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Symptoms, Infectious Pathway, Treatment, and History of Rabies in the United States

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Abstract: Rabies is a virus of the Lyssavirus family that is endemic to almost all parts of the world and claims over 55,000 lives every year. The virus is capable of being vectored through any warm-blooded animal and has a variable incubation time in its hosts. Once the disease finishes incubating and symptoms appear in the host, the disease is always fatal to humans. To prevent this there are several treatments available, but they can be expensive or difficult to obtain in parts of the world that have the most problems with rabies. To solve this vaccines have been created to inoculate patients and avoid the necessity for costly care after every encounter with a possible vector of rabies. In this paper the history of vaccines in the United States and the procedure for developing new vaccines is discussed, as well as how vaccines function in the body and the specific developments for new rabies vaccines. Symptoms, treatments and common vectors of rabies are addressed, as well as areas of the world that are most affected by the disease.

Introduction: Vaccines have played an important role in medicine for over two centuries. They are one of the most cost effective and long lasting solutions to infectious diseases, resulting in a 95% reduction of infections of vaccine preventable diseases in populations that are immunized. Smallpox has even been completely eradicated worldwide due to the intervention of vaccinations. The process of developing new vaccines is a continual one however, as new science and new diseases arise continually that mandate change to the current vaccines. One such disease is rabies. Rabies is a disease typically transferred though animal attacks, as saliva and brain tissue are the main vector by which it infects other organisms. It can affect any warm blooded animal, and is almost always fatal once infection takes hold. The only effective way to stop rabies has been to kill the virus before symptoms begin to appear in
patients. Vaccination is a key aspect of this process, and has made the disease almost obsolete in developed countries.

**History:** Cotton Mather was the first person to work on developing vaccines in the United States in 1720 in response to an epidemic of smallpox in Boston. Mather transferred immunity to patients by inoculating them with samples of the disease taken from patients who already had the disease. He would take samples of pus from an infected individual, and scrape the skin of a healthy person with a knife coated in the pus to give them the disease, but the method of infection made it a less severe case that the body could fight off more easily. Another man at the forefront of vaccine development was Edwin Jenner, who developed a smallpox vaccine from a similar disease, cowpox, in 1796 in Europe. His method was much the same as Mather’s, but the sample of infected tissue used was from a cow, not another person, making the infection easier to fight off for the patient. A colleague of Jenner’s in the United States named Waterhouse copied this method of vaccination, and began the first independent trials for smallpox vaccines in the U.S. in 1780. From this genesis of vaccinology in the United States, many advances have been made to both the process of development, distribution, and safety in the field of vaccinology. The explosion of science and technology related to the fields of vaccinology and immunology has led to the creation of many new methods of vaccination for many different diseases, but along with the advances came setbacks and unsafe handling and development in the U.S. Because of this, there have been several instances of contamination, unsafe handling, and general unsafe conduct throughout the history of vaccine development. Paralleling these developments there have been many implementations of government controls, organizations, and regulations on the fields of vaccinology and immunology that have led to the methods that are in place now for how vaccines are developed and distributed. One of the first
such laws was the Public Service Law of Hygiene in 1887, which monitors drug safety and regulations. Several years later, there was a large string of deaths due to improper vaccine handling and this led to the 1902 Biologics Control Act, or the Virus Toxin Law, which was followed rapidly by the 1906 Food and Drug Act. Both of these laws implemented controls on how manufacturers made vaccines, and forced them to be honest about their products, what they contained and the risks inherent in their use. Manufacturers also were required to implement controls and checks on their drug’s production to ensure that they were as advertised, and not a so called snake oil cure. Despite this, 100 people died due to a batch of contaminated vaccines not long after these laws were implements, which spurred the Food and Cosmetic Act of 1938 to be implemented, mandating animal testing for vaccines prior to the use by the general human populace. After these initial laws and government institutions were invoked, there were additional small refinements to the laws concerning the safe handling of vaccines over the next several decades, spurred on by incidents such as the 1955 case of children being infected with Polio, rather than immunized, or the 1982 case in which seven people died from cyanide poising due to cross contamination of Tylenol capsules. These cases led to anti-tampering laws, as well as some of the most recent laws passed by the FDA concerning vaccines. The PDUFA and FGAMA acts of 1992 and 1997, respectively, were major controls on how drugs are reviewed and tested prior to licensing and public distribution, as well as setting down guidelines as to how new vaccines were to be developed in the future.

Paralleling these instances of vaccine misuse and subsequent government controls being implemented, there were many developments and advances in vaccinology as well. New vaccines for new diseases were researched and released, as well as new and improved methods for their implementation. As stated, the first methods of vaccination were crude, involving
craping scabs and pus off infected individuals and putting those samples into cuts on healthy patients. Not long after this method was introduced, special farms were developed in which cows were infected with cowpox to be used in inoculating people, which was more controlled and had fewer accidental infections, since the infected samples were contained. However, a public mistrust of vaccines persisted, as any people perceived vaccination as an act against God, and considered it to be unsafe and suspect regardless. This began to change when World War I began, as all U.S. soldiers were vaccinated with very few complications and a very low death rate from the vaccines. In World War II, soldiers were vaccinated not only for smallpox, but for many other diseases as well, using newly developed techniques for tetanus, yellow fever, cholera, and typhoid, among others. The world wars gave the field of vaccinology a huge boost, as the military funded a lot of research into new and safer ways to vaccinate soldiers. This boost to the field led to the World health Organization (WHO) launching a global campaign against smallpox in 1967, which began with mass inoculations of populations. This method was slow and costly, however, so WHO developed a new technique for inoculating large numbers of people quickly and effectively by observing populations, and only vaccinating small, connected groups when an individual became sick so the disease would not spread at all. This technique led to the announcement in 1980 that smallpox had been completely eradicated worldwide, becoming the first disease to be entirely cured due to modern medicine. With such a great medical success, many new vaccines were developed and continue to be developed and refined for a variety of infectious diseases, one of which is rabies.

**Rabies Worldwide:** Rabies has been vaccine preventable since the 1800’s, yet it still remains an issue to this day (Willoughby). Not only is it still an issue, but the disease is actually rebounding. In 2010, Ney York had 40 documented cases of rabies, which is much higher than
the 2009 number of 28. Other states have also been reporting an increase in the number of recorded cases of rabies infected wild animals, and the CDC reported 6,690 animal and 4 human cases of the disease in 2009 in the United States and Puerto Rico. (Snow) These numbers may seem low, and while developed countries like the United States have lower incidences of the virus, it is a worldwide affliction, occurring everywhere on earth except Hawaii and Antarctica (Linscott). The World Health Organization reports more than 55,000 deaths annually from the disease, with 15 million people receiving post-exposure prophylaxis (PEP). This post-exposure treatment is estimated to save hundreds of thousands of lives each year, but it is relatively expensive and difficult to obtain such care in rural areas of the world. In remote villages in Asia and Africa the daily income can be as low as $1-$2, while PEP costs an average of $40-$49 (“Rabies”). This is part of the reason that 95% of human deaths from rabies occur in Asia and Africa (“Rabies”), with India representing 36% of the global mortality rate (India’s). Proper vaccination would prevent the need for much of the post-exposure treatment, thereby saving lives in these developing countries. A second contributing factor to developing countries having a much higher incidence of rabies is that they tend to have more wild dogs - India alone has been estimated to have as many as 25 million canines (India’s). 99% of the global rabies deaths in humans are a result of contact with rabid dogs (“Rabies”, Linscott) with 90% of all reported cases in Africa and India being vectored by rabid canines (Linscott). In developed countries a very successful strategy of controlling rabies has been to vaccinate animals. For instance, in the United States it is policy for all domestic pets to be vaccinated for rabies, but in underdeveloped areas of the world like India, this approach is simply not feasible due to the number of wild dogs present (India’s).
**Transmission:** Rabies is a RNA retrovirus in the *Rhabdoviridae* family (Snow). It is a global zoonosis, being naturally transmissible to humans from any vertebrate animal. The virus is part of a family of lyssavirus, of which the rabies virus is the genotype 1 lyssavirus. It is an acute, rapidly progressing encephalitis that is almost always fatal in all recorded cases, and is the only strain of lyssavirus present in the Americas. The composition of the virus, as well as all viruses in the *Rhabdoviridae* lyssavirus family, is a negative-sense, single stranded, enveloped RNA virus which contains only a single-surface glycoprotein, as well as a ribonucleoprotein core. (Willoughby) Transmission occurs through infected saliva via a bite, scratch, or puncture, as well as through contact with infected nervous tissue. Only eight percent of the reported cases of infection occurred through domestic animal encounters, although the majority of those cases were from cats. Most cases occur through wild animal transmission, with the only human-to-human infections being recorded in whole organ transplants (Willoughby). Of the recorded infections by wild animals in the United States, 34% of infections were from raccoons, 24% from bats, 23% from skunks, and 7.5% from foxes. There have been several disputed cases of the virus spreading through the air in laboratory settings, or in caves infested with bats, but there are difficulties in confirming these infection events (Snow). While the majority of infection events come from the animals listed above, any warm blooded animal can be a carrier for the disease, though the most likely transmission agents are bats, cats, dogs, coyotes, foxes, skunks, raccoons, and cattle (Pace).

**Symptoms:** There are several stages of disease progression post-infection, with an average incubation period of 20-90 days. While the virus can be dormant for years, in 90% of the recorded cases the incubation period is less than a year. As soon as the virus hits the central nervous system (CNS), it begins to spread to the peripheral nerves before the onset of symptoms.
Once the virus enters the CNS, the prodromal period begins, lasting anywhere from 2-10 days. This period is accompanied by non-rabies-specific symptoms such as pain, paresthesia at the site in infection, and flulike symptoms such as lethargy, headache and fever. The second stage is the acute neurological period, which also lasts 2-7 days. More specific signs arise in this time, such as anxiety, confusion, fever, hallucinations, insomnia and abnormal behavior. In animals, this can present itself as being abnormally friendly or nocturnal animals being active in the day. Paralysis can also accompany this stage of the infection. If the infection is allowed to proceed past this stage, it is almost always fatal, with fewer than 10 recorded cases of human survival. The final stage of the infection is presented as a coma and ultimately, death (Snow). How the virus causes death is as of yet unclear, since it is not very cytopathic or immunogenic, meaning that anatomic damage is minimal. Thus, there is minimal structural damage to any part of the nervous system. Many patients die within three days of hospitalization in endemic areas, as the virus is rapidly progressive. However many patients also die without any detectable antibodies to the disease, and autopsy reveals only minimal perivenular inflammation, with occasional viral inclusions, or Negri Bodies, in the hippocampus and cerebellum. Additionally, the neurons are generally only minimally apoptotic or necrotic. (Willoughby)

The virus must come into contact with a mucosal membrane or enter through broken skin to be infectious, as ingestion requires a very large dose of the virus to be infectious. Blood, urine, and feces have never been documented as infectious in either humans or animals, and the virus is quickly inactivated by desiccation and by direct sunlight. As mentioned, incubation periods can be highly variable in length, which is due to the activity of the virus. It replicates poorly and at low levels in muscle and skin tissue, which lends to the variable and prolonged cases of incubation lasting up to seven years, although there is no known mechanism of latent
infection. Once the virus comes into contact with neurons, however, it begins to replicate rapidly, as it is highly neurotropic. Once incorporated into the nervous system, the virus is transmitted rapidly by retrograde axonal transport, where it disseminates exclusively across the synapses at an average rate of one synapse every 12 hours. In this period dorsal root ganglia can also be infected, and while they add to the symptoms of the infection, they do not extend the infection at all. One of the factors that contribute to misdiagnosis of rabies is that the immune system is a highly specific immunological site, so once the rabies virus enters the CNS it can operate up to several days without any adaptive immune response being triggered in the body. This allows for several days in which the central nervous system is highly infected, but there are no signs or symptoms of the disease. Additionally, the initial symptoms are subtle and intermittent, which facilitates transmission of the virus as the infected individual does not display any signs of sickness, but can spread the disease. (Willoughby)

These factors and more contribute to the many cases of misdiagnosis of rabies, as well as a substantial number of cases that are never diagnosed. In rare cases, patients fulfill the diagnostic parameters for rabies, but have a diminished case of the disease, which suggests that there is a continuum of severity of infection caused by the lyssaviruses. This indicates that rabies may not always be fatal, and indeed there are several documented instances of a patient with no detectable neutralizing antibodies, despite having antibodies for the ribonucleoprotein of the rabies virus. However these cases are often disputed as to whether the individuals were ever actually infected with rabies which, as mentioned, is often misdiagnosed. In fact, 38% of the recorded cases in the United States have been diagnosed post mortem, as many patients die from rabies without any detectable immune response, and the incubation period of the disease is difficult to determine. For a diagnosis of rabies, the symptoms must be accompanied by acute
neurological syndrome, as well as confirmation from laboratory testing, due to the variable mimics of the lyssavirus. \textit{N-methyl-d-aspartate receptor} (NMDAR) and limbic encephalitis present similar symptoms as rabies, and all three diseases occur primarily in the limbic brain structures. Cerebral malaria is another disease commonly associated as rabies. (Willoughby)

\textbf{Treatment:} Post-Exposure Prophylaxis (PEP) is an effective treatment for rabies, and is a viable option to prevent infection up until a few days prior to the development of symptoms. It is the leading cure for rabies in the United States, and has rarely failed since the mid 1970’s, when cell-based vaccines were developed. The procedure is costly, so a preferred method of diagnoses is to capture the animal suspected of incurring transmission and testing it for rabies. If the tests are negative, no treatment is necessary. The only recorded cases of PEP not succeeding in preventing infection have been when the bites or scratches have been excessive, and around the head or neck, as this allows for a large amount of the viral agent to be introduced very close to the CNS and has a correspondingly short incubation period. As discussed previously, rabies is statistically always fatal. There are approximately 50,000 cases each year, and fewer than 20 patients have survived a rabies infection in the last 50 years. Thus, the most effective and truly only viable option at this point is to prevent infection, which requires both a rabies immune globulin (RIG) and a rabies vaccine. There are four steps to Post-Exposure Prophylaxis treatment. The first is to thoroughly clean the wound with antiseptic and water. Second, avoid suturing the wound immediately. Often, the infection spreads more quickly if it is covered immediately. Instead, suture the edges so the wound doesn’t expand, and only completely and professionally seal it after one to two weeks. Third, RIG of human or modified-equine origins should be used to bolster the immune system until the vaccine takes effect, 10-14 days later. RIG is administered to the wound directly, as it is not particularly effective intramuscularly.
Additionally, it is not needed if the patient has been inoculated for rabies more than seven days before exposure to the virus. The last step of PEP is the rabies vaccine. The common vaccine used today is a modern cell-based, inactivated version. The previous vaccine was comprised of infected nerve tissues and produced a high rate of autoimmune neurological syndromes in 1 out of every 400 or 500 patients, and only partially protected against the disease. While PEP has proven to be an effective way to prevent rabies infection, if the virus does take hold there is no cure, as neither RIG nor vaccination has proven effective in curing the symptoms in real life cases, although there have been successful trials of antivirals on the rabies virus in in vitro tests. As such, the most advisable course of action is in pre-exposure care through vaccination. The World Health Organization (WHO) has proposed several schemas for rabies immunization, which is to be delivered either intramuscularly or intradermaly, with four doses at day 0, 3, 7, and 14. (Willoughby)

Vaccines work by bolstering the immune system’s natural defenses and granting immunity to the disease for a period of time after the immunization event. This is accomplished by way of several different areas of study working together – vaccinology, proteomics, immunology, genomics, and others. Infectious diseases infiltrate the body through a variety of ways, either by air, ingestion, or in the case of rabies, through direct contact with a contaminated substance. Once the infectious agent is introduced to the body, the immune system begins to identify the foreign substances and destroy them through a variety of ways. Vaccines function by stimulating this natural immune response of the body to pathogenic molecules synthetically. A version of the virus is introduced to the body in a manner that is not infectious, typically as a killed form of the virus, so that the body’s immune response will be activated and fight off the weakened pathogen. After this process is complete, the patient’s immune system has the ability
to store the information of how to recognize and kill the pathogen if it is ever encountered again, thereby giving resistance to a full strength strain. This process is carried out by two different aspects of the immune system, the innate and the adaptive immune responses. The innate immune system is responsible for the first reaction to a pathogen and the genesis of a specific response to it. The adaptive system operates more slowly, taking days or even weeks to respond to an infection, but it is incredibly specific to each individual pathogen once it does respond. The adaptive immune system is also responsible for pathogenic memory, and is what allows the body to recognize an infectious agent and grant resistance.

The innate system detects pathogens with specialized cells called dendritic cells (DCs) which are grown in the bone marrow, but mature in every tissue in the body. When these cells encounter a foreign object in the body such as a pathogen they move to the lymph system and initiate the innate immune response, making the DCs the directors of the immune system. They are responsible for detection, signal transduction, and induction of the immune response through cells like T and B cells. The dendritic cells detect pathogens with specialized, specific receptors called Toll-Like Receptors (TLR), of which there have been 13 identified in humans. While there are other receptors, such as DDCA2 of CLR, TLRs are the most studied and seem to pay the most critical role in the immune response, along with a second class of receptors called MHC I and II. Once the pathogen is identified, molecules and cells such as cytokine, B cells ant T cells are induced to destroy the virus. The type of cells induced, as well as the pathway through which they are induced, is specific to each type of infection and is therefore a strong point of control when considering the development of new vaccines. Post infection, the CD4+ T cells are responsible for producing cytokines that allow killer T cells to recognize, with the help of CD8+ T cells, the antigens presented by the viral agents and destroy infected cells. After the T cells
and other molecules destroy the infected cells, the adaptive immune system takes over and codes the genetic material and antigens into B cells for future reference, when a similar pathogen is encountered. The B cells store the specific antigen presented by the infected cells and code the sequence into the receptors of the dendritic cells, so when a microbe that presents the same antigen is detected by the DCs, the signal pathway is already in place to induce the appropriate immune response and destroy the infection before it spreads. The manipulation of this process is what allows vaccines to be effective over long periods of time. By introducing the antigens that are presented by a virus without actually introducing the infectious agent, the immune system response is stimulated, the inactivated pathogen disposed of, and the antigens stored for use in detecting the virus in the future. However, since the immune response is so specific to each disease, much care is needed in finding which part of the immune system to stimulate artificially and how that induction may affect the patient. For this reason, new vaccines are developed continually as more information is gathered through study of immunology.

One of these new vaccines is a purified Vero cell rabies vaccine (PVRV). This vaccine was recently developed, and has not yet been licensed but has completed a successful phase I human clinical trial. The vaccine, SIIL PVRV, is a lyophilized sample containing inactivated purified rabies antigen of the PM3218 virus strain. The diluent is simply serine water, and the final reconstituted sample contained glycine, sucrose, and human serum albumin. The development of the vaccine began with a revival of the Vero ATCC CCL81 cells used as the transport for the viral agents. The revived cells were infected with working seed virus, and then washed with a virus medium. After the cells were transformed with the viral genetic material, they were grown in culture for 48-72 hour intervals, harvested, and the beta propiolactone was concentrated and the inactivated antigen purified via column chromatography. The final potency
of the vaccine was 4.35 IU/dose. The vaccine was then administered at day 0, 7, 21, and 42 to three test groups in doses of either 1ml intramuscularly or .1 ml intradermally. This vaccine is unique in that it is the first rabies vaccine to be clinically tested for both ID and IM routes initially, as opposed to the standard vaccines which were licensed for IM routes, and only later for ID. 54 days after the initial trial, the patients were tested for immunogenicity to the virus. All subjects showed protective levels of RVNA titres. As of 2006, this vaccine was licensed and operational in several states in India, but none in the United States. (Kulkarni)

The most common vaccination against rabies used in the United States currently is a human diploid cell rabies vaccine (HDCV). For decades, since the discovery in 1885 that rabies could be prevented with PEP after an encounter with the pathogen by Louis Pasteur and Emil Roux, rabies vaccines have consisted of increasingly virulent doses of infected tissue from animals. Until the late 1900s, all rabies vaccines were produced in vivo by inoculating animals with rabies, and then using their infected tissues for use in vaccines, just as the practice used to be with cowpox for treating smallpox. However in the 1970’s rabies cells were cultured successfully for the first time, which allowed for the development of the first truly effective rabies vaccine, HDCV. The process of inoculation was refined to be a treatment of five doses given subcutaneously at 0, 3, 7, 14, and 30 days with a booster shot on day 90. In an ongoing study, several patients from the initial trials of the HDCV were located and tested to see how effective the inoculation is over extended period of time. The strain of HDCV was prepared with a supernatant of Human Embryonic Lung Fibroblast Culture W138, which was recombinant with the Pitman Moore rabies virus. The patients who had received no booster vaccines for rabies in the convening 32 years since their inoculation displayed RVNA titers between .3 and .98 IU/mL, and after a single booster injection in 2007 the numbers raised to 2.6 and 20 IU/mL, showing that
the vaccine is highly effective at inducing cell memory of the adaptive immune system. After 32 years, the B cells and dendritic cells still recognize the antigens presented by rabies and induce an immune response strongly. (Fayaz)

Modern versions of the rabies HDCV have been tested for efficacy not only against the primary genotype of lyssavirus that is the rabies vaccine, but also for several of the other lyssaviruses in the family, such as the European bat lyssavirus (ABLV types-1 and -2), as well as the Australian bat lyssavirus. The virus strains used in the preparation of these modern vaccines are the RABV isolates, as well as CVS and a wild strain of wRABV and RV61. All the viruses were altered to grow in the BHK cells used as their vectors, and titrated with a 10-fold serial dilution. The results of the study found that the vaccine is effective at killing the other strains of lyssavirus in addition to the rabies genotype I, as long as they were above 5IU/mL. (Brooks)

While the current vaccine against rabies is effective against many strains of the same virus, and for many years post-inoculation, the disease remains a prevalent and deadly virus in the world. While few people die in the United States from the disease, there are many deaths in other countries, particularly developing countries. This is because, while the HDCV is effective, it is expensive and difficult to transport long distances as it needs to be refrigerated. Thus, developed countries do not have an endemic rabies problem since most livestock are vaccinated, and the treatment is readily available to the human public as well, but the disease remains an issue in developing countries. The response to this demand has been met in an attempt to create a DNA vaccine against rabies, which is inexpensive, easy to produce, and does not require refrigeration to be transported. A vaccine developed at the end of the 20th century uses viral DNA from the rabies glycoprotein as the immunogen. While this vaccine may prove to be effective at preventing the disease, it must be administered prior to an infection event, as it takes
up to 30 days for the vaccine to stimulate an effective immune response, and would be delivered prophylactically. (Stephenson)

The process of developing a vaccine has inherent risks. As mentioned, the immune system is a complex interlay of several disciplines, and crafting a vaccine that has the desired effect, with minimal side effects, and that can be created cost-effectively is a difficult task. If the target of the vaccine, to the dosage or amount of viral substance is inaccurate, vaccination can lead to anaphylaxis, residual encephalopathy, paralysis and even death. Because of the specificity required, there have been several incidents historically of injury caused by vaccinations. The government has implemented many controls to monitor the licensure and testing of new vaccines to prevent this. Now, government money often goes towards sponsoring the development of new vaccines, such as the 2004 Project Bioshield Act, which allotted $5.6 billion to the cause. Now, the development of any new drug or vaccine goes through rigorous stages of testing overseen by government entities such as the FDA. First, a committee is installed to oversee the initial development of the vaccine and ensure the science behind the idea is sound, the facilities to produce the vaccine are adequate, and that the proper procedures are observed for testing, licensure and distribution. This process can take from four to ten years to complete, and incorporates several checks.

**Vaccine Production:** First, the idea and science behind the vaccine need to be reviewed and deemed practical. If it is, the drug moves to process development, process transfer, manufacturing, and finally distribution. Process development alone can take up to a year to complete, as this is the stage that deals with the bioprocesses of the vaccine to determine the long term effects, efficacy, shelf life, stability, and safety of the drug. Animal testing takes place after these aspects have been determined to find out the proper dosage of the vaccine, and the
administration regime that proves most effective at raising the body’s immune response. After these processes are completed and the vaccine is deemed safe and effective, it moves in to human clinical trials for testing. If there are no negative results associated with the treatment in the subjects, and there is a positive reaction of the immune system, the vaccine moves into licensing, and finally distribution. The tests are not concluded at this point, however. Since once aspect of an effective vaccine is how long it induces immunity to the recipient, often clinical trials will be re-conducted after a decade or more, to confirm the hypothesized results from the initial process development, and to ensure that the vaccine is also safe in long-term use.

**Conclusion:** Vaccines are an important and integral part of modern medicine and are responsible for the near eradication in developed countries of many previously serious infectious diseases. New vaccines are continually being developed to combat new diseases, or to overhaul a less effective vaccine already inexistence. Rabies is one such disease. While a vaccine has been in existence for decades for the virus, it was not particularly effective. In the recent decades a much more effective vaccine was created, but it is expensive and difficult to transport to developing countries that still have problems with rabies. To address this problem new forms of a rabies vaccine are being developed and tested, under the rules and guidelines of safe and effective vaccine development set in place by government institutions.
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