**Rabies vaccine meets the laws of supply and demand**

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Rabies is a viral neuroinvasive disease that causes encephalopathy in mammals. Vaccination is the primary method of rabies prevention, given as both pre- and post-exposure prophylaxis. North America is currently experiencing a heightened rabies threat due to recent problems in vaccine production. Since 2007, the pharmaceutical industry has been struggling to meet North American demand for the rabies vaccine. The Food and Drug Administration (FDA) and the two vaccine-producing pharmaceutical companies, Sanofi-Pasteur and Novartis, are jointly responsible for the current supply shortage. This shortage of rabies vaccine has resulted in a rationed approach to delivering prophylaxis. Conservative measures such as avoidance behavior and vaccination of animals are to be used in place of pre-exposure prophylaxis. Public health officials must review all cases in which post-exposure prophylaxis is requested to ensure the limited supply of vaccine is appropriately distributed.

**Introduction**

Rabies is a viral neuroinvasive disease that causes encephalopathy in mammals. The most common vector for human infection is animal bites, and if untreated, rabies is almost always fatal. While rabies has been well controlled or eradicated in some areas of the world, death from rabies is not uncommon in Asia and Africa. Prevention of rabies by vaccination has been a mainstay of prophylaxis since the late 19th-century and is largely responsible for declining incidence in both animals and humans in North America.

North America is currently experiencing a heightened rabies threat due to recent problems in vaccine production. Since 2007, the pharmaceutical industry has been experiencing problems in meeting North American demand for the rabies vaccine. This has affected the front lines of medicine by causing a disturbance in the practice of rabies prophylaxis. Here we will discuss rabies and the rabies vaccine, the events that precipitated the current shortage in supply and how this production-related strain on resources has caused a reactionary change in the practice of medicine.

**Background and epidemiology**

Rabies is considered a zoonotic infectious disease. This implies transmission to humans and animals occurs via other animals. It is an RNA virus belonging to the family *Rhabdoviridae* and genus *Lyssavirus* and is contained in the saliva of infected mammals. After a bite occurs, the virus enters the central nervous system of the next host and causes non-specific prodromal symptoms followed by progressive encephalitis that is almost always fatal. Early symptoms include paresthesias, pruritis and pain at the site of viral entry. In humans the incubation period usually varies from several weeks to months. Diagnosing rabies is difficult due to the long and variable incubation time, as well as the lack of symptom specificity.

Historically, the most common vectors for rabies transmission have been domestic and stray dogs and cats. In the United States in 1946 over 8300 rabies cases were reported among dogs. By 2006, aggressive canine vaccination programs and improved stray animal control have resulted in a greater than ten-fold reduction in canine rabies cases. This has translated into a roughly ten-fold drop in human rabies cases in the United States. There has been an increasing rate of rabies in
traditionally forest-dwelling wildlife such as skunks, bats and raccoons. This is concerning as urbanization and suburbanization increases in North America and these animals are in greater contact with humans. Between 2000 and 2005, 40% of Canada’s 2238 confirmed animal rabies cases were skunks, 26% were bats, and 8% were raccoons. Only two rabies deaths have been reported in Canada since 1985 and both were caused by bat exposure. Responding to changes in the pattern of rabies transmission requires adequate supply and effective use of preventive measures.

The rabies vaccine and prophylaxis

Prior to the development of the first rabies vaccine by Louis Pasteur and Emile Roux in 1885, almost all rabies infections resulted in death. This early vaccine was developed by harvesting cells from nerve tissue of infected rabbits. Research into an attenuated strain of the virus led to the development of new vaccines including the human diploid cell rabies vaccine in 1967 and a newer, less expensive purified chick embryo vaccine. These are available as Imovax® by Sanofi-Pasteur and RabAvert® by Novartis, respectively. They are the only two rabies vaccines currently approved for use in Canada and the United States.

In humans, rabies vaccines are intended for pre- and post-exposure prophylaxis. Pre-exposure prophylaxis is indicated for those at high risk of contacting the virus, such as veterinarians, animal trappers, and travelers to certain regions in Asia and Africa. Post-exposure prophylaxis is given to those who have experienced open skin wounds as a result of an animal encounter. Individuals that have never received the vaccine and are in need of post-exposure prophylaxis also require rabies immunoglobulin to provide intermittent immunity. Post-exposure prophylaxis with rabies vaccine in humans has been validated as an effective and safe method of preventing infection, particularly when administered within 6 days of exposure. Thus, the recent shortage in rabies vaccine supply to North America has been of great concern, particularly to those in immediate need of prophylactic treatment.

Cause and implications of the vaccine shortage

A current shortage of rabies vaccine has resulted in a rationed approach to delivering prophylaxis in North America. Much like other elements of preventive medicine such as colonoscopies, the indications for receiving the rabies vaccine have become more stringent in response to strained resources. Unique to the shortage of rabies vaccine is that the origin of the resource constraint is not intrinsic to the healthcare system; there are no infrastructure, human resource or financial constraints limiting the use of rabies vaccine. The Food and Drug Administration (FDA) and the two vaccine-producing pharmaceutical companies, Sanofi-Pasteur and Novartis, are jointly responsible for the current supply shortage.

In June 2007, Sanofi-Pasteur began renovating its Imovax® production facility in France in order to comply with new requirements from the FDA and a French regulatory body. Prior to these renovations the company stockpiled a finite amount of vaccine that was expected to meet demand until the facility re-opened. Shortly after renovations began it became evident that the estimation of demand was incorrect and the stockpiled supply would be inadequate. Also at this time Novartis, which controls 50% of the North American rabies vaccine market, experienced FDA scrutiny and was asked to temporarily halt production of RabAvert®. Public health and industry officials have since declared that the rabies vaccine should be used for post-exposure prophylaxis only. Conservative measures such as avoidance behavior and vaccination of animals are to be used in place of pre-exposure prophylaxis. Public health officials must review all cases in which post-exposure prophylaxis is requested to ensure the limited supply of vaccine is appropriately distributed. RabAvert® was recently cleared by the FDA, and Novartis has been attempting to meet vaccine demand. However, as of October 2008, the Center for Disease Control (CDC) has not changed recommendations for prophylaxis and
has informed travelers to certain regions in Asia and Africa that pre-travel vaccination is not available. Current projections estimate the supply of vaccine to restore to normal in mid-2009 upon the re-opening of the Imovax® production facility.

Discussion

For many years the international pharmaceutical industry has acted alone and in conjunction with governments around the world to change the landscape of modern medicine. Positive economic pressure, such as the encouragement of research and development by government incentives, has translated into economic growth for nations and an intended improvement of quality of life of the masses. Stringent regulatory forces on the pharmaceutical industry have also had a trickle-down effect in which government bodies or other stressors temporarily shock the business of drug production, which in turn changes the way medicine is practiced. This is evident in the recent shortage of rabies vaccine in North America.

The practice of medicine in Canada has attempted to demonstrate flexibility and poise amidst a storm of stressors. Elements of healthcare delivery have crumbled in the face of limited resources while other areas have thrived on the heels of innovation. For example, some Canadians have had to seek more timely care in the United States or overseas. However, others have benefited from new models of primary care, allowing them to attain both timely and high quality care. While these examples are considered to be largely intrinsic to our method of healthcare delivery, it is important to note that external forces may also drastically change the practice of medicine.

The current philosophy of medicine in the Western World requires the efficient production of pharmaceutical agents as well as regulatory bodies to ensure the safety of the population. The nature of the pharmaceutical industry makes it necessary for the practice of medicine is agile and prepared to deal with sudden change.

References