ABSTRACT

Rabies is a fatal viral zoonotic disease transmitted to humans through bites or scratches by infected domestic and wild animals. It is present in all continents except Antarctica and mostly endemic in Asian and African countries. In countries like India and China, dogs are one of the major reservoir hosts for the transmission of this disease. This disease is unpreventable with the lack of awareness and proper treatment measures are not being followed up with patients who reside particularly in rural areas. It is because most Post Exposure Prophylaxis (PEP) needs are borne by patients who can least afford to yield. Rabies vaccines have come a long way following the development of a vaccine by Louis Pasteur in 1885 which is still being used to control rabies in animals and humans.

Keywords: Rabies, pathophysiology, PEP, vaccines
INTRODUCTION

Rabies is a disease entrenched in history, dating back to ancient Egypt. Caused by an RNA virus belonging to the Lyssavirus genus, rabies is capable of infecting all mammals. Rabies is primarily a disease of terrestrial and airborne mammals, including dogs, wolves, foxes, coyotes, jackals, cats, bobcats, lions, mongooses, skunks, badgers, bats, monkeys and humans. The dog has been, and still is, the main reservoir of rabies in India. Other animals, such as monkeys, jackals, horses, cattle and rodents, seem to bite incidentally on provocation, and the fear of rabies leads the victim to seek post-exposure prophylaxis. Rabies occurs in more than 150 countries and territories. With the expectation of some areas in the South Pacific, rabies persists as a major Public Health hazard in many countries across the world. It is estimated that the South East Asia Region accounts for approximately 60% of human deaths due to rabies in the world. Data available from 14 developing countries of Africa, Asia, South and Central America report a dog/inhabitant ratio of between 150/1,00,000 to 200/1,00,000. Stray dogs are mainly responsible for 99% of human infection. In India, some studies have estimated that there are as high as 17 million animal bites per annum and 20,000 human deaths occur due to rabies each year. Based on vaccine utilization, approximately 3 million people receive post-exposure treatment in our country. (1)

Figure 1: Wild animal (especially bats)

At first there might not be any symptoms. But weeks, or even months after a bite, rabies can cause pain, fatigue, headaches, fever, and irritability. Skunks, raccoons, dogs, cats, coyotes, foxes and other mammals can also transmit the disease. Human rabies is rare in the United States. There have been only 55 cases diagnosed 1990. However, between 16,000 and 39,000 people are vaccinated each year as a precaution after animal bites.

Intradermal Vaccines-

Over the centuries, a number of vaccines have been administered into the skin using a variety of instruments, from simple to sophisticated ones. At the same time as these progresses in administration techniques, advances in the field of immunology have led to an increased understanding of the basic mechanisms of innate and adaptive immunity and the skin has been
identified as an attractive site for vaccination, largely due to the presence of a dense network of immune-stimulatory antigen-presenting cells. The current renewed interest in ID route of vaccination has been largely driven by the perception that it might offer several advantages in terms of both immunogenicity, such as the reduction of antigen concentration (dose-sparing), the ability to improve immune response in low-responders and the avoidance of the need for adjuvants, and some practical issues as the easier and safer administration with the respect to conventional intramuscular route and the reduction in risk of needle-stick injuries for health care workers and blood vessels or nerves injuries for patients.

During the last century, the skin was the subject of numerous studies demonstrating the highly complex and dynamic interplay between the skin and the other components of the immune system [1] and for this reason has been proven to be suitable for vaccine delivery.

**Measles vaccination**

A small number of studies have been conducted to investigate the intradermal vaccine against Measles. The rationale of most of these trials was lower cost and easier administration of this vaccine. The results are conflicting: while some studies investigating reduced antigen dose ID vaccine versus standard dose SC vaccine, have shown the capability of both formulations to induce an equivalent immune response; others studies did not demonstrate the same. Therefore, this route of immunization cannot be considered alternative to current methods of vaccine administration.

**What is Rabies?**

Rabies is a serious disease. It is caused by a virus. Rabies is mainly a disease of animals. Humans get rabies when they are bitten by infected animals. At first there might not be any symptoms. But weeks, or even months after a bite, rabies can cause pain, fatigue, headaches, fever, and irritability. These are followed by seizures, hallucinations, and paralysis. Human rabies is almost always fatal.

Wild animals especially bats are the most common source of human rabies infection in the United States. Skunks, raccoons, dogs, cats, coyotes, foxes and other mammals can also transmit the disease. Human rabies is rare in the United States. There have been only 55 cases diagnosed since 1990. However, between 16,000 and 39,000 people are vaccinated each year as a precaution after animal bites. Also, rabies is far more common in other parts of the world, with about 40,000 – 70,000 rabies-related deaths worldwide each year. Bites from unvaccinated dogs cause most of these cases.

Rabies has terrified man since antiquity. The fear is by no means unfounded since the disease is invariably fatal and perhaps the most painful and horrible of all communicable diseases in which the sick person is tormented at the same time with thirst and fear of water (hydrophobia).
Fortunately, animal bites, if managed appropriately and timely the disease is preventable to a large extent. In this regard the post-exposure treatment of animal bite cases is of prime importance. Rabies vaccine is given to people at high risk of rabies to protect them if they are exposed. It can also prevent the disease if it is given to a person after they have been exposed. Rabies vaccine is made from killed rabies virus.

**PATHOPHYSIOLOGY CHANGES**

Rabies is a zoonotic disease that remains an important public health problem worldwide and causes more than 70,000 human deaths each year. The causative agent of rabies is rabies virus (RV), a negative-stranded RNA virus of the rhabdovirus family. Neurovasiveness and neurotropism are the main features that define the pathogenesis of rabies. Although RV pathogenicity is a multigenic trait involving several elements of the RV genome, the RV glycoprotein plays a major role in RV pathogenesis by controlling the rate of virus uptake and trans-synaptic virus spread, and by regulating the rate of virus replication. Pathogenic street RV strains differ significantly from tissue culture-adapted RV strains in their neurovasiveness. Whereas street RV strains are highly neuroinvasive, most tissue culture-adapted RV strains have either no or only limited ability to invade the CNS from a peripheral site. The high neurovasiveness of pathogenic street RVs is, at least in part, due to their ability to evade immune responses and to conserve the structures of neurons. The finding that tissue culture-adapted RV strains replicate very fast and induce strong innate and adaptive immune responses opens new avenues for therapeutic intervention against rabies.

**PHARMACOLOGICAL CHANGES**

If preventative treatment is sought promptly, rabies need not be fatal. Immunization is almost always effective if started within two days of the bite. Chance of effectiveness declines, however, the longer vaccination is put off. It is, however, important to start immunizations, even if it has been weeks or months following a suspected rabid animal bite, because the vaccine can be effective even in these cases. If immunizations do not prove effective or are not received, rabies is nearly always fatal with a few days of the onset of symptoms.

**Management of a patient following an animal bite** –

- Wound should be washed immediately with soap and water for 3-5 min.
- Wounds should be be cleaned thoroughly at the hospital with 70 % alcohol or provide iodine.
- Anti titaneous immunization should be inoculated when necessary.
- Antimicrobial should be prescribed if necessary to control bacterial infection.

**Symptoms**
The period between infection and the first symptoms (incubation period) is typically 1–3 months in humans. Incubation periods as short as four days and longer than six years have been documented, depending on the location and severity of the contaminated wound and the amount of virus introduced. Initial signs and symptoms of rabies are often nonspecific such as fever and headache. As rabies progresses and causes inflammation of the brain and/or meninges, signs and symptoms can include slight or partial paralysis, anxiety, insomnia, confusion, agitation, abnormal behavior, paranoia, terror, and hallucinations, progressing to delirium, and coma. The person may also have hydrophobia. Death usually occurs 2 to 10 days after first symptoms. Survival is rare once symptoms have presented, even with the administration of proper and intensive care. Jeanna Giese, who in 2004 was the first patient treated with the Milwaukee protocol, became the first person ever recorded to have survived rabies without receiving successful post-exposure prophylaxis. An intention-to-treat analysis has since found this protocol has a survival rate of about 8%.

Figure 2: Rabbies patient

Prevention

One promising preventive strategy that has been used since the early 2000s is the distribution of wildlife baits containing an oral vaccine against rabies. This strategy has been used in Germany to vaccinate wild foxes, which are frequent carriers of the disease in Europe. In the United States, veterinary researchers at Kansas State University have developed an oral vaccine for fruit bats; early trials of the vaccine have given promising results.

The following precautions should be observed in environments where humans and animals may likely come into contact.

Domesticated animals, including household pets, should be vaccinated against rabies. If a pet is bitten by an animal suspected to have rabies, its owner should contact a veterinarian immediately
and notify the local animal control authorities. Domestic pets with current vaccinations should be revaccinated immediately; unvaccinated dogs, cats, or ferrets are usually euthanized (put to sleep). Further information about domestic pets and rabies is available on the American Veterinary Medical Association (AVMA) web site. Wild animals should not be touched or petted, no matter how friendly they may appear. It is also important not to touch an animal that appears ill or passive, or whose behavior seems odd, such as failing to show the normal fear of humans. These are all possible signs of rabies. Many animals, such as raccoons and skunks, are nocturnal and their activity during the day should be regarded as suspicious. People should not interfere in fights between animals. Because rabies is transmitted through saliva, a person should wear rubber gloves when handling a pet that has had an encounter with a wild animal.

Garbage or pet food should not be left outside the house or camp site because it may attract wild or stray animals.

State or county health departments should be consulted for information about the prevalence of rabies in an area. Some areas, such as New York City, have been rabies-free, only to have the disease reintroduced at a later time. Preventative vaccination against rabies should be considered if one's occupation involves frequent contact with wild animals or non-immunized domestic animals. Bites from mice, rats, or squirrels rarely require rabies prevention because these rodents are typically killed by any encounter with a larger, rabid animal, and would, therefore, not be carriers.

**Diagnosis**

After the onset of symptoms, blood tests and cerebrospinal fluid (CSF) analysis tests will be conducted. CSF will be collected during a procedure called a lumbar puncture in which a needle is used to withdraw a sample of CSF from the area around the spinal cord. The CSF tests do not confirm diagnosis but are useful in ruling out other potential causes for the patient's altered mental state. This must be started at the earliest to ensure that the individual will be immunized before the rabies virus reaches the nervous system. However, people who present for treatment even months after a possible rabies exposure should be evaluated and treated as if the event had occurred recently. To bring out uniformity globally, the classification of animal bite for post-exposure prophylaxis has been based on WHO recommendations.

The two most common diagnostic tests are the fluorescent antibody test and isolation of the rabies virus from an individual's saliva or throat culture. The fluorescent antibody test involves taking a small sample of skin (biopsy) from the back of the neck of the patient. If specific proteins, called antibodies, that are produced only in response to the rabies virus are present, they will bind with the fluorescent dye and become visible. Another diagnostic procedure
involves taking a corneal impression in which a swab or slide is pressed lightly against the cornea of the eye to determine whether viral material is present.

**Treatment**

Rabies is 100% fatal disease and after development of rabies there is no treatment for it. Only method to prevent rabies is anti rabies prophylaxis. For the prevention of rabies presently two type of vaccine regimen are in practiced in India. In both regimen cell culture vaccine is used. In India, IDRV was recommended for use in the government sector in 2006.

Compliance to post-exposure vaccination is crucial to achieve optimum level of antibody titers. The present study was planned to assess the compliance of 4 dose Intra-dermal regimen (updated Thai regimen) over 5 dose intramuscular regimen (Essen regimen). It was observed that compliance was more in Intra-dermal regimen as compare to intramuscular regimen and it was found to be statistically significant. treatment approximately reduces by 80% of intramuscular regimen. A study conducted by Rohi K R, Mankeshwar R (2014) conducted study on 2051 patients, found that Intradermal regimen is more cost beneficial than Intramuscular (Essen) regimen. Present study showed that, 25.67% & 27.99% patients belongs to category III and 72.02% and 71.07% belongs to category II during year 2010-11 &2011-12 respectively. Pattern of distribution was found similar during both year. N.J. Gogtay et al (2014) found that maximum patients belonged to category II (78.3%) followed by category III (21.7%). Contrast to our study, Shah Venu, et al (2012) found that 67.8% were belonged category III followed by 19% to category I and 13.2% to category II exposure. Study shows that as prophylaxis treatment precede dropout rate increased, so counseling part and follow up is very important to avoid dropouts. As incomplete treatment offer no immunity against rabies so given doses become useless if patient is non-compliant to treatment.

**Intradermal injection**

Is the injection of a substance into the dermis, just below the epidermis. This route has the longest absorption time as compared to subcutaneous injections and intramuscular injections. As a result, it is used for sensitivity tests, like tuberculin and allergy tests, and for local anesthesia. Additionally, the body's Intramuscular regimens for rabies PEP. Three intramuscular schedules for category 2 and 3 exposures:

- The 5 dose regimen
- The 2-1-1 regimen
- The 4 dose regimen with RIG in both categories 2 and 3

Vaccines should be injected in into the deltoid muscle for adults and children aged 2 years and more. The anterolateral thigh is recommended for younger children.
Vaccines should not be injected into the gluteal region.

**Figure 3: Intra-dermal route of vaccine**

**Transmission**

Rabies is mostly transmitted to humans, and between animals, through the saliva of infected animals. Transmission is generally through a bite from any infected animal. Transmission between humans is extremely rare, although it can happen through organ transplants, or through bites.[citation needed] After a typical human infection by bite, the virus enters the peripheral nervous system. It then travels along the nerves towards the central nervous system.

During this phase, the virus cannot be easily detected within the host, and vaccination may still confer cell-mediated immunity to prevent symptomatic rabies. Once the virus reaches the brain, it rapidly causes encephalitis and symptoms appear. This is called the "prodromal" phase and at this time, treatment is usually unsuccessful. Rabies may also inflame the spinal cord producing myelitis.[citation needed].

**POST-EXPOSURE PROPHYLAXIS (PEP)**

Post-exposure prophylaxis (PEP) is the immediate treatment of a bite victim after rabies exposure. This prevents virus entry into the central nervous system, which results in imminent death. PEP consists of:

- Extensive washing and local treatment of the wound as soon as possible after exposure;
- A course of potent and effective rabies vaccine that meets WHO standards; and
- The administration of rabies immunoglobulin (RIG), if indicated.

All category II and III exposures assessed as carrying a risk of developing rabies require PEP. This risk is increased if:

- the biting mammal is a known rabies reservoir or vector species
- the exposure occurs in a geographical area where rabies is still present
• the animal looks sick or displays abnormal behavior
a wound or mucous membrane was contaminated by the animal’s saliva

**RABIES VACCINES**

**Nerve tissue based vaccines**

More than 100 years ago, Louis Pasteur and his colleagues developed the first crude rabies vaccine based on attenuated virus in desiccated nerve tissue. Nerve tissue vaccines (NTVs) were intended for post-exposure prophylaxis. Although continuously improved over the years, inactivated NTVs produced in the brains of sheep or goats (Sample) or suckling mice (Fuenzalida) are associated with neurological adverse reactions.

Thus, in about 0.3–0.8 persons per 1000 vaccines sensation to contaminating neuroproteins present in the vaccine causes severe allergic encephalomyelitis. Also, these vaccines are inferior to modern CCVs in terms of potency and immunogenicity. A complete post-exposure prophylaxis regimen using NTVs involves a prolonged and painful immunization course of 7–10, even up to 23 injections.

**Nerve tissue based vaccines**

**Table 1: Distance (eucledian) to the nearest case of annual rabies data and clustered dataset**

<table>
<thead>
<tr>
<th>Data set</th>
<th>Cases</th>
<th>Infected counties</th>
<th>Infected townships</th>
<th>Observed Mean Distance(kilometers)</th>
<th>Nearest Neighbor Ratio</th>
<th>z-score</th>
<th>Number of clusters detected by ST-DISCAN</th>
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<tr>
<td>2005 Year</td>
<td>2537</td>
<td>710</td>
<td>2012</td>
<td>9.674</td>
<td>0.305</td>
<td>−67.114</td>
<td>88</td>
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<tr>
<td>2006 Year</td>
<td>3279</td>
<td>899</td>
<td>2568</td>
<td>10.565</td>
<td>0.474</td>
<td>−57.653</td>
<td>135</td>
</tr>
<tr>
<td>2007 Year</td>
<td>3300</td>
<td>984</td>
<td>2721</td>
<td>11.442</td>
<td>0.546</td>
<td>−49.897</td>
<td>106</td>
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<tr>
<td>2008 Year</td>
<td>2466</td>
<td>858</td>
<td>2060</td>
<td>14.596</td>
<td>0.409</td>
<td>−56.134</td>
<td>47</td>
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<tr>
<td>2009 Year</td>
<td>2213</td>
<td>892</td>
<td>1900</td>
<td>14.321</td>
<td>0.633</td>
<td>−33.053</td>
<td>33</td>
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<tr>
<td>2010 Year</td>
<td>2048</td>
<td>817</td>
<td>1750</td>
<td>15.339</td>
<td>0.578</td>
<td>−36.546</td>
<td>40</td>
</tr>
<tr>
<td>2011 Year</td>
<td>1917</td>
<td>862</td>
<td>1685</td>
<td>16.316</td>
<td>0.449</td>
<td>−46.142</td>
<td>31</td>
</tr>
<tr>
<td>Clustered cases 2005–2011 Year</td>
<td>4823</td>
<td>0.306</td>
<td>−80.343</td>
<td>5ume480</td>
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A complete post-exposure prophylaxis regimen using NTVs involves a prolonged and painful immunization course of 7-10, even up

**THE MANUFACTURING PROCESS**

Manufacturing an anti-virus vaccine today is a complicated process even after the arduous task of creating a potential vaccine in the laboratory. The change from manufacturing a potential vaccine in small quantities to manufacturing gallons of safe vaccine in a production situation is dramatic, and simple laboratory procedure may not be amenable to a "scale up" situation.

**The Seed**

Manufacturing begins with small amounts of a specific virus (or seed). The virus must be free of impurities, including other similar viruses and even variations of the same type of virus. Additionally, the seed must be kept under "ideal" conditions, usually frozen, that prevent the virus from becoming either stronger or weaker than desired. Stored in small glass or plastic containers, amounts as small as only 5 or 10 cubic centimeters, but containing thousands if not millions of viruses, will eventually lead to several hundred liters of vaccine. Freezers are maintained at specified temperatures; charts and/or dials outside of the freezer keep a continuous record of the temperature. Sensors will set off audible alarm signals and/or computer alarms if the freezer temperature goes out of range.

**Growing the virus**

After defrosting and warming the seed virus under carefully specified conditions (i.e., at room temperature or in a water bath), the small amount of virus cells is placed into a "cell factory," a small machine that, with the addition of an appropriate medium, allows the virus cells to multiply. Each type of virus grows best in a medium specific to it, established in pre-manufacturing laboratory procedures, but all contain proteins from mammals in one form or another, such as purified protein from cow blood. The medium also contains other proteins and organic compounds that encourage the reproduction of the virus cells. As far as the virus is concerned, the medium in a cell factory is a host for reproduction. Mixed with the appropriate medium, at appropriate temperature, and with a predetermined amount of time, viruses will multiply.
In addition to temperature, other factors must be monitored, including the pH of the mixture. pH is a measure of acidity or basicity, measured on a scale from 0 to 14, and the viruses must be kept at a defined pH within the cell factory. Plain water, which is neither acidic nor basic (neutral) has a pH of 7. Although the container in which the cells are growing is not very large (perhaps the size of a 4-8 quart pot), there are an impressive number of valves, tubes, and sensors connected to it. Sensors monitor pH and temperature, and there are various connections for adding media or chemicals such as oxygen to maintain the pH, places to withdraw samples for microscopic analysis, and sterile arrangements for adding the components of the cell factory and withdrawing the intermediate product when it is ready.

The virus from the cell factory is then separated from the medium, and placed in a second medium for additional growth. Early methods of 40 or 50 years ago used a bottle to hold the mixture, and the resulting growth was a single layer of viruses floating on the medium. It was soon discovered that if the bottle was turned while the viruses were growing, even more virus could be produced because a layer of virus grew on all inside surfaces of the bottle. An important discovery in the 1940s was that cell growth is greatly stimulated by the addition of enzymes to a medium, the most commonly used of which is trypsin. An enzyme is a protein that also functions as a catalyst in the feeding and growth of cells.

In current practice, bottles are not used at all. The growing virus is kept in a container larger than but similar to the cell factory, and mixed with "beads," near microscopic particles to which the viruses can attach themselves. The use of the beads provides the virus with a much greater area to attach themselves to, and consequently, a much greater growth of virus. As in the cell factory, temperature and pH are strictly controlled. Time spent in growing virus varies according to the type of virus being produced, and is, in each case, a closely guarded secret of the manufacturer.

**Separation**

When there is a sufficient number of viruses, they are separated from the beads in one or more ways. The broth might be forced through a filter with openings large enough to allow the viruses to pass through, but small enough to prevent the beads from passing. The mixture might be centrifuged several times to separate the virus from the beads in a container from which they can then be drawn off. Still another alternative

**Selecting the strain**

The eventual vaccine will be either made of attenuated (weakened) virus, or a killed virus. The choice of one or the other depends on a number of factors including the efficacy of the resulting vaccine, and its secondary effects. Ru vaccine, which is developed almost every year in response to
new variants of the causative virus, is always an attenuated vaccine. The virulence of a virus can dictate the choice; rabies vaccine, for example, is always a killed vaccine.

If the vaccine is attenuated, the virus is usually attenuated before it goes through the production process. Carefully selected strains are cultured (grown) repeatedly in various media. There are strains of viruses that actually become stronger as they grow. These strains are clearly unusable for an attenuated vaccine. Other strains become too weak as they are cultured repeatedly, and these too are unacceptable for vaccine use. Like the porridge, chair, and bed that Goldilocks liked, only some viruses are "just right," reaching a level of attenuation that makes them acceptable for vaccine use, and not changing in strength. Recent molecular technology has made possible the attenuation of live virus by molecular manipulation, but this method is still rare.

The virus is then separated from the medium in which it has been grown. Vaccines which are of several types (as most are) are combined before packaging. The actual amount of vaccine given to a patient will be relatively small compared with the medium in which it is given. Decisions about whether to use water, alcohol, or some other solution for an injectable vaccine, for example, are made after repeated tests for safety, sterility, and stability.

**RABIES VACCINES FOR INTRADERMAL ADMINISTRATION**

Although injection of cell culture and embryonated egg vaccines by the intramuscular route results in higher antibody concentrations, extensive evaluations have shown that similar schedules based on ID injection of 0.10 ml of the vaccine induce equally high protection against rabies. Cost-effective ID regimens using selected CCVs have been successfully introduced for post-exposure prophylaxis in many developing countries, such as the Philippines, Sri-Lanka, Thailand, and India. ID regimens offer a safer and more effective alternative to the use of NTVs and a more economic alternative compared with the intramuscular use of CCVs. For administration by the intradermal route CCVs should meet the same WHO requirements for production and control as required for intramuscular rabies vaccines, including a test potency of at least 2.5 IU per single intramuscular dose. In addition, the immunogenicity and safety of the vaccine in question should be demonstrated inappropriate clinical trials using WHO post-exposure prophylaxis regimens. In countries approving this route of administration, the packet leaflets of such vaccines should state explicitly that they are authorized for intradermal use.
Rabies is a widely distributed zoonotic infectious disease and worldwide about 55,000 deaths are estimated to occur each year. China is the second after India in the annual incidence of human rabies cases. From 1950 to 2011 China experienced several serious human rabies epidemics. While over the past fifty years the annual number of cases has decreased, the epidemic situation remains serious in that a total of 1,917 cases were reported in 2011. Unsuccessful control of canine rabies and inadequate post-exposure prophylaxis (PEP) of patients are thought to be the main factors leading to the high incidence of human rabies in China. Notably each year rabies infections appeared in areas without previous history of infection.

Numerous studies have been conducted to investigate the epidemiology and transmission dynamics of human rabies in China across different temporal and geographical scales. Phylogenetic analysis of Chinese rabies viruses from 1969 and 2009 demonstrated that infection had been transmitted intra-provincially and extra-provincially due to human-related activities. Time-series analysis of human rabies in China has shown seasonal trends in infection in that number of cases in summer and autumn was higher compared to that in spring and winter.
Quality Control

To protect both the purity of the vaccine and the safety of the workers who make and package the vaccine, conditions of laboratory cleanliness are observed throughout the procedure. All transfers of virus and media are conducted under sterile conditions, and all instruments used are sterilized in an autoclave (a machine that kills organisms by heat, and which may be as small as a jewel box or as large as an elevator) before and after use. Workers performing the procedures wear protective clothing which includes disposable Tyvek gowns, gloves, booties, hair nets, and face masks. The manufacturing rooms themselves are specially air conditioned so that there is a minimal number of particles in the

WHO response

Rabies is included in the neglected tropical disease roadmap of WHO. As a zoonotic disease, it requires close cross-sectoral coordination at the national, regional and global levels. Out of 2051 patients, 1339 patients completed all the 4 doses, 347 patients took 3 doses, 264 patients received only 2 doses while 101 patients received only 1 dose of ID Anti Rabies vaccine.[11]

Rabies immunoglobulins (RIG) for passive immunization RIG should be administered in all category III exposures and in category II exposures involving immuno deficient individuals. Due to its relatively slow clearance, human rabies immunoglobulins (HRIG) is the preferred product, particularly in cases of multiple severe exposures. However, HRIG is in short supply and available
mainly in industrialized countries. Where HRIG is not available or affordable, purified equine immunoglobulin (ERIG), or F(ab’)2 products of ERIG should be used. Therefore, a skin test is mandatory prior to administration of ERIG and F(Ab’)2 products, according to guidelines by the manufacture RIG for passive immunization should not be injected later than 7 days after the initiation of post-exposure vaccination. The dose for HRIG is 20 IU/kg body weight, and for ERIG and F(ab’)2 products 40 IU/kg body weight. All of the RIG, or as much as anatomically possible (cave compartment syndrome!) should be administered indoor around the wound site(s). Any remaining RIG should be injected i.m. at a site distant from the site of vaccine administration.

**Drug- Imovax.-**

**Description**
The Imovax® Rabies Vaccine produced by Sanofi Pasteur SA is a sterile, stable, freeze-dried 9 suspension of rabies virus prepared from strain PM-1503-3M obtained from the Wistar Institute, Philadelphia, PA. The virus is harvested from infected human diploid cells, MRC-5 strain, concentrated by 13 ultrafiltration and is inactivated by beta-propiolactone. One dose of reconstituted vaccine contains less than 100 mg human albumin, less than 150 mcg neomycin sulfate and 20 mcg of phenol red indicator. Beta-propiolactone, a residual component of the manufacturing process, is present in less than 50 parts per million.

**Clinical pharmacology-**

**Pre-exposure immunization**

1. High titer antibody responses to the Imovax Rabies vaccine made in human diploid cells have been demonstrated in trials conducted in England (1), Germany (2) (3), France (4) and Belgium.

2. Seroconversion was often obtained with only one dose. With two doses one month apart, 8100% of the recipients developed specific antibody, and the geometric mean titer of the group.

3. Approximately 10 international units. In the US, Imovax Rabies vaccine resulted in geometric mean titers (GMT) of 12.9 IU/mL at Day 49 and 5.1 IU/mL at Day 90 when three doses were

**Post-exposure immunization**

Post-exposure efficacy of Imovax Rabies vaccine was successfully proven during clinical 19 experience in Iran in which six 1.0 mL doses were given on days 0, 3, 7, 14, 30, and 90, in 20 conjunction with antirabies serum. Forty-five persons severely bitten by rabid dogs and wolves received Imovax Rabies vaccine within hours of and up to 14 days after the bites.
Indications and usage

Imovax Rabies is a vaccine indicated for pre-exposure and post-exposure against rabies. Imovax Rabies vaccine is approved for use in all age groups. 17 Rationale of treatment - Physicians must evaluate each possible rabies exposure. Local or state public health officials 20 should be consulted if questions arise about the need for prophylaxis.

Contraindications

Do not administer to anyone with a known life-threatening systemic hypersensitivity reaction to any component of the vaccine (see WARNINGS, PRECAUTIONS, and DESCRIPTION

Warning

- Do not inject the vaccine into the gluteal area as administration in this area may result in lower neutralizing antibody titers.
- The product is provided in a single dose vial. Because the single dose vial contains no preservative, it is not to be used as a multidose vial for intradermal injection.
- posture and post-exposure immunization, the full 1.0 mL dose should be given intramuscularly.
- Serum sickness type reactions have been reported in persons receiving booster doses of rabies 10 vaccine for pre-exposure prophylaxis. The reaction is characterized by onset approximately 11 to 21 days post-booster, presents with a generalized urticaria, and may also include arthralgia, arthritis, angioedema, nausea, vomiting, fever, and malaise. None of the reported reactions were life-threatening. This has been reported in up to 7% of persons receiving booster vaccination.
- Rare cases of neurologic illness resembling Guillain-Barré syndrome, a transient neuroparalytic illness, that resolved without sequelae in 12 weeks and a focal subacute central nervous system disorder temporally associated with HDCV, have been reported.
- This product contains albumin, a derivative of human blood. Based on effective donor screening and product manufacturing processes, it carries an extremely remote risk for transmission of viral diseases and variant Creutzfeldt-Jakob disease (vCJD). There is a theoretical risk for transmission of Creutzfeldt-Jakob disease (CJD), but if that risk actually

Precaution-

When a person with a history of hypersensitivity must be given rabies vaccine, antihistamines 12 may be given. Epinephrine (1:1000) and other appropriate agents should be readily available 13 to
counteract anaphylactic reactions, and the person should be carefully observed after immunization.

**Drug interaction**

Corticosteroids, other immunosuppressive agents or treatments, and immunosuppressive illnesses interfere with the development of active immunity and predispose the patient to developing rabies. Immunosuppressive agents should not be administered during post-exposure therapy.

**Adverse interaction**

- Once initiated, rabies prophylaxis should not be interrupted or discontinued because of local or mild systemic adverse reactions to rabies vaccine. Usually such reactions can be successfully managed with anti-inflammatory, antihistaminic, and antipyretic agents.
- Reactions after vaccination with HDCV have been observed. In a study using five doses of HDCV, local reactions such as pain, erythema, swelling or itching at the injection site were reported in about 25% of recipients of HDCV, and mild systemic reactions such as headache, nausea, abdominal pain, muscle aches, and dizziness were reported in about 20% of

**Dosage and administration**

Parenteral drug products should be inspected for particulate matter and discoloration prior to administration, whenever solution and container permit. The syringe and its package should also be inspected prior to use for evidence of leakage, premature activation of the plunger, or a faulty tip seal. If evidence of such defects is observed, the product should not be used

**How supply**

Imovax Rabies vaccine is supplied in a tamper evident unit dose box with: One vial of freeze-dried vaccine containing a single dose (NDC 49281-248-58). One sterile syringe containing diluent (NDC 49281-249-01). A separate plunger is provided for insertion and use. One sterile disposable needle for reconstitution.

**Storage**

The freeze-dried vaccine is stable if stored in the refrigerator between 2°C and 8°C (35°F to 46).

**CONCLUSION**

Rabies is a highly contagious, dangerous and potentially fatal virus. It is carried by animals and can be easily contracted by humans as well as other animals. There are numerous symptoms of infection that will appear and there are many diagnostic tests that can confirm the presence of the virus. Treatment is available for rabies in the form of vaccinations. People within rural areas that are
heavily populated with stray canines or felines are considered to be at higher risk of contracting rabies.

REFERENCE

1. Rozario Menezes, Rabies in India: CMAJ. 2008 February 26; 178(5): 564–6


