Master of Public Health Field Experience Report

Identifying Gaps in Post-Exposure Rabies Prophylaxis in Hunan Province, China

by

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MASTER OF PUBLIC HEALTH

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Summary

My MPH Field Experience was completed in summer 2016 at the China CDC in Beijing. China experiences the second highest burden globally of human rabies deaths annually. Almost all of these deaths are due to canine rabies and transmitted from the dog population of China, in which rabies is endemic. Eliminating the disease from the dog population is the most significant way to reduce the incidence of the disease in humans. However, in the meantime, post-exposure prophylaxis (PEP) administered to the appropriate patients is necessary to reduce the number of fatalities due to the disease. During my field experience at the China CDC, I participated in a study to investigate the capabilities of clinics to administer rabies PEP successfully in Hunan Province, China. The study additionally followed potentially exposed patients at several clinic sites to identify gaps in post-exposure prophylaxis administration. This study found that wound washing, the first essential step in rabies PEP, is often neglected or inadequate; additionally, trained healthcare workers struggle to appropriately categorize patients according to their level of risk and therefore patients do not receive adequate PEP; furthermore, even patients whose risk levels are appropriately determined do not consistently receive the correct PEP either due to a lack of understanding among healthcare workers or due to lack of access to the necessary biologics. These gaps identified highlight some important target areas for improvement in the area of PEP delivery.

Subject Keywords: rabies, China, post-exposure prophylaxis

Table of Contents

List of Figures

List of Tables

Chapter 1 - Field Experience Scope of Work

Global Burden of Rabies

Rabies is a worldwide zoonotic disease of mammals with a case fatality rate approaching 100%.[1] According to the World Health Organization (WHO), rabies is present in more than 150 of the 195 UN member countries.[2] The disease causes an estimated 55,000 deaths annually according to the US Centers for Disease Control and Prevention (US CDC), with the vast majority of these deaths occurring in developing countries and in association with dog bites.[3] An estimated 45% of those deaths occur in southeastern Asia, and India has the highest incidence of rabies with around 20,000 deaths annually.[4] Rabies also causes significant mortality in Africa and the Middle East.[2] Rabies is considered to be widely underreported and has been designated a neglected tropical disease by the WHO.

Despite its high mortality, rabies is an entirely preventable disease when prompt post-exposure prophylaxis (PEP) measures are appropriately administered or when reservoir populations are controlled. In the majority of developing countries, rabies is endemic in the domestic dog population. The canine-adapted strain of the virus, transmitted from dogs to humans, is responsible for more than 99% of human rabies mortalities worldwide.[5] As with many infectious diseases, rabies surveillance data are lacking in the areas where the disease is most prevalent.[6]

The burden of rabies as a global public health issue is difficult to estimate due to widespread underreporting. A 2015 study on the global burden of canine endemic rabies attempted to estimate the physical, economic and social costs of rabies. This study estimated that canine rabies is responsible for 59,000 human deaths annually, for the loss of more than 3.7 million disability-adjusted life years,[i] and for approximately 8.6 billion US dollars in economic losses annually.[6] The cost of post-exposure prophylaxis administered was estimated to comprise 20% of those economic losses with over 29 million people receiving PEP annually in rabies endemic regions[19]; the loss of income while patients were seeking post-exposure prophylaxis was estimated to comprise another 15% of the economic losses due to this disease. The WHO estimates that 3.3 billion people around the world are at risk of exposure to rabies.[19]

Rabies Virology, Pathology and Diagnosis

The rabies virus is in the family *Rhabdoviridae*, genus *Lyssavirus*.[7] It is an enveloped, non-segmented, negative sense RNA virus that is 12 kb long. The rabies virus infects most mammalian species, but primarily affects bats, raccoons, skunks, foxes and dogs. It has the ability to form host-adapted strains that thrive in certain populations, such as the canine strain of the virus that circulates in dog populations globally. The viral genome encodes five proteins: a phosphoprotein (P) and a viral RNA polymerase (L) that associate with the helical ribonucleoprotein core, and function collectively to make the RNA-dependent RNA polymerase; a nucleocapsid protein (N) that covers the helical core, forming the ribonucleoprotein core; a matrix protein (M) that forms an inner membrane; and a transmembrane glycoprotein (G) that protrudes from the surface of the envelope. Protective antibodies are made to this glycoprotein (Figure 1.1).[8]

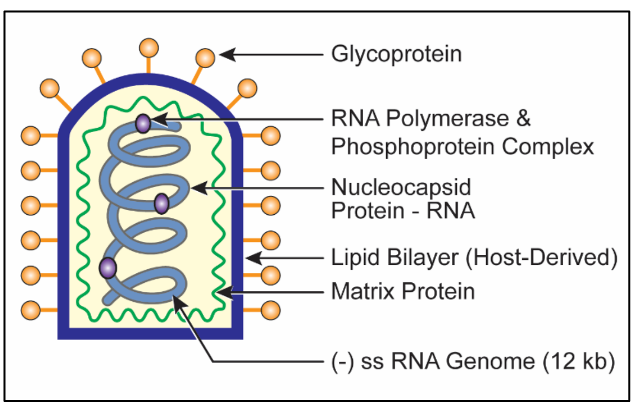

Figure 1.1 Structure of the rabies virus (Credit: Mal Hoover)

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[i] the disability-adjusted life year is a measurement of disease burden and represents the number of healthy, productive years lost to illness, disability or premature death

Rabies has a unique pathogenesis in that the virus disseminates via nerve fibers rather than via the blood or lymphatic system.[5] Once it is taken up by an unmyelinated axon terminal via endocytosis, the virus migrates via retrograde axoplasmic transport along the peripheral nervous system until it reaches the central nervous system; once within the spinal cord, it distributes rapidly.[9] Once it reaches the brainstem, the virus is spread to the peripheral nervous system and organs via the autonomic nervous system.[10] In the final stages of the disease, it is spread to the salivary glands along the facial and glossopharyngeal nerves. The virus is shed in high levels from the glandular epithelium of the salivary glands. Its high concentration in saliva enables effective transmission of the virus through bites. Few structural abnormalities are present in neurons infected with the virus, so the cause of the extreme neurologic dysfunction associated with rabies is not currently understood.[8] Current theories on rabies pathogenesis favor modulation of neuronal function rather than structure. There is evidence that the virus might decrease neurotransmitter functionality, particularly of serotonin and acetylcholine.[10] Housekeeping genes are downregulated in rabies-infected neurons. Additionally, functional ion channels such as voltage-dependent sodium channels exhibit decreased expression in rabies infected cells. The virus's ability to relatively conserve neuronal structure might aid in its unique ability to evade the immune system. Pathogenic strains of the virus also replicate slowly and keep production of the virus to a minimum to further reduce activation of antiviral host pathways.

The incubation period of the rabies virus in humans is variable; most commonly it is reported as being in the 20 to 60 day range, however it can be as short as 5 days or as long as several months, or even years.[11] In the initial stages of disease, clinical manifestations of rabies include non-specific signs of illness such as a fever, headache and malaise; occasionally pruritus or neuropathic pain at the bite site are present. Within a few days, the patient becomes neurologic, with usually one of two sets of signs depending on the form of the disease. Which form presents is believed to be based on whether the central nervous system or the peripheral nervous system is affected more significantly at time of presentation. In the encephalitic form, patients demonstrate more central nervous system signs including intermittent abnormal mentation and experience agitation, photophobia, hydrophobia, aerophobia, hyperventilation and hypersalivation. In the paralytic form of the disease, patients experience paralysis as the virus targets the peripheral nervous system. The encephalitic form usually progresses to include paralysis. In both forms of the disease, the patient usually progresses to a comatose state, and death occurs most frequently attributable to cardiopulmonary failure.

Rabies in animals must be diagnosed with a post-mortem test on the brainstem and cerebellum to detect viral antigens. Direct fluorescent antibody tests on these brain tissues are the preferred mechanism for diagnosing rabies in animals. Rabies diagnosis in humans is also confirmed via a post-mortem test, such as the fluorescent antibody test, direct rapid immunohistochemistry, ELISA, or RT-PCR, and less commonly by virus isolation.[11,12] Ante-mortem tests, although less specific, less sensitive and not considered confirmatory, are available for humans. These include viral antibody or antigen detection tests on serum, cerebrospinal fluid, urine, saliva or hair follicle biopsies from the neck region.

Rabies in China

China began recording information on human rabies cases in 1950.[13] The Chinese Notifiable Disease Reporting System was initiated in the 1950s to develop a system for communicable disease surveillance.[17] In 2003, after the outbreak of severe acquired respiratory syndrome (SARS) in China, surveillance was upgraded to an online platform, referred to as the Nationwide Notifiable Infectious Disease Reporting Information System (NIDRIS). After the implementation of NIDRIS, epidemiological information became more easily accessible and an increase in publications on diseases such as rabies has been observed.

For the last two decades, China has reported the second highest burden of human rabies deaths worldwide.[14] Between 1950 and 2010, 124,255 human cases of rabies were reported, with an average of 2,037 cases per year.[14] Several epidemics were observed during that period, with over 7,000 cases reported in 1981; over 5,000 cases per year throughout the remainder of the 1980s; and another epidemic in 2007 with 3,300 cases reported. Rabies is designated a notifiable infectious disease in China.[15] However, particularly in rural areas of the country, many persons die at home with the disease and so are not included in the official reported statistics, leaving estimates of the disease likely lower than they are in reality. In 2005, the Ministry of Health implemented a National Rabies Surveillance Campaign in focused areas of the country where the disease incidence was highest. Eventually, this campaign was expanded to include all areas of the country that are still reporting rabies. China has a goal to eliminate canine rabies by 2030.[16]

More than 85% of the human rabies cases reported in China occur in rural areas.[1] The disease has been geographically focused in the southern part of the country where the dog to human ratio is much higher than it is in the northern part of China. From 2004 to 2014, 52% of the total cases reported were from Guanxi, Guizhou, Guangdong and Hunan Provinces (Figure 1.2). However, in recent years, despite a decline in overall incidence, the geographic distribution of the disease has spread, with

Figure 1.2 Rabies Distribution in China: 2004 to 2014

more provinces and counties in the northern region of the country reporting rabies than previously.[17] In 2014, all provinces reported human rabies fatalities. Among rabies cases reported in China, males are more commonly affected, with a 2.3 - 2.4:1 male to female ratio.[15,17] Additionally, the age group that is most commonly affected among reported deaths is the 50 – 59 year old age group. Farmers in rural areas have the highest risk of dying from rabies.

Approximately 70% of households in rural areas of China keep dogs, and vaccination rates are very low.[14] Approximately 95% of the human cases of rabies in China are attributed to dog bites; cats and other animal species make up the remaining transmission sources. In 2005, the Ministry of Agriculture began an annual Rabies Immunization and Surveillance Program to reduce the prevalence of canine rabies, requiring vaccination of all types of dogs in urban as well as rural areas. Despite the regulations in place, vaccination of dogs is still quite uncommon in rural areas due to low levels of awareness and the high costs of vaccination usually at the owner's expense. Ecological and household surveys published in a 2014 study found a 36.4% immunization rate for dogs and 15.6% immunization rate for cats.[13] Campaigns to increase awareness, initiate canine mass vaccination, and improve the immunization rates are important components of the national Long-Term Animal Disease Prevention and Control Plan (2012-2020).[17]

China is the world's largest producer and consumer of rabies biologics, administering an estimated 12 to 15 million doses of PEP annually.[18] While exposed persons do not always seek PEP and therefore are at risk of developing the infection, national and provincial level retrospective studies of rabies cases reveal that a concerning percentage of cases did visit treatment centers for PEP. A 2008 study of rabies cases in Guangdong Province revealed that 12.3% of patients had gone to a PEP clinic for treatment after exposure.[22] A 2015 study by Ren et al of rabies cases in Zhejiang Province found that 14.9% of cases had visited a rabies PEP clinic after exposure.[15] A 2018 study of cases in Chongqing found that 12.2% of the patients had visited a hospital for medical treatment after exposure.[16] Due to the nature of these studies (all cases were deceased and the majority of interviews were conducted with family members of the deceased patient and performed after the death had occurred), the reasons for failure of PEP in these patients are not completely understood. Possible explanations include that the patient did not comply with the complete PEP vaccine schedule, while in other cases it was suspected that the appropriate PEP was not delivered by the healthcare staff at the PEP clinics.

China has a National Immunization Program, organized by the China CDC that covers fees for certain vaccinations. However, the human rabies vaccine is not included in this program so bite wound victims and potential rabies-exposed persons are responsible for covering the costs of PEP themselves.[17] Some provincial governments including Guizhou and Anhui have begun programs to partially alleviate the cost of PEP to patients; however these are still insufficient and leave a substantial financial burden on patients.[18]

Rabies Prevention and Biologics

Rabies prevention relies on two strategies – controlling the disease in canine populations to decrease the transmission of the virus to humans and appropriate risk-based pre-exposure or post-exposure prophylaxis in humans. Experts regard the eradication of endemic rabies in the canine population as the most important and most-cost effective way to prevent the disease. Areas of the world that experience extremely low rates of human mortalities from rabies have achieved this by mass vaccination of the canine population. The WHO regards a 70% vaccination rate of the dog population annually as necessary to maintain an immune barrier between the virus and humans.[15] Due to the low basic reproductive number[ii] of rabies, estimated to be between 1.05 and 1.72, some areas have achieved remarkable control of rabies with just a 64% vaccination rate of owned dogs.[20]

A study in 2017 in Chad examined the cumulative cost efficiency of PEP alone compared to PEP plus mass canine vaccinations. This study found that the financial costs of the two strategies broke even in the sixth year of use.[19] The reduction in PEP costs due to the degree of disease control was equivalent to the money spent on the canine mass vaccinations. A similar study in Bhutan demonstrated that within only three years, the cost of canine vaccination plus PEP was less than the cost of PEP alone.[20] PEP is found to be relatively expensive and has no impact on the canine reservoir so only functions as a last resort intervention.[20] Another controversial strategy for controlling the disease in canine populations that has been proposed and used in a few cases including in Indonesia and Bhutan is culling stray dogs.[20] However, aside from detrimental effects on the human-animal bond, this approach has proven to be more expensive and less effective in controlling the disease. Not only is euthanizing dogs more expensive than vaccinating them, but also the chaotic disruption this practice causes in dog social systems leads to increases in the number of dog bites.

Rabies PEP includes wound washing as well as two types of biologics, anti-rabies vaccines and rabies immunoglobulin (RIG). Rabies vaccines, when used

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[ii] Reproductive number, R_0, of a disease is the number of secondary cases that arise from a single primary case.

appropriately and in conjunction with wound washing and RIG if indicated, are highly effective with very few failures reported.[21] Rabies vaccines have been available for over a century, with the earliest vaccines being produced in 1885 by Louis Pasteur. These early vaccines were made of inactivated spinal cord tissue homogenates from infected rabbits; inactivation was not always successful however, so these early vaccines had the potential to induce rabies infection in the patient. Later vaccines made from sheep or eventually chick embryos and suckling mouse brains were more consistently inactivated, but the levels of myelin present still led to severe autoimmune reactions including fatal encephalitis. Human diploid cell culture vaccines and purified chick embryo cell vaccines became available in the mid-1970s; these vaccines are much safer and are recommended for use worldwide in persons at high risk of exposure and all persons who have been potentially exposed to rabies. The WHO has discouraged the use of nerve tissue vaccines (NTVs) since cell culture vaccines have been made available due to concerns about both the safety and efficacy of NTVs. China banned the use of NTVs in 1981.[22] WHO-approved rabies biologics including both anti-rabies vaccines and immunoglobulins are considered safe for use and the benefits always outweigh the risks of a potential adverse effect, even in pregnant and lactating women.[23] In the event of an exposure, there are no contraindications to administering PEP.

The WHO publishes specific risk-based guidelines on the post-exposure prophylaxis (PEP) measures for rabies exposures.[24] These guidelines are based on the categorization of exposure level as I, II or III, with Category III exposures carrying the greatest risk for rabies transmission. These guidelines are included in Table 1.1. The WHO also encourages an integrated bite management approach, which includes identifying the biting animal and quarantining it for observation when possible or euthanizing and testing it for rabies when quarantine is not available.

Retrospective analyses reveal that the majority of patients who succumb to rabies experienced a Category III exposure; however Category II exposures also result in deaths when not treated properly. A 2015 study found that 84% of cases had a Category III exposure while 16% had a Category II exposure.[15] A 2018 study found a similar trend with 75% of cases having died from a Category III exposure while just 25% had experienced a Category II exposure.[16]

Table 1.1. WHO Rabies Exposure Categories and Recommended PEP[24]

Categories of contact with suspect rabid animal	Activity/Wound Description	Post-exposure prophylaxis measures
Category I	Touching or feeding animals, licks on intact skin	None
Category II	Nibbling of uncovered skin, minor scratches or abrasions without bleeding	Immediate vaccination and local treatment of the wound Immunocompromised persons§ with a Category II exposure should also receive rabies immunoglobulin.
Category III	Single or multiple transdermal bites or scratches, licks on broken skin; contamination of mucous membranes with saliva from licks, contacts with bats.	Immediate vaccination and administration of rabies immunoglobulin; local treatment of the wound

§Immunocompromised persons include any patient with an illness such as HIV, TB or cancer or other illnesses known to suppress the immune system. Also included are patients that have been on an immunosuppressive medication for any reason prior to a rabies exposure.

All currently approved PEP regimens require multiple doses being administered days and weeks after the initiation of treatment during 3 to 5 clinic visits (see Table 3.1). This poses additional unforeseen burdens on patients receiving PEP. Due to the necessity of multiple visits to a clinic, patients can incur travel costs and lose wages and productive work time. These treatment regimens also require that patients remember to seek treatment up to 4 weeks after the exposure incident occurred and may be out of mind. In the case of Category III exposures (or in Category II exposures in immunocompromised or immunosuppressed persons), rabies immunoglobulin (RIG) administration should accompany the initiation of the vaccine series. These biologics are discussed in more detail in Chapter 3.

A Brief Introduction to the Chinese Center for Disease Control and Prevention

The China Center for Disease Control and Prevention (CDC) is an agency within the Ministry of Health of the People's Republic of China (PRC). It is based in Beijing, China with the national headquarters campus located in the northwest part of the municipality of Beijing in the Changping District. The China CDC was founded in 2002 when the existing national public health organizations were challenged by the SARS outbreak. The CDC emerged from a variety of previous national organizations involved in public health including the Chinese Academy of Preventative Medicine, the Industrial Health Institute, the Health Education Institute, and the Rural Water Supply Technical Guidance Center. Now, it is the official government-funded national public health institution of the PRC. The mission of the China CDC is "to create a healthy environment, promote health and quality of life by controlling and preventing disease, injury and disability so as to ensure the economic and social development and the national security" (China CDC, Internal Document). The China CDC strives to achieve three core goals embedded within this mission: (1) disease prevention and control, (2) scientific research and (3) workforce development.

The China CDC is structured into several Offices, including the Division of Infectious Disease Control, the Office for Public Health Management, and the Office for Non-Communicable Disease Control and Community Health (See Figure 1.3).[25] The agency also has a Public Health Emergency Center which handles outbreaks at a national level and manages a hotline; and a Technical Support group focuses on epidemiology, surveillance and information management. To fulfill its mission of workforce development, the China CDC conducts post-graduate education for students from around the country. The China CDC employs around 2,100 staff, the vast majority of whom are health professionals.[26]

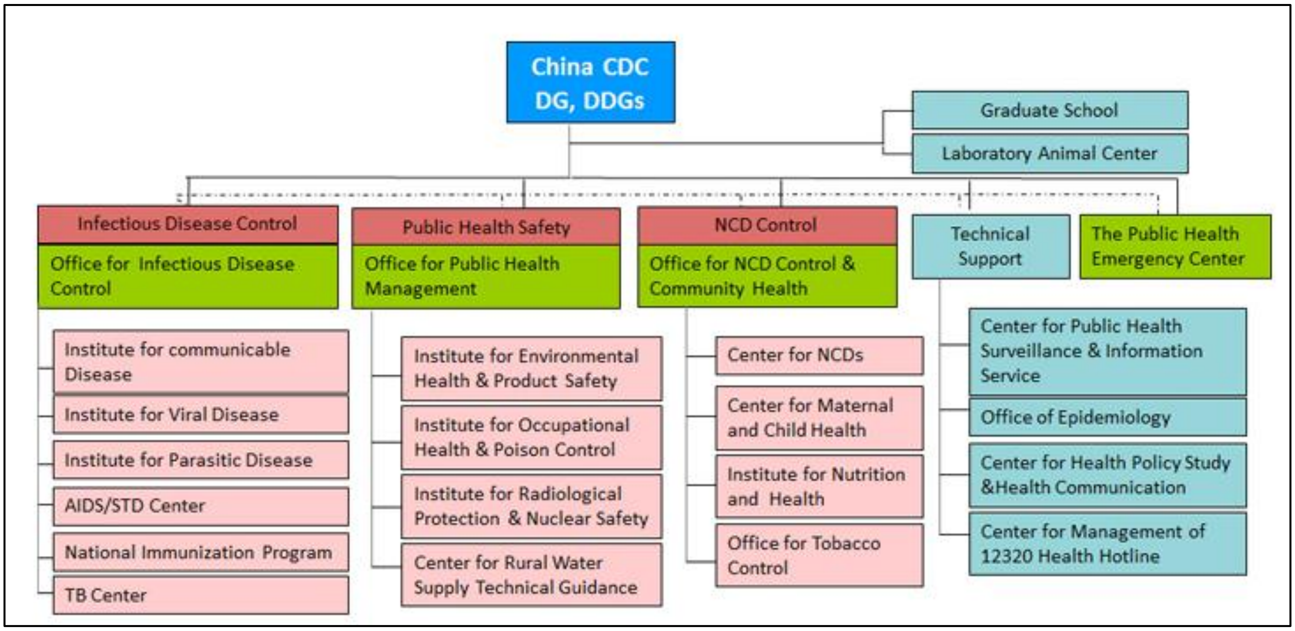

Figure 1.3 Organizational Chart of China CDC[25]

As the national public health agency, the China CDC is tasked with advising policy makers on issues affecting public health. The agency also coordinates projects, interventions, surveillance and information management within the hierarchy of local CDCs. The provincial health departments run provincial-level CDCs, prefectural and city health departments also operate CDCs and county health departments run county-level CDCs including township health centers and village clinics. Provincial, Prefectural/City and County CDCs all provide hospitals and other health facilities with technical agency guidance and assistance.

Preceptorship Mentor: Yu Li, MD, MSc

The mentor who guided me at the preceptorship site throughout the duration of my field experience was Dr. Yu Li. He trained as a medical doctor in China and then traveled to the UK to study non-communicable diseases and epidemiology. Eventually, his interests shifted from non-communicable diseases towards communicable infectious diseases. He returned to China after having obtained his master's degree in epidemiology to work for the China CDC in Beijing. He works as an epidemiologist in the Branch of Zoonotic and Vector-Borne Diseases, a group within the Division of Infectious Diseases.

His work with the China CDC primarily includes descriptive epidemiologic studies of diseases such as anthrax, rabies, avian influenza, severe fever with thrombocytopenia syndrome,[iii] dengue fever, and brucellosis. During my field experience, Yu Li mentored me in a broad variety of topics including public health communication and study design and analysis. He also shared with me his experiences, insight and knowledge on the China CDC and its functioning as a national public health organization.

Technical Guidelines for the Prevention and Control of Human Rabies in China

The China CDC identified rabies as a disease of serious public health importance. It has as its goal zero human rabies cases by 2025 and the eventual eradication of canine rabies by 2030. Five strategies for the control of rabies were identified: (1) eradicate canine rabies via immunization, registration and control of the canine population; (2) integrate human and animal surveillance information in a timely fashion; (3) implement quarantine where appropriate and restrict movement of dogs; (4) deliver complete and appropriate PEP by trained professionals; (5) increase public awareness, risk communication and social motivation. To implement strategy #4, the China CDC created a document entitled "Technical Guidelines for Human Rabies Prevention and Control 2016," (Technical Guidelines) which includes specific instructions on the administration of various rabies post-exposure prophylaxis biologics.[27]

The Technical Guidelines was drafted by the China CDC in January 2016 and is a comprehensive document on the topic of rabies in China. It includes information regarding the basic virology, laboratory diagnosis, clinical signs and presentation, pathogenesis, diagnostic criteria of clinical rabies. It also includes information on the epidemiology – globally and in China – of rabies, the disease burden, and the sources of transmission. Regarding rabies biologics, it contains information on the available and

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[iii] a recently emerging vector borne disease spread by *Ixodes* ticks

China Food and Drug Administration-approved vaccines, the approved regimens, immunology, serology and safety profiles of vaccines. It also covers the safety and mechanism of action of rabies immunoglobulin (RIG). Finally, it contains specific guidelines on how to administer PrEP and PEP, how to classify exposures and how to respond to adverse events following immunization.

The majority of the information presented in this document is in agreement with what is recommended by the WHO. However, only the intramuscular Essen and Zagreb regimens for anti-rabies vaccines (ARVs) are currently approved in China. Despite widespread WHO approval, the use of intradermal regimens is not permitted at this time in China. The majority of China uses purified equine rabies immunoglobulin (ERIG) rather than human rabies immunoglobulin (HRIG) or unpurified equine antisera. The WHO supports the use of purified ERIG as a life-saving and safe biologic. The document does mention an increased risk of serum sickness or adverse event with the use of ERIG instead of HRIG; but it also highlights the potential risk of blood-borne infections such as HIV or Hepatitis B and C that is associated with HRIG but not ERIG. In accordance with the WHO, the Technical Guidelines recommend the use of RIG in immunocompromised or immunosuppressed patients with a Category II exposure as well as in all patients with a Category III exposure. To determine the category of exposure, the presence of intact skin must be examined. The Technical Guidelines recommend using an alcohol wipe to stimulate pain and detect any skin damage smaller than the eye can detect that may be present on a potentially exposed area. As is recommended by the WHO, wound washing is recommended for a minimum duration of 15 minutes. Finally, in accordance with the WHO, the Technical Guidelines emphasize that there are no contraindications to administering PEP.

Project Introduction

Due to the high burden of human rabies cases in China as well as the reports of PEP failures discussed above, the Branch of Zoonotic and Vector-Borne Diseases was tasked with investigating rabies PEP. The US CDC office in Beijing joined efforts with the China CDC to fund and assist in the conduction of this project. The Branch created a project to develop tools to assess preparedness of rabies PEP clinics, training of healthcare workers at these clinics, as well as specific medical practices regarding the delivery of rabies PEP by clinic staff. Goals included evaluation of the accuracy of exposure classification and appropriate treatment selection per the national and WHO PEP guidelines and identification of gaps in PEP knowledge and practices. The group selected Hunan Province as the location to conduct the pilot project to assess the tools developed. Hunan Province was selected due to the area's high incidence of human rabies cases. Two assessment tools were created in the format of surveys and tested in a pilot study over the period from May to August, 2016 in Shuangfeng County, Hunan Province. This project was the main focus of my field experience. It is discussed in detail in Chapter 3 of this report.

Chapter 2 - Learning Objectives

1. Observe a large-scale governmental public health organization in operation under the supervision of a mentor.
2. Observe international collaboration efforts between public health organizations of China and the United States working towards a common identifiable public health goal, the elimination of rabies.
3. Participate in the assessment of rabies post-exposure prophylaxis clinics in China, experiencing and contributing to an epidemiological project to better understand the disease and its control.

Activities Performed

Table 2.1 Activity Table

Objective	Activity	Product(s)
1	Attended regular meetings on the Hunan Province pilot project to observe epidemiologists and public health professionals interacting, designing the survey and implementing the survey.	Survey 2 (Provided at defense)

1	Read internally created documents and presentations about the founding of the China CDC, the organizational structure, mission and activities.	
2	Edited the Technical Guidelines for Human Rabies Control and Prevention (2016) document so that future versions of the document can be made available in English. Improved its grammar, mechanics and readability.	Edited Technical Guidelines in English (Provided at Defense)
2	Wrote an abstract for a paper which my mentor and colleagues at China CDC had written on anthrax epidemiology. This was then published in the Emerging Infectious Diseases journal of the US CDC (Vol 23:1, Jan 2017)	Abstract (Provided at Defense)
2	Conducted a literature review on Rabies Post-Exposure Prophylaxis focusing on developing countries, methods of evaluating PEP delivery and effectiveness of biologics	Literature review (See Chapter 3 of this Report)
1, 3	Managed data collected from Survey 2. Created a legible Chinese/English key to Survey 2 to facilitate easier retrieval and understanding of data.	Survey Bilingual Keys (Provided at Defense) Data file, cleaned
3	Formulated questions about rabies PEP delivery in China and used the data generated from the surveys to answer the questions	Results and Discussion (See Chapter 3 of this Report)
2	Participated in dialogue between the staff members at the US CDC office in	

	Beijing and the China CDC staff members at the Branch of Zoonotic and Vector-Borne Diseases	

Products Developed

When I began my field experience, the Survey 1 had just been conducted and Survey 2 was still in the design phase. I participated in the design of this Survey 2. However, because I had recently arrived and was just becoming immersed in the project, my participation was primarily in an observational role. I listened to the investigators plan the format of the survey and decide which questions to include and how to organize them in the survey. Once Survey 2 was released, both surveys were sent to a student for translation into English; the resultant product was not very understandable in English. My task was to work with the translated surveys and the investigators to make a bilingual copy that was understandable in English for the purpose of communicating with the US CDC or with future potential English language journals that may publish any findings based on these surveys. (At this time, I do not have permission to share the surveys publicly, so they will be made available for review to my committee, but not attached as appendices in the official K-Rex submission of my report.)

Before I arrived at my field experience, my mentor sent me a copy of the Technical Guidelines for Human Rabies Control and Prevention (2016) that had been developed by a taskforce at China CDC earlier that year. This document, although translated into English, was not fluent and so I was tasked with editing this document and returning an improved copy to my mentor. Editing this 65-page document was time consuming, but also allowed me to learn a lot about the management of rabies and PEP in China. This document will be revised as necessary and newer editions published for use.

My mentor had submitted a manuscript on anthrax to the Emerging Infectious Diseases journal of the US CDC and received comments from the peer reviewers. I worked with him to improve this manuscript. The abstract also needed to be rewritten in accordance with the requirements of the journal and in smooth English, so after reading the manuscript and speaking with him about the project, I wrote an abstract. This manuscript was re-submitted with revisions and accepted for publication.

I also spent a portion of my time at my field experience reading about rabies. I initially spent time reading about the virus, pathogenesis and diagnosis. To complement this, I spent two days at the State Key Laboratory for Rabies Diagnostics, also a component of the China CDC and located on the same campus as my field experience site in Beijing. While there, I met with investigators and learned about their research, I observed laboratory protocols for sample handling and processing. I then continued my literature review studying rabies PEP biologics, challenges and costs. Since my career interests are in global health, I focused on the use, access and success of PEP programs in developing countries of rabies-endemic regions. I learned about the gaps in PEP delivery as well as gaps in current understanding and research regarding rabies PEP.

Chapter 3 - Capstone Project

Literature Review

To gain a better understanding of rabies post-exposure prophylaxis procedures, challenges and studies around the world, and in particular, regions of the developing world where canine rabies is endemic, I conducted a literature review. Within the last few years, there have been several studies addressing this neglected tropical disease and in particular investigating post-exposure prophylaxis, which is one of the main avenues for controlling the disease in the human population. Post-exposure prophylaxis is expensive, frequently not readily available due to cost and supply, and often patient compliance is low.

Demographics of Persons Seeking PEP and Animals Associated with Exposures

A common theme among all studies investigating rabies post-exposure prophylaxis is that males are at a higher risk of exposure. Studies conducted in many countries including Sri Lanka (55.0%)[28], Pakistan (87.0%)[40], Central African Republic

(53.8%)[29], Iran (84.5%)[30], India (71.6%)[31], and Ethiopia (62.8%)[32] showed a higher percentage of males among persons presenting for bite wounds. This trend is in accordance with studies that evaluate human rabies cases; a study in China showed 70% of cases were male.[15] Most studies also reveal a higher risk among younger persons, with children under 15 usually overrepresented among patients seeking PEP.[40,28,29,32,52,53] However, studies in Iran and India have shown the opposite trend with adults overrepresented among PEP-seeking persons.[30,31] Additionally, a 2015 study in China by Ren et al. showed that 61% of patients that had died from rabies were aged 40 to 65 years.[15] Another study in China by Zhou et al. found that the age group of 50 – 59 years was the most overrepresented with 20.5% of cases from that group.[17] The vast majority of rabies-associated bites are from dogs, and in most cases, the dog is owned by someone that the victim knows. In Sri Lanka, unvaccinated owned dogs and cats were the main source of potential exposures.[28]

WHO-Approved PEP Regimens

Currently, the World Health Organization has approved 6 different PEP vaccine regimens for rabies exposures (see Table 3.1). Adherence to these guidelines and completion of these schedules is essential for preventing rabies infection after an exposure. Most countries that deal with endemic rabies advocate following the WHO guidelines for rabies PEP. Failure rates are low where complete PEP is appropriately administered. Treatment failures occur when the vaccine series is not completely administered or when passive immunity in the form of rabies immunoglobulin is not directly applied in Category III or Category II immunocompromised cases. The WHO indicates that all these protocols achieve equivalent seroconversion and adequate protection.[40] Vaccine manufacturers must prove that their products achieve the appropriate seroconversion rates via the intradermal route in order to qualify for WHO approval in those regimens.

Table 3.1 WHO-Approved PEP Anti-Rabies Vaccine Regimens[50]

Intramuscular Route (0.5 – 1.0 ml at each site, depending on vaccine)	
5-dose ("Essen") Regimen	1 dose each on days: 0, 3, 7, 14, 28
4-dose ("Zagreb") Regimen (also referred to as "2-1-1")	1 dose at each of 2 sites on day 0; 1 dose each on days: 7, 21
Modified 4-dose Regimen‡ + RIG* *RIG must also be administered ‡May not be used on sick or immunocompromised persons§	1 dose each on days: 0, 3, 7, 14
Intradermal Route (0.1 ml at each of 2 sites)	
Updated Thai Red Cross Regimen	1 dose at each of 2 sites on days: 0, 3, 7, 28
PEP for patients who have already received Pre-Exposure Prophylaxis (PrEP)	
Intramuscular	1 dose each on days: 0, 3
Intradermal	1 dose at each of 4 sites on day 0

§Immunocompromised persons include any patient with an illness such as HIV, TB or cancer or other illnesses known to suppress the immune system; this also includes patients that have been on an immunosuppressive medication for any reason.

Post-exposure vaccination can now be offered via intradermal (ID) as well as the traditionally accepted intramuscular (IM) injection routes.[21] Due to the high density of antigen-presenting cells in human the dermis and epidermis, ID vaccination requires a substantially smaller volume to be effective. This has the potential for greatly reducing the cost of PEP. As a result, the WHO officially recommends the use of ID vaccines in all areas where PEP resources are in short supply. Each vaccine product that is to be used for ID use must be tested for safety and efficacy, and approved by the country. The universal use of ID vaccines has encountered some resistance, in part due to the fact that more advanced technique and therefore training is required to successfully administer a vaccine intradermally and achieve a visible skin bleb. If the bleb is not seen, the vaccine is not considered effectively administered and must be repeated.[60] As mentioned in Chapter 1, currently in China, ID rabies vaccine regimens are not approved for use. Reasons cited for this include that there is no shortage of vaccine production in the country; that clinicians and manufacturers are not interested since the demand is already met with the current production supply; and that the technical demands of administering the vaccine via this route are too high for medical staff.[33]

National Policy Adherence to WHO Guidelines

The WHO advocated phasing out all nerve-tissue vaccines by 2006 due to concerns over their efficacy and the incidence of serious adverse effects.[34] Many countries made serious efforts to increase production of cell-culture anti-rabies vaccines or increase importation of those products in order to adhere to these WHO guidelines. Currently, a few countries still routinely use nerve-tissue vaccines instead of cell-culture vaccines, including Pakistan and Myanmar[40] as well as Ethiopia.[35]

Currently two forms of rabies immunoglobulin are available and approved by the WHO for use in PEP: human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG).[36] HRIG is more expensive and has a limited availability; ERIG is less expensive and has wider availability, but an impeding factor to the use of ERIG is the perception that it is unsafe for use. As a heterologous biologic, ERIG has a slightly higher risk for inducing a hypersensitivity reaction as well as a slightly higher risk for causing serum sickness; it is also eliminated faster by the patient than HRIG. However despite common perceptions to the contrary, the risk of serum sickness with modern purified ERIG biologics is quite low.[37] A 2011 study demonstrated an overall adverse event rate of 1.5% with use of ERIG.[45] A 2007 study of over 70,000 patients in Bangkok found a 1.83% adverse event rate with ERIG compared with a 0.09% adverse event rate with HRIG, however the majority of all adverse events were very mild.[38] The same study also found 0.7% of patients receiving ERIG developed serum sickness compared to 0.006% of patients that received HRIG. Earlier forms of ERIG were available as an unpurified serum and were associated with higher risks of serum sickness and other adverse effects. Many healthcare workers perceive that ERIG causes severe and frequent adverse reactions and therefore choose not to use it,[39] whereas in reality its use has been documented with very few adverse reactions.[40]

According to the most recent WHO position paper on rabies vaccines published in January 2018, The WHO does not recommend the use of a skin-sensitivity test prior to the use of ERIG; however due to the reputation of ERIG as being associated with a high risk of serum sickness and other adverse reactions, this practice is popular in many countries where ERIG is still used. The WHO has stated that there is no evidence to support the use of the skin-sensitivity test.[41] Despite this, the skin-sensitivity test remains on the package insert for ERIG products including FAVIRAB and Equirab.[42,43] And one WHO website still contains a statement that says "A skin test must be performed prior to the administration of ERIG."[44] A study published in 2011 reported the sensitivity and specificity of the skin sensitivity test to predict an adverse event to be 41.9% and 73.9% respectively.[45] The WHO's most recent position paper on rabies advocates using whichever rabies immunoglobulin is available in all cases where it is indicated and being prepared to treat any adverse reactions that, though rare, may occur. The use of the skin-sensitivity test may be harmful to the successful administration of PEP. For example, in Sri Lanka, the ERIG skin sensitivity test is used and if positive, HRIG is used instead. HRIG is more costly, and in some cases this is a deterrent to the use of any rabies immunoglobulin product for fear of a potential reaction, placing patients at a higher risk of developing rabies infection.[28]

The WHO advocates wound washing as the first and one of the most essential steps in preventing rabies infection after exposure. The available literature on wound washing's effects on rabies transmission is quite old, but studies conducted in 1957 and 1962 on guinea pigs indicated that local treatment of wounds might prevent rabies transmission.[46,47] Wound washing should consist of 15 minutes under running water with soap (water alone can be used if no soap is available), followed by infiltration with chlorhexidine or iodine.[48] Most countries follow this guideline in their official policies despite lack of implementation at point-of-care; however Iran recommends wound washing for 5 minutes, which is not considered adequate by the WHO.[30]

Availability and Cost of Rabies Biologics

Rabies biologics, particularly rabies immunoglobulin (RIG) whether equine or human in origin, are not readily available throughout much of the world where rabies is endemic. Frequently, availability and supply are still an issue for vaccines as well as for RIG; this is especially true in remote areas due to transportation difficulties, costs and the challenges of maintaining the cold chain, required for all rabies biologics including vaccines and RIG.[34] The cost of post-exposure prophylaxis per patient varies widely from country to country depending on the sources of biologics, the frequency of the use of RIG plus vaccines compared to the use of vaccines alone, the route and regimen selected (ID versus IM).

The ID route regimen was introduced recently and is recommended by the WHO in areas where economics are of a particular concern due to the decreased volume of vaccine required. In countries where it is approved, it can provide dramatic cost savings. A 2016 study in Pakistan comparing the use of the Essen 5-dose IM regimen with the Thai Red Cross ID regimen found 80% cost savings when using the ID route instead of the IM routes due to the use of 1 vial per patient for the ID route compared with 5 vials per patient for the IM route.[40] In Sri Lanka, the cost of ID PEP per patient was found to be around $173 USD according to one study in 2016.[28] In Ethiopia, NTVs cost 5 to 23 USD per person, whereas cell culture vaccines, which are of limited access, cost 80 USD per person.[49] RIG is not available at all in Ethiopia. In 2018 in Vietnam, PEP was estimated to cost about 153 USD per person.[23] In Pakistan, where cell culture vaccines are of limited availability and where government hospitals are still routinely supplied nationally produced NTVs, the cost of PEP per patient was found to be 12 USD on average (when using cell culture vaccines); however it was lower (5.70 USD) when the Thai-Red Cross ID regimen was used, and higher (27.35 USD) when the Essen IM regimen was used.[40] Because vaccines are still all currently manufactured and produced in 0.5 ml or 1.0 ml vials, in order to realize the potential cost savings of ID regimens, multiple PEP patients must present within a 6 hour time period because once reconstituted, the vaccine must be refrigerated at 2 to 8 degrees Celsius and is only valid for 6 to 8 hours.[50] Studies are being conducted to evaluate the validity of rabies vaccines after days and even a week after reconstitution; however to date the WHO does not recommend the use of any rabies vaccine that has been reconstituted for more than 6-8 hours.[51]

In the Central African Republic, rabies PEP is only available at one facility in the whole country, which is located in Bangui, the capital of CAR.[29] RIG in this country is only available from certain NGOs and in rare exceptions. In Iran, RIG is only rarely available, so only vaccines are used even when RIG would be indicated in many cases.[30] In Cambodia, RIG is cost-prohibitive so is almost never used; the wholesale cost of single dose of ERIG is equivalent to 25-50% of a Cambodian farmer's monthly salary.[39]

Patient Compliance in Rabies PEP

Low patient compliance is often cited as a concern and a cause for rabies PEP treatment failures. Over the last few years, several studies on compliance have been carried out to investigate overall compliance rates in patients completing the PEP treatment course as well as comparing compliance rates between different regimens. A 2016 study in Pakistan found a 73% overall compliance rate[40]; a 2015 study in India found an overall PEP compliance rate of 76.5%.[52] Two additional studies in India investigated the difference in compliance rates between ID and IM regimens of PEP. A 2015 study found compliance for the IM route to be 62.8% and that of the ID route to be 70%, but that the difference was not statistically significant.[31] Another study completed in 2016 found the compliance among the 5-dose Essen IM route patients to be 60.0% and that of the 4-dose ID route to be 77.0% and that this difference was statistically significant.[53] A study published in 2018 of rabies PEP non-compliance risk factors in Cambodia not surprisingly found that lower income and increased distance from a clinic site were associated with higher rates of non-compliance.[54] This study additionally found that being male, being between 15 and 49 years, and requiring more than 3 visits to complete the PEP course were all associated with higher rates of non-compliance. Given that the costs associated with ID routes of PEP can be significantly lower and that patient compliance may be higher, ID regimens may become the more widely accepted method of administering PEP, particularly in areas where rabies is endemic and costs are a major concern.

Identifying Gaps in Rabies PEP in China

In order to investigate compliance with WHO and national rabies PEP guidelines in China, the China CDC designed a pilot project to develop an assessment tool for rabies PEP administration at several clinics designated as PEP centers. The first phase of the project encompassed an assessment of the clinic capabilities, infrastructure, human resources and available biologics. The second phase of the project tested a tool to evaluate the frequency of appropriate (in accordance with national guidelines) PEP administration. The project aimed to identify gaps in healthcare workers' (HCWs) knowledge and implementation of PEP in order to target these particular gaps in future training courses for personnel at rabies PEP facilities.

The site selected for the pilot study was Shuangfeng County located in Hunan Province in the southeast part of China (See Figure 3.1). In 2015, Hunan Province was identified as one of the provinces reporting relatively high numbers of human rabies cases. The population of Shuangfeng County is approximately 850,000; annually, Shuangfeng County administers 5,000 courses of post-exposure prophylaxis, or 588/100,000 persons (China CDC internal documents). Shuangfeng County has a Prefecture-level CDC clinic, which is a tertiary care hospital. Shuangfeng County has urban areas as well as semi-urban and rural areas, and it also has a rabies PEP clinic in each town within the county.

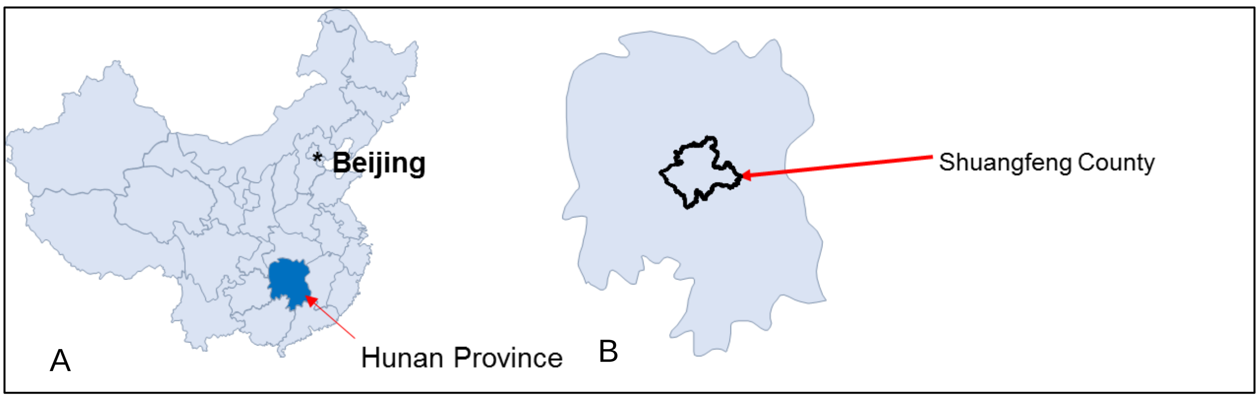

Figure 3.1 A Hunan Province, PRC**; B** Shuangfeng County within Hunan Province

The project consisted of two surveys. Survey 1 evaluated 16 PEP clinics in Shuangfeng County; the goal of Survey 1 was to identify capabilities of each clinic site regarding personnel, facilities and hours, biologics, equipment and information management. Included were the Prefecture-level CDC clinic (a tertiary care facility) and 15 township clinics. Survey 2 was conducted at seven clinic sites randomly selected from the first group, following patients presenting for bite or scratch wounds from admission to discharge. A total of 196 patients' experiences were observed by Hunan Provincial level CDC officials over the period of a few weeks. The healthcare workers at the various sites observed were unaware of the project topic or goals. The observations were recorded electronically using iPads into a survey questionnaire that was designed by staff at the China CDC in Beijing.

I was assigned to this project for the main component of my field experience at the China CDC. When I arrived in summer 2016, the project had already been initiated, and the results of Survey 1 had been collected but not yet analyzed (See Figure 3.2). Survey 2 was still in the design phase when I arrived; this is the point at which I became involved in the project (see Chapter 2). As part of the project, China CDC investigators were scheduled to travel to Shuangfeng County, and I was supposed to travel with them. However, due to serious flooding that occurred throughout China, particularly in Hunan Province, during much of summer 2016, roads were closed and destroyed, and all non-emergency travel was cancelled by the China CDC. As a result, I was unable to view the clinic sites or the region of the country in which the survey was conducted. Although this hampered my participation in conducting and understanding the project, I participated to the fullest extent possible. It was also a lesson in an important aspect of working in global public health – unforeseen circumstances such as weather events can disrupt studies.

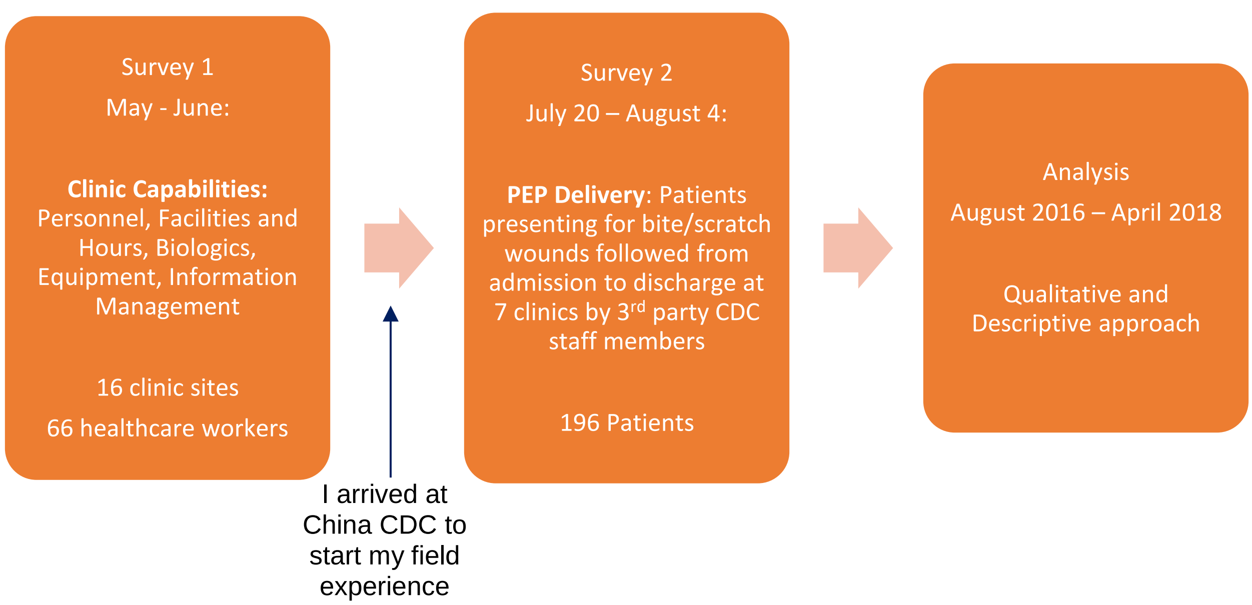

Figure 3.2 Pilot Project Design and Timeline

Results of Survey 1

Clinic General Information

The first component of Survey 1 asked a series of questions regarding general information about the clinics such as whether or not they were licensed to administer rabies PEP, what hours they were open, what information appeared on their signage, whether they were a stand-alone vaccine clinic or part of a larger healthcare facility and how spaces on the site were designated to various treatments. The 16 clinics for Survey 1 were randomly selected from Shuangfeng County. All 16 clinics were licensed to practice and administer rabies PEP. Thirteen of the 16 clinics were open 24/7, and the remaining 3 clinics were open during normal business hours but on call 24/7; 2 of these 3 clinics had their phone numbers posted prominently for the public to view in case of emergency. None of the clinics had a specifically designated outpatient service for rabies PEP. Twelve of the 16 clinics were operated under a vaccination outpatient service and the remaining 4 were affiliated with a hospital or general clinic setting. Nine of the clinics were equipped with a specifically designated area for wound care.

Human Resources

A total of 66 healthcare workers (HCWs) staffed the 16 clinics surveyed. The number of healthcare workers per clinic site ranged from 1 to 7, with a median and an average of 4. The survey asked for information regarding basic demographics of the personnel including gender and age (See Figure 3.3). The majority of HCWs were found to be female (53%) and the age group over 40 years old was the largest (47%).

The survey also identified education level, type of medical training as well as occupation or role within the clinic of each healthcare worker. None of the HCWs at any of the 16 sites surveyed had obtained graduate education; the largest group had received a secondary education (47%); followed by 45.5% that had attended vocational college (See Figure 3.4). Personnel were also surveyed regarding their medical training. In China, medical training to become a doctor, or a licensed medical practitioner, consists of 5 years after secondary education is completed. Half of the clinics in the survey had at least one licensed medical practitioner on staff (See Figure 3.4). Licensed assistant medical practitioners in China attend school for 3 years to become an

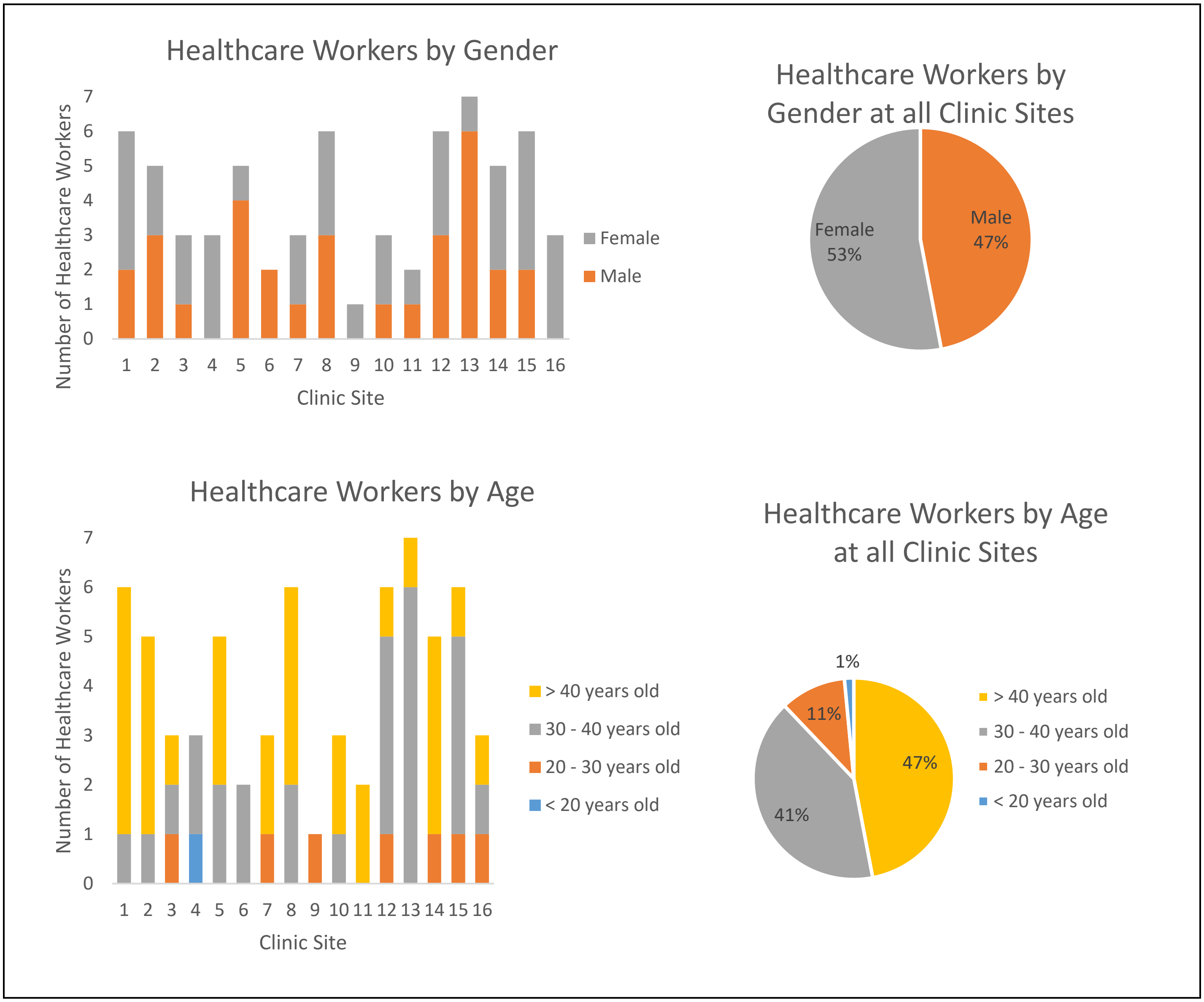

Figure 3.3 Healthcare Worker Demographics of 16 Clinic Sites surveyed in Shuangfeng County: Age and Gender

assistant physician. Of the 8 clinics that did not have a licensed medical practitioner on staff, four had a licensed assistant medical practitioner. Four clinics had neither a licensed medical practitioner nor a licensed assistant medical practitioner on site.

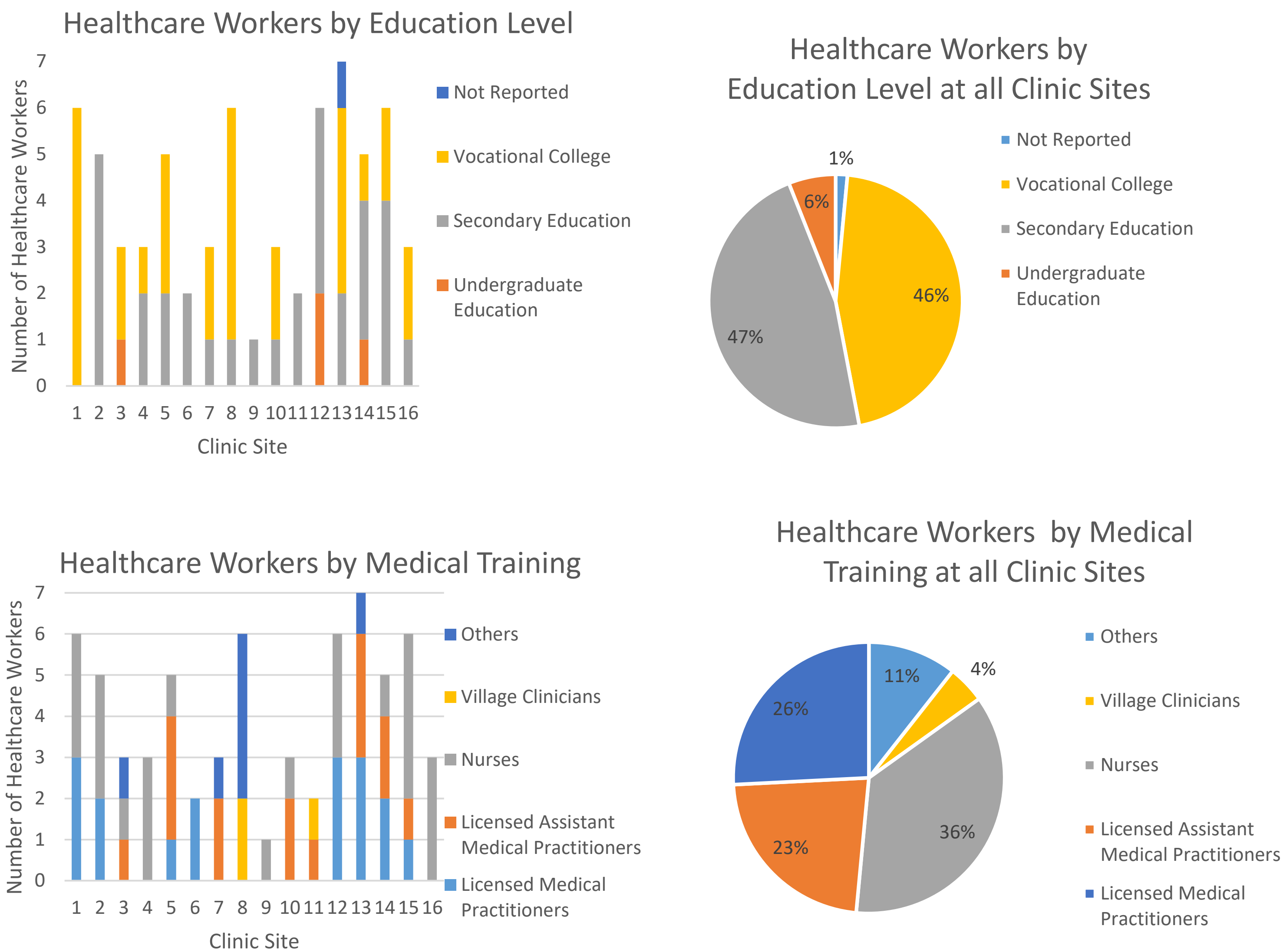

Figure 3.4 Healthcare Worker Demographics of 16 Clinic Sites surveyed in Shuangfeng County**:** Education level and Medical Training

Nurses comprised the largest portion of HCWs. Two facilities had only nurses. One clinic had no licensed medical practitioners, licensed assistant medical practitioners or nurses, but instead had village clinicians. Four percent of the HCWs fell into the medical training category of village clinicians. Village clinicians are a significant component of rural China's healthcare system; in areas with no or limited physicians, they are responsible for providing primary care. The system of village clinicians was initiated in the 1950s by the central government of the PRC and has grown tremendously since then, being managed and overseen on the local level.[55] Village clinicians complete short-term training specific focused on providing basic primary medical care to a community. The training lasts three, six or twelve months, and then the village clinician must pass an examination before returning to practice medicine in the home community. Within the clinics, personnel are allocated to positions in public healthcare, general practice, surgery or other; no HCWs surveyed work in specific disease control roles (see Figure 3.5). All the HCWs at the 16 clinic sites surveyed reported that they had received training in rabies PEP from a health department at or above the county level. All but one HCW reported training in emergency management of vaccine reactions.

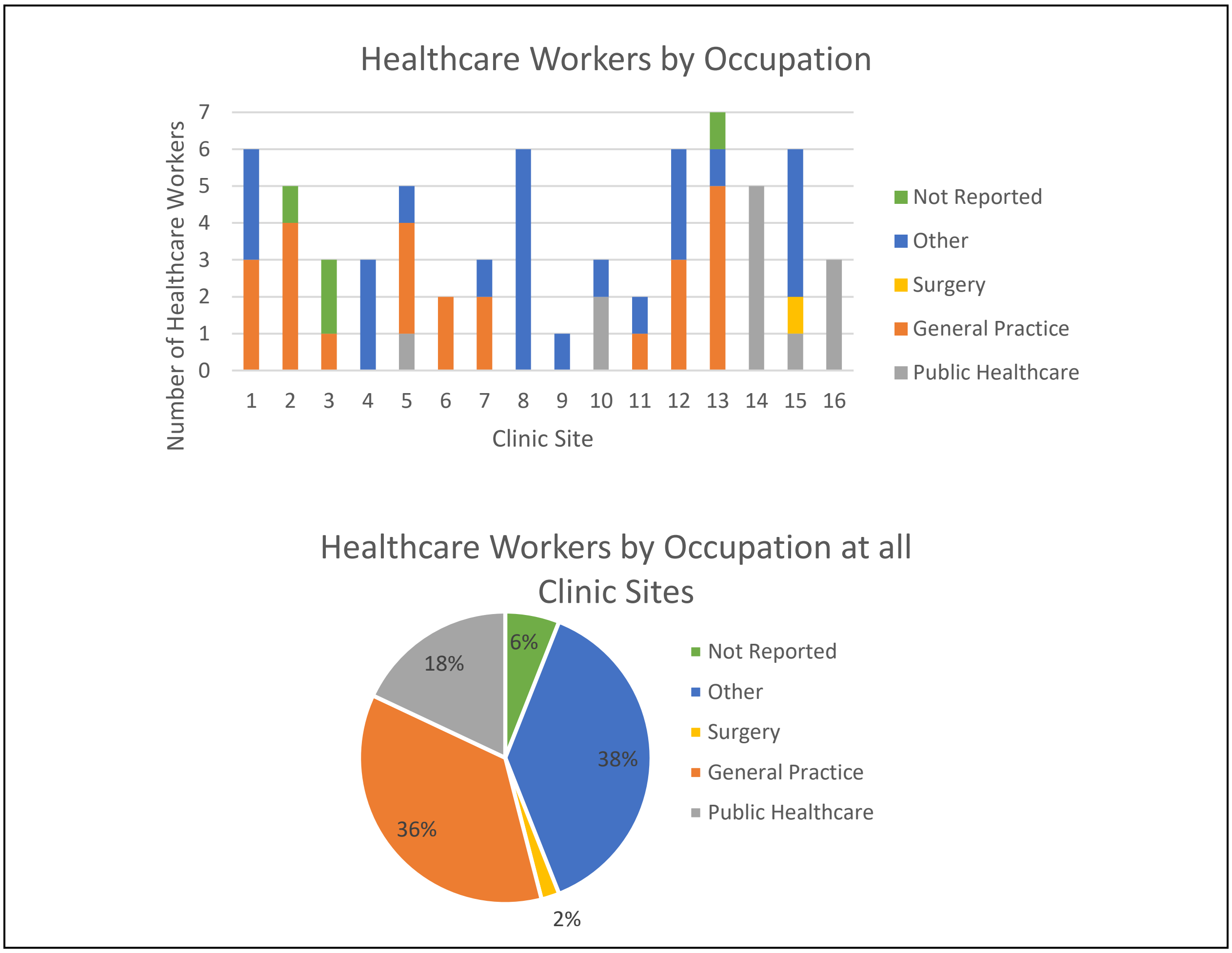

Figure 3.5 Healthcare Worker Demographics of 16 Clinic Sites surveyed in Shuangfeng County**:** Occupation

Biologics

The first survey assessed the 16 clinics' supply of rabies biologics including anti-rabies vaccines in stock, the protocols used to administer those vaccines as well as rabies immunoglobulin, and the price charged per person for these biologics. All 16 clinics followed the Essen 5-dose IM vaccination protocol. The price charged per person for the PEP vaccine series ranged from 290 RMB (45.79 USD) to 375 RMB (59.21 USD) at an average of 327 RMB (51.69 USD). Clinics varied greatly in terms of how much vaccine was kept in stock, ranging from 0 doses to 102 doses, with a median of 19.5 doses. Only one of the 16 clinics surveyed (the tertiary hospital) had RIG available; this clinic had HRIG, at a price of 250 RMB/vial (39.47 USD). HRIG is dosed according to IU per kilograms of body weight, so the survey questioned whether clinics had scales to weigh patients; 9/16 clinics had capabilities to weigh patients. All 16 clinics had refrigerators to store the vaccines; 12 of the 16 clinics monitored their vaccine storage refrigerators with a thermometer, and the products were stored at a range from 4 to 9 degrees Celsius. WHO recommends vaccines be stored at an ideal temperature range of 2 to 8 degrees C.[56]

Wound Cleaning Capabilities

All 16 clinics surveyed reported that they did not have the proper wound cleaning equipment for administering professional PEP. However, when asked about the specifics, many clinics did have the necessary components of soap and wound disinfectants, so there is possibly a comprehension gap among HCWs in terms of what constitutes professional rabies PEP wound cleaning. Fourteen of the clinics surveyed had a soap product with which to clean the wound, and in all cases this was bar soap. All 16 clinics had a disinfectant product with which to disinfect the wound after washing, the most common one being iodine. The WHO approves the use of 70% ethanol or iodine as wound disinfectants in the case of rabies exposures.[57]

Equipment and Drugs for Managing Vaccine Reactions

Vaccine reactions, although not common, do occur in response to administration of all vaccines including rabies vaccines. Reactions may vary from mild erythema (redness) and pruritus (itchiness) at the injection site to a life-threatening anaphylaxis.

Staff at China CDC wanted to assess rabies PEP clinics' abilities to treat a severe vaccine reaction should one occur following PEP administration. Additionally, perceived issues with safety are sometimes an impedance to patients seeking and to healthcare workers providing rabies PEP, so preparedness to handle situations such as vaccine reactions is essential to combat these perceptions. Some of the clinics did not report their emergency capabilities on this section of the survey. Figure 3.6 shows the number of clinics that have and do not have a variety of emergency medical equipment. Several of the clinics lacked some of the basic medical equipment required to manage an anaphylactic event. Figure 3.7 shows the proportion of clinics that have and do not have a variety of emergency medical drugs to respond to a vaccine reaction. Almost all the clinics had epinephrine (15/16) and dexamethasone (13/16) to use in case of severe vaccine reaction. One clinic had neither epinephrine nor dexamethasone despite the fact that this clinic did have licensed medical practitioners on staff. (The use of corticosteroids such as dexamethasone is not preferred in the event of a vaccine reaction following rabies PEP administration because the suppression of the immune system can interfere with the efficacy of the vaccine.) Other emergency medical drugs were variably available to clinics. Twelve of the clinics had emergency generators or other solutions to deal with temporary electrical power outages.

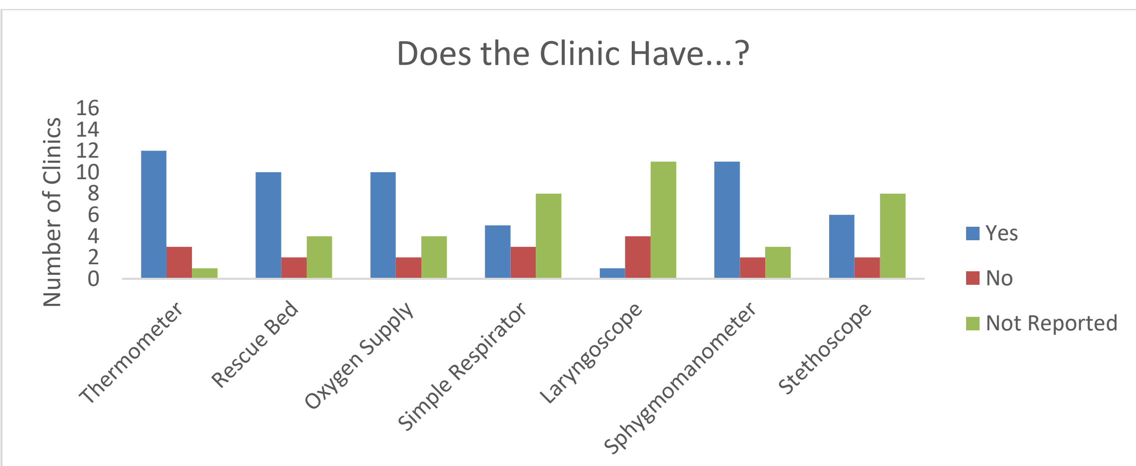

Figure 3.6 Number of Rabies PEP Clinics having Emergency Medical Equipment

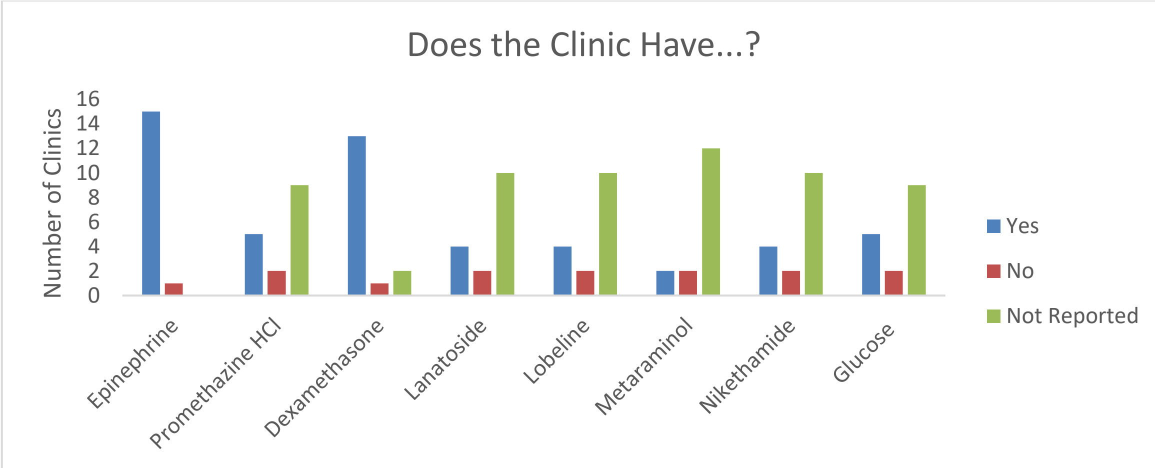

Figure 3.7 Number of Rabies PEP Clinics Having Emergency Medical Drugs

Information Management

Record keeping and information management was the final area of clinic site capabilities that were assessed in Survey 1. Ten of the 16 clinics surveyed use and store informed consent forms for their patients. All 16 clinics report that they record relevant information for bite/scratch victims regarding the wound, exposure source, and patient information. All clinics record this information electronically.

Results of Survey 2

Design of Survey 2

Survey 2 was conducted at 7 clinic sites randomly selected from the original 16 clinic sites included in Survey 1. The sites included the county-level clinic of Shuangfeng County (the one clinic that had RIG available on site) as well as six other clinic sites that were distributed around the county in urban, semi-urban and rural sites. The questionnaire was conducted by local CDC staff who visited the clinics and observed any patients presenting for bite or scratch wounds who agreed to be included in the study. Serious flooding in the area prevented China CDC staff members from traveling from Beijing to the site. The schedule of the data collection also had to be altered and postponed due to the flooding as some of the clinics could not be accessed. At the end of the data collection window, which spanned from July 20, 2016 to August 4, 2016, only 6 of the 7 selected clinics had seen patients that qualified as bite/scratch wound victims and therefore potential rabies exposures. A total of 196 patients were included in the data, which followed these patients with bite/scratch wounds from intake to discharge. The number of patients at each clinic site ranged from 0 to 111 (Figure 3.8). Previous data on normal numbers of bite/scratch wound patients presenting to these clinics or in this area is not available for comparison. Consequently, it is not possible to ascertain if this is a typical sampling of this area.

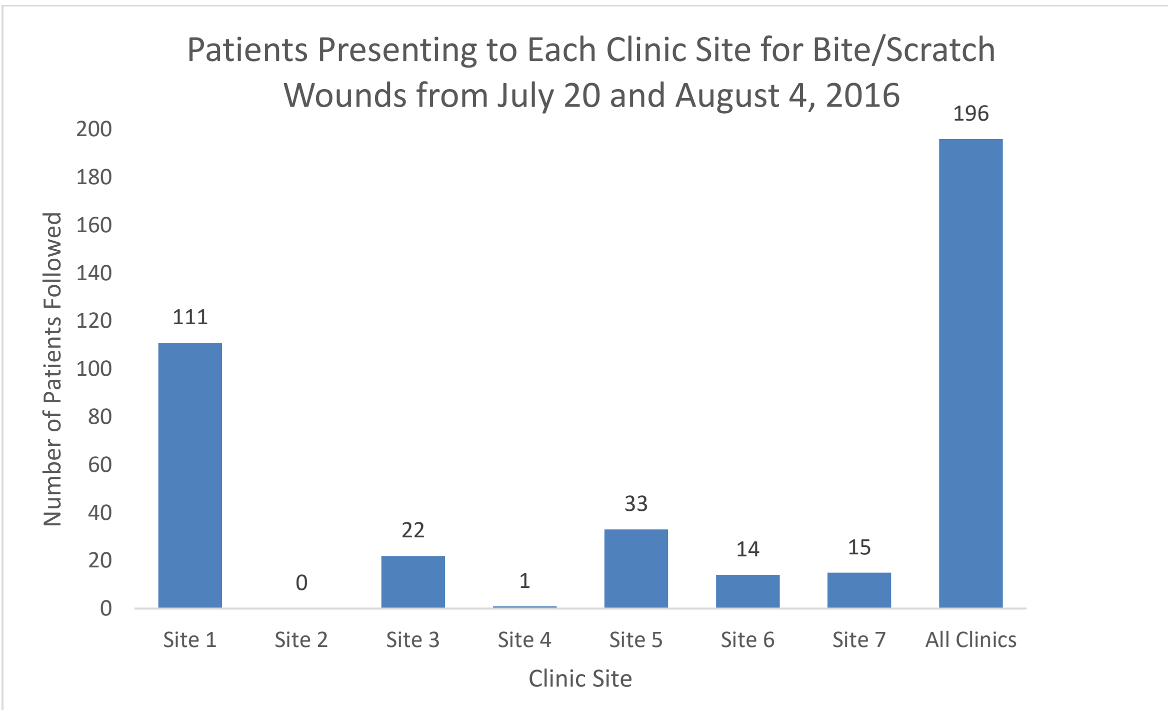

Figure 3.8 Number of Patients Followed at Each Clinic Site for Bite/Scratch Wounds.

Survey 2 was composed of four sections to evaluate the exposure, history-taking by the HCW and the treatment administered. Additionally, the initial survey questions collected information on the patient's age and sex to evaluate the basic demographics of persons presenting for possible rabies exposures to compare these to previously published demographics for rabies PEP in China and other places. The first section ("Section 1: Intake Inquiry") evaluated the exposure source, collecting information about the animal species, ownership and vaccination status. Section 1 also evaluated the wound, collecting information about location, depth and time of occurrence, as well as what the patient had done to treat the wound at home. This section then asked for the healthcare worker’s categorization of exposure, and the patient’s medical history regarding previous rabies vaccination, known immunocompromised conditions or use of immunosuppressive drugs and drug or vaccine allergies.

The remaining three sections of the survey evaluated the three phases of PEP that can be administered after potential rabies exposures. The second section of the survey (“Section 2: Wound Care”) evaluated the specifics of the wound washing that occurred at the clinic, including the source of water, the duration of the washing, the use of soap and disinfectant. The third section of the survey (“Section 3: Anti-Rabies Vaccines”) targeted the use of post-exposure prophylaxis anti-rabies vaccines. It asked questions regarding whether or not vaccines were administered, which regimen was initiated, and whether or not the product was within its validity period. Section 3 also asked some very specific questions regarding injection technique that were added by the Hunan Provincial level CDC staff members who wanted to investigate whether or not healthcare workers in the area were adequately trained on administering vaccines, including anti-rabies vaccines. The final section of the survey (Section 4: Rabies Immunoglobulin) questioned the use of post-exposure prophylaxis rabies immunoglobulin including the administration techniques and dose administered to evaluate if a correct dose was given, since RIG is administered on a body-weight basis.

Section 1 Results: Intake Inquiry

Of the 196 persons presenting to the 6 clinics during the survey period, 108 were male (55%) and 88 were female (45%). The age of the patients ranged from < 1 year old to 89 years old, with 44% of persons being aged 20 years or younger and 30.6% of persons being males aged 20 years or younger (Figure 3.9). The median age for all patients was 31 (quartiles: 9.8 – 51.3) years. On average, males were found to be significantly younger than females. The median age of exposed males was 15 years and of exposed females was 41.5 years.

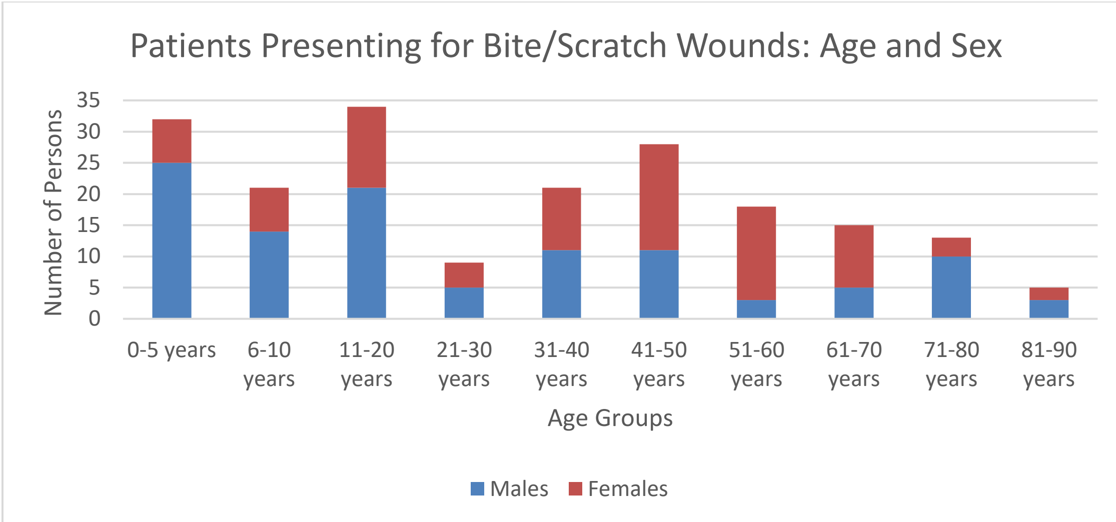

Figure 3.9 Demographics of Patients Presenting for Bite/Scratch Wounds: Age and Sex

In all cases, the HCW inquired about the bite/scratch wound source. The majority (71%) of wounds were caused by dogs; cats were the next most frequent source followed by rats (Table 3.2). In one case, the source of the wound was reported to be unknown (in this case, the patient was a 10 year old child); and in one case, the wound was reported to be caused by a human. Domestic (owned) dog bites comprised 48% of all wound sources and domestic (owned) cat bites comprised 14% of all wound sources. 67 of the 94 domestic dogs (71%) were reported to be owned by the bite/scratch wound victim's own family, while only 27 dogs (29%) were owned by another family. Out of the 122 cases caused by domestic dogs and cats, in only 3 cases did the HCW on the case inquire about the biting animal's rabies vaccination status; of these three, only one animal was reported to be vaccinated.

Table 3.2 Wound Source: Species, Ownership, Vaccination Status (when applicable)

	Number	*% of Total*	*% of Domestic animals*
Dogs	**140**	**71.4**	
Owned by patient's family	67	34.2	
Owned by someone else	27	13.8	
Unknown	15	7.7	
Not inquired	31	15.8	
Cats	**38**	**19.4**	
Owned by patient's family	26	13.3	
Owned by someone else	2	1.0	
Unknown	2	1.0	
Not inquired	8	4.1	
Domestic animals (owned dogs and cats)	122	62.2	
Vaccinated	1		0.8
Unvaccinated	2		1.6
Not inquired	119		97.5
Rats	**16**	**8.2**	
Human	**1**	**0.5**	
Unknown	**1**	**0.5**	

In all 196 cases, the HCW asked about the time of the exposure in year, month, day, hour format. Six surveys contained illogical information about the exposure time, so these data entries were excluded from this analysis. The survey also contained an entry time; this data point was compared to the reported exposure time in order to approximate a time from the wound occurrence to the patient's presentation at the clinic. Of the remaining 190 cases, the average time elapsed from wound exposure to presentation was 6.9 hours. The average time elapsed did not vary greatly by clinic site. The minimum time elapsed was 0 hours, the maximum time elapsed was 87 hours, and the median for all patients was 3 hours. Only 10 (5%) of the potential exposures occurred at an interval of 24 hours or more prior to presentation.

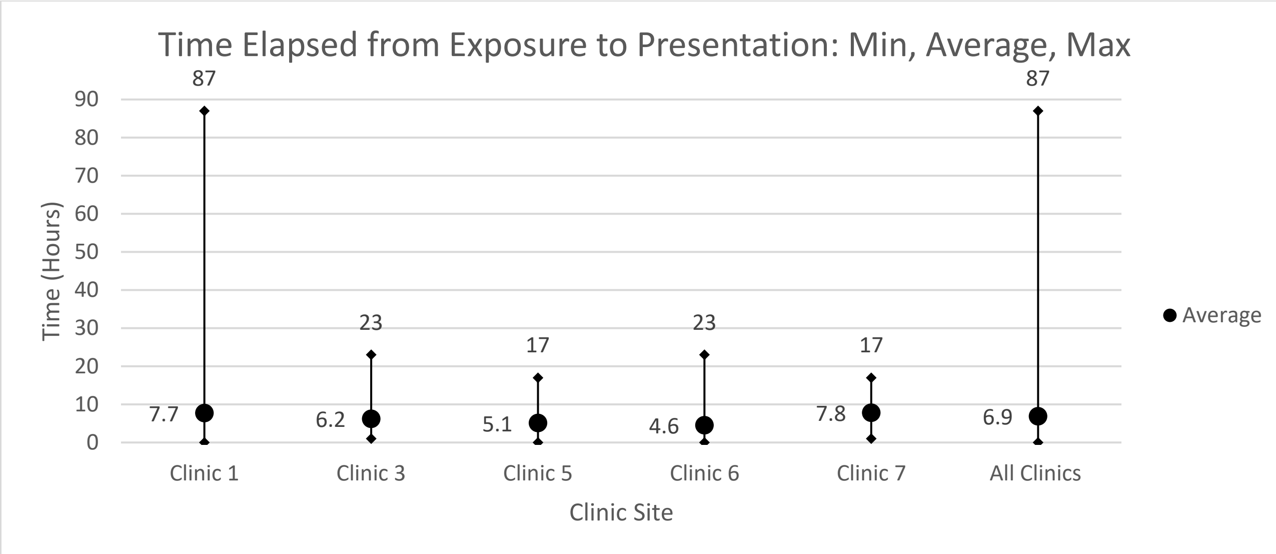

Figure 3.10 Time Elapsed from Wound Occurrence to Presentation at Rabies PEP Clinic

The anatomic location of the wound was recorded in all cases – in four of the cases, multiple sites for the wounds were noted. The lower limbs were the most common location for bite/scratch wounds to occur (64.3% of patients had a wound on the lower limbs) followed by the hands (26.6% of patients had a wound on the hand) (Table 3.3).

Table 3.3 Anatomic Location of Patients' Bite/Scratch Wounds

Wound Location	**Number**	**% of Patients with a Wound in this Location**
Head and Face	1	0.5
Neck	1	0.5
Body	8	4.1
Upper Limbs	12	6.1
Hands	52	26.5
Lower Limbs	126	64.3
Multiple Locations	4	2.0

In order to accurately categorize the exposure as Category I, II or III per the WHO guidelines (Table 1.1), the survey collected information about the method of exposure. The results of this information are contained in Table 3.4. The most common route of exposure was a penetrating skin bite or scratch, constituting 44.4% of all the cases. Based on the WHO categorization scheme of exposure types, 2.5% of the patients, or 5 persons, experienced a Category I exposure to rabies; 52.6%, or 103 persons, experienced a Category II exposure to rabies; and 44.9%, or 88 persons, experienced a Category III exposure to rabies.

Table 3.4 Exposure Method and WHO Category of Rabies Exposure

WHO Exposure Category	Exposure Method	Number of Patients	%	Number of Patients	%
I	Touching/feeding animals	0	0	5	2.5
	Lick on intact skin	4	2		
	“Other”	1	0.5		
II	Nibbling at exposed skin	35	17.9	103	52.6
	Minor scratch or abrasion without bleeding	68	34.7		
III	Penetrating skin bite(s) or scratch(es)	87	44.4	88	44.9
	Lick on area of broken skin	1	0.5		
	Open wound or mucous membrane contamination	0	0		

In all Category II and Category III rabies exposures, the wound site must be washed with soap and water repeatedly for a duration of 15 minutes and ideally scrubbed with a disinfectant solution after it has been washed. Out of a total of 191 Category II and Category III exposure cases (according to the WHO categorization), the HCW asked the patient whether or not the wound had been washed prior to presentation in 163 cases (85.3%). In most of these cases (146, or 89.6%), the HCW asked additional details about the wound washing such as what materials were used and the duration of the wound washing. These results are displayed in Table 3.5. Only a total of 17 patients (9% of Category II and III patients) reported washing their wounds at home for a duration greater than or equal to 15 minutes; of those, only 6 (3.1% of

Category II and III patients) used soap and water repeatedly according to the guidelines. Only 31 (16.2%) of Category II and III exposed persons were asked about their use of a wound disinfectant prior to presentation. Of those 31 persons, 8 used iodine, 4 used alcohol, 1 used hydrogen peroxide, 2 did not report the product used, and 16 had not used a disinfecting product.

Table 3.5 Wound Care Prior to Presentation in Category II and III Exposed Persons

No. of patients (%)	*Method of wound washing*	*Wash period duration ≥ 15 minutes (%)*
39 (20)	Washed with Water alone	7 (4)
21 (11)	Washed with Soap once	4 (2)
15 (8)	Washed with Soap and water, repeatedly	**6 (3)**
71 (37)	Did not wash prior to presentation	N/A
17 (9)	HCW did not ask details	N/A
28 (15)	HCW did not ask about wound washing at all	N/A
191	Total WHO Category II and III patients	**17 (9)**

At intake, the HCW assigned an exposure category to each patient. This exposure categorization was then compared to the WHO exposure categorization determined by the survey responses regarding exposure method, depicted in Table 3.4. For each patient, we compared the HCW's categorization to the WHO categorization. These comparisons are displayed in Table 3.6. Of the WHO Category I exposures, 3/5 (60%) were categorized as Category II by the healthcare worker. One-fourth (49) of the total 196 exposures were categorized differently by the HCW when compared with the WHO standard scheme. 23.5% of patients were under-categorized. 1.5% of patients were over-categorized. Category II patients were most likely to be categorized in the same way by WHO and HCW. Only 58% of the WHO Category III patients were categorized correctly; 3/88 (3.4%) of Category III exposures were categorized as Category I exposures. No WHO Category I or Category II exposures were classified as a Category III exposure by the HCW. Categorization was also compared between the various clinic sites; the percent of patients that were categorized according to the WHO classification scheme at a given clinic site ranged from 27% to 100% (Table 3.7). Only two of the clinics assigned Category III exposures to patients during the study period indicating a trend for HCWs to under-categorize patients.

Table 3.6 Exposure Categorization: WHO compared to Healthcare Workers

WHO Category	# Patients	Exposure Category applied by HCW	# Patients	%
I	5	I	2	40
		II	3	60
		III	0	0
II	103	I	9	8.7
		II	94	91.3
		III	0	0
III	88	I	3	3.4
		II	34	38.6
		III	51	58

Table 3.7 HCW Exposure Categorization in Accordance with WHO by Clinic Site

Clinic Site	*Classified According to WHO*	*Classified differently from WHO*	*% Classified According to WHO*
Clinic 1	106	5	95
Clinic 3	6	16	27
Clinic 4	1	0	100
Clinic 5	17	16	52
Clinic 6	13	1	93
Clinic 7	4	11	27
Total	147	49	75

The survey also assessed the relevant medical history questions that the HCW could ask the patient. In 114 (58%) cases, the HCW asked about the patient's rabies vaccination status. Of these patients, 89 (78%) had never been vaccinated against rabies previously, and 6 (5%) had been vaccinated fully and reported the date of their vaccination. One of these patients was designated a Category III exposure but would not require RIG according to WHO guidelines. The other 5 were Category II exposures, and so would require a PEP regimen for persons that have received PrEP (See Table 3.1).

In 18 cases (9.2%), the patient was asked about possible immunocompromised status due to immune diseases such as HIV/AIDS, TB, or cancer. Five of these 18 patients reported an immunocompromised status. All 5 of these patients were considered to be Category II exposures by the HCW; all 5 received anti-rabies vaccines; however none received RIG despite this being the WHO recommendation. Twenty-six patients (13%) were asked about any history of drug/vaccine allergies; 2 reported a history. No patients were asked about the use of immunosuppressive drugs such as corticosteroids.

Section 2 Results: Wound Care

Thorough wound washing with soap and water repeatedly for 15 minutes followed by cleaning the wound with an appropriate wound disinfectant is the ideal way to initiate treatment for all Category II and Category III exposures. The WHO recommends that this occur as soon as possible after exposure, and further recommends that all wounds should be treated as a fresh wound no matter how long after exposure they present. Only one patient's wound was washed by a HCW in the study; in 153 cases, the patient or the person accompanying the patient was instructed to wash the wounds themselves with the available facilities (Figure 3.11). In all 154 cases that the wound washing was observed and included in the survey, running water from a tap with pressure was used and soap was also used; however, in only 96 (62.3%) of these cases did the wound washing duration last greater than or equal to the full required 15 minutes. In 98 (63.6%) of the 154 cases, a wound disinfectant was used. In all Category II and III exposures – using either the WHO or the HCW's categorization scheme, approximately one half of the patients had their wounds appropriately washed (Table 3.8).

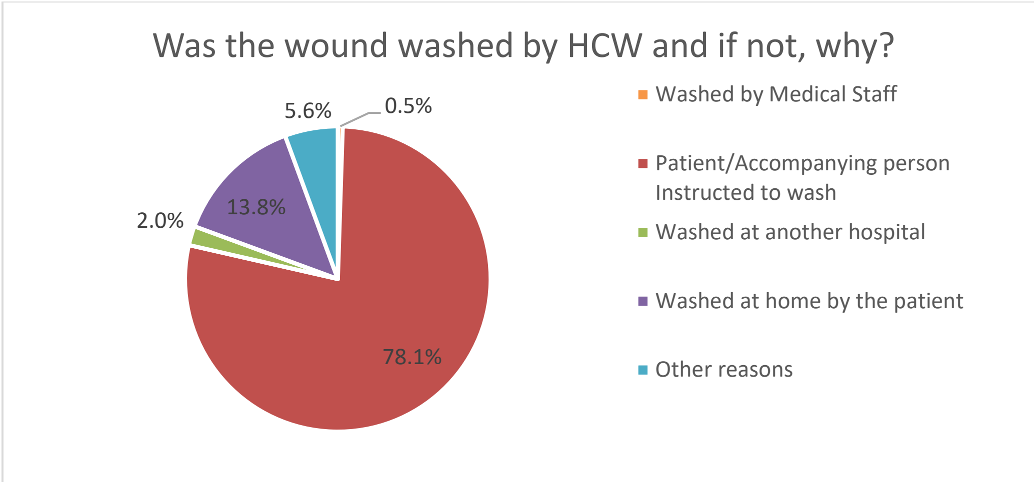

Figure 3.11 Was the wound washed by the Healthcare Worker; if not, why?

Table 3.8 Was the wound washed appropriately in Category II and III Exposures?

		# of patients whose wound was washed (%)	*Appropriately washed (%)*
WHO Category II and III (191 patients)	by HCW:	1 (0.5)	0 (0)
	by patient/accompanying person:	151 (79)	95 (49.7)
	by another hospital:	4 (2)	?
	at home:	26 (13.5)	4 (2.1)
	Not washed:	9 (5)	N/A
			Total: 99/191 = 51.8%
HCW Category II and III (182 patients)	by HCW:	1 (0.5)	0 (0)
	by patient/accompanying person:	140 (77)	85 (47)
	by another hospital:	4 (2)	?
	at home:	27 (15)	6 (3)
	Not washed:	10 (5.5)	N/A
			Total: 91/182 = 50%

Section 3 Results: Anti-Rabies Vaccines

According to WHO and national guidelines, all patients with a Category II or III exposure to rabies should receive one of the approved regimens of anti-rabies vaccines beginning on the day they present. Section 3 of Survey 2 evaluated if the patient received anti-rabies vaccines and if not, why; which regimen was initiated. It also evaluated whether the first dose was applied in an appropriate anatomical location; whether the vaccine was expired; whether appropriate record-keeping was maintained. Additionally, Section 3 included a series of questions about sterility and injection technique which were added by the Hunan Provincial level CDC staff members and are beyond the scope of this report.

The survey results for the use of anti-rabies vaccine show a very high rate of the use of anti-rabies vaccines. 195 of 196 patients received the first dose of an ARV series during the visit to the clinic site (Table 3.9). Even all the Category I exposures (as determined by the WHO classification scheme or by the healthcare worker's scheme) received the first dose of anti-rabies vaccine despite this not being the recommendation of the WHO or national guidelines. In all uses of vaccine, the 5-dose Essen regime was initiated via administration into the deltoid muscle. This is the approved WHO site for administration of the vaccine, with the exception that in small children it may be injected into the anterolateral thigh muscle. In two instances, the vaccines administered were past the expiration date. The reason for this was not asked by the survey. In 124 (64%) cases in which vaccine was administered, the HCW wrote the appropriate information on the record; in 69 (35%) cases, the healthcare worker did not; and in 2 (1%) cases, there was no record. The only patient not receiving anti-rabies vaccine was a Category III exposure (classified as such both by the WHO and by the HCW). The patient was referred to another facility for treatment.

Table 3.9 Patients receiving ARV by Exposure Category (WHO and HCW)

Exposure Type	*# Total Patients*	*# Patients receiving ARV*	*# Patients not receiving ARV (%)*
WHO Category I	5	5	0 (0)
WHO Category II	103	103	0 (0)
WHO Category III	88	87	1 (1.1)
HCW Category I	14	14	0 (0)
HCW Category II	131	131	0 (0)
HCW Category III	51	50	1 (2.0)

Section 4 Results: Rabies Immunoglobulin

According to the WHO and national guidelines, all persons with a Category III rabies exposure should receive RIG. Additionally, both the WHO and national guidelines also recommend the use of RIG in any Category II exposed patient who may be immunosuppressed due to a pre-existing condition or the use of immunosuppressive medications. In the study population, a total of 38 persons received RIG. All of these persons were classified as Category III exposures by both the WHO scheme and the HCW. Out of the 51 persons determined to have a Category III exposure by the HCW, only 38 (75%) received RIG; of the 13 persons categorized by an HCW as Category III who did not receive RIG, only one had previously been vaccinated for rabies, so did not require RIG. Additionally, of the 5 persons that were determined to be likely immunocompromised due to pre-existing conditions and that were determined to have a Category III exposure by the HCW, zero received RIG despite the WHO and national guideline recommendations. There were however 87 previously unvaccinated Category III exposures and 2 immunocompromised Category II exposures. A total of 89 persons should have received RIG; of these, 38 (43%) did.

Table 3.10 Patients Receiving RIG by Exposure Category (WHO and HCW)

Exposure Category	*# Total Patients*	*# Receiving RIG*	*# NOT Receiving RIG*	*% Receiving RIG that should*
WHO Category I	5	0	5	-
WHO Category II	103	0	103	-
(II – Immunocompetent)	(101)	(0)	(101)	-
(II – Immunocompromised)	(2)	(0)	**(2)**	0%
WHO Category III	88	38	**50***	43%
HCW Category I	14	0	14	-
HCW Category II	131	0	131	-
(II – Immunocompetent)	(126)	(0)	(126)	-
(II – Immunocompromised)	(5)	(0)	**(5)**	0%
HCW Category III	51	38	**13***	75%

*1 of these Category III patients reported previous rabies vaccination and so according to the WHO and national guidelines did not require RIG administration.

Section 3 also inquired about the reason cited for not administering RIG in each case. Of the 14 cases categorized by the HCW as a Category I exposure, the HCW did not recommend RIG administration in 2 cases; the patient did not consider it to be necessary in 10/14 cases; and in 2/14 cases, the lack of RIG at the clinic was cited as the reason it was not administered. According to WHO and national guidelines, the reason cited in all 14 cases should have been that the HCW did not recommend RIG administration since the HCW had categorized it as a Category I exposure.

Of the 131 cases categorized by the HCW as a Category II exposure, the reasons that RIG was not administered were cited as follows: the HCW did not recommend RIG administration in 106 (81%) cases (of which 2 were reported to be immunocompromised and therefore should have been recommended to receive RIG); RIG was considered to be cost-prohibitive in 2 (1.5%) cases (of which 1 was reported to be immunocompromised); the patient considered the administration of RIG to be unnecessary in 10 (7.6%) cases; the clinic site did not have RIG available to administer in 13 (9.9%) cases (of which 2 were reported to be immunocompromised). According to WHO and national guidelines, the 5 patients classified as having Category II exposure by the HCW and being immunocompromised should have been recommended to receive RIG; in the other 126 cases, the reason cited should have been that the HCW did not recommend RIG administration due to the fact that the HCW had categorized the wound as a Category II exposure.

Of the 13 cases categorized by the HCW as a Category III exposure that did not receive RIG, the reasons that RIG was not administered were cited as follows: the HCW did not recommend its administration in 7 (53.8%) cases; the patient considered RIG administration to be unnecessary in 5 (38.5%) cases; the clinic referred the patient to the county level hospital to receive RIG in 1 case (7.7%). RIG administration should have been recommended by the HCW in all of these cases due to the high level of risk. With the exception of the one case that was referred, these cases all occurred at the one site that did have RIG in stock.

Human rabies immunoglobulin should be administered directly in the wound site at a weight-dependent dose of 20 IU/kg. Any remaining volume that does not fit in the wound site should be injected into a muscle site away from the wound.[58] The patient's bodyweight was measured in 24 of the 38 cases (63%) that received RIG; according to the weight reported in the survey and the number of 200 IU vials reported to be used for the patient, the patient was under dosed in 11 of these 24 cases (45.8%). In total, 89 patients should have been administered 20 IU/kg RIG upon presentation due to a Category III exposure without previous vaccination or a Category II exposure with immunocompromised status. Of these, 14.6% were given RIG at a dose sufficient for their measured body weight.

Discussion

This study highlights some significant gaps in the delivery of rabies PEP in Hunan Province, China. As discussed in Chapter 1, China delivers an estimated 12-15 million doses of PEP each year.[6] However, failures of PEP are seen; studies have found that around 12 to 15% of patients who died from rabies did seek treatment at a medical clinic after exposure.[15, 16, 22] This study sought to identify gaps in the process of PEP delivery that lead to failures and ultimately deaths in patients seeking PEP. Gaps were identified in clinics' preparedness to treat fully and appropriately as well as handle potential adverse events associated with PEP. Gaps were also identified in the history-taking process of HCWs, particularly in regards to immunocompromised status of patients and wound washing. HCWs also demonstrated an inability to classify exposures in accordance with WHO guidelines despite training. Other issues were discovered in the inadequacies of wound washing that occurred on clinic sites, in patient selection for anti-rabies vaccines, in the underuse and under-dosing of rabies immunoglobulin, and in the ability of HCWs to follow WHO recommendations consistent with their categorization of exposure status. Overall, HCWs do not appear to be appropriately trained and equipped to appropriately manage rabies exposures. There is a demonstrated lack of understanding of the risk-based approach to rabies PEP.

Comparison of findings to other currently published data on rabies PEP

Animal bites and therefore potential rabies exposures are consistently reported to be more common among males and are usually reported to be more common among younger persons. In our results, 55% of potentially exposed persons were male; 44% were twenty years or younger; and almost one-third of all patients were males twenty years or younger. These findings are consistent with the demographic distribution of potential rabies exposures in other countries and studies. Animal bites are more common to occur in children than adults and young males are more likely to be animal bite victims than are young females. A 2008 study published in the *Journal of Nursing, Social Studies and Public Health* examined risk factors of dog bites in children.[59] This study found that children struggled to identify body language, in particular negative body language such as fear or aggression. This struggle was more prevalent among boys than girls. Additionally, in many parts of the world where rabies is endemic, boys are more likely to be outside than are girls, making them more likely to be exposed to a dog bite. Parental concern over a bitten child could lead PEP to be more likely sought for children after a potential exposure than members of other age groups making them overrepresented in these studies.

The vast majority of rabies exposures originate from dog bites. In our study, we found the same result, with 71.4% of the bite/scratch wounds originating from dogs. Ren et al. 2015 found 71% of bites to originate from domestic animals in Zhejiang Province, China.[15] Domestic dogs, owned either by the patient's family or another family, comprised the largest group of bite sources in our study, which is also consistent with other published findings.[28] Due to low prevalence of rabies vaccination in dogs in many parts of the world, unvaccinated dogs are responsible for the majority of exposures and disease transmission of rabies. In this study, the majority of the patients were not asked about the vaccination status of the biting animal by the healthcare workers.

The question often arises as to whether or not the rabies vaccination status of the biting animal should be considered in the PEP decision process in canine-endemic areas. In areas of the world that are canine rabies free, as long as the dog or cat is apparently healthy and available for observation, the initiation of post-exposure prophylaxis may be delayed while the animal is held for a 10-day period of observation. If the animal is disease free at the end of the 10-day period or the animal is euthanized and tests negative for rabies, a rabies exposure can be ruled out. However, the WHO does not recommend delaying the initiation of PEP in areas where canine rabies is endemic. Instead they recommend starting PEP and ideally observing the animal for the 10-day period. If the animal is still healthy at the end of the 10-day interval or dies/is euthanized and tests negative, the PEP series may be transitioned to PrEP (given on days 0, 7, and 21 or 28), i.e. the day 14 dose may be skipped.[60] There is one, albeit impractical, exception. If the animal is vaccinated, WHO guidelines indicate that PEP may be delayed for the period of observation; however they state that the vaccine must not only be current, but also must be confirmed via laboratory to be effective. However, since rabies titers are neither routinely nor cheaply performed on dogs in rabies endemic areas, this suggestion is not practical in most settings.

Strengths identified in PEP Capabilities and Administration

This study identified a few areas of strength in the clinics' capabilities and healthcare workers' knowledge and execution of appropriate PEP. All the clinics report a capability for information management. A majority of clinics were open for treatment 24/7 for emergency treatment of potential rabies exposures, and the ones that were not open 24/7 were on call during hours they were closed. Additionally, all but one clinic had ARV doses in stock, with a median of 19.5 doses stored per clinic.

Patients presented to rabies PEP treatment centers relatively soon after exposure to an animal bite/scratch. WHO and national guidelines recommend PEP be initiated "as soon as possible" after an exposure, but exact timelines are not given for the initiation of treatment as all exposures, no matter how recent, should be treated as if fresh. A previous study conducted in China about PEP-seeking behaviors defined a delay in PEP as an interval greater than 24 hours between exposure and administration of PEP.[61] Only 10 (5%) exposures were reported to have occurred at an interval of 24 hours or longer prior to presentation. Another strength identified through Survey 2 was that all Category II exposed persons received anti-rabies vaccine as a component of their PEP treatment in accordance with national and WHO guidelines. All but one Category III exposed person also received ARV and this person was referred elsewhere.

Gaps identified in PEP Capabilities and Administration

The immediate goal of this study was to identify gaps in rabies PEP in Shuangfeng County, Hunan Province. Survey 1 highlighted several of these gaps. Only one clinic of the 16 clinics surveyed that were licensed rabies PEP centers reported having RIG in stock or the ability to administer RIG. Additionally, clinics reported a lack of both emergency medical equipment and emergency rescue drugs that are necessary to handle a severe adverse event associated with vaccine administration. One area that looked like it might be a strength in Survey 1 was that all healthcare workers at the 16 clinics surveyed reported that they had been trained in rabies PEP at a county level health department or higher. Unfortunately, Survey 2 revealed a weakness in the PEP training system because the HCWs did not demonstrate adequate knowledge or implementation of PEP.

Preventing human fatalities due to rabies hinges upon correct categorization of exposures. Therefore it is dependent on the HCWs' ability to correctly categorize rabies exposures. Categorizing an exposure as higher than appropriate does not expose the patient to potential death by rabies but it results in a waste of expensive and limited biologics resources. Categorizing an exposure as lower than appropriate risks a patient's life as the potential for rabies infection increases with inadequate post-exposure prophylaxis. The WHO recommends assigning a Category I exposure classification only if the history is reliable and supports it. In this study, 1 in 4 patients were misclassified when comparing the HCW's classification with the WHO classification. 23.5% of exposures were under-categorized. All the healthcare workers reported having gone through county-level or higher rabies PEP training. Despite this, they still did not use the appropriate classification scheme. Only 40% of WHO Category I exposures were classified as such; Category II exposures were categorized appropriately in 91.3% of cases; and Category III exposures in 58% of cases. More accurate classification, particularly of Category III exposures, would narrow a major gap in rabies PEP administration and potentially reduce the number of treatment failures.

An alarming gap identified by this study is the frequency at which inadequate wound washing occurs. Only approximately one half of Category 2 and 3 patients in this study received a thorough wound washing either at home prior to presentation as reported to the HCW during intake or at the PEP facility after presentation. Wound washing is the first step in preventing rabies infection after an exposure has occurred. This is an area that should be targeted by future training programs for healthcare workers as well as public awareness campaigns since wound washing can occur either at a treatment center or before presentation. In half of cases, the wound was washed for a duration of less than 15 minutes, potentially leaving the patient exposed to infection with the virus.

Another gap identified was inappropriate patient selection for PEP vaccines, since several Category I exposed patients were administered ARV. Only one person did not receive ARV as part of the PEP treatment since that person was being referred elsewhere for treatment. According to WHO guidelines, only Category II and Category III exposures constitute a medical exposure to rabies and therefore should be treated with PEP ARVs. Overuse of the vaccine is an error that will not threaten the life of the patient; however its use is not recommended for these patients and could be an unnecessary cost or waste of biologics. In areas where resources are very limited, patient selection for ARV is crucial. The overuse of the vaccine in Category I exposures could indicate insufficient understanding about the risks and associated precautions among HCWs.

According to WHO guidelines, all immunocompromised persons with Category II exposure should receive rabies immunoglobulin due to the likelihood that they will not have a protective immune response to the vaccine. In this study, HCWs frequently did not include this in their history-taking, only asking 9.2% of patients about immunocompromising disease and 0% of patients about immunosuppressive medications. HCWs classified 5 immunocompromised persons as having Category II exposures (only 2 of these persons had a Category II exposure according to the WHO classification scheme). None of these persons received RIG, indicating that this may be another gap in PEP understanding. Of those 5 persons, 2 were not recommended to receive RIG by the HCW; for another two patients, there was no RIG available at the treatment site; and for the fifth patient, RIG was cost prohibitive.

In 14 of 38 (36.8%) cases of RIG administration, the patient was not weighed for the dose calculation; in 11 (28.9%) additional cases, the patient was weighed but was under-dosed. The reason for the under-dosing was not assessed by the survey but could potentially be due to calculation errors by HCWs, misinformation or misunderstanding about the required dose, or patient concern about cost. Under-dosing of RIG could leave a patient undertreated and at risk of developing rabies infection despite PEP being administered.

The reasons cited for RIG not being administered in cases that were categorized as Category III exposures by the HCW indicate a lack of understanding of the WHO/national guidelines for PEP. Although lack of access to biologics or inability to cover the associated costs may be insurmountable reasons to administer RIG in a given case, the healthcare worker not recommending its administration should not occur. RIG should be recommended if available in all Category III exposures. In 5/13 (38.5%) cases that did not receive RIG despite HCW classification as Category III exposure, the reason cited for not administering RIG was that the patient did not want to receive the appropriate treatment or did not think that the appropriate treatment was necessary. This trend indicates that HCWs may not be able to effectively communicate the risks associated with rabies exposures and the importance of following PEP protocols.

Project Limitations

The design of this study did not enable an assessment of compliance among patients or HCWs. Several published studies have evaluated compliance rates in different regions or with different PEP regimens. The scope of this project did not enable tracking patients through the entire course of the PEP administration; it only allowed evaluation of the initiation of PEP.

As an observational study, this project is limited by a high degree of systematic bias. Participants had to voluntarily agree to be followed in the study, allowing for selection bias. The selection of the study area itself was influenced by the fact that there was a strong interest from the local CDC staff members to participate and assist in the study. Information bias is present as well. A significant portion of the data was collected by selective recall of patients being asked questions. HCWs may have also been influenced in their history-taking and actions taken since they were being observed by a third party CDC staff member. The data was generated by these third party CDC staff members, so the quality of the observer information also lends bias to the results. Since expected or baseline values were not known for the area, no sample size determinations were performed. However, the sample size was very small with fewer than 200 participants in Survey 2 and only 16 in Survey 1. Statistical analyses were not performed on the data and a more qualitative descriptive epidemiological approach was taken for the data analysis.

The severe flooding that occurred may have altered the sample size as well as the distribution of the samples since the clinics may have been affected differently by the flooding. It is unknown how the flooding during summer 2016 may have affected the study results.

Due to the study design and limitations, caution must be taken in interpreting the results of this study. However, there is likely some truth to the trends and gaps that were detected by this study. Based on these results, these tools can be modified and used in future studies in which sample size determinations can be performed and bias better controlled for in the design.

Future Studies / Projects

Future studies could be designed to be of sufficient length to investigate compliance of both patients and HCWs or facilities in administering the whole treatment regimen. The study could be designed to evaluate the methods used by HCWs or clinics to try to promote patient compliance. Examples might include patient reminders, patient education about the subsequent visits to receive the remaining doses of PEP.

The current national technical guidelines on rabies PEP in China do not address the use of ID vaccine regimens. As discussed previously, ID vaccines can have benefits of being more cost-effective; in particular in higher volume facilities this could prove a good solution. Use of ID vaccines in China may prove useful in areas where cost prohibits the use of currently approved IM vaccines.

A future project to attempt to narrow some of the identified gaps would be to create a training session on rabies PEP for healthcare workers, in particular emphasizing categorization of exposures, the specifics of wound washing, as well as patient selection for ARV and RIG. Failure to correctly identify Category II and Category III patients or to appropriately select patients to receive ARV and RIG can lead to under treatment of persons exposed to rabies, PEP failures and mortality. Training sessions should be designed to highlight a few main points that are currently identified as gaps in PEP such as the duration of wound washing, the exposure categories, and that immunocompromised patients should always be recommended to receive RIG with both Category II and III exposures. Providing rabies PEP clinics with simple visual aids to facilitate easy retrieval of this information may also help reduce the frequency with which PEP is administered inappropriately.

Conclusion

As recent epidemiological investigations of rabies in China have pointed out, the disease still has a high incidence in the country, particularly in the southeastern region. With hundreds to thousands of reported human rabies cases each year, but high overall uses of PEP in the country, it is important to identify gaps in appropriate treatment delivery from the time of exposure to completion of PEP. Increased public awareness of the risks of rabies, methods of exposure, and benefits of PEP treatments is necessary to increase PEP-seeking behaviors. However, once patients arrive at a rabies PEP site, they should not become a treatment failure as is seen occasionally in China. Therefore, the purpose of this study was to pilot an assessment tool to assess gaps in PEP administration at initial clinic presentation. This tool having been tested, can be modified, improved and used elsewhere in the country.

The study design was unique in that healthcare workers were observed by a third party, so the data enabled the researchers to identify what HCWs are asking or not asking, doing or not doing throughout the intake and initial treatment process. This perspective enabled review of HCWs' categorization of wounds and comparison to the WHO categorization. History-taking is an important aspect in managing potential rabies exposure cases. The design of this study enabled evaluation of the relevant history-taking skills of HCWs in rabies PEP clinics.

Several important gaps were identified in the PEP process. These can be targeted specifically in the future with training programs, which should be offered on a frequent basis to refresh staff's knowledge and skills and accommodate for staff turnover. First, staff and the public are not adequately informed on the importance and protocols for wound washing after exposure to an animal bite/scratch. Second, staff that have been trained in rabies PEP are not able to consistently identify risk and categorize exposures. This leads to potential under-treatment of persons exposed to rabies, which ultimately may result in treatment failures, despite these persons having sought care at a licensed rabies PEP facility. In particular, HCWs should be urged to recommend the use of RIG to all Category III patients and Category II patients who are immunosuppressed; and if RIG is unavailable at the clinic site, patients should be referred to another facility for its administration.

PEP is a necessary but not sufficient component of rabies control (Figure 3.12). Not examined by this study, but critical to the control of human rabies in China is the control of the disease in the dog population. Ultimately, as has been acknowledged in the national strategies to achieve the goal of zero human deaths from rabies in China, canine rabies needs to be eradicated. No post-exposure prophylaxis system alone is sufficient to control human rabies; appropriate PEP must be coupled with canine rabies control programs. And once canine mass vaccination programs are initiated, the demand for PEP should decrease as long as appropriate education accompanies these programs.[20] The Ministry of Health and the Ministry of Agriculture must learn to work together to effectively communicate on issues, projects and initiatives to target rabies in populations comprised of both humans and dogs. Effective collaboration between the veterinary and public health sectors has been proven to increase the success of rabies control programs.[62] The areas of the world such as Western Europe and the Americas that have largely eradicated canine rabies have demonstrated effective control of the disease. Until the time that rabies is controlled in its canine population, China's PEP system needs to be improved in order to reduce the significant loss of life to rabies in the country.

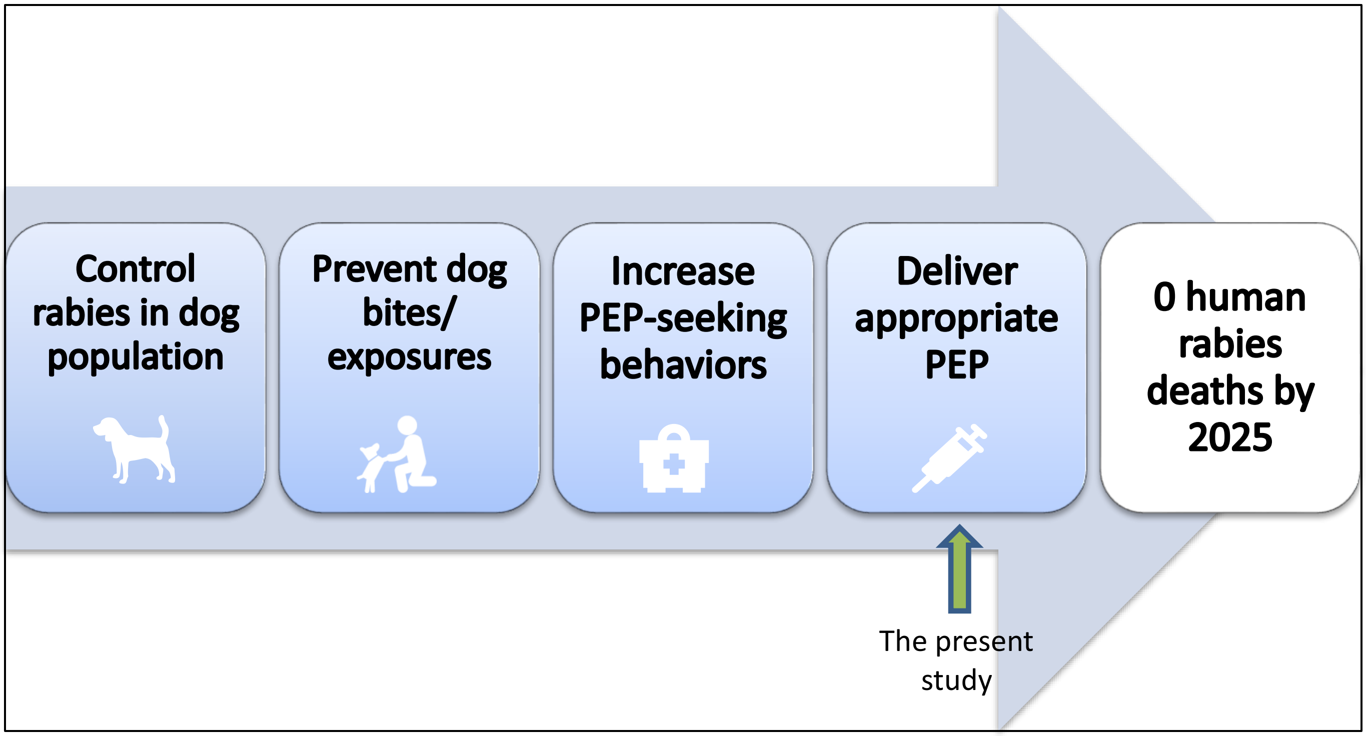

Figure 3.12 Components of achieving rabies control

Student Attainment of MPH Foundational Competencies.

Evidence-based Approaches to Public Health

1. **Apply epidemiological methods to the breadth of settings and situations in public health practice:** Participating in the study design and data analysis allowed me to apply epidemiological methods of an observational study to the investigation of an infectious disease and its treatment in a variety of clinics. Reading a large number of studies that were conducted on a similar topic, but of different designs and targeting related questions in different areas of the world, enabled me to learn about study designs that were not specifically used in my project or field experience, but will still be relevant to my career in public health.
2. **Select quantitative and qualitative data collection methods appropriate for a given public health context**: Designing the second survey and reviewing and analyzing the data generated by both surveys enabled me to learn about data collection methods. The surveys were created in an online

interactive platform that could be accessed on a tablet remotely by the project creators and data analyzers at China CDC as well as by the local CDC officials who completed the surveys while observing PEP practices at the point-of-care facilities. The survey design phase was mostly completed by the time I arrived at the China CDC, so I was more involved with the later stages of design and then the distribution and completion phases of the second survey. Completing the data analysis on my own however enabled me to reflect on the data collection methods and the manner in which questions were framed, the answer options phrased and recorded and to think about how I might design a survey in the future.

3. **Analyze quantitative and qualitative data using biostatistics, informatics, computer-based programming and software, as appropriate**: The majority of the data analysis was performed using Microsoft Excel 2013. This project was the first time that I analyzed data in an epidemiologic survey setting rather than in a benchtop laboratory setting. I had an original data set of survey responses that was raw and included illogical pieces, duplicates, incomplete information and other elements common to raw data sets collected from surveys. I learned about cleaning data as I went through the process. As I analyzed data, I had to think about the questions I wanted to use the data to answer and decide which analyses to perform and how to transform the data into a usable the format. I also created all the results tables and charts. This process forced me to think about the best way to present the results, in order to create visually informative and clear images.
4. **Interpret results of data analysis for public health research, policy or practice**: The Discussion section of Chapter 3 includes my interpretation of the results of Survey 1 and Survey 2. I plan to convey all of this information to my mentor at the China CDC and hope that this information will be transmitted to persons who are capable of designing future studies or implementing future projects and training programs for rabies. If the staff there are receptive to my ideas, I would like to design a few graphics for

distribution at rabies PEP clinics regarding wound washing and the use of RIG.

Public Health & Health Care Systems

5. **Compare the organization, structure and function of health care, public health and regulatory systems across national and international settings:** I listened to presentations on the structure and organization of China CDC as well as local CDCs. I learned how they are integrated into the centralized national office in Beijing. I learned about the communication as well as gaps in communication between the Ministry of Health and the Ministry of Agriculture particularly for zoonotic and vector-borne diseases. I observed cooperation and participated in dialogue between the US CDC office in Beijing and the China CDC national office in Beijing on a joint project that was funded by the US CDC but implemented by the China CDC.
6. **Discuss the means by which structural bias, social inequities and racism undermine health and create challenges to achieving health equity at organizational, community and societal levels**: Although the surveys conducted in this project did not specifically gather information regarding social determinants of the disease, the literature available on rabies epidemiology, post-exposure prophylaxis costs and access quite clearly demonstrates that rabies is a disease of the poor in developing countries. Seeking medical treatment presents the most significant burden to the poorest members of society in terms of travel costs and lost wages due to time away from work as well as in many cases the direct costs of the PEP treatment itself. Rabies post-exposure prophylaxis is particularly troublesome in this regard as it requires repeated visits over a period of up to 4 weeks. Often children are the ones exposed, so a parent must take time to take the child to the clinic, if the PEP course is to be completed. In many developing countries, the elimination of canine rabies poses an enormous challenge due to the high costs of vaccinating dogs, costs that often rest on the shoulders of the owners who may not be able to afford the vaccines.

Planning & Management to Promote Health

7. **Assess population needs, assets and capacities that affect communities' health**: The first survey assessed capacities of Shuangfeng County's healthcare system to effectively administer rabies PEP to exposed persons. Analyzing the results highlighted some deficiencies in providing effective PEP – most notably that many people in the county do not have access to RIG at their local treatment centers. This biologic is life-saving in an area where rabies incidence is so high.
8. **Apply awareness of cultural values and practices to the design or implementation of public health policies or programs:** As a guest in a foreign country's national public health organization, I was provided ample opportunities by my field experience to acquire awareness of cultural values and practices. Within the specific context of this project, I was unable to visit Shuangfeng County due to the flooding (discussed previously), and therefore did not have as many opportunities to understand the local cultural values and how they related to this project.
9. **Design a population-based policy, program, project or intervention**: This particular competency was not specifically attained during my field experience; however, I hope that subsequent work, which I would like to be involved in, may include the design and implementation of a population-based project to target appropriate PEP administration, as previously mentioned in the form of graphics that could be distributed. Also, if PEP training programs for HCWs are to be redesigned, the results of this analysis may contribute to the design of those programs.
10. **Explain basic principles and tools of budget and resource management**: I was not involved in the financial planning of this project so this competency was not specifically addressed at the field experience site.
11. **Select methods to evaluate public health programs**: The project that I was involved in had as one of its goals the creation and testing of a tool to assess rabies PEP in clinics around China with Shuangfeng County as the pilot site. Through completing this project, I learned about strengths and

weaknesses of a survey method for evaluating a public health program. A weakness was its inability to evaluate outcomes and long-term compliance. Additionally, it was subject to a high degree of information and selection bias as discussed in the Limitations section above.

Policy in Public Health

12. **Discuss multiple dimensions of the policy-making process, including the roles of ethics and evidence**: This particular competency was not addressed at my field experience. The group I worked with was primarily focused on the collection of data and interpretation of results, which were then handed over to other groups within the China CDC to be used in informing policy.
13. **Propose strategies to identify stakeholders and build coalitions and partnerships for influencing public health outcomes**: This particular competency was not addressed at my field experience site.
14. **Advocate for political, social or economic policies and programs that will improve health in diverse populations**: I did not participate in activities that targeted this competency during my field experience.
15. **Evaluate policies for their impact on public health and health equity**: This particular competency was not addressed at my field experience site.

Leadership

16. **Apply principles of leadership, governance and management, which include creating a vision, empowering others, fostering collaboration and guiding decision making:** My work on the data analysis and interpretation enabled me to apply leadership skills in terms of looking at the data and deciding how to approach it, and independently determining what questions I wanted to answer in regards to the data.
17. **Apply negotiation and mediation skills to address organizational or community challenges**: This particular competency was not addressed at my field experience. With a language barrier between me and my coworkers at the site, I was unable to attain this competency during my field experience.

Communication

18. **Select communication strategies for different audiences and sectors:** This competency is being addressed with my project after completion of the field experience; I have to decide how and what I want to present to whom from these results. As mentioned before, I have been considering different communication strategies for the public, for healthcare workers at rabies PEP clinics, as well as for staff members in public health working at the China CDC in terms of designing future projects and how to address some of the gaps identified.
19. **Communicate audience-appropriate public health content, both in writing and through oral presentation:** I have not yet addressed this competency, but as the goals listed #18 are achieved, I will address this competency.
20. **Describe the importance of cultural competence in communicating public health content**: This competency was not specifically addressed at my field experience site. However, I was acutely aware of the importance of cultural competence and continually working to improve my own levels of cultural competence throughout my field experience, from interacting with coworkers to learning about specific challenges, situations, and my host organization's structure and the healthcare systems associated with my project as I was a guest in another country.

Interprofessional Practice

21. **Perform effectively on interprofessional teams**: This competency was not specifically addressed on my field experience as everyone I worked with was an epidemiologist.

Systems Thinking

22. **Apply systems thinking tools to a public health issue:** This competency was not specifically addressed on my field experience. However, I did review some of the available literature on comparing costs among strategies using PEP alone, using PEP in conjunction with mass dog vaccination and using PEP with canine vaccination and One Health communication. Some of these

studies use systems thinking approaches to objectively analyze approaches to rabies control in endemic regions.[62, 63]

Student Attainment of Infectious Diseases and Zoonoses Core Competencies – Area of Emphasis

1. **Pathogens and Pathogenic Mechanisms: Understand and be able to describe the ecology and modes of disease causation and infectious agents such as bacteria, viruses, parasites and fungi:** This competency was addressed through gaining an understanding of the pathogenesis of rabies virus.
2. **Host response to pathogens and immunology: Describe the current understanding of host immune response to infection and understand the role of vaccination in infectious disease control:** This competency was addressed through gaining an understand of human host response to rabies, and an in-depth exploration of the role of vaccination, with a particular emphasis on rabies PEP vaccination and RIG administration and its role in disease control. I also read literature about the vaccination of dogs in controlling the disease in canine-endemic areas.
3. **Environmental and ecological influences: Understand the influence of space/geography, insect vectors, toxic plants and other toxin sources as well as infectious agents on infectious disease and food safety:** The influence of space and geography was addressed in my field experience through the study of how living in different spatial areas – rural, semi-urban, urban – affects a person's risk of rabies exposures and access to PEP. Additionally, in my field experience but beyond the scope of the rabies PEP project, I worked on some projects regarding severe fever with thrombocytopenic syndrome, a newly emerging disease believed to be transmitted by *Ixodes* ticks.
4. **Disease surveillance and quantitative methods: Understand how disease events and risk factors for disease are quantified and compared:** I assisted

in the editing of a paper and writing of an abstract about anthrax surveillance in China.

5. **Effective communication: develop and demonstrate effective strategies to communicate public health/ infectious disease issues to a variety of audiences:** This competency was addressed as discussed in #18 and #19 in the previous section.

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