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Rabid Response: Unpacking the history of the rabies virus to examine resource allocation

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Abstract

Rabies is a neurological disease transmitted by the bite of an infected animal and has assured fatal consequences if untreated. Despite the existence of an effective vaccine, the virus kills more than 50,000 people every year, primarily in low-income countries where dog-mediated strains of rabies persist. The long history of the disease has seen many transitions in disease context but also given rise to salient socio-cultural narratives that shape control and elimination campaigns. Effective future address of the disease requires knitting together historical lessons with frameworks of resource allocation.

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Introduction

For people ever bitten by a dog, it is likely they were queried about the possibility of developing rabies. This rare degenerative virus, when left untreated causes violent, uncontrollable and painful symptoms leading to nearly assured death. In the United States, Canada, Western Europe or most island nations the query was likely an overreaction -- rarely there does anyone die of canine-mediated rabies. If one seeks treatment for a possible exposure in these regions they are likely to be availed of post-exposure prophylaxis (PEP), an effective, life-saving treatment when delivered in a timely manner. In low-income countries across the world, however, rabies remains endemic in dog populations presenting a higher risk of disease transmission to humans. In these settings a lack of access to medical care, shortages of such biologics and inability to pay render those most at risk of the ravages of the rabies without the resources they need. This global inequity appears neither just nor efficient, but it is our starting point.

This project is centered on the dimensions of a single disease: rabies. But the questions that overarch extend to all health conditions and well-being as a whole as they concentrate on how resources in public health can be better allocated to improve health equity across the globe. It is a sisyphean task, as global and local understandings of health, burdens of disease, policy, technology and culture are fluid entities that mandate constant consideration. Efforts and inventions of the past two centuries have transformed rabies from the most-fatal of conditions to a completely preventable condition, which inspires hope for the progress yet to be made

especially if global inequality in terms of risk, resources and response to the disease can be addressed. Though rabies virus is an age-old disease, other zoonotic pathogens are constantly emerging; in the past 30 years, 75 percent of emerging diseases have been zoonoses (WHO 2015a). Moreover, overall 6 in 10 infectious human diseases are zoonotic in nature (CDC 2013). The lessons drawn from rabies can not only translate across diverse regions but also be applied to new and emerging diseases that will afflict human and animal populations alike.

Rabies is an ancient virus that today is estimated to kill 59,000 people per year (Hampson 2015). It is prevalent in more than 150 countries and present on six of the seven continents (WHO 2015b). More than 3 billion people worldwide live in regions with endemic canine-rabies, the strain responsible for 99 percent of rabies deaths in humans (CDC 2011). In addition to the death count, the burden of rabies is measured at 3.7 million disability adjusted life years (DALYS -- a metric that combines the toll of morbidity and mortality) with annual economic losses of $8.6 billion USD (Hampson 2015). Of the economic burden, Hampson (2015) estimates 55 percent of the figure is contributed by premature death, 20 percent from direct costs of PEP, 15.5 percent from lost wages and indirect costs of seeking treatment, 6 percent for cost of livestock losses to rabies, and only 1.5 percent on outlays in the veterinary sector for dog vaccinations (p. 1-2).

Technically, rabies is an "acute progressive encephalitis caused by a neurotrophic virus of the genus *Lyssavirus* in the order *Mononegavirales*, in the family *Rhabdoviridae*" (Kipanyula 2015). The *Rhabdoviridae* family of viruses contains more than 150 different strains known to infect vertebrates, invertebrates and plants, though rabies is a disease exclusively of mammals. Within the *Lyssavirus* serotype there are 10 viruses, each often associated with the animal they primarily infect. The viral package with its distinct bullet-shaped appearance is approximately 70 nm wide and 170 nm long, making it impossible to see with the human eye and thus an undetectable agent for much of human history. Further, the ability to differentiate

the antigenic shifts that define unique strains of rabies transmitted by different species is of relatively recent advent. Thus historical notes identifying animal strains centers on transmission rather than etiology.

Rabies transmits through the saliva of infected animals, being inoculated into the body of new mammalian hosts through an open wound, most often a bite. Once deposited into skin or muscle tissue, the pathogen finds its way to cells of the peripheral nervous system, beginning its slow crawl towards the brain. Rabies is only transmissible once the virus has migrated to the salivary glands, a relatively short stop from its destination in the brain. By the time a creature is driven to bite others it often has just a few days left to live. As a disease of the nervous system rather than the blood, for centuries rabies complicated attempts to identify and isolate a pathogenic agent. Rabies also confounds science because of the long latency period between bite exposure and symptomatic development. In humans the incubation period can last from as little as a week to a full year. In non-human mammals this waiting game can be just as variable. The symptoms of the disease manifest differently in each case, but are often described as either furious and paralytic rabies. Though once the muscle pain, spasms, blurred vision, aversion to water, excessive salivation, lethargy and so on begin, there is no turning back. Usually once symptomatic it takes little more than a day before death comes about. In humans, these symptoms often align with other neurodegenerative diseases, making rabies deaths difficult to identify even by clinical examination. Humans, for the most part, are a dead end or accidental host of rabies as transmission rarely occurs between people. However, this is not to say that human to human transmission scenarios are not impossible especially in healthcare settings. There have been several instances of rabies transmitted through organ donation (Monroe 2015).

More than a 130 years ago, the assured fatality of rabies in humans and animals was overthrown by Louis Pasteur's invention of a vaccine that can be administered both preventatively and prophylactically. In high-income countries, preventative vaccination for

rabies in humans is standard in veterinary and animal control fields, as well as often recommended to travelers to canine-endemic regions. In the same regions, rabies vaccination of domestic dogs and cats is regulated in municipalities that govern the ownership and licensing of pets. The prophylactic administration of the vaccine in humans capitalizes on the long latency of the disease to stimulate an immune response before clinical symptoms develop. The five shot regimen begins as soon as possible after an exposure to stimulate an immune response to the virus. Until the virus reaches the brain, the onset of illness can be prevented to great effect with nearly 99 percent of those who receive PEP recovering full health. However, until symptoms develop it is impossible to test a human victim for presence of the pathogen to confirm an exposure has occurred.

The success of Pasteur's vaccine when delivering promptly and in full has meant there has been little evolution in the technical treatment of the rabies in the ensuing century. The challenge that persists is a matter of connecting those involved in exposure scenarios to the lifesaving biologics. The United States utilizes around 50,000 courses of PEP each year, tallying 2-3 annual deaths, while a country like Tanzania experiences more than 2,000 fatalities and frequently experiences shortages of the lifesaving biologics (CDC 2016; Shim 2009). Further, the cost of administering PEP is comparatively high to vaccine interventions for other diseases, and the cost varies wildly by location. In the U.S., the full course of treatment typically exceeds $3000 dollars, while in most sub-Saharan African countries the total comes to approximately $100 (Kriendel 1998; Shim 2009). Seemingly large price tags for their respective regions, these are the prices of administering the only effective, and lifesaving, treatment for rabies.

Across the world divergent epidemiological and cultural contexts precipitate different perceptions of rabies transmission dynamics but also necessitate distinct strategies for vaccination, prevention and treatment programs. Approximately 95 percent of human deaths take place in countries where rabies is enzootic in dog populations, meaning it is characterized

by ongoing transmission throughout the canine species. In these low income countries the greatest burden of disease is falls within the health sector, yet it is the veterinary sector that is responsible for control of animal vectors. The lack of interdisciplinary programs and sustained attention to the disease undermines dog vaccination campaigns and delivery of timely and affordable of PEP to those who may have been exposed. In these high risk locations, rabies is one disease of many that exact high burdens of morbidity and mortality, often further disproportionately affecting the most vulnerable sectors of society: children, marginalized rural populations and those of the lowest socioeconomic classes (Hampson 2008).

In high income countries, where veterinary, public health, and political projects have rolled back the geographic extent of the disease canine rabies has been relegated to the status of "a notoriously underreported and neglected disease of low-income countries" (Hampson 2015, p. 1). Yet, even though the greatest risk of transmission has been eliminated, rabies continues to attract investment and attention. Today in countries like the United States and United Kingdom, rabies, while limited, is mediated through wildlife populations -- primarily skunks, foxes, raccoons and bats. Though incidence of human rabies is exceedingly rare here, the disease weighs greatly in public consciousness. In the United States, this attention paid has the effect of driving annual public health expenditure on the disease to more than $510 million dollars (CDC 2016).

Collective preoccupation with rabies is not a new phenomenon; it is particularly underpinned by the long history of the disease. Rabies was one of the first conditions to be documented in texts chronicling signs, symptoms, transmission and treatment of ancient maladies (Wasik and Murphy 2012a). The disease was a feature of early medical experimentation, and helped establish the science and success of vaccination (De Kruif 1926). Controlling rabies was a challenge for colonial governments, with the disease increasingly was codified in law under Victorian rule, all along playing upon cultural fears of violence, sexuality

and repression (Steele and Fernandez 1991; Pemberton and Worboys 2007; Kete 1988). Throughout its history the disease has influenced the way humans relate to their environment, especially dogs, at many points conjuring a collective hysteria that outstrips the toll and prevalence of the disease. In the United Kingdom, rabies has been a catalyst for debates over public well-being versus individual rights; considered as psychosomatic, or imagined, disease; proffered as representative of the moral failings of lower classes and women; and utilized to advocate isolationist policies (Pemberton and Worboys 2007). At present, rabies is marked by distinction between those places where canine strains remain prevalent, and the spaces where the disease is characterized by wildlife rabies.

First, by tracing back through the annals of rabies understandings and history, a narrative of fatality, fear, and ineffective but imaginative remedies arises. Throughout there is a sense that the sociocultural weight of the disease outstripped the actual burden and incidence, and these salient fears of rabies continue to inform present day inequity. Through the lens of political economy and cost-effectiveness frameworks for resource allocation, we'll look at the how rabies is addressed in the United States and Tanzania, and ways in which perceptions of the disease manifest in respective interventions. Lastly, a look to the future will draw on recent innovations and policy prescriptions to consider the character of rabies address going forward.

A Brief History of Rabies

Rabies is one of the oldest-known diseases to afflict humankind. However, the early history of the disease was in fact two: a marked separation between rabies -- a disease of dogs -- and hydrophobia -- an affliction of the same symptoms in humans. In the writings of the early Greek, Roman and Egyptian scholars who first documented rabies, varying levels of parallel and connection are drawn between the two conditions. These early descriptions of symptoms in dogs

and humans hold remarkable salience to present-day understanding of the manifestation of rabies in both species.

Around 3000 BC, Aristotle wrote in the *Natural History of Animals* of dogs suffering from an irritation and madness that was transmitted to all other animals they may bite (Wasik and Murphy 2012a). Hippocrates wrote of persons who seized and convulsed when frenzied by water. In both humans and animals today symptomatic rabies is characterized by throat pain and spasming that makes it difficult to drink or swallow, and in turn fosters distinctive drooling or frothing at the mouth (Steele and Fernandez 1991). Mesopotamia's Codex of Eshnunna, from circa 1930 BC, charges the owner of any dog displaying rabies-like symptoms is responsible for preventing the dog from biting any human, and should a bite occur such owner would be steeply fined (Wasik and Murphy 2012b). Shortly after the advent of AD, Plutarch writes loosely of the danger of biting dogs and the diseases they spread (Wasik and Murphy 2012a). Lucian, a Roman writer, similarly identified the bite of rabid dogs as an avenue of transmission but also wrote of human-bite transmission (Steele and Fernandez 1991), in which an afflicted person could spread the disease to a larger group of individuals by biting them all -- a particularly fearful trope that persists today. Other Roman scholars would identify saliva as the fluid critical for transmission of rabies, an observation perhaps aided by the excessive salivation that accompanies furious canine rabies (Wasik and Murphy 2012a).

Steele and Fernandez (1991) argue that aggregated together, the writings of these ancient scholars demonstrate the wealth of understanding on rabies within the constraints of the time. Further, they posit that the disease occurred with such a frequency that it was readily observable and the number of human and animal victims offered ample room for experimenting with new theories of rabies and accompanying treatment. While these early men were astute in their observation of the disease, they also inaugurated a long tradition of speculating on the cause of rabies to a less successful end. Pliny and Ovid pioneered the tongue worm theory in which it was

believed the membrane (known anatomically as the frenum linguae) which attaches the tongue to the floor of the mouth contained within it a pathogenic worm (Wasik and Murphy 2012b). The practice of cutting out the small flap in dogs would be utilized through the nineteenth century as a preventative strategy (Steele & Fernandez 1991). Greek philosopher Celsus believed that every animal bite was a threat to humans and that canine saliva was inherently poisonous. He advised that all bites should be treated with a regimen of caustics, burning, bloodletting and sucking to remove the venom. Similarly, while Celsus' ideas of generation would go on to be discounted, these practices of wound treatment continue on even to the present. They are especially prevalent today in situations where access to the health care services and prophylactic biologics are not easily available.

Some scholars did include rabies in the classes of diseases caused by bad humors or pestilent air, but for the most part early scholars were correct in sussing out its mainly canine-mediated nature. What they could not truly remedy, however, was the disease's certain fatal result. In addition to the aforementioned cures meted out, some truly bizarre strategies were applied in response to rabies. It was recommended to salt and eat the flesh of the offending dog (Wasik and Murphy 2012a). Another strategy included drowning a puppy of the same-sex as the dog who had bitten the person, and then having the human victim eat the liver raw (Steele and Fernandez 1991). Pliny, also of tongue-worm fame, suggested burning hair picked from the tail of the dog, and then inserting the ashes into the wound (Wasik and Murphy 2012a). This treatment lives on today in name and spirit with 'hair of the dog' hangover cures which calls for alleviating alcohol-induced symptoms with more alcohol consumption.

The historic documentation of rabies cases up to the Middle Ages leads to the conclusion that epizootics were relatively rare, with the disease most often occurring as the result of single dog bite incidents. However, around 1000 years ago reports of increasingly large outbreaks of rabies begin to proliferate, as well as the sense that rabies was circulating among dog and

wildlife populations. It is unclear however whether this shift was the result of an epidemiological transition in the disease's context and transmission patterns or a reflection of an advance in understanding of rabies.

Around 900 AD a rabid bear entered Lyon, France terrorizing the townspeople and biting more than 20 in their attempts to kill it. At least six of these people went on to develop symptoms and were subsequently smothered to death by relatives and neighbors (Wasik and Murphy 2012b). This idea that sufferers of rabies -- both human and animal -- must be put out of their misery crops up regularly throughout this history. But layered into the benevolent aim of alleviating pain is the reality that as long as individuals, and especially dogs, are symptomatic they are at risk to transmitting the disease to others. Thus such killings become a strategy to limit any further spread of the rabies. As with the disease itself, it is not the cumulative incidence of such an act of killing, either in preventative or palliative motive, that inspires anxiety but rather the moral and emotional consequences that might occur. The weighty notion that an individual either failed one's duty to either protect a loved one from pain or they themselves were responsible for ending a life was not a task frequently faced. Yet the powerful possibility of such a decision leads to salience in personal and public imagination.

One of the first well documented, large scale rabies outbreaks came in 1271 as a pack of rabid wolves assailed humans and livestock in the northern German region of Franconia, leaving more than 30 individuals dead (Wasik and Murphy 2012b). Between the 15th and 17th centuries, epizootics in dogs, wolves and foxes were common across western Europe, and noted as far east as Turkey. By the 17th century, the myriad superstitious treatments of rabies had caught the attention of the Sorbonne which published a declaration against them (Wasik and Murphy 2012a). One of the most notable treatments singled out in this document was the miracles believed to be conducted at the Basilica of Saint Hubert in Liege, Belgium (Wasik and Murphy 2012a). Dog bite victims and sufferers of hydrophobia would pilgrimage to the church

to seek *la taille*, a holy rabies treatment. Individuals would be tied to a metal ring that remains affixed to the wall today. They would be slashed across the forehead and a thread of Saint Hubert's vestments placed within the wound, then bound up by a priest for nine days. In such time the afflicted would remain within the church, praying and fasting (Wasik and Murphy 2012a). None of the sources in which I read about the miracles of Saint Hubert offered any estimation of the number of patients treated nor anything close to a success rate, but the proliferation of this account signals the prevailing reverence and tendency to seek divine intervention when faced with this most fatal of diseases.

In 1703, a Spanish priest residing in Mexico reported a case of human rabies to his colonial superiors only to be told rabies was not a concern in the New World (Steele and Fernandez 1991). There is disagreement among scholars over whether this constitutes the first report of rabies in the Americas. If so, there is chronological evidence that rabies was part of the Columbian Exchange, travelling across the Atlantic in the same direction as smallpox, measles, influenza and yellow fever. However, several studies of health conditions in the pre-Columbian Americas identify circumstantial evidence of rabies incidence, but only of the bat-mediated variety (Vos 2011). The prospect that rabies was a disease that existed in both hemispheres, and thus developed as two parallel strains is an intriguing one but to date still speculative.

In the second half of the 18th century, canine-mediated rabies spread throughout colonial America in British, French and Spanish territories, but it also jumped across species into skunk, wolf and fox populations. The first epizootic documented in the New World began in Boston in 1768 (Steele and Fernandez 1991). Mainly evident in dogs and foxes, rabies also exacted a large toll on livestock, especially cattle and pigs. Outbreaks on the islands of a Jamaica and Hispaniola in 1783 were so widespread that all dogs were ordered killed in Kingston and Port-au-Prince (Wasik and Murphy 2012a). The newly independent United States saw a series of outbreaks that steadily spread westward from the Atlantic moving with the expanding pioneer

frontier. In South America in the early 1800s, rabies extended into Peru, running north to south and on into Chile, leaving a trail of disease fatalities and slaughtered dogs (Steele and Fernandez 1991). In 1819, the Governor General of Canada, the Duke of Richmond, was bit by his pet fox and subsequently died of hydrophobia (Wasik and Murphy 2012a). In 1859, soon-to-be President Lincoln sought 'madstone' treatment for his eldest son Robert, who had bitten by a possibly rabid dog (Wasik and Murphy 2012b). Common in this era, a madstone, or moonstone, was a hairball from the gut of a deer or farm animal that when rubbed on the site of the bite wound was said to ward off rabies.

Back in Europe, the disease escalated and intensified especially in France, Germany and England, and tumult of the Napoleonic Wars increased incidence of rabies in Ukraine and Austria (Steele and Fernandez 1991). Outbreaks of rabies in London throughout the 1750s and early 1760s brought about widespread culls in which it was ordered all dogs be shot on sight and individuals were offered bounties for the number of kills made (Wasik and Murphy 2012a). The bloody and cruel result of these events would help shape the discussion about rabies in the UK for nearly a century to come as individual owners felt their rights to own pets had been violated, and animal rights activists coalesced around acknowledging the welfare and need to protect all creatures. Similar seeds planted around this time included a fissure between classes which was evidenced in rhetoric delineating pedigreed dogs and street curs, as well as William Pitt's 1796 Dog Tax which at five shilling was designed to be prohibitively costly to the working poor (Pemberton and Worboys 2007). Further, the hunting dogs of the elite were often excluded from control and muzzling policies while the lap dogs of women and street mutts of the working class were subjected to such legislation despite hunting being a major arena of rabies transmission (Pemberton and Worboys 2007). Even as rabies became increasingly political and legal fodder, the dimensions of the disease were still being adjudicated in the medical and veterinary fields.

In 1792, James Mease, an American medical student of Benjamin Rush at the College of Philadelphia accurately described the disease as one of the nervous system rather than a bloodborne affliction. While he posited spontaneous generation as the root cause of the disease and offered the administration of jimsonweed or *Datura stramonium* as a remedy, Mease was also one of the first to identify the similarities between the delayed onset of rabies and that of tetanus (Wasik and Murphy 2012a). Early in the nineteenth century Rush himself, a noted American author and doctor educated in Edinburgh, published a list of causes of rabies, and while bite of a rabid animal was named first it was quickly followed up by cold night air, eating beechnuts, a fall, and the involuntary association of ideas (Wasik and Murphy 2012a; Wasik and Murphy 2012b). Rush was one of the best and brightest for his time, but his writings demonstrate how a stagnation in the understanding of rabies led to a proliferation of alternative theories on the cause of the disease.

In their cultural history of the disease, Murphy and Wasik (2015a) write "science understood rabies little better at the start of the nineteenth century that it did at the end of the second." A symptom of the stasis in understanding the disease was the increasing popularity of the theory of spontaneous generation as the ultimate origin of rabies. This viewpoint found its most prominent and ardent advocate in British veterinarian George Fleming. He claimed that rabies arose out of the unnatural condition of domesticated dogs who were kept isolation, which had a restrictive effect especially on sexual behavior. He posited that one route of disease generation occurred when male dogs were sexually frustrated and excess semen that could not be ejaculated then became pathogenic (Pemberton and Worboys 2007). His foil, William Youatt, a veterinary authority in the mid-1800s, was firmly of the belief that rabies arose from inoculation -- most often the bite of an infected dog -- and as such incidence of disease could be controlled through policies of muzzling and confinement. Further, he argued that dog bites could be successfully treated through cauterization, even claiming to have been bitten thousands

of times by mad dogs in the course of his work. This claim ultimately undermined his credibility in arguing against spontaneous generation as surviving such a quantity of would-be fatal bites proved dubious to many in the field (Wasik and Murphy 2012a). Throughout the second half the nineteenth century, these two and many other veterinary and medical professionals would be called to testify in panels of British Parliament and hash out their differences in the public press, creating a stark dichotomy over the effect of isolation and quarantine in policy proposals for control of the disease.

In Britain, between 1830 and 1860, rabies seemingly took a backseat to other matters of public health and general order. Yet the emotive nature of the disease meant periodic smaller outbreaks of madness in the dog population still received media coverage and stoked public anxiety (Pemberton and Worboys 2007). The attention paid in every strata of society from government to academia to the clinic to media to the street leaves one to postulate the disease was widespread, but between 1837 and 1902, at which point the disease was eradicated from the island nation, there just were 1,225 hydrophobia deaths recorded in the UK (Pemberton and Worboys 2007). Over this 60 year period, that levels off to less than 20 human deaths per year in a population of 38,000,000, making it unlikely that ordinary Britons ever encountered the disease, yet the fear of certain fatality weighed widely. Then and now the disease's outsize position in the media, public imagination and political policy perpetuates an overblown magnitude of attention and unequal distribution of resources.

The most important development in the history of rabies, and the ability to control the disease was Louis Pasteur’s vaccine invention. Born in 1822 in Arbois, France, the one-day revolutionary scientist led a young life that was relatively rural and happy, but just before his ninth birthday, a rabid wolf attacked livestock and several men in the area, resulting in eight human deaths and untold damages. A young Louis witnessed one victim brought into the local blacksmith shop where his wounds were cauterized with hot iron (Steele and Fernandez 1991).

Pasteur would go on to become a talented student at the Ecole Normale Superieure where he later founded his Institut Pasteur, earning his degree in physics and becoming a professor of chemistry. What drew his imagination though and stimulated his burgeoning skill in original research design were solutions to problems that he felt would be of practical use to the French people. His pioneering discoveries on the microbial processes that linked fermentation, spoilage and preservation in wine and food sparked investigation into the degeneration that occurred in diseased tissues (Steele and Fernandez 1991).

Vaccination depends the stimulation of the immune system to recognize and respond a select disease. It centers on the introduction of a weakened or less virulent form of the disease and was originally pioneered in Asia nearly 1,000 years before the work of Pasteur. The practice of injecting small amounts of pus from an active smallpox sore was found to induce a less deadly form of the disease that then conveyed immunity from future infections (Steele and Fernandez 1991). Spreading through Europe in the seventeenth century, variolation was used as a reactive measure to already occurring smallpox outbreaks rather than as a preventative step which limited the impact. That all changed in 1798 when Edward Jenner, a British physician, confirmed the folklore that those exposed by virtue of lifestyle to cows, and cowpox, did not find the same affliction from smallpox as the general population (Steele and Fernandez 1991). Jenner found that by inoculating *Variolae vaccinae* into humans with no previous exposure to either smallpox or cowpox he could stimulate protection from both diseases. In utilizing the less virulent cowpox, Jenner induced immunity across species with lower risk and lower cost that allowed him to scale his vaccination to the masses and setting forth a two-century march to eradication of smallpox.

Pasteur initially employed Jenner's techniques in his quest against chicken cholera, but it was work in anthrax that won him celebrity and brought him in league with the veterinary community. After isolation and attenuation via oxygenation of the *anthrax bacillus* germ in his

own laboratory, Pasteur moved to a local farm where he set up a randomized control trial with 50 sheep (De Kruif 1926). Over the course of a month 25 of the animals received two doses of Pasteur's weakened vaccine, while the rest remained unvaccinated. When after 30 days all the animals were given a shot of live bacterial culture, those in the control group died, while the sheep who had been progressively inoculate survived. The showmanship and success of the experiment built a name for Pasteur and curried legions of admirers in professional and public circles (Gelfand 2002).

After chicken cholera and anthrax, the choice of rabies as his disease of inquiry was in keeping with the zoonotic field, but carried a much greater public profile, if not a large burden. Pasteur's desire to alleviate human suffering, especially that of children, was in part born of losing three of his own to typhoid and cancer (Gelfand 2002). As his work shifted toward medical applications, Pasteur capitalized on growing public attention to draw resources and young minds to work in his laboratory. Pasteur's decision to focus increasingly on infectious disease research brought him together with Emile Roux, a medical student who had written his dissertation on rabies. Murphy and Wasik (2015a) describe 'the meticulous zeal' and 'monastic devotion' both men displayed in their study of animal and human diseases as particularly fruitful for their relationship and beneficial in the long-run. Their commitment to rigorous scientific standards would serve them well as their work came under public scrutiny (Gelfand 2002).

In 1874, the Pasteur laboratory was granted two rabid dogs by veterinarian M.J. Bourrel who himself had sought a cure for the disease to little effect other than to confirm saliva as the contagious agent (De Kruif 1926). The veterinarian had suffered his own tragedy with hydrophobia when his nephew was bitten, infected and died while working with rabid dogs in Bourrel's laboratory (Wasik and Murphy 2012a). Pasteur gathered samples from the saliva of the dogs and a young hydrophobia victim, but could not isolate a pathogen that satisfied Koch's

postulates of isolation, inoculation, infection and reisolation (De Kruif 1926). However, he was not deterred. While it could not be cultured in scientific media, Pasteur's technicians developed techniques of maintaining and manipulating the disease in living tissue. By formulating a process to strengthen and weaken the virus, they laid the groundwork for the field of immunology and the creation of other vaccines. Yet, the utilization of dogs and rabbits as living reservoirs, and a crucial skull trepanation technique, by which contagious material was directly injected into the brain of the animals, drew the outrage and opposition of many including anti-vivisectionists who challenged the ethics and conduct of Pasteur (Pemberton and Worboys 2007; Gelfand 2002).

Opponents decried the invention of a whole new of strain 'laboratory rabies' that while more easily manipulated was more uniformly virulent. They claimed if it ever escaped into the wild it would decimate all vulnerable species (Gelfand 2002). However, the prospect of a cure for rabies and hydrophobia outweighed any efforts to terminate Pasteur's work. His audacious and controversial research would bear remarkable fruit; not only did Pasteur observe that he could create a preventive vaccine but that also the long incubation period of rabies allowed a time window in which a 'cure' could be delivered that would act upon the same principles of induced immune response to allow the body a chance to fight off the disease (De Kruif 1926). With the dogs in his laboratory Pasteur perfected the processes of vaccination and post-exposure treatment, yet he remained hesitant to attempt the process on a human-being, wary of the fatal consequence of any flaw. Pasteur even pondered proffering himself as patient zero, but a July 1885 dog-attack on a nine year old boy in Alsace provided the prompt for Pasteur to finally put his work to the test. After Joseph Meister had been bitten 14 times by a rabid dog, his frantic mother sought out Pasteur pleading that any risk was worth it. For the first time, attenuated viral material from a rabbit spinal cord was injected into a person (Pemberton and Worboys 2007). For the next two weeks, the young Meister received daily inoculations, and to

collective delight and surprise, he survived. On October 26, 1885, Pasteur announced to the world his cure for the most fatal of conditions.

Beginning as soon as possible after the exposure incident, Pasteur's treatment delivered escalating doses of the vaccine for the ensuing 15 days. As countless patients sought his service, Pasteur established an 11 o'clock hour of vaccine administration to all who arrived in the garden of his laboratory. However, the scientist himself could not deliver the treatment for he was not a licensed doctor. Instead it was Joseph Grancher who would inoculate the masses who gathered daily, as the other members of the laboratory recorded extensive notes on the conditions of exposure and demographic details of each patient. As news of his success trumpeted around the world, high profile patients arrived at Pasteur's laboratory from across France, England, Russia and the United States. Pemberton and Worboys (2007) describe the fanfare that surrounded the Pasteur Institute: "the enterprise became theater; the innoculations attracted spectators and Parisians seemed to relish the mixture of advanced science, heroic medicine and suffering humanity."

Even as many celebrated his innovation, Pasteur and his team still had to answer to critics and account for the notable cases of vaccine failure. The first fatality was the 80th case treated; in the first two years, 30 patients had died after receiving treatment in Pasteur's garden (Gelfand 2002). Each case of failure was explained away with case specifics -- a severe bite, injury to the head or neck, delay in treatment after exposure -- while pointing to the thousands who had successfully been treated (Gelfand 2002). However, critics countered by claiming the success rate was artificially inflated by the treatment of scores who had not actually been exposed to rabies (Pemberton and Worboys 2007; Gelfand 2002). Colonial officials and experts in India argued that rabies was nowhere near as deadly as Pasteur claimed and that the disease could be treated successfully with a series of homeopathic strategies, similar to anti-venom practices at the time (Wasik and Murphy 2012a). The difficulty at the time of confirming rabies

exposure without the onset of symptoms meant there would always be disparity on statistics of the disease.

In 1886, deaths in two high profile British cases led to the creation of a Parliamentary panel to investigate Pasteur's treatment, especially the accusation that he had created a whole new strain of the disease which had appeared in the demise of both men (Pemberton and Worboys 2007). The newly termed paralytic rabies stoked mass fear of a mutant disease ready to lay waste to a vulnerable population, but the committee found the condition was merely the product of a heightened state of observation. Paralytic, or dumb rabies as it can be called, was not a new affliction, just one less readily impressionable when compared to the violent outbursts that characterize furious rabies. In 1887, the British Panel released their support of Pasteur's work based on the assessment of over 90 case studies including the two Britons who had died. Interestingly the report placed great weight on eradicating canine rabies in the country rather than concentrating resource on building their own Pasteur Institute, which was seen as a reactionary rather than preventative measure. This recommendation was landmark for the time as legislative efforts often treated hydrophobia and rabies as separate disease to be dealt with each in their own accord.

Through it all, Pasteur and his team kept administering shots to all who arrived at his garden every morning. Even as he was transforming the course of veterinary and medical practice "it was a point of principle to offer no privileges nor to accept any payment" (Pemberton and Worboys 2007). Because time was of the essence in administering the shots - and Pasteur became increasingly sure of his process - it became important to expand the sites in which one could obtain treatment. As the 1890s dawned a series of Pasteur Institutes began to crop up around the world. Initially in colonial outposts, today the 33 centers link the work of more than a 1000 scientists in 120 countries (Pemberton and Worboys 2007). These centers remain important locales for new medical research, but their utility in serving as sites to seek PEP is

undermined by their urban locations away from the rural regions in which the greatest risk of canine mediated rabies persists.

Pasteur's vaccination for dogs and humans was fundamental to eliminating canine-mediated rabies in many industrial nations. However, across the American frontier wildlife strains of rabies were a perpetual threat for settlers. On his expeditions throughout the West before he became president, Theodore Roosevelt wrote of the dread inspired among plainsmen by the skunk. In the United States the animal was termed a 'phobey cat' as a diminution of hydrophobia, while in Canada skunks were known as 'L'enfante du diable' or child of the devil. There are apocryphal stories of epizootics among skunks in which the melting snow of spring would reveal scores of dead animals. In one year there were so many a park ranger describes piling the bodies in cords -- a measure 4 feet by 4 feet by 8 feet, normally reserved for stalking wood (Steele and Fernandez 1991). However, high rates of fatality in the case of skunk bites, leads to the conclusion "not that all skunks carried the disease but the species is compelled to bite humans only when they are infected" (Steele and Fernandez 1991).

Not only were skunks a concern, but wolves and foxes as well as potential vectors for rabies. So much so that in 1827, the U.S. War Department solicited its representatives in Indian Country to seek out the cures for hydrophobia employed by Native tribes. This quest to learn from indigenous ways thinly veils the racism that equated Native Americans with animals and enabled the exploitation and extermination of countless communities. Wasik and Murphy (2015a) describe the aggregation of Native Americans with wolves and the resulting consequence: "As wolf and native were both beaten back over centuries of brutal eradication, the frontier attitude toward both seemed to soften -- from outright hatred and fear to a sort of colonial condescension." (2012a, p. 115-116)

Throughout the eastern United States today, raccoon-variant rabies is the strain of the disease most prevalent, though it was not present in the region until the late 1970s. Traditionally

found exclusively in the far southeast, raccoon hunters from West Virginia trapped and transported more than 3000 raccoons up into Appalachia from Florida, bringing not only fresh hunting fodder but also rabies (CDC 2008). From there the epizootic transmission of rabies has exploded along the eastern seaboard, and today continues expanding west and north. Raccoon variant rabies presents more challenges than fox variant because of their wily nature -- they are known to hitchhike -- and because they more frequently live in proximity to humans and display less timidity.

In many places the greatest wildlife threat comes from bats that carry the virus. Infection via the small flying mammals has long confounded efforts to trace the exposure contacts because bats can swoop on silent wings and their bite is often not enough of a disturbance to wake a sleeping person. In 1906, there was a mysterious blight among cattle in Brazil, that perplexed because the rabies-like symptoms could not be traced to any canine exposure but were later determined to be caused by vampire bats who fed on the blood of the cows (Steele and Fernandez 1991). This collision of vampirism and rabies not only fosters disease transmission but is the kind of condition that sets aflame imaginative and fearful reactions. Protocols in most U.S. states are conservative in regards to administering prophylaxis for potential bat-exposures, which has led to concern at several incidents in which large groups of people were believed to be exposed.

Enzootic rabies in canine populations was eradicated across the developed world beginning with the United Kingdom in 1902, who achieved this much sought after status only after decades of polemic debate over quarantine and muzzling laws. The restraint of dogs was increasingly governed by politicians while owners were charged with taking responsibility for the actions and securing the wellbeing of their pets. When the case count in the UK among dogs was ultimately lessened to zero, it became a point of national pride throughout the 20th century, with Prime Minister Margaret Thatcher even employing the status in the service of British

exceptionality (Pemberton and Worboys 2007). But the Brits did not live without fear of a return of rabies -- long holding onto quarantine laws on all dogs travelling from overseas and running several public service campaigns to warn against the illegal import of animals. When the Channel Tunnel, linking Calais, France with Kent, England, was inaugurated in 1994, the fears populating the minds of Britain were not ones of migration or military security, but rather the possibility a rabid fox might stray through the 31 mile tunnel to unleash a new epizootic across the UK's island fortress. During the planning stages in 1985 a poll taken near the proposed English entrance found more than 85 percent of residents believed the construction of the tunnel would make the spread of rabies virtually unstoppable (Wasik and Murphy 2012a). Outcry over the risk led to electric mats being incorporated into the design and installed at intervals throughout the tunnel to first deter and then decimate any possible animal invasion.

The long history of rabies is marked by divergences between an understanding of the transmission dynamics of rabies, while most responsive treatment long had little effect in reducing its diabolical and deadly nature. Wherever it has gone rabies has inspired a sense of dread in communities and individuals that produces wild and often excessive responses to the disease. The large and emotive nature of the disease's history never quite matched the prevalence of disease as historians have been able to ascertain. While the burden and character of rabies plays out differently across the high and low income countries disproportionate responses echo on today perpetuated in particular dread and uncertainty characteristic of understandings of rabies.

Socio-Cultural Narratives

United States: low incidence, high resource

One of the places that rabies has long existed in Western popular culture is through literary deployment as a device to invoke fear and convey madness. There have been myriad

works published in the last 100 years which each in their own ways invoke rabies, especially canine mediated strains. In Their Eyes Were Watching God (1937) Zora Hurston Neale deploys a rabid dog to precipitate the death of a character, Tea Cake. Despite the life Janie Crawford has constructed for herself the devastating power of nature still holds supreme as the hurricane and subsequent rabid dog attack lead to Tea Cake's insanity and the danger he poses to Janie. In the end, Janie shoots Tea Cake in self defense as he becomes increasingly violent and uncontrollable, however this ultimate rift between husband and wife would not be possible without the insertion of rabies. The virus is central to the plot arc of Of Love and Other Demons (1994) by Gabriel Garcia Marquez, as it is the bite of a rabid dog that causes Sierva Maria's supposed demonic possession and her subsequent isolation in the convent. The magical realist style of the Garcia Marquez blurs the distinction between divine and human, and further between nature and nurture. Not only does nature win out in precipitating the death of Sierva Maria, but those responsible for caring for the young girl consistently neglect or exploit her for their own gain. While the scene in To Kill a Mockingbird (1960) by Harper Lee involving a rabid dog is fleeting, the implications of the moment ripple on. Atticus Finch's decisive action to kill the dog alters his children's perception of his personality as reserved and calm. The event serves to support Atticus's resistance of general madness in the book which most often displayed by the town's anger at his defence of Tom Robinson. However, this incident with Atticus as the jury and executioner of the rabid dog juxtaposes with his participation in the judicial process, and belief that ultimately the innocence of Tom will prevail. In Old Yeller (1969), Fred Gipson deploys rabies as an emotional gut punch as the disease sets up the imminent death of the family dog, but not only must the dog die but the risk he poses in exposing the family necessitates that young Travis Coates shoot him. For much of the narrative, rabies lurks in the background of family life and several incidents are tinged with the fear that either a person or the livestock would be exposed to the virus. The disease is the manifestation of the irrepressible

danger found in the wilderness, and despite every effort to tame and conquer ultimately it is the whims and ravages of nature will win out. This construction of the deadly domination of nature draws further parallels in vampire literature. In fact, the first cases of the disease observed and identified in cattle in Brazil in the early 20th century were mediated by bats termed 'vampiros' (Steele and Fernandez 1991). The tradition of vampirism also draws connections into monster and zombie lore which increasingly has leapt off the page and taken to screens big and small.

Further, there exists a permeating lexicon of rabies and related imagery of dogs as violent and pathogenic. First, most evidently, there is an adjective defined by the Oxford English Dictionary as denoting such animal or object as "furious, raging; wildly aggressive or violent." Initially appearing in the late 16th century 'rabid' is often employed today to describe fandom of teenage pop stars and sports teams, both extending upon and obfuscating its viral roots. In 18th century England, 'the dog days of summer' was termed to describe the period that coincided with the astrological prominence of Sirius the dog star, and a seeming rise in the incidence of rabies in the hottest days of summer (Pemberton and Worboys 2007). As noted earlier, 'hair of the dog' hangover cures are the descendent of a rabies remedy that called to place a hair of the offending dog into the site of the bite. Additionally, the practice and term of burying the dead 'six feet under' comes from the close relationship between humans and dogs. Such a burial was in part designed to be deep enough that dogs would have great difficulty disinterring the body (Murphy and Wasik 2015a).

This salient presence of rabies in language and literature reify themes from the disease's history that endow it in the individual and collective mind in ways that make the virus seem more prevalent than any case count of the disease conveys. First, the uncertainty that characterizes many exposure scenarios and the guesswork over whether bite victim would develop symptomatic rabies led to historical projections of rabies as a psychosomatic illness (Pemberton and Worboys 2007); after being bitten by a dog, often uninfected, individuals would

whip themselves into such an anxious state that they would begin to exhibit disease symptoms without actually being infected. In 1886, a French veterinarian, Dr. Portanier, extrapolated on an average of 70 to 80 rabies deaths per year in the country to suggest that "for every four thousand Frenchmen who believed themselves to be in the process of becoming rabid, only one would have that unhappy success" (Kete 1988, p. 101). It has never been easy to predict whether or not a bite incidence will develop with fatal consequences; an oft-repeated refrain is that Pasteur himself at times difficulty divining whether a patient had truly been exposed to a rabid bite or was manifesting a maddening anxiety (Gelfand 2002). While 'anxious rabies' has fallen by the wayside, incertitude remains within estimating the burden of rabies as social stigma of the disease drives those suffering out of formal clinics where cases are reported, and convergence of the symptoms with other diseases complicates diagnosis (Hampson 2015). In the United States, failure to identify rabies as the cause of death has led to organ transplantation that also transmitted the virus to the recipient patients (Monroe 2015).

Ambiguity over the disease also persists as current practice for determining if an animal is infected with rabies takes a two prong approach: quarantine and testing. First, in municipalities across Western Europe and North America it is the standard for dogs and cats who bite a human to be put in isolation and monitored for any symptom of disease. Rabies can only be transmitted once the virus has travelled up to the nervous system to the salivary glands, and from there it does not have far to go attack the brain and precipitate demise into death. If the animal was infectious at the time of the bite incident, within 10 days it will be showing symptoms of rabies or already have succumbed to the disease. Option two depends on harvesting tissue from the brainstem for post-mortem examination. What underpins both these scenarios is access to the animal in question who did the biting and facilities necessary to carry out the quarantine or laboratory to conduct the autopsy. These necessities are unattainable in

many cases, the latter especially in low income settings where dog ownership and confinement are more fluid and in wildlife variant situations where the bite-encounter may be fleeting.

The second theme from the history of rabies that governs present conceptions and campaigns against the disease is the human-dog interface. In the second half of the nineteenth century, the theory of spontaneous generation arose in part as a critique of confining domestic dogs in conditions that challenged natural or innate behavior, but it was also driven by an uncertainty of the changing profile of man. In her appraisal of the French context of rabies outbreaks in this period Kathleen Kete describes rabies phobia "as shaped by an anxious awareness of the costs of modern life, by bourgeois ambivalence toward a world of their own making" (1988, p. 102). To overcome this cultural apprehension of dogs, and ambiguity about the role of humans, new constructions of the relationship between man and dog had to be set forth.

In the United Kingdom it was upon the agitation by animal rights activists who paradoxically were rallied to organize in response to Pasteurian experimentation with laboratory animals (Gardiner 2014). By setting up a series of free and mostly unregulated clinics, groups including the People's Dispensary for Sick Animals of the Poor (PDSA) shifted the course of veterinary practice towards small companion animals by framing a moral argument that both pets and their owners of all socioeconomic strata deserved quality care; "Instead of an assumption that animals required protection from their ignorant or willfully cruel owners, neglect and suffering were framed primarily in the context of social disadvantage" (Gardiner 2014, p. 481). Expanding veterinary practice upon dogs allowed the arena in which widespread vaccination and mechanisms of quarantine could be carried out. It was also part of a larger trend in which England became proud to be a nation of 'dog-owners' (Pemberton and Worboys 2007).

Canine endemicity was in the United States was eliminated through programs and policies governing the vaccination of dogs such that herd immunity was achieved with more than 70 percent of dogs vaccinated. Thus since 1980, wildlife has accounted for more than 90 percent of all rabid animals reported in the United States. The 5 species considered primary reservoirs include raccoons, bats, skunks, foxes, and in Puerto Rico, mongooses (CDC 2016), however each strain can still transmitted across species. For example, most cases of rabies found among cats in the United States are bat-variant (Monroe 2015).

Recently the historic mismatch between public health response and disease realities has been manifested in mass exposure scenarios, in which a large group was considered at risk for rabies and correspondingly administered PEP. An incident with rabid kittens in Concord, New Hampshire in 1994 set off a massive wave of investigations, interviews, and post-exposure treatment of 665 people which totaled a cost of about $1.1 million for biologics alone at the time of the incident (Noah 1998). In late October, a kitten that had been recently purchased from a pet store died and tested positive for a raccoon-variant rabies. In the ensuing investigation, the CDC found a local raccoon that also tested positive for rabies and three other kittens from the same pet store that had died under suspect circumstances but were unavailable for testing. Extrapolating the dates the known and likely rabid kittens were in the pet store, the CDC identified 30 other kittens of which 27 were euthanized and tested negative for rabies, one more was quarantined and the remaining two could not be located (CDC 1995). However, given the environment of the pet store -- kittens were allowed to roam freely -- and the uncertainty over which kittens had been present, possibly rabid, and in contact with customers, a widespread media campaign was conducted to alert the community to the possible exposure. In phone interviews with more than 1000 individuals who had frequented the store during an estimated month-long period, most exposures were identified as being low risk such as petting, holding and nuzzling the kittens (Noah 1998). Still more than half of those surveyed were administered

PEP. This scenario underlies the need for strong surveillance and tracing methods in situations where there is high circulation among animals and people, especially when the animals in question are less than 3 months old -- the standard age of pet vaccination. It also begs the need for advancement in diagnostic capacity so that when the offending animal is unavailable for testing or there is question as to whether an exposure incident occurred at all, a screening test can narrow the instances in which PEP is administered.

In early 2014, 922 Air Force trainees and instructors were assessed for possible rabies exposures after bats were found in the sleeping quarters at Joint Base San Antonio-Lackland in Texas. Based on risk assessments and reported sightings and contact -- though no confirmed bites -- more than 200 soldiers were administered PEP including HRIG at a cost of more $400,000 (U.S. Medicine 2014). It is the largest mass exposure incident ever documented for the armed forces, and subsequent surveys of the dormitories found that between 400 and 600 bats had been nesting in the walls over a span of several years. However, of the Mexican Free Tailed bat specimens that were submitted for testing all returned negative results (Joint Base San Antonio 2014). Given the degree to which bats were found to have a long-term presence at the base, and the lack of prior investigations into possible rabies exposures it seems an overextension in this instance to vaccinate a fifth of those who were present at the time given no bats tested positive and no soldiers reported a direct bite incident.

In the United States, collective attention paid to rabies results in large allocations of resources, but these understandings are not applicable to other disease contexts where different routes of transmission and conceptions of dogs predominate.

Tanzania: high incidence, low resource

In Tanzania, rabies is known in Kiswahili as *Kichaa cha Mbwa* (madness in dogs), considered to be a disease spread by 'neglected' dogs who although they have owners are free-

roaming and lazy (Bardosh 2014). High levels of awareness about rabies are underpinned by local experiences of human cases (Bardosh 2014). The discrete and memorable nature of transmission events, as well as visible and violent symptoms intensified fear and apprehension over the disease especially for those who held a primary experience of having neighbors or relatives die of rabies or needing to seek treatment after a dog bite. Across 16 villages in a select survey area of rural Tanzania, there were just over three human rabies deaths per year between 1995 and 2008. Based on a total population of more than 30,000, this implies an annual rate of 10.7 cases per 100,000 people which is far higher than the estimated incidence for the region (Bardosh 2014). This higher than expected prevalence supports the belief that human rabies deaths are greatly underreported, but also that rabies is a somewhat familiar occurrence that echoes on through the fear it inspires. An individual's experience of rabies informs knowledge of the disease as well as opinions of vaccination campaign and attitudes towards dogs.

The nature of dog ownership in Tanzania, and sub-Saharan at large, is characterized by free-ranging animals, however “it is noteworthy that only a small proportion of the dog population is ownerless, therefore making most of the dog population accessible for vaccination” (Kipanyula 2015, p. 5). However, within families dogs are often cared for by children who have little agency within the household to decide to seek out vaccination clinics or allocate any resources for a vaccine (Kipanyula 2015). The perceived utilitarian value of dogs often dictates their care and management; the majority of participants in the Bardosh (2008) survey cited security as the primary reason for owning dogs. 98 percent of those interviewed said they owned domestic dogs for the purpose of providing protection to members of their family or crops and livestock. Alternative answers included keeping dogs for hunting, companionship, as symbols of wealth, to ward off spiritual forces and act as capital assets when selling puppies (Bardosh 2014).

The root cause of transmission of rabies is posited to be wildlife contact with dogs living in agro-pastoralist communities near game reserves or national parks (Bardosh 2014). There is evidence of enzootic rabies among wildlife canine-species, but the degree and direction of transmission across domestic and feral populations is less clear. However, this narrative places the blame for perpetuated transmission on the living condition of already marginalized rural and impoverished populations. Further, this feeds into the perceived intractability of the problem in rural Africa "because of poor infrastructure, limited capacity, and the misperception that large populations of wild carnivores are responsible for disease persistence" (Hampson 2009).

The characteristic uncertainty of rabies is extended in this setting because the disease is characterized by irregular epidemic cycles. Though there is noted intensity of transmission in summer harvesting season which also aligns dog-mating season, harkening back to Victorian England's identification and naming of 'the dog days of summer,' seasonal variation and capriciousness of outbreaks undermines attempts to foment communal and political support for sustained vaccination of domestic dogs (Pemberton and Worboys 2007; Hampson 2009). This also factors into forecasting an expected number of PEP courses needed in a particular location. Before administration the PEP vaccine needs to be kept in a cold chain, and has a variable date of expiration (usually under a year) which combined with its relative expense makes the vaccine difficult to distribute and unlikely to be stockpiled in more rural clinical settings (Hampson 2008). Shortages of lifesaving biologics are an oft cited cause of persistent mortality despite the preventable nature of rabies. In a study of the Serengeti and Ngorongoro Districts of Tanzania, 10 percent of suspected rabies exposures that attended a medical facility did not receive PEP because none was available (Hampson 2008).

In Africa each year, an estimated 200,000 individuals received some form of post-exposure treatment which ranges anywhere from washing the wound to delivery of a full PEP

regimen, however few individuals in low income countries ever receive human rabies immunoglobulin (HRIG), which conveys passive immunity until the vaccine stimulates the body to produce its own antibodies (Knobel 2005). However, many rabies victims did not seek medical attention until after symptomatic onset at which point PEP is no longer effective. Faced with the prognosis of demise into fatality with no effective course for care, individuals retreat from clinical settings where their deaths may not be accounted for (Hampson 2009). Accordingly surveillance systems "have been shown to substantially underreport the number of deaths from rabies. For example, in Tanzania more than 100 human rabies deaths are estimated to occur for each officially reported case" (Hampson 2008). Limited and incomplete data on the public health burden of rabies, marshalling political support, community participation and sustained investment has proved detrimental to efforts to achieve herd immunity-requisite levels of vaccination in the domestic dog population.

Presently in spaces where attempts to achieve requisite levels of vaccination coverage in the dog population have fallen short, there is "emphasis on the need for local bylaws to punish dog owners who did not vaccinate their dogs" (Bardosh 2014, p. 10). The other reactionary mechanism to ongoing transmission of rabies in the dog population is culling. In disease ecology literature, pathogens are often given a sense of agency and strategy they employ to spread disease. With rabies this mechanism plays out levels of both symptomatic and societal reaction. First, when primarily dogs develop rabies, they are stimulated to exhibit rare and aggressive behaviors, including the proclivity to bite other dogs and humans thus inoculating the virus into its next victim. To this end, the virus has manipulated its own transmission, ensuring it does not die out as it kills its host. The short window of opportunity for transmission drives the aggressive manifestation of rabies.

But the pathogen's agitation to ensure its continuing transmission and incidence extends beyond the mechanisms of symptomatic development; rabies sparks a sense of dread capable of

moving populations and policy in ways that ultimately do little for the control of the disease. Dog culling has long been the reactionary measure deployed to a rabies outbreak in which attempts to stop the disease hinge on limiting all possible hosts. However, the indiscriminate killing of domestic animals often leads to popular backlash that plants the seeds of skepticism and mistrust of government, hampering future public health initiatives. Further, in the age of vaccination establishing herd immunity becomes imperative. While the 70 percent threshold of vaccination is an impractical target for human populations because of the high cost of the vaccine and low likelihood of exposure, in dogs it has become one of the foremost tools responsible for eradicating canine rabies.

This effort is undermined by the practice of culling, or killing, the dog population when there is a rabies threat or outbreak. Culling sweeps do not discriminate between dogs vaccinated and unvaccinated, rather guided by reactionary fear in to attempt to wipe away all possible vectors. As a consequence all investment in vaccines administered to dogs, and any progress towards population immunity, is also wiped away. In many countries that remain canine endemic, turnover in the dog population is relatively high, making it difficult to sustain the target level of vaccination; culling only magnifies this problem. Rabies is a particularly nefarious disease that secures transmission in micro and macro ways. By aggressively driving infected animals to slobber and bite, the virus fosters a situation in which it it primed to be passed on to a new host even as the current one is in rapid decline. While less directly the result of pathogenic mechanism, on a population level rabies engenders dread that manifests in reactionary policies counter to effective control. Understanding salient socio-cultural perceptions of the disease is essential to then engaging, applying and critiquing mechanisms of resource allocation that seek to explain how and why medicine, money and man-power are distributed as they are.

Frameworks of Resource Allocation

Questions of resource availability and corresponding allocation have long existed because scarcity of biologics, the finances to pay for and the infrastructure to deliver health care are not new problems. There are numerous frameworks that aim to rationalize the allocation of public health and medical resources, each of which offers us some descriptive or normative dimension. Two approaches -- political economy and cost effectiveness -- each elucidate certain dimensions that define the public health redress of rabies.

Political Economy

This model of assessing resources seeks to explain distributions not based on efficiency, merit or justice but rather political power and participation. Public health and medical care are not isolated fields nor are the actors that participate in them constrained from influence and action in larger socio-economic, cultural and political structures (Breiger 2006). To understand the realities of public health challenges as well as the possible avenues for intervention, attention must be paid to larger power contexts.

The political economy approach specifically examines the role of economic and class distributions that influence perceived social and health problems, and the public and political priorities they drive (Hart 1971). This is particularly relevant to an exploration of rabies, for those most impoverished, both across the globe and within countries, carry the highest risk and consequence of rabies while receiving a smaller share of access to lifesaving medicines and funding for preventative measures (Hampson 2015). This inequitable and inefficient distribution can be viewed through Julian Tudor Hart's 1971 treatise *The Inverse Care Law* which demonstrates the mechanisms by which medical care is disproportionately concentrated among populations with relatively lower morbidity and mortality.

Hart (1971) coined 'the inverse care law' to describe the distribution of primary care services across space and socio-economic status in the post-World War II United Kingdom. He

identifies cycles of professional development and political priorities which compound to concentrate staffing, equipment and funding in communities which carry the least burden of need, while those who suffer disproportionate risk and consequence are neglected. Manpower, material and monetary resources tend to go to wealthier regions where there is already better health outcomes (Hart 1971). Hart (1971) posits that higher income groups know how to make better use of the services offered and delivered, because of accumulated education and collective expectation that such care be robust and readily available. Higher income groups are often concentrated in urban spaces or seats of political power, where they have the agency and visibility to demand care that meets their high expectations.

The Social Progress Index (SPI) is an aggregate measure of basic human needs, foundations of wellbeing and opportunity within and across countries (Porter 2016). In 2015, the United States ranked 16th overall in the composite index, and was 8th in the opportunity metric which measures personal rights, inclusion in society and access to advanced education (Porter 2016). Comparably, Tanzania was 116th in the overall ranking and 98th in opportunity (Porter 2016). Citizens of the U.S on the whole are better able to avail of structures and circumstances by which they can articulate, expect and access quality health care.

On a global level, the United States has the capacity to internally marshall resources for its own perceived need. The country is not an official recipient of any donor assistance for health (DAH). Meanwhile, in 2013 Tanzania received $1.1 billion dollars in DAH, with nearly a third of that figure directly funded from the United States government (IHME 2016). Money allocated for aid in public health often comes with strings attached mandating use that reflects the priority of the donor. Accordingly, Tanzania and other sub-Saharan countries that receive similar flows of aid are constrained in their spending and priorities. Further, a legacy of structural adjustment policies enforced by international financial institutions upon many low income countries in exchange for debt relief has had a particularly lasting effect of the veterinary

sector (Bardosh 2014). Accordingly, state capacity to address animal health and the animal interface of zoonotic diseases is greatly limited across the African continent.

Hart (1971) points out that high use rates of medical services and health resources are not necessarily emblematic of high morbidity but rather strong health seeking behaviours and an expectation of health care delivery and fulfilment. On average Americans visit the doctor three times per year while only 31 percent of women in Tanzania have a post-natal care visit (CDC 2014; USAID 2010).

In the U.S. there exists a cultural tradition that projects rabies in every animal bite; an understanding of the fatal, yet preventable, nature of the disease; and an expectation of medical intervention. Accordingly, is estimated each year around 50,000 courses of PEP are administered in the U.S. (Monroe 2015); such a high allocation of medicines may be the reason there are only two to three deaths per year. Yet, the prevalence of the rabies found in animals, both domestic and wildlife, does not match such an allocation of PEP regimens.

In 2014, the CDC reported 6,034 cases and the year before there were 5,865 animals that tested positive (Monroe 2015). For the risk of rabies to warrant the prescription of 50,000 courses of PEP one would expect a much higher prevalence of the disease in wildlife and domestic animal populations. In the United States, bat variant rabies are the most common strains to become symptomatic, and thus fatal, in humans. However, it should be noted, that tabulations of symptomatic rabies developments does not assess all possible exposures, including those where PEP may have been successfully administered. With the long history of attention towards canine and to a lesser extent feline and terrestrial wildlife rabies, individuals, physicians and officials are adept at recognizing possible exposure scenarios (Hsu 2017). However, bat-variant strains while transmitted through the same bite mechanism do not often possess the same confrontational event; bat exposures have been known to occur while a person

was sleeping none the wiser of being bitten nor able to detect the very small bite marks once awake.

In part driven by a trend of 22 of 37 clinically diagnosed cases of rabies since 2003 being bat variant, nearly 30,000 bat specimens are submitted for testing to the CDC, state and local health departments each year (Monroe 2015). Of the 28,154 tested in 2014, only 1,756 or 6.2 percent were positive for rabies (Monroe 2015). The only species to return more positive tests were racoons with 1,822 (Monroe 2015). Even these numbers portray a sense of selection bias; for a specimen to be submitted for testing it likely had to involved in a bite incident or portray some sort of abnormal behavior. Neither veterinarians, public health officials nor the general public is able to clearly grasp the prevalence of rabies in wildlife and domestic animal populations. Thus the narrative of the disease continues, just as it has been historically, to be dominated by one-off scenarios that perpetuate collective fear, rather than facts and figures that would paint a more detailed picture of variation in risk and burden. The thousands of PEP regimens delivered demonstrate a collective sense of dread risk, alongside the wherewithal and privilege to seek medical attention, not any disproportionate risk.

Further, Hart (1971) states “medical services are not the main determinant of mortality and morbidity; these depend most upon the standards of nutrition, housing, working environment, and education, and the presence or absence of war.” This is true of canine-mediated rabies, which has been progressively rolled back into its present day status as a neglected tropical disease. Rabies is prevalent in places that lack basic sanitation infrastructure, tolerate a culture around free-roaming dogs, shoulder high rates of other preventable conditions complicated by low levels of literacy and access to health services, and exacerbated by the inability to pay for any services received.

In a 2008 study of rabies exposures and treatment in rural Tanzania, Hampson et al found that risk of rabies stratified by age, wealth and geography. Finding that individuals

between 5 and 15 years of age composed 65 percent of all possible exposures echoes other literature finding that children are at an elevated risk of transmission which is in part because they have a higher probability of being bitten on the head or neck (Hampson 2008). Children are often responsible for the care and management of dogs, and because of their short physical stature are likely to suffer severe bites. The other group considered to be at elevated risk in the study were agro-pastoralist populations who were characterized by low socioeconomic status and lived at greater distances from district hospitals (Hampson 2008). Both of these traits place individuals at a disadvantage in seeking effective care following an exposure incident. Among the study participants four major means of raising funds for PEP were reported -- family savings, borrowing money, selling household properties, payment by the owner of the rabid animal -- but these differently utilized by individuals of different income status (Hampson 2008). For those identified in the study as high socioeconomic status more than 70 percent funds to pay for PEP treatment came from family savings, while those of low socioeconomic status primarily depended on loans or selling off property (Hampson 2008). Socioeconomic status also delineated the time it took for individuals to seek clinical attention for a possible exposure; 100 percent of individuals classified by high socioeconomic status sought care within three days while less than 40 percent of the low socioeconomic individuals did so in the same period (Hampson 2008). This is confounded by the delay in seeking treatment relative to distance from the district hospital. The farther from a hospital the longer after an exposure until the first course of PEP is administered. Impoverished, rural communities in Tanzania are those most at risk of the disease, yet individuals often have to bear greater indirect costs to seek care at great distance while taking on greater precarity to pay for lifesaving PEP.

While collective understanding of determinants and drivers of disease has expanded exponentially in the past few centuries, the health picture surrounding rabies is still marked by uncertainty and inequity. Of the 59,000 rabies deaths around the world 95 percent occur in

Africa and Asia, and yet the disease continues to attract money and medicines in Western Europe and the North America where it is no longer canine-endemic (CDC 2016). Allocations of facilities, staff, funds, time, biologics, are made according to projected or estimated need and costs, not the ones to be actually incurred, but they are also concentrated in the places where politically active and powerful constituencies demand they be.

Hart (1971) writes "No act of courage is required of the individual doctor (or of the administrator) by going where or allocating resources to the place that already has the expectation of high quality delivery of health care." The challenge is then to be courageous enough to question the current distribution, to problematize and seek remedy for biologics shortages that occur in canine-endemic countries, to limit over-administration of PEP in the U.S., and to challenge the specific socio-cultural superstructure of rabies which underpins all the above. The frame of political economy analysis seeks to expand upon the forces which influence resource allocation. As rabies is a disease characterized by great socio-cultural weight, identifying the groups that are best able to articulate their fears of the disease and seek out care, is not just a project of identifying differential risk but also power dynamics that concentrate care and resources among politically active and visible communities. With an eye towards improving equity in the burden and corresponding investment understanding the political economy of the disease is particularly important because of the persistent risk of canine-mediated rabies in low income countries, and within such countries in young, rural and impoverished populations.

Cost Effectiveness

Scientific and sanitation advances have rendered many previously fatal and widespread conditions treatable and controllable, but they have also opened up limitless possibilities for accrual of costs. In order to rationalize individual and governmental health spending, cost effectiveness models seek to measure the efficacy and productivity of an intervention or

treatment. Defining cost effectiveness for post-exposure rabies prophylaxis ties together the cost of the biologics administered, the related health care costs of administration and delivery, the probability of rabies transmission and the value of a life.

Relative to many other medical interventions, the biologics delivered prophylactically for rabies are quite expensive, and their costs vary greatly across the globe. In Tanzania, a dose of the vaccine procured through the government costs about 11,000 Tanzanian shillings (~USD $10), Frequently government supplies are not available and patients pay 25,000 shillings (~USD $20) per vial of vaccine from private clinics or chemists (Shim 2009). Recommended vaccine schedules require four or five doses, bringing the cost somewhere between USD $40-100, in a country where the World Bank (2016) placed gross domestic product per capita measured in purchasing power parity (GDP/PPP) in 2015 at $2672 (Cost of PEP ±5% of annual GDP/PPP). There is similar high cost variability in the United States. A study of PEP delivery the U.S. in the early 2000s found the cost of biologics ranging between $113 and $679 for a single dose of vaccine (Dhankhar 2008). Additionally, PEP in the U.S. and high-income countries includes a dose of human rabies immunoglobulin (HRIG) which is administered with the first dose of vaccine and costs an average of $761 (Dhankhar 2008). All told the cost of the medicines alone in the United States is between $889-4831 (Dhankhar 2008, Kreindel 1998), where per capita GDP/PPP was $56,115 in 2015 (Cost of PEP ±7% of annual GDP/PPP). In both locations, the cost of care escalates when direct costs of medicine delivery and follow-up appointments are tabulated, also increasing with the indirect costs of taking time off work or traveling to a clinic to seek care. Relative to average income, the cost of PEP administration is about the same in Tanzania and the United States. It is undeniable that across locations treatment for rabies is expensive.

Cost-effectiveness scenarios thus measure the return on that investment. Rabies' fatal dichotomy -- symptomatic development nearly always yields death while prompt administration

of vaccine doses while HRIG is nearly 100 percent effective in preventing onset of the disease -- plays a big hand in determining the equation (Shim 2009). Should PEP not be administered following actual exposures the loss of life and corresponding value to such lost years, can be relatively enormous, especially considering that children are disproportionately represented in suspected bite victims (Hampson 2015). Shim's (2009) Tanzanian study looks at the return on PEP through quality adjusted life years (QALYs), a metric that quantifies burden of disease by assessing the quantity and quality of life should an intervention be applied; on a scale between 1 and zero, the upper band represents one year of perfectly healthy life while zero represents death. By dividing the costs of PEP by the metrics of the effectiveness and application of of such treatment, the study produces estimates for the costs of QALYs from both healthcare -- only medical costs -- and societal perspectives -- direct and indirect costs to the patient and provider. It was found that considering a normal life-expectancy of 51 years in Tanzania, cost effectiveness per QALY was $27 from a healthcare perspective and $32 for a societal valuation (Shim 2009). To evaluate the degree of relative cost effectiveness, the price of gaining additional healthy years is measured relative to GDP per capita, which makes rabies interventions an attractive investment. With similar aim but differing methodology, Dhankhar's study (2008) of cost-effectiveness in the U.S. applies "the average present value of expected future earnings … assuming an average lifespan of 75 years" to come up with the valuation of a human life at $1,109,920 in 2004 dollars. The study then weighs the cost of treatment and the probability of a true rabies exposure to measure cost effectiveness and cost savings, finding that "so long as the risk of the patient getting rabies is deemed greater 0.7% then giving PEP will be cost-saving" (Dhankhar 2008).

Layered into both of these analysis is the reality that often it is unknown whether a rabid exposure has occurred, and also the increasing finding that not all rabid animal exposures result in the development of symptoms. The first point results from the fact that offending animals are

often not available for testing and confirmation, thus probability of exposure is determined through behavioural clues, animal vaccination history and context of the possible exposure. The second is an important paradox that underlines persistent lack of knowledge about the disease. Tracing more than 1000 bite-injuries in northern Tanzania between 2002 and 2006, Shim's (2009) team constructed a probability tree based on hospital and clinical records, community-based surveillance activities and retrospective interviews to determine the likelihood of various bite scenarios resulting in the development of rabies. Bites to the head and neck occurred less frequently than bite injuries to the arms, legs and trunk, but resulted in a higher probability of developing rabies given an exposure with a rabid animal. Surprisingly, though, the probability of developing rabies, given a bite by a rabid animals and without prompt delivery of PEP is just 0.19 (Shim 2009, Table 1), which undermines cultural narratives of violently assured death when any exposure to rabies is not treated. Dhankhar similarly presents data that estimates the risk mortality resulting multiple bites to the face and neck from a laboratory confirmed dog or cat is only between 60 and 70 percent (2008, Table A1). While these findings do not challenge the progression from symptomatic rabies to death, it does call into question the likelihood of such symptoms developing in the first place. However, this is impossible to test or confirm in any sort of controlled trial because while it might be found that the risk of developing symptoms after a known rabies exposure is less than currently understood to be, those unlucky enough to develop symptoms would die, an outcome preventable given standard measures of care -- PEP -- thus no ethical research review board would, or should, ever sanction such a study.

Further problematic with cost-effectiveness models that evaluate a mortality-preventing intervention is the need to place a cost on a human life. Drawing on predicted future wages and respective life expectancy, each study creates a valuation. The stark dichotomies of outcome for rabid exposures creates high qualities of return on investment through QALYs. A rabid exposure without prompt PEP results in near assured fatality of a most painful variety, while the

administration of a full regimen of shots alleviate the risk and return the patient to their normal health. This is further compounded by the fact that 40 percent of victims are under age 15. With relatively young victims, effective administration of PEP has the potential to yield more years that an intervention for a health condition that might strike later in life.

The valuation of components in cost-effectiveness models vary across time and space. While public health is often envisioned at the global level, it is governed at the national and conducted at the local. In each of these settings, there are different conceptions and financial realities of what it means to be cost effective. For the United States, financial costs of medical care are buttressed by a web of insurance, price negotiations and government subsidies. Even as health insurance is extended unevenly to the population of the United States, there remains a systemic aversion to rationing or redistributive mechanisms which allows for overspending on unnecessary procedures and services (Teutsch 2012). Conversely in Tanzania, Kipanyula (2015) found the cost of PEP must be born by the victim, the family or in some cases the owner of the offending dog.

Despite the comparatively high costs of PEP delivery, and the variability in assessing exposures and the probability a suspected rabies exposure results in death, cost-effectiveness models advocate for the widespread application of the PEP. In Tanzania, the baseline threshold found for being 'very cost-effective' was that at least 1 percent of all people who were administered PEP were actually exposed to rabies. However, outlining that PEP is still cost-effective when 99 percent of those receiving a dose were not truly exposed, calls into question the utility in applying cost-effectiveness models when the benefits of the intervention cannot be measured with certainty. Budget devotions to public health and medical interventions are constrained at every level from the household to the global health community, necessitating interventions that are not just cost-effective but efficient. When applied to cases of known rabies exposures, PEP is incredibly effective in reducing mortality and yielding high returns on

investment. For countries like Tanzania, widespread and readily available access to PEP is fundamental to preventing rabies deaths among populations most at risk. However, in the United States where risk is reduced as rabies is only mediated through wildlife population if cost-effectiveness justifications are taken to their logical ends, PEP would be administered in a manner so widespread that more than 90 percent of biologics could be administered in cases where there was no true rabid exposure. This would only serve to perpetuate the collective historical tendency to apply a public health and perceptive response that does not match the medical and epidemiological realities of rabies.

Future of Rabies Control and Address

In the last 15 years, there have been three developments that each have the possibility to alter the way rabies is understood and treated. In 2004, the first documented case of survival of post-symptomatic rabies without vaccination took place, leading to a protocol that undercuts the certain fatal outcome of rabies when PEP is not administered. Second, Canada's National Advisory Committee on Immunizations shifted its policy in bat-exposure scenarios in 2009, trending away from widespread PEP administration to more judicious application. Finally, the World Health Organization has set 2030 as the target year for elimination of canine-mediated rabies.

First, for more than a century, Pasteur's vaccination remained the sole course of treatment available for rabies. It worked to such great effect that there was little incentive to develop new strategy or technology. However, the multi-shot course was of little use for patients and physicians when rabies had progressed to the symptomatic phase of the disease; for them there was no recourse. That changed in 2004 when fifteen year old Jeanna Giese fell ill, presenting with vomiting, fatigue, loss of coordination, and disruptions in vision and speech. She was transferred to the care of Dr. Rodney Willoughby at Children's Hospital of Wisconsin in

Milwaukee with an ominous case history of a bat bite four weeks earlier. After testing for other causes of the symptoms and having the CDC return a positive on rabies antibodies in her cerebrospinal fluid, Willoughby set about designing a novel course of treatment.

As the doctor had never before seen a case of the disease, he focused on literature that supported excitotoxicity as the mechanism that facilitated mortality. There are competing theories to the way rabies inflicts the brain and body but a prominent belief is that disease operates by manipulating neurotransmission to overstimulate the cells of the brain driving cardiac, muscular, nervous and other bodily systems to exhaustion and death (Wasik and Murphy 2012a). Willoughby postulated that given time to rest and instigate an immune response the body might be able to fight off the infection. In consultation with Giese's parents and the doctors on his team, Willoughby induced a coma by employing ketamine in combination a variety of antivirals and sedatives. A tense week of waiting was rewarded when tests revealed the number of viral antibodies in Giese's system had multiplied. And yet, when the sedatives were removed, Giese's body was slow to recover stimulating fears she would forever be rendered debilitated by her treatment. Against all odds, she recovered, slowly and surely regaining function of her limbs and speech through therapy. In the course, she made history as the first documented case of survival of rabies after symptomatic onset in which no vaccine had been administered. From Giese's case came the Milwaukee Protocol published by Dr. Willoughby laying out the treatment he had administered and in the course disrupting thousands of years of belief on the assured fatality of the disease after onset.

Since the success of Giese's case, the Milwaukee Protocol has held mixed results. Administered more than 35 times, five patients have survived, though with varying degrees of recovery. Perhaps the most successful case beyond Giese is that of eight-year old Precious Reynolds, who was brought to UC Davis Medical Center in Northern California in 2011 with severe flu-like symptoms (Wasik and Murphy 2012a). Likely exposed by a stray cat she'd

encountered at recess, Reynolds had not received any post-exposure treatment until her doctors placed her in a ketamine induced coma. Her recovery was even quicker and more robust than Giese's, with some pointing to the youth and athleticism of both patients as key to their fortuitous outcomes. Many physicians dispute the efficacy and ethics of the Milwaukee Protocol but "the survival rate ... is wildly impressive when compared with that imposing baseline of zero, buttressed by thousands of years of medical history" (Wasik and Murphy 2012b). Some doctors challenge Willoughby's excitotoxicity theory of pathogenicity, reifying the more traditional encephalitis, or swelling of the brain, theory. Other critics point to the high cost of the treatment

While the development of the Milwaukee protocol adds to the compendium of possible rabies treatments, the common ability to diagnose the disease before symptoms develop is no more advanced than when Pasteur was in residence in Paris. As new campaigns to fight disease are inaugurated and funds dedicated, there must be a prioritization of new research and technology for rabies, and every other condition. The lack of innovation partly determined by the dramatic course of the disease which leaves little room for intervention once symptoms have set on. But in the time that's passed the capacity to test, see and treat microscopic organisms has grown exponentially. Is it not due time that we seek to develop a diagnostic test to detect rabies virus at the site of a possibly rabid bite, or even along the neural pathway as the germs make their way towards the brain. Even as the case of Giese and others opens possibilities for rabies survival previously unimagined, the Milwaukee Protocol is not a course of treatment possible or affordable in regions where rabies inflicts the greatest burdens of mortality.

Second, in 2009 Canada altered its recommendations for PEP application in bat-in-the-bedroom scenarios marking an important policy shift and example in countries where canine-mediated rabies have been eliminated. In places where only wildlife strains remain present, the animal that contributes the most to case totals in both domestic pets and humans is bats, yet because of their small body and tooth-size it is often difficult or impossible to determine if an

exposure has occurred. Presently in the United States, and until the policy shift in Canada, the documents which advise physicians and public health officials advocated PEP administration for all cases in which a bat was found in the company of an individual -- a sleeping person, a child, someone intoxicated or cognitively impaired -- who could not reliably recall or observe a potential exposure.

Noting the rarity of human rabies cases related to bats in Canada -- approximately one every 5 years -- the National Advisory Committee on Immunizations (NACI) kept the definition of direct contact as a bat touching or landing on a person, but narrowed the former advisement that all bat-in-the-bedroom instances should be treated prophylactically. Now, unless adults report a bite, scratch or saliva contact with a prior wound or mucous membrane, PEP is not advised. With children observation and recall of an incident is more unreliable which the NACI recognizes with greater flexibility in recommending prophylactic intervention. The most notable change regards when a bat is found in the room with a child or an adult who is unable to give a reliable history. “Analysis conducted in Canada estimated that a case of human rabies related to bedroom exposure to a bat (i.e., finding a bat in the room of a sleeping person with no recognized physical contact with the bat) is expected to occur in Canada once every 84 years. In addition, it has been determined that, to prevent one case of rabies from bedroom exposure to a bat, using a conservative estimate, 314,000 people would need to be treated” (Public Health Agency of Canada 2015).

Cost effectiveness assessments of PEP encourage widespread use, because the intervention is highly effective in terms of QALYs gained, if there is a rabid exposure. However, in this case there seems a conclusion that administering PEP for bat in the bedroom scenarios exceeded the comparative threshold for the cost-effectiveness of PEP found by Shim (2009) and Dhankhar (2008). Those studies set forth that about one percent of PEP administrations need to be true exposures of rabies to justify the financial cost. From a political economy standpoint,

this decision recognizes Canada's relatively low burden of rabies and risk of contraction in the specific scenario described. In scaling back the threshold for PEP administration, this policy steps away from concentrating resources where they are already readily available, and seeks to limit the excessive use of biologics.

The Canadian Department of Health found the prior allocation of medicines disproportionate to risk and costs, and responded with a policy change. The ramifications of this recommendation remain to be seen. Assessing whether a there is a reduction in PEP courses administered or if a human rabies case arises out of the kind of scenario adjudicated above will determine if more judicious use of PEP can be legislated in countries where a low burden of rabies is driven primarily by wildlife exposures.

Finally, 2030 is the date by which the Global Alliance for Rabies Control (GARC) composed of the World Health Organization (WHO), Organization for Animal Health (OIE), Food and Agriculture Organization (FAO) and the Gates Foundation, has set a target to eliminate canine-mediated rabies. The project rests on five pillars to address various aspects of the disease:

> "The **socio-cultural** approach will encourage the promotion of responsible dog-ownership, and dog population management practices, including dog vaccination. The **technical** approach will strengthen animal health and public health systems to ensure sustainable, safe, efficacious and accessible dog and human vaccines and immunoglobulins, and promote and implement mass dog vaccination as the most cost-effective intervention to achieve dog-mediated human rabies elimination. A good **organizational** set up will ensure sufficient supply of quality-assured canine rabies vaccines through vaccine banks. **Political** commitment will be crucial in promoting the One Health concept and intersectoral coordination through national and regional networks while implementation will necessarily require **investments** in rabies elimination strategies" (WHO 2016, emphasis from original text).

All of these dimensions of rabies control make sense on paper, but the challenge now comes in putting them into practice. With every 'top-down' intervention there are risks that new large-scale control programs will encounter fairly stereotypical challenges of working in low income countries where overlooking critical social, cultural, political and economic contexts

undermines effectiveness (Bardosh 2014). The technical prioritization of vaccine delivery is bolstered by the existence of an effective vaccine for both humans and dogs. The catch comes in ensuring the access to such treatment, both by means of physical distance and cost. On the human front, the rarity of exposures often means hospitals do not have sufficient supplies of the time-sensitive prophylactic. For dogs, the effectiveness of vaccination campaigns depends on provision of free vaccines, and adequate awareness of such an offering in the community, because individuals and families often do not have the disposable income to prioritize for such an expenditure. Understanding and mitigating the time and financial cost barriers is essential to widespread vaccine availability and uptake.

Thus, improving on organizational flows may be one of the most important elements proposed by GARC. Shortages are frequently cited in situations where PEP would otherwise be administered. While it is not a zero-sum equation between overuse of PEP and HRIG in countries where canine-rabies has been eradicated and a need in canine-endemic regions, judicious use of the biologics should be prioritized everywhere. Throughout its history rabies has been emphasized beyond the extent of the burden it exacts, marshalling reaction and resources based on the emotive profile of the disease. Building strong organizational relations depends on knitting together diverse structures of national health care, international programs, non-governmental energies and local particularities.

Interventions against rabies have the feature of both being very cost effective and relatively expensive. Funds dedicated for elimination strategies must walk this contradiction, while also being wary of the nature of diminishing returns in eradication programs. Only one disease has ever been completely eradicated -- smallpox -- but as polio, guinea worm and others have chased the elusive zero reported cases, millions of dollars have been siphoned into eradication efforts. The rationale for addressing canine-mediated rabies currently rests on the persistent number of deaths despite the existence of an effective vaccine, and proven strategies

for dog control, surveillance and vaccination. However, to avoid narrow implementation that fails to encompass both sides of the human-animal interface of rabies, funding must be applied to multidisciplinary programs. Eliminating canine-mediated rabies needs to involve both veterinary and public health sectors; acknowledging that as a zoonotic diseases rabies exacts the greatest burden in humans while the most cost-effective and sustainable course of address comes in vaccinating dogs mandates participation on both parts (Bardosh 2014).

And finally, essential to GARC's project is understanding and applying socio-cultural understandings of rabies. Collective understandings of the disease are not even across place and time but they can hold a salient quality that remains even after the disease context has shifted. Perceptions of the disease and specifically dogs are influential to shaping the application and success of elimination programs. Understanding the conception of dogs in a society is central to the deployment of vaccination campaigns that are the most cost effective method of seeking elimination (Kipanyula 2015). While investigation of societal perceptions and education about the dimensions of rabies are important to the effort, external influence should not be overstated in dictating a community's relationship with dogs, nature and rabies. Across the world, even if canine-rabies should be increasingly and progressively eliminated, rabies will continue to draw attention and investment due to its long history of fatality and fear.

Conclusion

The long history of rabies has led us to a moment of contradictions with inequity alongside hope, uncertainty meeting new scholarship, intractability challenged by new investment. The disease remains one that carries great socio-cultural weight across diverse epidemiological contexts which plays a great hand in determining allocations of medical resources as well as possibilities for policy prescriptions and control interventions. Even as the geographic extent of canine rabies is limited to low income countries, and the Global Alliance for

Rabies Control seeks to roll it back further, rabies will always be a part of our ecosystem. As a disease that inflicts more species than just humans and dogs, in various other mammalian hosts, especially bats, rabies is not a candidate for full eradication, thus reaching sustainable levels of herd immunity in dog populations and judicious use of PEP will remain a constant project. Ideally, increased investment and success of dog vaccination programs can lessen the risk of rabies to such a degree that expenditure and consumption of PEP may be reduced. For the foreseeable and extended future sustained and widespread dog vaccination programs will be necessary across high and low income countries. We have lots more to learn about rabies, and to the degree that improved data may aid public health officials and the general public in making decisions on the redress and risk of rabies, these investments are necessary. It's also fundamental to recognize that we have an age-old relation with this deadly virus, and that the perceptions and policies held today are the result of centuries characterized by a fear and uncertainty, but also remarkable medical innovation that has rendered rabies a preventable condition. By improving understanding of the disease in all its contexts, educating on the risks and proper courses for treatment, as well as prioritizing attention and funds to where rabies remains prevalent in canine populations, may we seek to reach a more equitable and sustainable burden of rabies around the world.

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