Wildlife Rabies: Past, Present, and Future

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Abstract:

Rabies is a fatal viral disease that infects the central nervous system and has afflicted humankind for millennia. Though vaccines have largely stopped the threat of the disease in the developed world, complete eradication of the disease is only possible through the vaccination of wildlife. Efforts to do so have involved population control, oral vaccines, and the trap-vaccinate-release method. However, these vaccines are limited to certain species and difficult to distribute globally, so rabies is still rampant in Asia and Africa. This literature review discusses the history of rabies vaccination in wildlife, its effectiveness around the world, and what new technology scientists are developing to combat rabies in wildlife.

Introduction:

Rabies lyssavirus, more commonly known as rabies, has spread worldwide to scourge both human and animal kind for millennia and is now responsible for thousands of human deaths every year, predominantly in Asia and Africa. It has the highest mortality rate of any disease on Earth (1). A zoonotic virus, it can be transmitted between humans and animals, and it is commonly spread through broken skin or mucous membranes. These membranes are typically ruptured and infected through animal bites, as the virus is secreted in the saliva of an infected animal (2).

Rabies is also a neurotropic virus, meaning it attacks the nervous system. Once in an infected organism's body, the virus replicates slowly enough that it doesn't raise any alarm in the immune system, allowing it to spread uncontrollably (3). It replicates enough to bind to the nicotinic acetylcholine receptors at a neuromuscular junction (Figure 1; 4). This allows the virus to migrate through the peripheral nervous system during an incubation period that typically lasts 2-3 months (2). It eventually reaches the central nervous system and replicates in the spinal cord's motor neurons and dorsal root ganglia, from which it enters the brain (4). It passes through the blood-brain barrier, where cells from the immune system can't reach. Even if T-cells from the immune system do pass through this barrier, the rabies virus kills them. Once in the brain, the virus causes neural dysfunction through disrupting the function of proteins. There, it results in encephalitis, or deadly inflammation of the brain. The virus also spreads back out through the body to organs and especially to the organism's salivary glands. Three symptoms of rabies, hypersalivation, hydrophobia, and aggression, make sure there is both enough saliva for the virus to easily be transmitted and make the organism more likely to bite another organism, ensuring a continuation of the virus (3).

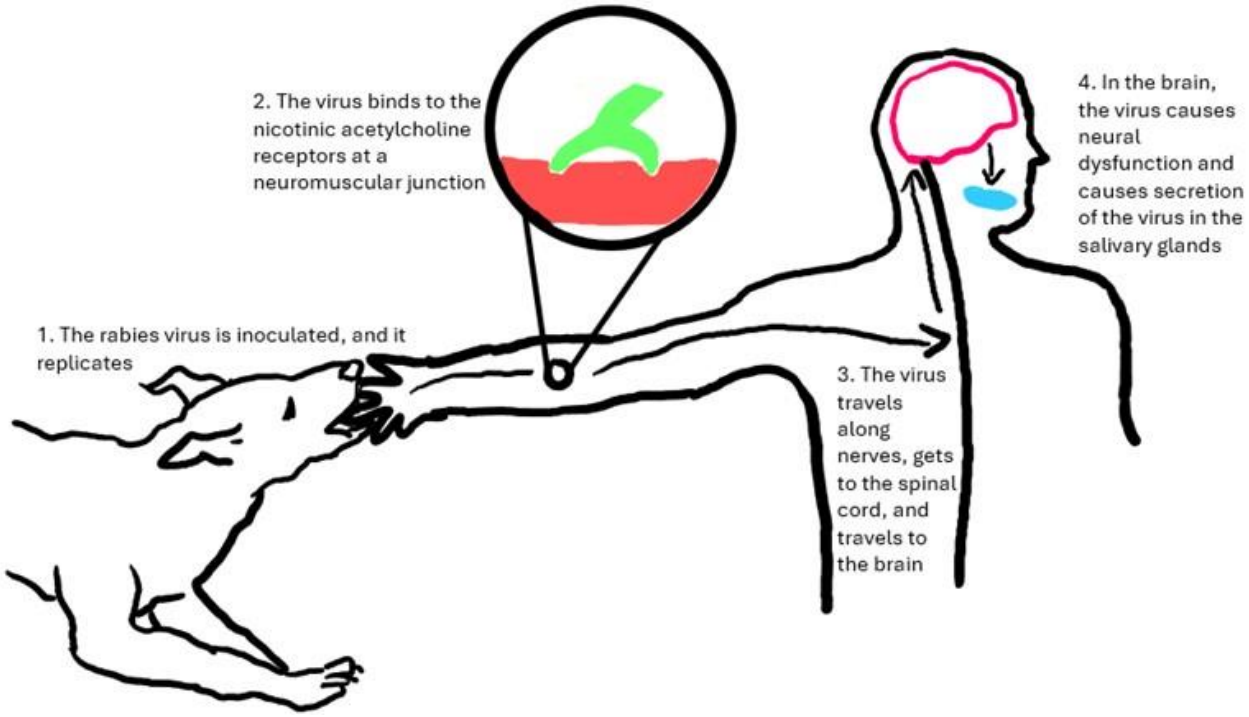

Figure 1. The path of rabies through the body: replication at the site where the membranes are ruptured, binding to the nicotinic acetylcholine receptors, moves along nerves to dorsal root ganglia and then to the brain.

There are two types of rabies: encephalitic and paralytic. Scientists have yet to definitively identify the pathophysiologic differences between these different forms, but the symptoms of each have been defined. Encephalitic rabies is much more common (80% of cases), and infected individuals are hyperactive, hydrophobic, and die within days. The progression of paralytic rabies, on the other hand, is more gradual and pernicious. It slowly paralyzes the muscles until the infected individual is comatose or suffers from respiratory failure (1).

Though fatal, rabies is preventable. The first rabies vaccine, effective on dogs and humans, was developed in 1885 by Louis Pasteur (2). Thanks to scientific progress and public health awareness, the rabies vaccine has essentially eradicated the virus in the domestic pet populations of developed countries, so people in these nations have a low risk of contracting rabies. Indeed, 90% of rabies cases in the United States are from wildlife (5), a testament to how effectively the domestic pet population has been vaccinated. In less developed nations, access to vaccines is limited and people are much more likely to get the virus. Yet even after being infected with rabies, humans can survive – provided that they have access to post-exposure prophylaxis (PEP) which, for rabies, is a series of four vaccines. In the case that the individual is unvaccinated before exposure, they receive rabies immunoglobulin in addition to the vaccines (2). Scientists are still working on eliminating rabies in wildlife, which have, in recent years, become the disease's most widespread carriers in the United States as more domesticated animals get the vaccine (6).

The primary purpose of this literature review is to delve into the historical attempts to combat wildlife rabies and assess future plans for eradicating the virus.

The History of Wildlife Rabies:

People have known about rabies for thousands of years and have always feared it. The first written record of a rabies-like disease is in Babylon's Esmuna Code, written around 2300 B.C. (7). For as long as people have known about rabies, they've created various homeopathic cures to combat it, often with limited effect. For example, Celsus, a Roman scholar, suggested holding victims of rabies underwater to cure them (7). Among the Plains Indians of America, people that were thought to be infected rabies were wrapped in a buffalo hide and swung through a fire, then plunged into cold water (8). In 18th century America, madstones, the calcified hairballs of ruminants, were common cures for rabies, as it was thought they had special healing powers (Figure 2; 7). It wasn't until Pasteur's vaccines that humanity had an effective way to combat rabies. From his work, scientists such as Emile Roux, Claudio Fermi, and David Semple were able to create the vaccines used today (7).

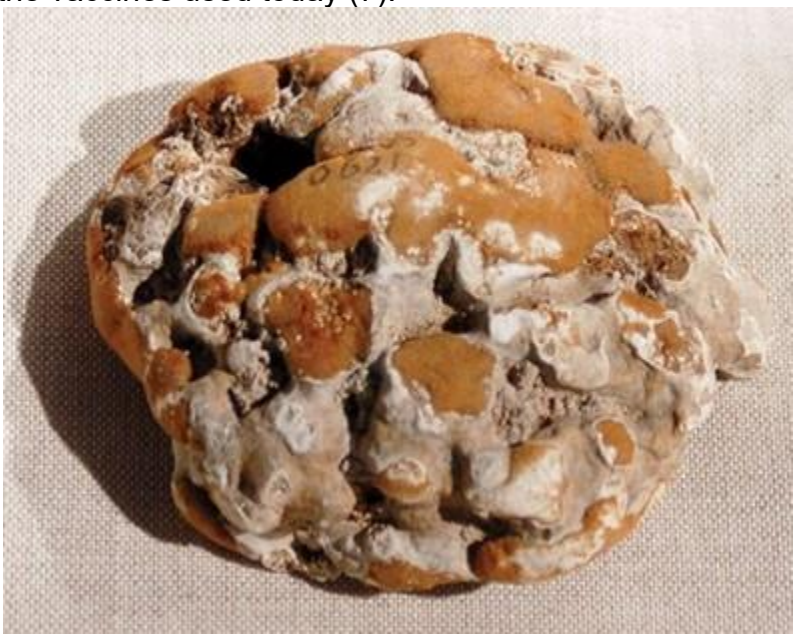

Figure 2. A madstone was used for curing rabies in 18th century America (9).

Through phylogenetic tracing, it was determined that rabies, along with other lyssaviruses, likely originated in Old World bats (10). From there, it spread among mammals and eventually got to the bats and skunks of the Western Hemisphere. Before European colonizers, however, there was no record of rabies in dogs in the Americas (10). The introduction of canine rabies through the colonists' dogs allowed the spread of the virus to other North American mammals such as foxes, wolves, and racoons, and increased the incidence of cases of human rabies overall.

In previous centuries, domestic animals caused the greatest number of rabies cases, as they had the most contact with humans. In the 1900s, however, when a greater focus on rabies vaccines developed, more pets received vaccines and wildlife became the more serious carrier

(1). The specifics of rabies in North American wildlife have fluctuated over time. While foxes were the largest group of carriers in the early 50s, raccoons and bats took their place as different methods, such as fox depopulation and the invention of oral vaccines, were developed (Figure 3; 11).

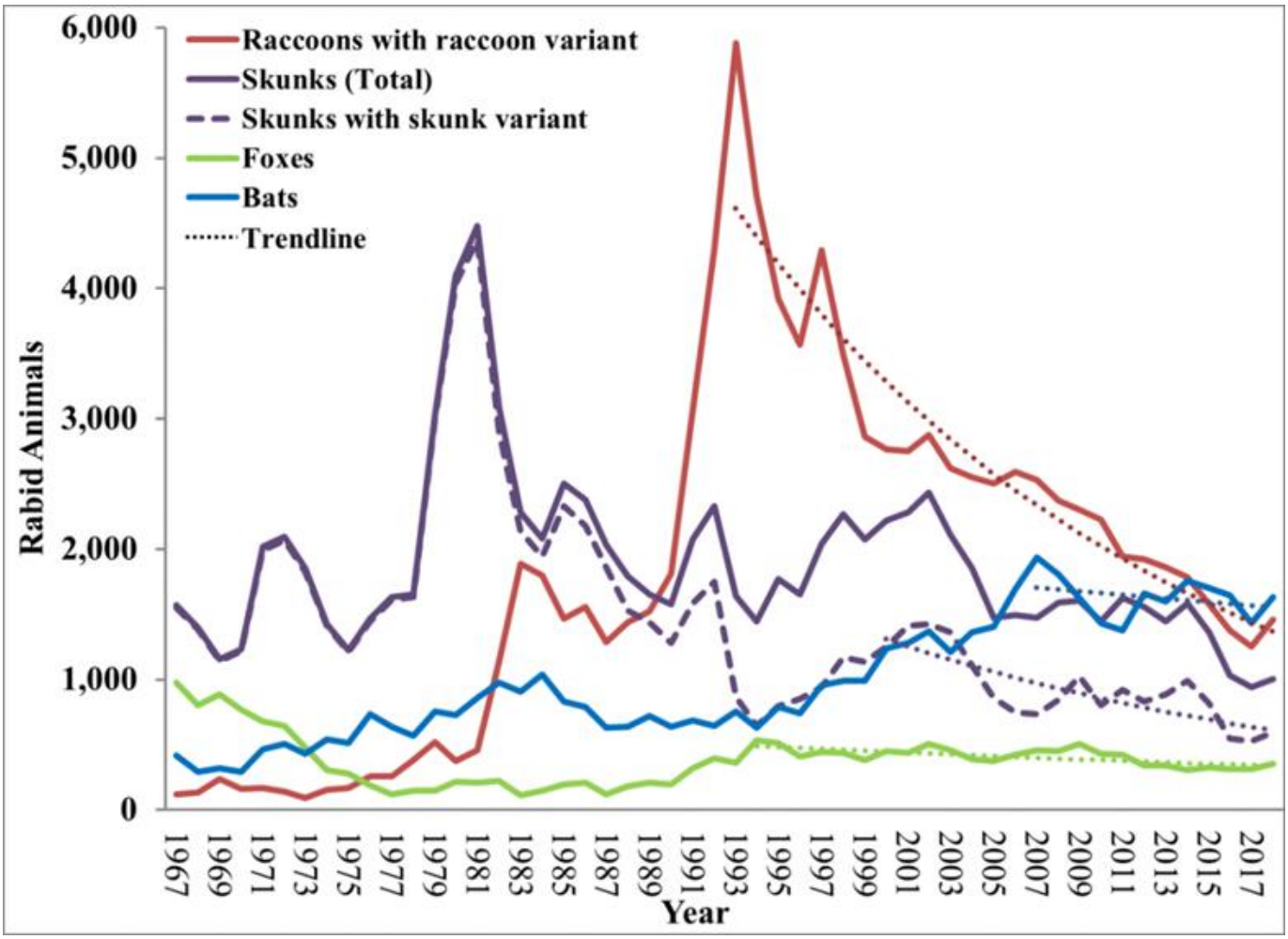

Figure 3. The number of rabid animals across different species in the United States has changed over time (12).

As can be seen in the graph, there have been spikes in the population of rabid animals in various species throughout history, such as skunks around 1980 and raccoons in the early 1990s. These spikes were often the result of increased animal populations. For example, the raccoon spike was the result of the translocation of racoons from the southeastern United States, augmenting the raccoon population and spreading diseases (13). Though people have always tried to eradicate rabies in general, these outbreaks in particular have resulted in increased efforts to combat wildlife rabies.

Methods of Controlling Wildlife Rabies:

Depopulation was the first method to keep wildlife rabies in check and has been used for all of human history, as it used to be the only possible method. This technique involved culling large populations of the species of animals known to carry rabies, usually right before breeding season. In the past few decades, this method was sometimes combined with a chemosterilant, a chemical compound that stops reproductive processes and reduces the population of a rabies vector species (14). Though straightforward, it was generally labor-intensive and inefficient at preventing rabies spread (15). Depopulation also overwhelmed animal shelters with euthanasia demands (14). Given it was impossible to eradicate an entire population of animals, the spread of rabies continued. It also raised questions of ethics and the rights of wild animals. Opponents of the depopulation method argued that it was unfair to kill the animals solely because they had rabies (16). Some argued the opposite, however, saying that it would be unethical not to kill them, as they would suffer and increase the risk of human health problems. Depopulation is still sometimes used today in conjunction with other methods. In Ontario, for example, when there was an outbreak of raccoon rabies, depopulation was first used before oral vaccines were administered (17).

To augment the effects of depopulation and create a more ethical approach, scientists in the late 1970s worked to create the oral wildlife vaccine, Raboral V-RG, that is widely used today. Oral vaccines place this vaccinia rabies glycoprotein in sachets for wild animals to eat (Figure 4) (18, 19). These sachets are often covered with fishmeal, vanilla, or another strong-smelling substance to bait animals into eating them. The sachet breaks open, releasing the liquid vaccine in the animal's mouth. The animal then creates antibodies in response to the vaccine that can be used if they actually are infected with rabies in the future. In rural areas, the bait is typically scattered from an aircraft. In urban areas, it's distributed by hand so as to not harm humans living in the area (19).

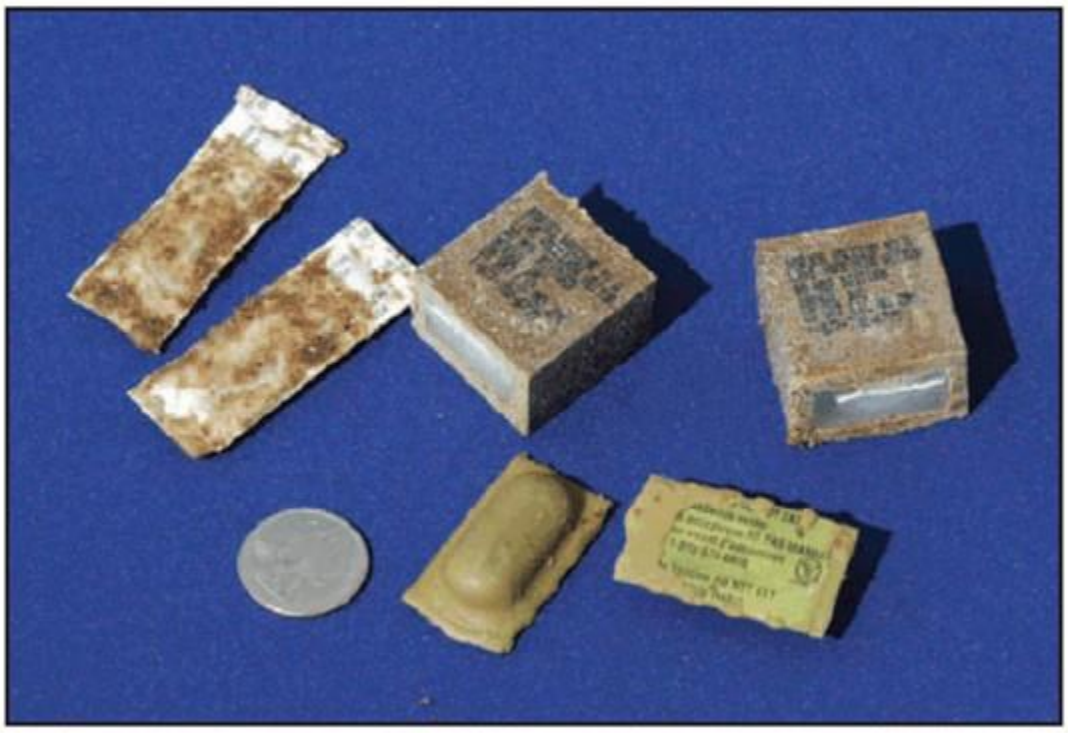

Figure 4. Bait containing oral vaccines, with a coin for size comparison.

They were tested extensively before being put into the field and were found to have no negative effects on the animals or the environment, unlike depopulation, which can often throw an ecosystem out of balance (20). However, that's not to say oral vaccines don't have any problems. Their biggest issue is their exorbitant cost – around $1 - $1.5 for each piece of bait (21). Though this might not sound like much, given that each outbreak of rabies is commonly treated with around a million sachets (21), the costs can quickly add up. Additionally, these vaccines also only last for a year, so even if they do drive down rabies cases, they have to continually be administered at high costs (22). All that being said, the oral vaccination method has been used with devastating effectiveness against wildlife rabies. For example, in Texas, oral vaccines were first used against the fox rabies variant in 1996. From 2015 onwards, there hasn't been a single case of that strain of rabies in the area (23). Additionally, from 1989 to 1995, oral rabies vaccines were successfully used in Ontario to eliminate the arctic fox variant rabies found there. This method of wildlife rabies control has completely eliminated wildlife rabies from Belgium, France, and Luxembourg (23). At the moment, it doesn't seem feasible to complete eliminate wildlife rabies from North America like has been done in these European countries simply because North America is so much bigger.

Trap-vaccinate-release or trap-vaccinate-neuter-release procedures are sometimes used instead of oral vaccines. These procedures can be more effective than oral vaccines because the vaccine is injected intramuscularly or parenterally rather than passing through the digestive system as with oral vaccines (24). Both trap-vaccinate-release vaccines and oral vaccines are not harmful to pregnant animals because the rabies in the vaccine is inactivated. However, the mother does not pass her immunity along to offspring (25). Trap-vaccinate-release procedures are not used annually, or as preventative measures, but when cases of rabies are discovered as the numbers of immunized animals fall (26). Unfortunately, trap-vaccinate-release procedures are also labor-intensive and extremely expensive at about $616/ (21). That being said, the trap-vaccinate-release method is still effective, as seen with the rabid raccoon population in Central Park. It was able to contain the spread of rabies and stop rabies from being a major problem in New York City (26).

Why Rabies is Still a Problem:

Though vaccines can successfully stop wildlife rabies, the difficulty lies in ensuring access to the vaccine. Rabies is primarily a problem in Africa and South Asia, as the countries there lack access to convenient, affordable vaccines for humans or wildlife (27). Clinics are often far away and expensive for individuals, and many governments cannot afford to implement a broad vaccination program. In the US, for example, about $500 million is spent annually on rabies control (28). It is estimated that in Africa, anywhere from $800 million to $1.55 billion is needed to eliminate rabies entirely (29). The continent's current $240 million budget (30) is nowhere near that number.

In these countries with lower socioeconomic statuses, rabies vaccination initiatives often do not take priority for government funding. In a country like South Sudan, where millions of people are food insecure (31), governments must allocate limited funds to the more pressing issues. Wars, natural disasters, and corruption further increase the difficulty of implementing rabies control when communities struggle to have basic human rights met. Few countries have long-term plans for combating rabies (32).

Furthermore, public awareness about rabies transmission, seriousness, and PEP is lacking. After coming into contact with possibly infected wild animals through a bite or scratch, many people decide not to seek medical attention because it's often dismissed as something that will heal on its own (33). There is a far greater chance of death if people don't receive the vaccine immediately, and this lack of awareness contributes to a great number of deaths each year. These deaths are often not reported as rabies, which contributes to governments being less willing to fund programs against rabies because the problem doesn't seem as bad as it actually is (34). Even if people try to get PEP, they often only get the first vaccine in the series when four vaccines are needed (33), either out of lack of funds or lack of awareness.

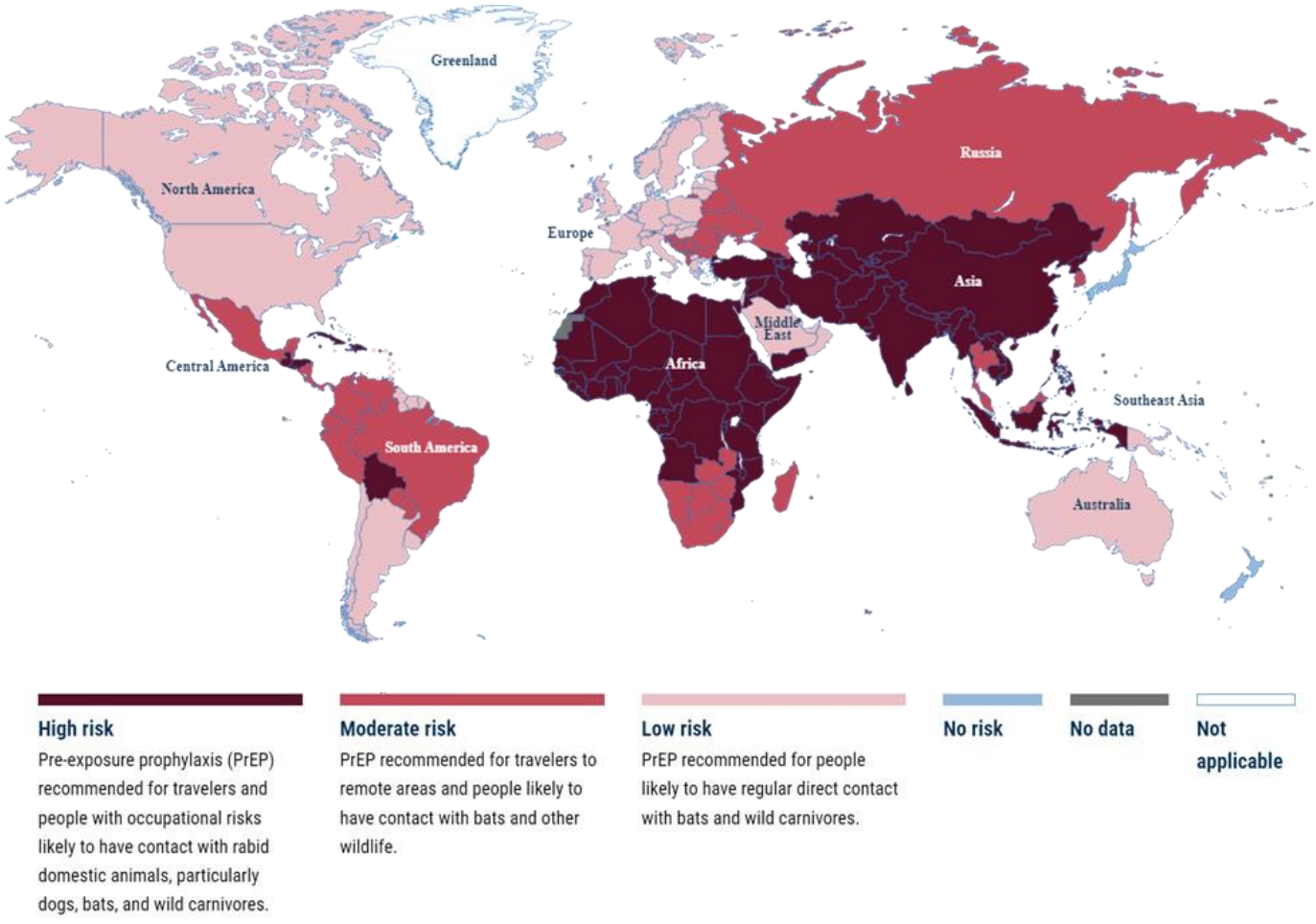

Figure 5. The incidence of rabies cases worldwide is highest in Asia and Africa (35).

As seen in the map (Figure 5), rabies is still a problem even in countries with higher gross domestic products (GDPs). These countries can also lack public awareness. In China, for instance, there is misinformation and counterfeit vaccines that make it harder for people to get real treatment when they need it (36). Additionally, because of lack of scientific knowledge, rabies is still a rampant problem in these areas due to the lack of vaccines for bats. Across Latin

America in particular, bats are the biggest vectors of rabies (37). However, they are difficult to vaccinate as capturing each individually is labor intensive, and it is difficult to implement oral vaccines with an insectivore (38). Scientists are currently developing transdermal vaccines so that a smaller population of bats can be captured, vaccinated, and serve as a nidus to spread the vaccine around their roost (38).

Effects of Wildlife Rabies:

Wildlife rabies can pose a significant threat to endangered animals. If a rabies outbreak threatens endangered animals, there is a greater possibility of extinction. Depopulation is no longer an option as a control method. Vulnerable species require specific programs to protect them from the virus. In late 2003, there was an outbreak of rabies among Ethiopian wolves, killing off dozens of the already endangered species. Each wolf had to be vaccinated to save the species (39). Blanford's Fox and African Wild Dogs are other examples of endangered species whose populations struggled under the strain of rabies (40).

While wildlife rabies poses a serious threat to human and animal health around the world, they can also pose a serious threat to the global economy. Livestock can easily be infected by rabid bats, hurting the cattle industry and especially the farmers who raised the livestock (41). It's estimated that Africa loses about $280 million annually from rabies-infected cattle (29). As cattle is shipped around the world, it spreads the virus to the people who slaughter them and eat them. Bats infecting cattle is one of the biggest problems with rabies in Brazil, where hematophagous bats attack livestock (41). Farmers have resorted to depopulation of bats through poison (41). Furthermore, rabies can negatively impact tourism, as tourists can contract rabies when they visit countries where rabies hasn't been eradicated, making others believe that these countries are unsafe (42). Even though pre-exposure prophylaxis is an option for tourists going to countries where rabies is a concern, about 70% choose not to get it because of the cost, the time required, or because of the perceived low risk (43). However, the chance of getting rabies is never 0, and when tourists do get rabies, they likely discourage others from going to these countries and reduce tourism, harming the country's economy and reducing income that could go towards fighting rabies.

The Future of Wildlife Rabies Control:

A highly effective way to eliminate wildlife rabies infections would be to implement worldwide programs to vaccinate stray dogs, but most countries do not have the bandwidth or resources to support that (30). There should be more international support in aiding countries with lower gross domestic products in their fight against rabies, yet that is difficult to achieve. Though there are already charities in existence, such as the Global Alliance for Rabies Control, that promote the worldwide fight against rabies, they are underfunded and can find it difficult to combat rabies (44).

Another alternative to allocating money would be to raise public awareness and education. If more people knew about the danger of animal bites and scratches, more people would likely be able to go to clinics and get treatment before symptoms show, at which point the virus has reached the brain and there is little to no hope of recovery (1). Additionally, new legislature could be put in place to make rabies a notifiable disease, meaning that it must be reported by law. By making rabies a notifiable disease, people would have to report cases of it. There are currently many unreported rabies cases, as it is often misdiagnosed (45). With more cases of reported rabies, countries would have a more accurate prevalence of rabies in the

country and could use that data to garner more initiative support. This method would be effective in India especially, which has 36% of the world's rabies cases due to the high population of stray dogs. In India, though thousands die of rabies each year, there is not a proper rabies surveillance system in place because the virus is not notifiable. Additionally, because many cases are in rural areas, the virus seems to be scattered and is not of the highest priority. Making rabies notifiable would make it more of a national concern, and more infrastructure could be put in place to save thousands of lives (45).

From a scientific perspective, new innovations could be made to squash the last vestiges of rabies that remain in the Americas, particularly among bats. Aerosols and transdermal vaccinations are currently being tested and show promise (38). Scientists could also work towards developing a form of post-exposure prophylaxis that only requires a single vaccine. Currently, four doses of the vaccine are needed to ensure the creation of long-lasting antibodies, but a single vaccine would reduce the cost and make it easier for people to obtain the vaccine (46). Through these methods, rabies will hopefully soon become a problem of the past.

Conclusion:

Rabies has always harmed both humans and animals in the past, but that doesn't mean it has to in the future. Science has come a long way since the days of holding people underwater to cure them of rabies. Through point infection control, increased public awareness, and more government initiatives against rabies, the deaths from rabies, the threat to endangered animals, and the danger to the economy, can be things of the past. Rabies is a completely preventable disease so long as humanity takes the necessary steps.

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