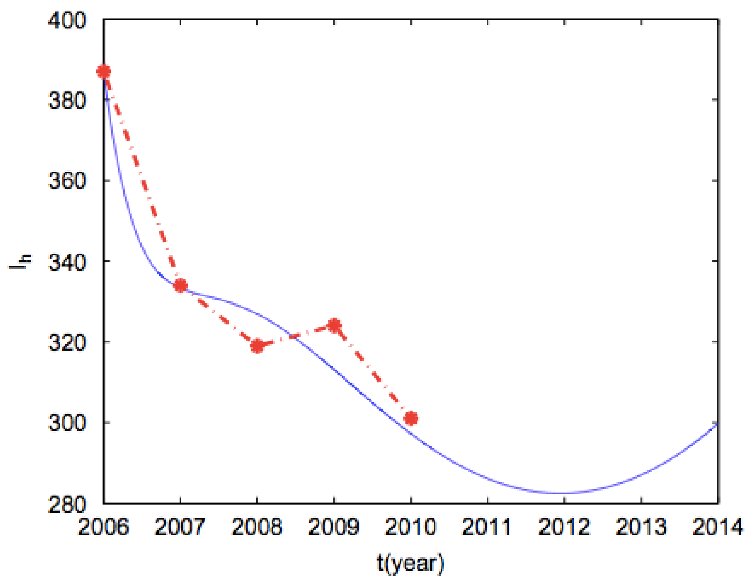
In 2006, rabies was responsible for approximately 3,200 deaths in China, trailing only behind India. There is a structured and efficient nationwide surveillance network for zoonotic diseases, created in 2003 (Si et al., 2008). This program has increased the surveillance and overall reporting of cases related to human deaths in China, including rabies. Underreporting and quality control issues are still common issues however, and will vary dependent on the funds that a province has to put towards disease surveillance (Lawson and Lin, 1994). This surveillance network however does not specifically focus on the root of the problem: the increasing dog population due to lack of sterilization and increased numbers of pet dogs (Si et al., 2008). When China implemented a strict regimen regarding canine rabies control during 1990-1996, rabies cases dropped 95.5% nationally and the GDP increased as well, showing a positive relationship between economic growth and improved health and safety conditions (Si et al., 2008).

Even though rabies is a reportable disease in the Guangdong Province, the province still needs to implement a surveillance system for canine rabies cases, improve their reporting system, as well as the diagnostic facilities to test positive cases. Once reporting increases, then there should be an increase in cases, hopefully to establish a true estimate of the burden rabies has on this country.

The government has implemented public advertising of PEP, instructing people to seek treatment, and providing information on the facilities where they can find prophylaxis (such as local clinics and hospitals). The government was also influential in increasing the monitoring of vaccine quality (through batch controlling) and location, so that viable vaccines are distributed where they are most needed (Fu, 2007). Research in rabies epidemiology and surveillance has also increased in government research facilities and universities, resulting in increased training of local personnel for diagnosis (Fu, 2007, CDC, 2011). Increased research in these areas also is an improvement to establishing a strong surveillance system.

One study indicates that the Guangdong Province has a more severe rabies problem than other provinces (Hou et al., 2012). The Guangdong Province has the third highest annual incidence of deaths due to rabies in Mainland China (Davlin and VonVille, 2012; Hou et al., 2012). Rabies is responsible for approximately 300 deaths in the Guangdong Province annually, and though cases decreased, they are on the rise again (Figure 12). The red dotted line on the graph in figure 11 represents reported data on these rabies cases, and the smooth line represents the model output projecting the expected number of rabies cases in the future under current conditions, showing a clear expected increase (Hou et al., 2012).

Figure 11 - Simulation of Human Rabies Infections in the Guangdong Province



(Hou et al., 2012).

There is no structured canine rabies control program currently in the Guangdong Province, and the province is drastically lacking diagnostic tools and facilities (Si et al., 2008). Local clinics possess the required approved and effective rabies prophylaxis.

All 244 human deaths from rabies in the Guangdong Province in 2004 were due to an absence or ineffective provision of PEP, including concerns about improper storage and dosage delivered (Si et al., 2008). This illustrates that proper community and health worker rabies education and exposure care should be increased in this province. The Guangdong Province has the ability and the resources to accomplish the goal of decreasing and eliminating canine rabies related deaths in their country.

4.2.4 Canine Rabies Prevention in China and the Guangdong Province

There are approximately 130 million dogs living in China (Davlin and VonVille, 2012; Hu et al., 2008), with estimates ranging between 80 and 200 million (Tang et al., 2005), and over 5 million puppies born annually (Zhang et al., 2011). According to recent estimates, there are over 3 million dogs in the Guangdong Province (Hou et al., 2012).

Independent government departments manage the dog populations and local police departments control dog registration (Yang and Dong, 2012). Veterinarians vaccinate dogs, however, vaccination and registration of dogs is not required throughout China (Hu et al. 2009; Yang and Dong, 2012). Registration and vaccination would significantly reduce human rabies cases if it were required (Tang et al., 2005).

It is estimated that the vaccination rate of domestic dogs is less than 32.8% in this province, which sells approximately 400,000 canine rabies vaccines annually (Hou et al., 2012). In China, 0% of stray dogs are estimated to be vaccinated for rabies (Yang and Dong, 2012). If these estimates are accurate, this results in millions of dogs unvaccinated and susceptible to rabies with rising dog populations across China, with just as high of a percentage in the Guangdong Province.

Domestic dogs were the cause of 66.5% of reported rabies cases from 2003 to 2004, with a majority of human rabies cases reported in rural areas (Hou et al., 2012). In the Guangdong Province, 18.2% of rabies cases are a result of stray dog bites (Hou et al., 2012). Eighty-nine percent of all human rabies cases in Guangdong are due to dog bites, and an inaccurate dog census makes this issue more difficult to control and resolve.

There is not a complete canine rabies surveillance system or vaccination program in place within the Guangdong Province (Davlin and VonVille, 2012; Yang and Dong, 2012), which makes determining the burden of this disease and caring for bite victims of unvaccinated dog challenging. There are also no organized and regulated yearly population or rabies control programs regarding stray dogs in the Guangdong Province (Si et al., 2008). Stray dogs are dealt with through culling and vaccination in most areas of China (Hou et al., 2012) including the Guangdong Province, though programs are not common and easily can be replaced by cheaper and more effective immunization programs (Zhang et al., 2011).

4.2.5 Availability of Prophylaxis in China and the Guangdong Province

In 1998, nearly 5 million people received PEP in China (Davlin and VonVille, 2012). In the last decade, that number has only gone up. Rabies is a continued public health and safety issue in China, with millions of people receiving the vaccination series annually (Davlin and VonVille, 2012).

The Guangdong Provincial CDC recommended using 3 different rabies prevention vaccinations (Si et al., 2008). These were PVRV produced by Aventis Pasteur, in Lyon France; PCEC, produced by ChengDa Biologicals, in Shengyang, China; and primary hamster kidney cell vaccine (PHKCV) produced by Lanzhou Institute of Biological Products, in Lanzhou, China (Si et al., 2008). Hamster kidney cell-derived rabies vaccines are also being manufactured in Russia and China. These vaccines are being manufactured in various potencies, will have various shelf lives, and dependent on the manufacturer, so will the PEP treatment schedules (Wilde et al 2005). Another important part of prophylaxis, RIG, is available in the Guangdong Province and across China. While this may be crucial for many high risk exposures, RIG is not being covered under any national health care programs, decreasing overall access to this biological in economically challenging locations (Hou et al., 2012).

There are also many other vaccine products made by much smaller companies or institutes in China. These products have little to no quality control and therefore lack consistent efficacy and satisfactory quality for the rabies virus (Si et al., 2008). The standard PEP schedule in China was the ‘Essen’ 5-dose intramuscular regimen, but others are used in China as well (Si et al., 2008).

5 Policy and Management Context: Economic Costs of Rabies

5.1 Number of People Globally That Need Prophylaxis Annually

Total cost of rabies PEP per person is variable and is dependent on the country, region, and manufacturer. In most situations, rabies prophylaxis is a fairly expensive drug and there are often shortages in supplies and vaccinations in many developing countries (Haupt, 1999). A way of decreasing the cost is to use a procedure of intradermal vaccination. This uses smaller doses of vaccine, usually equaling 0.1 mL per dose. This allows one vial of vaccine to be used with multiple patients (Malerczyk, 2012).

In 2009, over 7 million people were receiving PEP treatments every year (Hampson et al 2009). However, according to the World Health Organization updated in March 2013, over 15 million people are now receiving PEP annually (WHO, 2013).

5.2 Costs of the Rabies Vaccine and Prevention in the United States

In the early 1990's, an average of 25,000 PEP treatments were given to humans in the United States annually at an estimated individual cost of $1,200-$1,500 per patient (Wilde et al 1999). This was an annual cost of approximately $37 million (Wilde et al 1999) for the United States during that time. As exposure to rabid animals or animals suspected of being rabid is common, an estimated ~40,000 people are receiving PEP each year in the US currently (McCollum et al., 2012; Moran et al., 2000). This range of cost for the vaccine is still appropriate. The current average cost of a series of rabies PEP shots in the US is around $1500-$2500 for each treated patient (Rupprecht et al., 1996; Vaidya et al., 2010; Table 1). With PEP still at a similar high cost per exposure, combined with RIG, the total cost per patient is closer to $4000 (Shwiff et al., 2007). The cost annually in the US totals approximately $160 million for PEP and RIG, a vast increase of annual cost since the 1999 article by Wilde et al (1999), as previously sourced.

The total cost of rabies PEP is an expensive vaccine series. The median charge for one dose of human diploid cell vaccine (HDCV) was $311 (with a range of $113 to $679) (Dhankhar et al., 2008). For the rabies PEP vaccine series, WHO usually requires four to five doses of the vaccine. In that same article, the average cost for a 6.3ml dose of human rabies immunoglobulin (HRIG) was $761 (ranged from $326-$1,434) and the average cost for the first emergency room visit cost $122 (ranged from $97-$156) (Dhankhar et al., 2008).

There are usually 1-2 cases of human rabies reported each year in the United States, and are usually caused by traveling and bats (Shwiff et al., 2007). The US spends approximately $300-400 million every year on public health costs related to wildlife and canine rabies protection (CDC, 2012, Sterner and Smith, 2006). Money is spent on prophylaxis (of which thousands receive annually in the US), educational programs and seminars across the country, and on continued vaccination programs for domestic animals and wildlife (the remaining rabies challenge in the US).

Other costs available within the Dhankhar et al. article (2008) were emergency room, physician visits, and hospital costs. Overall costs will decrease significantly if emergency room visits are not used (ER visits significantly increase costs). The average cost for a return visit to the emergency room for future doses of prophylaxis ranged from $48-$156. The cost of the first physician visit equaled an average of $105 (ranging $59 to $125), and follow-up visits averaging $100 (ranging $59 to $129). Hospital and physician costs totaled an average of $1,027 (ranging from $584-$1,423), which included the initial visit as well as the four following doses of PEP (Dhankhar et al., 2008). In 2004, these various charges averaged a total cost of $4,042 (ranging from $1,634 to $8,415). These numbers were from an article in the Vaccine of Massachusetts in 2004, and costs may have increased since this time in the area.

Hospital, physician and emergency room costs were not readily available for Thailand and the Guangdong Province to properly compare, though more research in this area would be beneficial to determining the full burden of the costs rabies has in these countries.

Table 1 – Comparison of Pre and Post Exposure Cost Estimates

	United States		Thailand		Guangdong	
	Pre	**Post**	**Pre**	**Post**	**Pre**	**Post**
Human Costs (USD)	$700/ treatment (3 shots)	$1500-$2500/ treatment (4 shots) $4000 including RIG	$2-$7.25 (ID) and $18.75-$34.5 (IM)	$28.75-$47.25 (ID) and $64.5-$74.5 (IM)	Na	$12.5-45/ treatment (5 shots)
Canine rabies vaccine Costs (per dog : USD)	~$20	-	~$1.3	-	$1-8	-

Key: (ID)- intradermal (IM)- intramuscular

Table 1: (Chulasugandha et al., 2006; (Hu et al., 2008; Kaare et al., 2009; Lembo et al., 2010; Cleave-land et al., 2006; Meltzer and Rupprecht, 1998; Dr. Chris McKinney, 2013; Si et al., 2008; Shwiff et al., 2007).

5.3 Economics of Prevention and Rabies Control

The most economically efficient and cost-effective way of decreasing human rabies cases is through population control and rabies prevention through vaccination in the domestic dog reservoir (Bögel and Meslin, 1990; Knobel et al., 2007). Risks of human rabies can be nearly eliminated by effectively controlling the disease in domestic dogs and increasing the availability of PEP (Knobel et al. (2009). A large percentage of Africa and Asia’s rural population is impoverished. Globally, rabies claims the largest numbers of lives in these two regions (Knobel et al., 2007).

The rabies vaccine series, travel, and housing are all expenditures that are of concern to people in rural areas (Cleaveland et al., 2006). One study in Tanzania showed that only 33% of families who had needed PEP were able to afford the care by themselves (Kaare, 2009; Knobel et al., 2007). In order to pay for this treatment people will often have to borrow money or sell land, livestock, and other properties (Haupt, 1999; Knobel et al., 2007; Lembo et al., 2010). It is not uncommon for people in Thailand and the Guangdong Province, particularly in rural areas to spend a large percentage of their annual income on rabies treatment (Song et al., 2009). This high cost deters many people to refrain from receiving the vaccine (Song et al., 2009; Zhang et al., 2011).

Tanzania is reported to spend greater than $400,000 of its annual health budget on PEP (Knobel et al., 2007). Through increased canine vaccination and rabies control, Tanzania is reported to save nearly $12,060 per 100,000 people annually (Kaare, 2009; Knobel et al., 2007). This saving is a significant portion of the annual health budget, showing how economical it is to control and eliminate rabies at the source of the majority of infections: the domestic dog.

The United States has eliminated the canine rabies variant from the country through large-scale canine vaccination programs and rabies vaccination requirements. The economics of rabies transmission and rabies programs within the Guangdong province or Thailand has not thoroughly analyzed (through available information), however research has begun to explore this.

Though pre and post exposure prophylaxis is highly effective if delivered appropriately and used early enough after exposure to rabies, there is still the issue relating to cold chain requirements. This is the range of temperatures that the biological agent needs to be stored and/or shipped in order to stay viable before injection. This is a requirement for the currently available vaccine, costing billions of dollars and the loss of thousands of doses annually from waste, transport, and storage (Dhankhar et al., 2008; Zhang et al., 2012). A common apprehension in rural areas is whether the vaccine will be viable or not, or whether economically challenged families are spending what little money they have on a defective series of vaccines, a common situation in Africa and Asia (Knobel et al., 2007).

In most countries and regions, rural areas are at highest at risk because of the lack of access to care and the high costs required to receive a vaccine. Increased time spent in hospitals takes crucial time away from the ones who are the only paycheck for the households in these areas.

Access to PEP is expensive and unreliable in rural areas, and because the vaccine series is longer and more complex than others, it is also logistically demanding, increasing the cost of transportation, health clinic visits, and income loss (Knobel et al., 2007). Income loss is also a critical cost when patients begin to present symptoms, a significant issue for larger families in rural areas with less job availability (Knobel et al., 2005).

A concerning cost is the loss of land and livestock either through payment options in order to afford prophylaxis (a common process) or through rabies deaths (Knobel et al., 2007). The manufacturing and delivery costs associated with the rabies vaccination are considered to be confidential business information. Costs like production, time used to transport vaccine shipments, storage, waste, and medical delivery should be considered for infectious diseases and implementing public health programs such as rabies control programs and will vary widely by country/region.

Table 2 - Comparing Total Estimates Costs and Exposure Annually for the United States, Thailand, and the Guangdong Province

	United States	Thailand	Guangdong
Total Preventative Costs (USD)	$300-400 million [1]	~$30-60 million [2]	Na
Canine Rabies Vaccine Sold	na	na	~400,000
Number of Estimated Canines	78 million	~7 million	3 million
Population (US Census, World Bank)	~310 million	~69.5 million	~104.4 million
Human PEP Received	~40,000	~400,000	Na
Human Cases per year	~3 deaths (2012)	<25 deaths (2011)	~300 deaths (2012)
Average Annual Income (USD)	~$50,000 (2013)	~$8,200 (2007)	~$3,000 (2008)
Cost of Human Life [3]	$10 to 100 million/life	$2 to 5 million/life	Na

[1] Preventative costs directed towards animal vaccinations

[2] Preventative costs directed towards human and animal costs

[3] Total Preventative Costs divided by human deaths

Table 2: (Shwiff et al., 2007; Denduangboripant et al., 2005; Si et al., 2008; Thai Visa Forum, 2007; Kaare et al., 2009; Lembo et al., 2010; Hou et al., 2012; Thiptara et al, 2011; CDC, 2012, Sterner and Smith, 2006)

5.4 Various Economic Costs in Asia

Economically, rabies is a very costly disease in developing nations, and particularly so in rural areas, due to the high demand for PEP and the distance usually necessary to travel in order to receive medication (Kamoltham et al., 2003). The collective cost (direct and indirect) of PEP is equal to 5.8% of annual per capita gross national income in Africa ($40 per treatment) and 3.9% ($49 per treatment) in Asia (Lembo et al., 2010; Meltzer and Rupprecht, 1998; Knobel et al., 2005). In Asia, the estimated total cost of rabies is roughly $563 million (Gongal and Wright, 2011; Knobel et al., 2005).

5.4.1 Economic Costs in Thailand

Thailand has increased the public health awareness of rabies and the dangers of being in contact with a rabid animal. Increased awareness has increased the understanding, knowledge, and acceptance of going to a hospital or clinic to receive PEP. Many Thai locals will insist on receiving PEP, regardless of whether the dog was known to be vaccinated for rabies or not. This aspect of rabies control is controversial within the governments, who are paying for PEP for animal bite patients. Most PEP in Thailand is given out without information on whether the dog was rabid or not (Kasempimolporn et al., 2007). This presents a large financial burden that could be significantly reduced if better protocols were put in place.

The cost of human rabies protection in Thailand varies, though is reasonably inexpensive for locals and travelers as a result of government subsidized healthcare. Vaccine quality will also vary throughout the country, though PEP failure has never been mentioned as an issue or concern in Thailand. The average number of PEP series given to humans annually in Thailand is approximately 400,000 treatments (Denduangboripant et al., 2005; Table 2). We can assume that the annual national cost put forth for human rabies prevention equals an estimated total of $30-60 million USD spent based on the vaccine costs and the amount of PEP received (Table 2).

Prices will range from $2 USD-7.25 USD (intradermal) to $18.75 USD-$34.50 USD (intramuscular) for the complete PrEP regimen. Rabies PEP costs will range from $28.75 USD-$47.25 USD (intradermal) to $64.50 USD-$74.50 USD (intramuscular) per treatment (Chulasugandha et al., 2006; Table 1). ERIG or HRIG are required to be administered to high risk-exposed patients. Costs are from $27.50 (ERIG) to $75 (HRIG), and these costs will double in the private sector (Chulasugandha et al., 2006; Table 1).

In order for the government to reach more patients and to conserve funds, the World Health Organization pushed recommendations to use the intradermal regimen with the PVRV vaccine (0.1 ml per dose) and the PCECV vaccine (0.2 ml per dose). These were introduced in the late 1980's and 1990's. These are now considered to be the common Thai Red Cross Intradermal regimen and each patient is given 0.1 ml of PCECV or PVRV on days 0, 3, 7 (2 sites each day) and on days 30 and 90 (1 site each day)

(Sirikwin, 2001; Kamoltham et al., 2003; Garden, 2009). Thailand is one of the Asian countries using the ID PEP technique, and it has been documented to be safe, immunogenic, and efficacious (Malerczyk, 2012). A specially trained professional or staff should perform this 2-site vaccination method (Wilde et al., 1999). The intradermal method is currently used, with the PCEC and PVRV rabies vaccines, mainly in Thailand by about 90% of clinics and hospitals and the Thai Red Cross (Chulasugandha et al., 2006, Haupt, 1999). The ID method is assumed to be the main reason that cheap, dangerous nervous tissue-derived vaccines (NTV) were replaced across the country (Garden, 2009). IM vaccinations are used in approximately 42% of hospitals and clinics in Thailand (Haupt, 1999).

In order to vaccinate the 6-10 million dogs in Thailand (Table 2), at an average canine vaccine cost of $1.30 USD (Kaare et al., 2009; Lembo et al., 2010; Cleaveland et al., 2006; Table 1), we can assume a total cost ranging from $7.8-$13 million USD would be needed to vaccinate the entire canine population. A total cost ranging from $5.46-$9.1 million USD would be needed to vaccinate approximately 70% of the population.

5.4.2 Economic Costs in the Guangdong Province

There are no published annual costs put forth for rabies prevention in the Guangdong Province due to the lack of a specific program or surveillance system against canine rabies in this province (Hou et al., 2012). However, a recent publication states that the Hunan and the Guangdong Province has included PEP expenses into a new "rural cooperative medical imbursement coverage" (Yin et al., 2012). This would include the vaccine and full PEP treatment for those in rural areas. This change in medical coverage has already been reported to have greatly increased accessibility of healthcare and medical availability and affordability for those in the rural areas of these two provinces and is looking to do the same in other high-risk areas of China as well (Yin et al., 2012).

The qualities of the rabies vaccines vary throughout the Guangdong Province depending on the source and pricing. Rabies vaccinations for domestic animals in the Guangdong Province are considered expensive to most of the population and are questionable in quality and availability in this province (Yang and Dong, 2012). The average number of PEP treatments distributed annually in the Guangdong Province is not published, which doesn't allow for an estimate for how much is being spent in this province each year on PEP.

Assuming canine rabies vaccinations will be similar in price across China, average costs will range from $1-8 USD per vaccinated dog in the Guangdong Province as well (Hu et al., 2008; Table 1). With the average number of dogs in Guangdong Province (approximately 3 million canines), in order to vaccinate all of the dogs in this province, we can roughly estimate that $3-24 million USD would be required to fully vaccinate the total canine population in the Guangdong Province.

Improvements in the quality of human rabies vaccines have led to the increase in cost of the vaccine in China (Hu et al., 2009). With the average annual income per capita being $3000 USD (Table 2), and the rabies vaccine cost within the range of $12.50-$45.00 UDS (Table 1) in the Guangdong Province, it is a costly expense for most people (Si et al., 2008). This averages up to 0.42-1.51% of a family's average annual income, and would be significantly higher if travel costs and hospital expenses were included for those coming in from rural areas for treatment (Si et al., 2008).

Healthcare across China is variable, and health status and the quality of care is commonly dependent on socioeconomic status (Lawson and Lin, 1994). The demand for modern, affordable, safe vaccinations is increasing, and cell culture vaccines are not always in sufficient supply in many provinces. Nervous tissue vaccines (NTVs) were banned throughout China in 1981, though they are still sought and used as cheaper and less effective prophylaxis in underdeveloped remote regions (Si et al., 2008). Because of the side effects and the dangers of using NTVs, there is a push to completely take them off the market across China (Si et al., 2008). Rabies NTVs are a continued problem globally, where their use is still common because of their decreased economic cost (Haupt, 1999).

6 The Human Component of Protection

6.1 Social/Societal Costs to Rabies Infections

There are many societal costs and opinions that are influenced through culture and religion in addition to economic costs, and are compounded once a person or a community is infected with rabies. It has been documented that rabies is influenced through factors such as socioeconomic distribution in cities and countries, usually having higher case burdens in impoverished, undereducated, and rural regions (Fang et al., 2010; Kaare et al., 2009). For example, in the Amazon, people often don't understand the significance of being bitten by a bat, and thus will not seek medication (Gilbert, et al, 2012). There are documented records of locals not believing a bat bite was a big deal, or actively avoiding modern medical care because of traditional beliefs (Gilbert, et al, 2012). These beliefs (religious or culturally influenced) may cause clouded judgment towards the threats and dangers of this virus and disease in various countries and regions. These beliefs will impair a person's understanding the true concerns of the virus.

The manifestation of clinical signs and symptoms of rabies are very concerning and will inevitably induce fear and significant psychological suffering and possible fear for loved ones, attending physicians, and those who witness them in the surrounding community (Cleaveland et al., 2006; Knobel et al., 2007).

Over 3 billion people in Asia are at risk for contracting rabies (WHO, 2013). Within developing countries, including many parts of Thailand and the Guangdong Province, communities are at risk if the animals around them are not vaccinated and they have limited access to medical services. Groups of people at higher risk within this continent are poor and developing communities, males and children. It has been documented that males are statistically more likely than females to get bitten (Si et al., 2008). A contributing factor to this increased risk group would be that males have more contact with stray dogs during the course of the day in these developing areas. Children and teens 0-20 years are one of the age groups largest at risk globally, including Thailand and the Guangdong Province (Mitmoonpitak et al 1998; Cleaveland et al., 2006; Dodet et al., 2008; Hampson et al., 2008; Si et al., 2008). It has been shown that the largest percentage of those bitten are 14-16 years of age and under (Mitmoonpitak, 1997; Pancharoen et al., 2001; Si et al., 2008), and approximately 50% of all human rabies deaths are in children under 15 years old (Briggs, 2010). This is predicted to be the case because children are bitten most on the face or neck, both of which carry an increased threat of contracting rabies than other parts of the body (Knobel et al., 2007; Gong et al., 2012). These locations also have been shown to have a shorter incubation period before the appearance of symptoms (Gong et al., 2012), increasing the need for access to PEP immediately.

With each human life lost, there are broken families, decreased workers and community members, decreased overall community health, and a diminished trust in the government and medical workers. With a larger percentage of males usually dying from rabies (Si et al., 2008) in developing nations, this (and possible future rabies bites) is a real concern for families that need to be provided for (Wilde et al., 1999). Even before their deaths, rabies will affect these people, decreasing their ability to work and provide when lethargy, physical symptoms, and decreased immune system symptoms arise with the disease.

Globally, rabies is responsible for tens of thousands of deaths and millions of dollars every year (WHO, 2013; Gongal and Wright, 2011; Knobel et al., 2005). The maturity of control programs in countries across the globe varies, and thus leads to various environmental and community difficulties. The direct and indirect costs of rabies has been estimated in developed and developing countries and reporting accuracy will be dependent on the level and stage of the implemented surveillance system.

Increased rabies cases will affect population dynamics in various communities. With rural communities and children comprising most deaths, this could lead to structural changes in the population dynamics. Increases in rabies related deaths also has an impact on how people work outdoors as well as travel to large populated cities with high dog populations and strays.

With the increase of rabies cases in an area, there is always a possibility for spillover into other domestic animals and wildlife, which has also occurred in threatened species, harming chances of population survival. Increased cases of rabies would escalate environmental/ecosystem problems in an area. An overall goal in any location or region is to create herd immunity, or specific percentage of vaccinated canines. Once there is sufficient herd immunity in the domestic dog population (WHO suggests 70% vaccination rate of the entire canine population), spillover events should not occur from wildlife, and human rabies cases should significantly decrease.

7 Challenges and Recommendations for Control and Intervention for Canine Rabies Programs in Thailand and the Guangdong Province

7.1 Challenges and Long-Term Economically Efficient Solutions

There is no one-size-fits-all solution to canine rabies control. There are methods that have been proven to successfully reduce or eliminate human rabies deaths for many countries, however the complexity and resulting success of programs will vary depending on funds, governmental and public support, and of course the canine population dynamics in that country or region. Ideally, every person should be able to afford the proper safe and effective PEP vaccines in order to save their life, so decreasing PEP and HRIG/ERIG costs represents the most important hurdle to overcome in these regions.

Thailand's overall challenges include decreasing the threat of human rabies deaths through controlling the canine populations and increasing the funds necessary for the government to continue subsidized healthcare and PEP treatments. Continued surveillance and increased support for annual canine vaccination programs will also be a challenge to overcome in future years.

The Guangdong Province similarly needs to control canine populations, and should eliminate the use of culling as a strategy (even combined with vaccination and PEP use) due to the more cost-effectiveness of vaccination and PEP combined. Their government is beginning to fund PEP treatments in rural areas, which will significantly make a difference in who receives healthcare services, and the next step for this would be to have funds that will continue to support this action. Increased disease surveillance and the creation of a canine rabies vaccination program would be the next stage for the Guangdong Province to take in rabies control.

The proven steps to accomplish the goals of rabies elimination include increased public education regarding rabies and wound safety, prevention of exposures through vaccination of canines and precautionary measures, more accessible availability of vaccines to those in increased risk situations, and the administration of PEP to all persons exposed (Rupprecht and Gibbons, 2012; Hampson et al. 2008; WHO, 2013). Attempted increased collaboration among various human and animal health and government sectors is also an encouraged solution to increase public awareness and surveillance in an area (Hampson et al., 2008). These goals are all steps that Thailand and the Guangdong Province can take in order to decrease their rabies cases and deal with the overwhelming stray dog populations.

Through current research, in the Guangdong Province and in Thailand, the most effective methods of controlling canine rabies is through combined culling of infected dogs and annual canine vaccination programs (Hou et al., 2012). Continued study also shows that dog birth reduction and large scale culling of domestics and strays can be supplemented with large-scale vaccination methods (Hou et al., 2012). One study however showed that to have an equal effect, culling needs to be approximately ten times the vaccination rate (Zhang et al., 2011). This study showed that culling alone would never be able to have the same cost-effectiveness as vaccination in large-scale canine rabies control.

The Global Alliance for Rabies Control, or GARC, created World Rabies Day in September 2006. World Rabies Day is an annual event where hundreds of thousands of people participate across the globe to raise awareness for rabies. Since its establishment, World Rabies Day has vaccinated over 7.7 million animals for rabies across the globe (GARC, 2013). In the last three years GARC has distributed educational information about rabies prevention to over 182 million people in over 150 countries (GARC, 2013).

An increase in public safety education with a focus on domestic and wild canines is necessary to begin and continue each year in the various provinces in China. By educating children at an earlier age on the dangers of getting bitten by a stray dog within the Guangdong Province, many hundreds of deaths could be prevented each year. Rural areas should be targeted in rabies control programs and special preference and education should be given to those living in these areas highest at risk (Hampson et al., 2011).

One economical way to continue vaccinating animals throughout the year is to use community members as volunteers. By training locals as volunteers and using trained local veterinarians or doctors to administer vaccinations, it is unnecessary for one person to travel extensively to do a “vaccine day” only once or twice a year. It can be done more often, such as once a season instead. Rabies is often misdiagnosed as other common ailments in developing countries, and is often only properly diagnosed when enough symptoms present themselves or after multiple people have died in an area (Briggs, 2010). By having more people aware of early symptoms and the dangers of getting bitten by an unvaccinated animal, prophylaxis communities will be more prepared to handle events and prevent unnecessary deaths.

7.2 Increased Research and Technology for Vaccines and Patients

One possible solution to economic loss of lost vaccines due to barriers regarding the cold chain is a new technology discovered by researchers at Tufts University. Researcher Dr. David Kaplan and his team have created a silk-infused vaccine for the MMR (Measles, Mumps and Rubella) vaccine series (another vaccine with a sensitive cold chain) (Kaplan et al, 2012; Zhang et al., 2012). This addition interacts with the antigen-part of the vaccine which triggers the immune response embedded into the silk produced by the silkworms. The silk and the antigen will bind and maintain the vaccine, preventing the antigen from degrading regardless of the storage temperature (Zhang et al., 2012). This would result in the vaccine being effective for months to years in a much larger range of temperatures (critical for transportation from country to country and into rural areas). Depending on final production and market costs, this technology would economically save millions yearly in vaccines and transport costs.

Intradermal vaccinations are a technique that was created for PEP in order to use a decreased amount of the dose when compared to intramuscular regimens of vaccination (Kamoltham et al., 2003). This reduced-dose technique has saved millions of lives since its development in the 1980's, and saves up to 80% of the cost of the vaccine (Briggs, 2010). With millions receiving the rabies vaccination series annually in this region, this technique would immediately decrease the cost of PEP used in both of these locations and the amount of vaccine available.

The direct rapid immunohistochemical test (dRIT) is another new technology that was created by the CDC in order to identify the rabies virus and all representative Lyssaviruses. The test can be read in under an hour, and requires a light microscope, which is 10 times less of the cost as a fluorescence microscope required for the direct fluorescent antibody test (DFA) (Dürr et al., 2008). The DFA is used globally and is also considered by WHO as the "gold standard" for the testing of the rabies virus (Dürr et al., 2008). This is a new technique, and it is recommended that developing and impoverished countries properly learn and use this method for rabies testing. Because of the quick response time and 100% specificity and sensitivity, the dRIT can also easily be used in the field (Dürr et al., 2008).

There have been 6 documented cases (ACIP, 2008) in which patients from the US who have survived the disease of rabies after the onset of symptoms due to vaccination previous to the appearance of symptoms or an extensive experimental treatment. The experimental treatment, also known as the "Milwaukee Protcol" is very intensive rounds of PEP and HRIG as well as an induced coma (CDC, 2011). Other rare and misunderstood instances of rabies survival that continue to be researched are human cases in the Amazon that seem to have developed a type of immunity to a strain of rabies (Gilbert et al, 2012). Research is being done to further understand why this occurs in this population and if increased survival is a possibility in other locations globally.

7.3 Strategies to Control Dog Populations for Rabies Elimination

Many strategies have attempted to reduce the stray dog population in order to control rabies cases. It has been proven that elimination of dogs alone through mass killing does not decrease rabies cases in the long run (WHO, 2013; ACIP, 2008). Community and stray dogs have a short life expectancy and because of this have a very rapid population turnover. This also hinders programs with >1 year intervals for mass vaccination campaigns (Kasempimolporn et al, 2007). Another technique to reducing populations is surgical sterilization through spay and neutering. Due in part to rapid turnover in these stray dog populations and the large cost, this is not an efficacious way to sustainably reduce large populations of animals (Kasempimolporn et al, 2007; WHO, 2010), like the larger populations of stray dogs in Asian countries such as Thailand and China.

The best rabies control programs, economically and in regards to overall human health consistently use PEP, sterilization, and vaccination of canines, rather than just providing PEP (Zinsstag, 2009). Dog populations will bounce back after culling methods alone (Knobel et al. 2007), but using sterilization and a goal of a 70% vaccination rate combined, is a more socially acceptable, effective and cheaper long-term solution (Zinsstag et al., 2009). Once the vaccination rate of dog populations has reached 70%, rabies transmission cycles will be broken (Kasempimolporn et al, 2007; WHO; CDC). Controlling rabies within dog populations and reducing human bite injuries, the demand for PEP significantly decreases (Cleaveland et al., 2003; Cleaveland et al., 2006, Hampson et al., 2008).

8 Conclusion - Summarizing the Conservation Medicine Issue and Importance of the Problem of Canine Rabies

Rabies is a neglected disease and should have the focus of legislators responsible for defining global policies and programs, especially in developing nations (such as those highlighted in this study). In order to find a solution to this global problem using a conservation medicine approach, multi-organizational and international cooperation is necessary among governments, public health agencies, doctors and veterinarians. By using public and private partnerships with different focuses regarding animal and human health, animal welfare, public education, communication, and economics (Briggs, 2010), solutions can be defined and goals will become easier to achieve. Proper policies such as increased promotion of good pet ownership, creating and enforcing leash laws, support for spay-neuter programs, control of stray animals, and mandatory animal vaccination regulations, will allow dog populations to become healthier, resulting in population control and stabilization (Rupprecht, 2004). Technologies are also increasing to treat and prevent the spread of rabies. With the development of intradermal vaccination regimens, dRIT, and "Blueprint for Rabies Prevention," there is attention being brought to this issue, but people and countries need to be motivated to use these available technologies. Japan, Canada, the United States, and parts of Western Europe are locations that have eliminated canine rabies in the 20^{th} century, (Rupprecht, 2004) and many others are close behind them as well. And with support and work, the rest of the world could learn from these examples and put in programs to better manage and ultimately eliminate rabies.

Canine rabies can be properly handled in Thailand and the Guangdong Province through increasing education and awareness, sterilization programs, availability to health care and services, required registration and licensing of dogs, safely and effectively eliminating the stray dog populations, and increasing the research done on the pathophysiology of rabies (Wilde et al, 2005; Jackson, 2003; Dodet et al., 2008; Yang and Dong, 2012). Learning and understanding what the molecular properties of the virus are that allow different sets of clinical symptoms in humans and canines is also critical to finding a cure to this disease (Wilde et al, 2005).

Control and prevention of canine rabies, however, is definitely worth the attempt and is a possibility in Thailand and the Guangdong Province. This would be useful to just eliminate a large portion of the risk in these areas, which both have millions of people at risk to this disease.

According to statistics and the progress of their control program at this time, Thailand is on the right track to obtaining rabies-free status by 2020 (Tenzin and Ward, 2012). Based on China's history of decreasing rabies deaths and its prevalence, with the proper assistance and following WHO's guidelines, it is estimated that China could eliminate human rabies cases by 2020 as well (Yang and Dong, 2012), meaning the Guangdong Province with the proper guidelines can accomplish this goal as well, if not in a sooner time period.

Global elimination of canine rabies is feasible (Rupprecht, 2004), as is dog population vaccination (Davlin and VonVille, 2012), though it will take an extensive amount of support, time, effort, and resources to accomplish this goal. Through the application of these suggested methods of awareness, canine population control and cost effective human and canine vaccination, significant steps towards this goal can be accomplished to increase overall public health and safety in the Guangdong Province and Thailand.

9 Author's Note

Though rabies is a neglected disease and largely underreported, it is still a highly published topic. With over 15,000 articles on Web of Science and Scopus, over 12,000 on Pubmed, and an astonishing 45,000+ on OVID just on the topic of "rabies" itself, it was outside the scope of this project to read or filter through them all. Once searches were filtered to “English articles only,” “China” and “the Guangdong Province” had considerably less articles than “Thailand” did when paired with “rabies” or “canine rabies,” which agrees with what Devlin and VonVille (2012), who expressed that publications from China were not as abundant as other countries, despite the higher number of people affected by rabies in that country.

There were limitations to completing this case study. A lack of information is the number one way that this review could be affected. Rabies itself does not have that problem, however when focusing on a specific strain or location, obvious gaps in the information are seen quickly during a literature search.

By choosing specific locations to focus on, narrowing down the literature was much easier. Thailand was a good decision with over 93% of all of the articles on “Thailand and rabies” being in English and over 97% of the articles on “canine rabies and Thailand” being in English. Focusing on a Province in China however, or any country that English is not the primary language, limits the peer-reviewed articles by over 50% in every situation looking at “rabies” or “canine rabies” in China or the Guangdong Province. This was a largely limiting factor due to deadline constraints and no access to a translator for this review.

Web of Science, PubMed, Scopus, Ovid, and Google Scholar were the online databases used to collect scientific articles for this review. It is likely that this review is subject to author bias in the inclusion of articles, researching articles relating to “China” “Thailand” “the Guangdong Province” and “rabies” or “canine rabies.”

This review shows that there is research being done on rabies in these locations, but some of the research is not accessible unless there is a way to translate the information. With only two articles specifically focusing on the Guangdong Province and canine rabies in this study, a significant gap can be seen in the information of rabies in the area. Knowing this, I would be interested in further research on rabies in China to learn and understand the most current in-country research on the disease in the various areas of China.

10 Citations Used:

[Anonymous] (2009) Proposed new WHO rabies control guidelines (Highlights from the WHO consultation on human and dog rabies prevention and control, Veyrier du Lac, France, October 7-9, 2009). Asian Biomedicine 3:751-4.

Barrett S (2004) Eradication versus control: the economics of global infectious disease policies. Bulletin of the World Health Organization 82:683-8.

Blanton JD, Dyer J, McBrayer J, Rupprecht CE (2012) Rabies surveillance in the United States during 2011. Javma-Journal of the American Veterinary Medical Association 241:712-22.

Blanton JD, Palmer D, Dyer J, Rupprecht CE (2011) Rabies surveillance in the United States during 2010. Javma-Journal of the American Veterinary Medical Association 239:773-83.

Bögel K, Meslin FX (1990) Economics of Human and Canine Rabies Elimination - Guidelines for Program Orientation. Bulletin of the World Health Organization 68:281-91.

Briggs DJ (2012) The role of vaccination in rabies prevention. Current Opinion in Virology 2:309-14.

Briggs DJ (2010) Reducing the global burden of rabies. International Health 2:161-2.

Burki T (2008) The global fight against rabies. The Lancet 372:1135-6.

CDC (2010) Rabies in Domestic Animals, 1958-2008. Available: http://www.cdc.gov/rabies/resources/publications/2008-surveillance/domestic-animals.html. [Accessed June/15, 2013].

CDC (2010) Terrestrial Rabies Reservoirs in the United States, 2009. Available: http://www.cdc.gov/rabies/resources/publications/2009-surveillance/reservoirs.html [Accessed February/20, 2013].

CDC (2011) Diagnosis in Humans and Animals. Available: http://www.cdc.gov/rabies/diagnosis/animals-humans.html [Accessed August/10, 2013].

CDC (2011) How is Rabies Diagnosed? Available: http://www.cdc.gov/rabies/diagnosis/index.html [Accessed May/25, 2013].

CDC (2011) Medical Care. Available: http://www.cdc.gov.ezproxy.library.tufts.edu/rabies/medical_care/index.html [Accessed August/10, 2013].

CDC (2011) The Rabies Virus. Available: http://www.cdc.gov/rabies/transmission/virus.html [Accessed June/15, 2013].

CDC (2012) Rables in Wild Animals, 1960-2011. Available: http://www.cdc.gov.ezproxy.library.tufts.edu/rabies/resources/publications/2011-surveillance/rabid-wild-animals.html [Accessed May/20, 2013].

CDC (2013). Possible Side Effects From Vaccines. Available: http://www.cdc.gov.ezproxy.library.tufts.edu/vaccines/vac-gen/side-effects.htm#rabies [Accessed August/10, 2013].

Christian KA, Blanton JD, Auslander M, Rupprecht CE (2009) Epidemiology of rabies post-exposure prophylaxis—United States of America, 2006–2008. Vaccine 27:7156-61.

Chulasugandha P, Khawplod P, Havanond P, Wilde H (2006) Cost comparison of rabies pre-exposure vaccination with post-exposure treatment in Thai children. Vaccine 24:1478-82.

Chuxnum T, Choomkasien P, Thongcharoen P (2011) Epidemiology of human rabies in Thailand, BE 2546-2550 (2003-2007 AD).

Cleaveland S, Costa P, Lembo T, Briggs D (2010) Catalysing action against rabies. Veterinary Record; 2010.167: 11, 422-423.3 ref .

Cleaveland S, Keyyu J, Auty H, Lembo T, Hampson K, Lankester FJ, et al. (2012) Domestic animal health programmes to protect wildlifeKaresh W, Machalaba C (editors), Animal health and biodiversity: preparing for the future. Compendium of the OIE Global Conference on Wildlife. Paris, France: Paris, pp 91-100.

Cleaveland S, Kaare M, Tiringa P, Mlengeya T, Barrat J (2003) A dog rabies vaccination campaign in rural Africa: impact on the incidence of dog rabies and human dog-bite injuries. Vaccine 21:1965-73.

Cleaveland S, Kaare M, Knobel D, Laurenson MK (2006) Canine vaccination - Providing broader benefits for disease control. Veterinary microbiology 117:43-50.

COE C, CARROLL N, ZENKER P, THOMPSON S, LOFGREN J, ADAMS J, et al. (1995) Human Rabies - Alabama, Tennessee, and Texas, 1994 (Reprinted from Mmwr, Vol 44, Pg 269-272, 1995). Jama-Journal of the American Medical Association 273:1327-8.

Coleman PG, Fevre EM, Cleaveland S (2004) Estimating the public health impact of rabies. Emerging Infectious Diseases 10:140-2.

Crump JA, Murdoch DR, Baker MG (2001) Emerging infectious diseases in an island ecosystem: the New Zealand perspective. Emerging infectious diseases 7:767.

Damrongplasit K, Melnick GA (2009) Early Results From Thailand's 30 Baht Health Reform: Something To Smile About. Health affairs 28:W457-66.

Davlin SL, VonVille HM (2012) Canine rabies vaccination and domestic dog population characteristics in the developing world: A systematic review. Vaccine 30:3492-502.

Denduangboripant J, Wacharapluesadee S, Lumlertdacha B, Ruankaew N, Hoonsuwan W, Puanghat A, et al. (2005) Transmission dynamics of rabies virus in Thailand: Implications for disease control. Bmc Infectious Diseases 5:52.

Dhankhar P, Vaidya SA, Fishbien DB, Meltzer MI (2008) Cost effectiveness of rabies post exposure prophylaxis in the United States. Vaccine 26:4251-5.

Dodet B, Meslin F (2001) Rabies Control in Asia: Proceedings of the Fourth International Symposium Organised by the Mérieux Foundation, Hanoi, Viet Nam, 5-9 March 2001: John Libbey Eurotext.

Dodet B, Goswami A, Gunasekera A, de Guzman F, Jamali S, Montalban C, et al. (2008) Rabies awareness in eight Asian countries. Vaccine 26:6344-8.

Dr. Chris McKinney (2013) Regarding price of rabies in clinics in NY.

Dürr S, Naissengar S, Mindekem R, Diguimbye C, Niezgoda M, Kuzmin I, et al. (2008) Rabies Diagnosis for Developing Countries. Plos Neglected Tropical Diseases 2:e206.

Dürr S, Mindekem R, Kaninga Y, Moto DD, Meltzer MI, Vounatsou P, et al. (2009) Effectiveness of dog rabies vaccination programmes: comparison of owner-charged and free vaccination campaigns. Epidemiology and infection 137:1558-67.

Fang LX, Ping F, Ping DY, Hui BG, Yan YX (2010) Socioeconomic status is a critical risk factor for human rabies post-exposure prophylaxis. Vaccine 28:6847-51.

Ferguson M (1991) Progress Towards Rabies Control. Trends in biotechnology 9:7-11.

Fooks AR (2007) Rabies - the need for a 'one medicine' approach. Veterinary Record 161:289-90.

GARC (2011) World Rabies Day Available:http://cherrillscrittercare.wordpress.com/2011/09/28/world-rabies-day/ [Accessed April/20, 2013].

Zhen F. Fu (2007) Current Rabies Vaccines, Avaiability and Use in China. Available: http://www.niaid.nih.gov/news/events/meetings/Viral%20Infections/Documents/fu.pdf [Accessed June/10, 2013].

Garden D (2009) Rabies research in Thailand. Asian Biomedicine 3:213-20.

Georgia Department of Public Health (2012) Rabies Frequently Asked Questions. Available: http://health.state.ga.us/pdfs/epi/zvbd/RabiesFAQ.pdf [Accessed August/10, 2013].

Gilbert AT, Petersen BW, Recuenco S, Niezgoda M, Gomez J, Alberto Laguna-Torres V, et al. (2012) Evidence of Rabies Virus Exposure among Humans in the Peruvian Amazon. American Journal of Tropical Medicine and Hygiene 87:206-15.

Gong Z, He F, Chen Z (2012) Risk Factors for Human Rabies in China. Zoonoses and Public Health 59:39-43.

Gongal G, Wright AE (2011) Human Rabies in the WHO Southeast Asia Region: Forward Steps for Elimination. Advances in preventive medicine 2011:383870.

Grace D, Gilbert J, Randolph T, Kang'ethe E (2012) The multiple burdens of zoonotic disease and an ecohealth approach to their assessment. Tropical animal health and production 44:67-73.

Guo Z, Tao X, Yin C, Han N, Yu J, Li H, et al. (2013) National Borders Effectively Halt the Spread of Rabies: The Current Rabies Epidemic in China Is Dislocated from Cases in Neighboring Countries. Plos Neglected Tropical Diseases 7:e2039.

Hampson K, Cleaveland S, Briggs D (2011) Evaluation of Cost-Effective Strategies for Rabies Post-Exposure Vaccination in Low-Income Countries. Plos Neglected Tropical Diseases 5:e982.

Hampson K, Dobson A, Kaare M, Dushoff J, Magoto M, Sindoya E, et al. (2008) Rabies Exposures, Post-Exposure Prophylaxis and Deaths in a Region of Endemic Canine Rabies. Plos Neglected Tropical Diseases 2:e339.

Hampson K, Dushoff J, Bingham J, Bruckner G, Ali YH, Dobson A (2007) Synchronous cycles of domestic dog rabies in sub-Saharan Africa and the impact of control efforts. Proceedings of the National Academy of Sciences of the United States of America 104:7717-22.

Hampson K, Dushoff J, Cleaveland S, Haydon DT, Kaare M, Packer C, et al. (2009) Transmission Dynamics and Prospects for the Elimination of Canine Rabies. Plos Biology 7:462-71.

Haupt W (1999) Rabies – risk of exposure and current trends in prevention of human cases. Vaccine 17:1742-9.

Hemachudha T, Mitrabhakdi E, Wacharapluesadee S (2001) Clinical aspects of human rabies, Rabies Control in Asia: Proceedings of the Fourth International Symposium Organised by the Mérieux Foundation, Hanoi, Viet Nam, 5-9 March 2001, pp 10.

Hemachudha T (2005) Rabies and dog population control in Thailand: Success or failure? Journal of the Medical Association of Thailand 88:120-3.

Hou Q, Jin Z, Ruan S (2012) Dynamics of rabies epidemics and the impact of control efforts in Guangdong Province, China. Journal of theoretical biology 300:39-47.

Hu R, Fooks A, Zhang S, Liu Y, Zhang F (2008) Inferior rabies vaccine quality and low immunization coverage.

Hu R, Tang Q, Tang J, Fooks AR (2009) Rabies in China: an update. Vector-Borne and Zoonotic Diseases 9:1-12.

IMOVAX (2012) Rabies Vaccine: IMOVAX Rabies. Available: http://www.fda.gov/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM133484 [Accessed May/20, 2013].

Jackson AC (2013) History of Rabies Research. Rabies: Scientific Basis of the Disease and Its Management :1.

Jackson AC (2003) Rabies virus infection: an update. Journal of neurovirology 9:253-8.

Jentes ES, Blanton JD, Johnson KJ, Petersen BW, Lamias MJ, Robertson K, et al. (2013) The Global Availability of Rabies Immune Globulin and Rabies Vaccine in Clinics Providing Direct Care to Travelers. Journal of Travel Medicine 20:148-58.

Kaare M, Lembo T, Hampson K, Ernest E, Estes A, Mentzel C, et al. (2009) Rabies control in rural Africa: Evaluating strategies for effective domestic dog vaccination. Vaccine 27:152-60.

Kamoltham T, Singhsa J, Promsaranee U, Sonthon P, Mathean P, Thinyounyong W (2003) Elimination of human rabies in a canine endemic province in Thailand: five-year programme. Bulletin of the World Health Organization 81:375-81.

Kasempimolporn S, Mitmoonpitak C, Chaiyabutr N, Supakorn K, Brahmasa R, Sitprija V (1996) Maternal antibodies against rabies in Thai puppies. A preliminary study. Journal of the Medical Association of Thailand = Chotmaihet thangphaet 79:36-9.

Kasempimolporn S, Sichanasai B, Saengseesom W, Puempumpanich S, Chatraporn S, Sitprija V (2007) Prevalence of rabies virus infection and rabies antibody in stray dogs: A survey in Bangkok, Thailand. Preventive veterinary medicine 78:325-32.

Knobel DL, Cleaveland S, Coleman PG, Fevre EM, Meltzer MI, Miranda MEG, et al. (2005) Re-evaluating the burden of rabies in Africa and Asia. Bulletin of the World Health Organization 83:360-8.

Knobel D, Kaare M, Fèvre E, Cleaveland S (2007) 17 - Dog Rabies and its Control. In: Rabies (Second Edition), Alan C. Jackson, William H. Wunner (editors), Oxford: Academic Press, pp 573-XIX.

Kongkaew W, Coleman P, Pfeiffer DU, Antarasena C, Thiptara A (2004) Vaccination coverage and epidemiological parameters of the owned-dog population in Thungsong District, Thailand. Preventive veterinary medicine 65:105-15.

Krebs JW, Long-Marin SC, Childs JE (1998) Causes, costs, and estimates of rabies postexposure prophylaxis treatments in the United States. Journal of public health management and practice : JPHMP 4:56-62.

Kureishi A, Xu L, Wu H, Stiver H (1992) Rabies in China: recommendations for control. Bulletin of the World Health Organization 70:443.

Lawson JS, Lin V (1994) Health Status Differentials in the People's Republic of China. American Journal of Public Health 84:737-41.

Lembo T (2012) The global elimination of canine rabies: feasible or fantasy? BSAVA Congress 2012, The ICC/NIA. Birmingham, UK: Quedgeley, pp 96-98.

Lembo T, Hampson K, Kaare MT, Ernest E, Knobel D, Kazwala RR, et al. (2010) The Feasibility of Canine Rabies Elimination in Africa: Dispelling Doubts with Data. Plos Neglected Tropical Diseases 4:e626.

Lembo T, Partners Rabies Prevention (2012) The Blueprint for Rabies Prevention and Control: A Novel Operational Toolkit for Rabies Elimination. Plos Neglected Tropical Diseases 6:e1388.

Lin, Xu(2013) Top 10 largest provincial economies in China 2012. Available: http://www.china.org.cn/top10/2013-02/21/content_28016802.htm. [Accessed June/15, 2013].

Lumlertdacha B, Wacharapluesadee S, Denduangboripant J, Ruankaew N, Hoonsuwan W, Puanghat A, et al. (2006) Complex genetic structure of the rabies virus in Bangkok and its surrounding provinces, Thailand: implications for canine rabies control. Transactions of the Royal Society of Tropical Medicine and Hygiene 100:276-81.

Malerczyk C (2012) Rabies Pre-Exposure Vaccination in Rabies Endemic Countries. J Vaccines Vaccin 3:e114.

Manning SE, Rupprecht CE, Fishbein D, Hanlon CA, Lumlertdacha B, Guerra M, et al. (2008) Human rabies prevention -- United States, 2008: recommendations of the Advisory Committee on Immunization Practices. MMWR Recommendations & Reports 57:1-28.

McCollum AM, Blanton JD, Holman RC, Callinan LS, Baty S, Phillips R, et al. (2012) Community Survey after Rabies Outbreaks, Flagstaff, Arizona, USA. Emerging Infectious Diseases 18:932-8.

Meltzer MI, Rupprecht CE (1998) A review of the economics of the prevention and control of rabies part 1: Global impact and rabies in humans. PharmacoEconomics 14:365-83.

Meltzer MI, Rupprecht CE (1998) A review of the economics of the prevention and control of rabies part 2: Rabies in dogs, livestock and wildlife. PharmacoEconomics 14:481-98.

Meng S, Sun Y, Wu X, Tang J, Xu G, Lei Y, et al. (2011) Evolutionary dynamics of rabies viruses highlights the importance of China rabies transmission in Asia. Virology 410:403-9.

Mitmoonpitak C, Tepsumethanon V, Wilde H (1998) Rabies in Thailand. Epidemiology and infection 120:165-9.

Moran GJ, Talan DA, Mower W, Newdow M, Ong S, Nakase JY, et al. (2000) Appropriateness of rabies postexposure prophylaxis treatment for animal exposures. JAMA: the journal of the American Medical Association 284:1001-7.

Murphy J, Kok H, Wong L, Loo B, Torreggiani W, Kilbride E, et al. (2013) The Global Burden of Disease. Instructions for Authors 106.

Murray CJL, Vos T, Lozano R, Naghavi M, Flaxman AD, Michaud C, et al. (2012) Disability-adjusted life years (DALYs) for 291 diseases and injuries in 21 regions, 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. Lancet 380:2197-223.

National Bureau of Statistics of the People's Republic of China (2011) Communiqué of the National Bureau of Statistics of People's Republic of China on Major Figures of the 2010 Population Census. Available:

http://www.stats.gov.cn/english/newsandcomingevents/t20110429_402722516.htm [Accessed August/10, 2013].

Pancharoen C, Thisyakorn U, Lawtongkum W, Wilde H (2001) Rabies exposures in Thai children. Wilderness & environmental medicine 12:239-43.

Panichabhongse P (2001). The epidemiology of rabies in Thailand: a thesis presented in partial fulfillment of the requirement for the degree of Master of Veterinary Studies .

Petersen BW, Rupprecht CE (2011) Human rabies epidemiology and diagnosis. Non-Flavivirus Encephalitis :247-78.

Prakash M, Bhatti VK, Venkatesh G (2013) Rabies menace and control – An insight into knowledge, attitude and practices. Medical Journal Armed Forces India 69:57-60.

Puanghat A (2001) Human rabies in Thailand.

Puanghat A, Hunsoowan W (2005) Rabies situation in Thailand. Journal of the Medical Association of Thailand 88:1319-22.

RabAvert (2012) RabAvert Package Insert. Available: http://www.fda.gov.ezproxy.library.tufts.edu/downloads/BiologicsBloodVaccines/Vaccines/ApprovedProducts/UCM312931.pdf [Accessed July/20, 2013].

RABORAL (2013). Raboral V-RG. Available: http://www.raboral.com [Accessed July/10, 2013].

Randall DA, Williams SD, Kuzmin IV, Rupprecht CE, Tallents LA, Tefera Z, et al. (2004) Rabies in endangered Ethiopian wolves. Emerging infectious diseases 10:2214.

Roebling A, Johnson D, Blanton J, Levin M, Slate D, Fenwick G, et al. (2013) Rabies Prevention and Management of Cats in the Context of Trap–Neuter–Vaccinate–Release Programmes. Zoonoses and public health .

Rupprecht CE (1996) Rhabdoviruses: rabies virus. Medical microbiology, 4th edn.University of Texas Medical Branch at Galveston, Galveston .

Rupprecht CE, Hanlon CA, Hemachudha T (2002) Rabies re-examined. The Lancet infectious diseases 2:327-43.

Rupprecht, Charles E., David R. Shlim (2013) Infectious Disease Related to TravelAvailable:http://wwwnc.cdc.gov.ezproxy.library.tufts.edu/travel/yellowbook/2014/chapter-3-infectious-diseases-related-to-travel/rabies [Accessed August/10, 2013].

Rupprecht CE, Smith JS, Krebs J, Niezgoda M, Childs JE (1996) Current issues in rabies prevention in the United States health dilemmas. Public coffers, private interests. Public health reports 111:400.

Rupprecht CE, Gibbons RV (2012) Prophylaxis against rabies - Reply. New England Journal of Medicine 352:1609-10.

Rupprecht CE, Hanlon CA, Hemachudha T (2002) Rabies re-examined. Lancet Infectious Diseases 2:327-43.

Rupprecht CE, Smith JS, Fekadu M, Childs JE (1995) The ascension of wildlife rabies: a cause for public health concern or intervention?. Emerging Infectious Diseases 1:107-14.

Rupprecht C (2004) A tale of two worlds: Public health management decisions in human rabies prevention. Clinical Infectious Diseases 39:281-3.

Shwiff SA, Sterner RT, Jay MT, Parikh S, Bellomy A, Meltzer MI, et al. (2007) Direct and indirect costs of rabies exposure: A retrospective study in Southern California (1998-2002). Journal of wildlife diseases 43:251-7.

Si H, Guo Z, Hao Y, Liu Y, Zhang D, Rao S, et al. (2008) Rabies trend in China (1990–2007) and post-exposure prophylaxis in the Guangdong province. BMC infectious diseases 8:113.

Sirikwin S (2001) Increasing the availability of modern rabies vaccine in countries infected with dog rabies: experience from Thailand.

Song M, Tang Q, Wang D, Mo Z, Guo S, Li H, et al. (2009) Epidemiological investigations of human rabies in China. Bmc Infectious Diseases 9:210.

Sriaroon C, Sriaroon P, Daviratanasilpa S, Khawplod P, Wilde H (2006) Retrospective: Animal attacks and rabies exposures in Thai children. Travel Medicine and Infectious Disease 4:270-4.

Sterner RT, Smith GC (2006) Modeling wildlife rabies: Transmission, economics, and conservation. Biological Conservation 131:163-79.

Tang X, Luo M, Zhang S, Fooks A, Hu R, Tu C (2005) Pivotal role of dogs in rabies transmission, China. Emerging Infectious Diseases 11:1970-2.

Tenzin, Wangdi K, Ward MP (2012) Human and animal rabies prevention and control cost in Bhutan, 2001–2008: The cost–benefit of dog rabies elimination. Vaccine 31:260-70.

Tenzin, Ward MP (2012) Review of Rabies Epidemiology and Control in South, South East and East Asia: Past, Present and Prospects for Elimination. Zoonoses and Public Health 59:451-67.

Thai Visa Forum (2007) What's the Average Thai Salary? Available: http://www.thaivisa.com/forum/topic/104961-whats-the-average-thai-salary/ [Accessed July/20, 2013].

The China Perspective (2013) The China Perspective: Guangdong. Available: http://www.thechinaperspective.com/topics/province/guangdong/ [Accessed May/20, 2012].

Thiptara A, Atwill ER, Kongkaew W, Chomel BB (2011) Epidemiologic Trends of Rabies in Domestic Animals in Southern Thailand, 1994-2008. American Journal of Tropical Medicine and Hygiene 85:138-45.

United Nations (2008) Thailand Info. Available: http://www.un.or.th/thailand/economy.html [Accessed May/20, 2013].

US Census Bureau (2013) State and County Quick Facts. Available: http://quickfacts.census.gov.ezproxy.library.tufts.edu/qfd/states/00000.html [Accessed August/12, 2013].

Vaidya SA, Manning SE, Dhankhar P, Meltzer MI, Rupprecht C, Hull HF, et al. (2010) Estimating the risk of rabies transmission to humans in the US: a delphi analysis. Bmc Public Health 10:278.

Warrell M (2012) Current rabies vaccines and prophylaxis schedules: preventing rabies before and after exposure. Travel Medicine and Infectious Disease 10:1-15.

Wasi C, Chaiprasithikul P, Thongcharoen P, Choomkasien P, Sirikawin S (1997) Progress and achievement of rabies control in Thailand. Vaccine 15:S7-S11.

WHO (2013) Rabies. Available: http://www.who.int.ezproxy.library.tufts.edu/rabies/en/ [Accessed June/20, 2013].

WHO Geneva (2010) Weekly epidemiological record No. 32, 2010, 85, 309–320. Available: http://www.who.int/wer/2010/wer8532.pdf [Accessed June/15, 2013].

Wilde H, Khawplod P, Khamoltham T, Hemachudha T, Tepsumethanon V, Lumlerdacha B, et al. (2005) Rabies control in South and Southeast Asia. Vaccine 23:2284-9.

Wilde H, Tipkong P, Khawplod P (1999) Economic issues in postexposure rabies treatment. Journal of Travel Medicine 6:238-42.

World Bank (2013) World Bank Search: Thailand. Available: http://search.worldbank.org.ezproxy.library.tufts.edu/data?qterm=thailand&_topic_exact%5B%5D=Economic+Policy+%26+Debt [Accessed June/20, 2013].

Wu X, Hu R, Zhang Y, Dong G, Rupprecht CE (2009) Reemerging Rabies and Lack of Systemic Surveillance in People's Republic of China. Emerging Infectious Diseases 15:1159-64.

Yin C, Zhou H, Wu H, Tao X, Rayner S, Wang S, et al. (2012) Analysis on factors related to rabies epidemic in China from 2007–2011. Virologica Sinica 27:132-43.

Zhang J, Pritchard E, Hu X, Valentin T, Panilaitis B, Omenetto FG, et al. (2012) Stabilization of vaccines and antibiotics in silk and eliminating the cold chain. Proceedings of the National Academy of Sciences 109:11981-6.

Zhang J, Jin Z, Sun G, Sun X, Ruan S (2012) Spatial spread of rabies in China. Journal of Applied Analysis and Computation 2:111-26.

Zhang L, Wilson DP (2012) Trends in notifiable infectious diseases in China: implications for surveillance and population health policy. PloS one 7:e31076.

Zhang Y, Xiong C, Xiao D, Jiang R, Wang Z, Zhang L, et al. (2005) Human rabies in China. Emerging infectious diseases 11:1983.

Zhang J, Jin Z, Sun G, Zhou T, Ruan S (2011) Analysis of Rabies in China: Transmission Dynamics and Control. Plos One 6:e20891.

ZHU WY, LIANG GD (2012) Current Status of Canine Rabies in China. Biomedical and Environmental Sciences 25:602-5.

Zinsstag J, Duerr S, Penny MA, Mindekem R, Roth F, Gonzalez SM, et al. (2009) Transmission dynamics and economics of rabies control in dogs and humans in an African city. Proceedings of the National Academy of Sciences of the United States of America 106:14996-5001.