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Review Article

Review on Rabies Vaccine: As Prevention and Control Option of Rabies

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Abstract

Rabies is a fatal viral disease of animal and human. It gets infection via bites from infected animals. It affects all animals include human and it is fatal with continuous increase of case in the world mostly developing country. Rabies continues to pose a severe burden to public health and is ranked one of the most fatal diseases. This is why we need to review about rabies vaccine as prevention and control option of it. Recently, dogs remain the main source of rabies. Since the first development of the rabies vaccine by Pasteur, human rabies vaccines have been improved and refined. Current cell culture rabies vaccines for humans and animals are highly efficacious, safe, and easily accessible in developed country, which in turn has enabled the control of rabies in these regions. The vaccine have long developmental history with modification, it is inactivated or killed vaccine. These vaccines are given as pre exposure prophylaxis as prevention by immunization and post exposure prophylactic treatment with or without rabies immunoglobulin as treatment, here post exposure as wound treatment and immunization due to its long incubation period of the disease. In most developing country people have clear understanding on the danger of the disease but believe to cure with different traditional and religious treatment rather than seeking effective post exposure prophylaxis. Post exposure prophylaxis consists of immediate wound cleansing and disinfection, followed by vaccination. Vaccines which are tissue culture mostly used but fewer efficacies and immunogenic but developing country use it still now including Ethiopia while cell culture is efficacious and immunogenic but it is expensive and used in developed country even if more or less efficacious vaccination in every aspect is best especially rabies.

Keywords: Post Exposure; Pre Exposure; Rabies; Rabies Immunoglobulin; Vaccine

Introduction

Rabies is a viral zoonotic neglected disease caused by a negative sense single stranded RNA virus from the Genus Lyssavirus [1]. Although a wide range of animals can become infected and transmit the disease, only mammals from the Carnivora and Chiroptera (bats) Order act as reservoir for the disease [2].

It affects all warm blooded mammals and the virus shades in the saliva of clinically ill animals and is transmitted through a bite. Once clinical symptoms appear, it is almost 100% fatal. It is vaccine preventable and can be controlled through vaccination of exposed humans and source animals, mostly dogs [3].

Globally mortality resulting from rabies is estimated between 40,000-70,000 deaths annually, with nearly all deaths occurring in developing countries [4]. These potentially preventable deaths occur in Africa and Asia where animal movement control, vaccination programs and post exposure prophylaxis are not universal [5]. The domestic dog is an important vector in the transmission of human rabies, contributing about 97% of all rabies related deaths in humans worldwide [6,7].

In Ethiopia, rabies is one of the most feared infectious diseases and it has been diagnosed from various parts of the country [8]. Rabies is a major public-health problem in most of the parts of the developing world, where the dog plays a principal role as a reservoir and transmitter of the disease to humans. Human rabies, transmitted by dogs, is an important public health issue in Ethiopia [9].

Rabies vaccine is a vaccine used to prevent rabies. It can be used to prevent rabies before and for a period of time after exposure to the virus. The immunity that develops is long lasting after a full course doses are usually given by injection into the skin or muscle. After exposure vaccination is typically used along with rabies immunoglobulin, and also mostly recommended and useful high risk be vaccinated before potential exposure. Vaccines are effective in humans and other animals. Vaccinating of dogs is very effective in preventing the spread of rabies to humans and may be safely used in all age groups [10].

It has been more than 100 years since the first vaccine was developed for pre-exposure vaccination and post-exposure prophylaxis by Louis pasture on June 6, 1885. Create awareness, educate the people, dog vaccination and the availability and accessibility of high quality Post-exposure prophylaxis (PEP) are keys for rabies prevention and control. Modern rabies vaccines produced on cell cultures or embryonated eggs are both safe and efficacious. At present, most of Asian countries have moved towards modern

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rabies vaccine usage, by import or local production. In Thailand, discontinuation of sheep brain vaccine (Semple vaccine) production in 1989 and of suckling mouse brain (Fuenzalida) vaccine in 1993, and importation of increasing quantities of modern vaccines have played a major role in the drastic reduction in the number of cases of human rabies in the country [11].

Due to the high cost of modern cell culture rabies vaccines, outdated nerve tissue origin rabies vaccines are still administered to most socioeconomically disadvantaged people who are at an increased risk of exposure. Additionally, most modern cell culture rabies vaccines are imported into developing countries and because of many countries impose an extra importation tax to them, the cost it is increased [12].

Some people develop a brief period of redness and pain at the injection site and other may have fever, headaches, or nausea. After exposure to rabies there is no contraindication to its use. Vaccines made from nerve tissue are used in a few countries, mainly in Asia and Latin America, but are less effective and have greater side effects. Their use is thus not recommended by world health organization [10].

The most common tool for disease control in veterinary medicine has been vaccination, with success influenced by vaccine efficacy and the proportion of the population inoculated [13]. Although primarily designed to address the disease in the animal host, veterinary control programmers have a positive contribution in preventing human infection and clinical illness. Veterinary vaccines have historically been produced from attenuated strains, although molecular techniques are facilitating development of safer and more efficacious vaccines which make diagnosis easier. Vaccination of a particular host protects not only key target populations, but can also serve as a barrier to protect human and veterinary health. Clearly, this learned from rabies vaccination of carnivores [14,15].

Therefore the objective of this paper is:

- To review about rabies vaccine as prevention and control option of rabies

Literature Review

Rabies virus and its virulence

The causative agent Rabies Virus (RAV) is the species of the genus Lyssa virus in the family Rhabdoviridae, means bullet or rod shape. The RABV genome is a single-stranded, negative-sense RNA virus, which encodes five structural proteins nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G) and RNA-dependent RNA polymerase (L) [16].

The negative-sense RNA genome is tightly encapsulated by N, P, and L proteins to form a ribonucleic protein complex that is responsible for virus replication in the cytoplasm within infected cells. The RAV G protein is the only viral protein exposed on the surface of the virus and the major determinant of viral pathogencity, and also the major protective antigen responsible for inducing protective against it applied things. RAV is very fragile outside of the animal host, and is rapidly inactivated by drying or exposure to ultraviolet (UV) light [17].

After entry via the endocytic pathway, virus replication and transcription take place in neuronal cells in cytoplasm inclusions termed Negri bodies [18,19]. The virus attacks the central nervous system, causing progressive paralysis, encephalitis and coma. Once symptoms occur, rabies is a fatal infection. The rabies virus multiplies at the site of inoculation then uses the peripheral nervous system to migrate and ascend to the central nervous system, ultimately causing encephalitis. In a rabid animal or person, the virus is present in saliva, tears, cerebrospinal fluid, and neurologic tissue (brain, spinal cord, and peripheral nerves). Transmission of rabies is most likely to occur following a bite from a rabid animal. Non bite exposure to mucous membrane (eye, nose). Rabies virus does not enter the blood stream, so blood is not an infectious fluid and also not present in the urine, feces, or milk, and cannot penetrate intact skin. No known effective treatment for rabies, so the disease is considered universally fatal once symptoms of rabies have started. Fortunately, the relatively slow incubation period of rabies allows for the successful initiation of rabies Post-Exposure Prophylaxis (PEP) for most patients [20].

There are an estimated 60,000 human rabies related deaths worldwide each year. Of these, most cases occur in Asia and Africa [21]. About 98% of the human cases occur in developing countries that possess large number of dogs, many of which are stray [22]. Domestic dogs are considered to be the main source (>90%) for human rabies in Africa. Once the symptoms have appeared, the disease ends almost always fatally [23].

Historical development of rabies vaccine

Rabies infection is always fatal unless prompt post exposure treatment is administered before symptoms begin. Until 1885, when Louis Pasteur and Emile Roux developed a vaccine, all human cases of rabies were fatal as the case fatality rate almost 100%. In 1885, Louis Pasteur experimented with rabies vaccination by using the term virus (Latin word for 'poison') to describe the agent. At that time, Pasteur did not discriminate between viruses and other infectious agents but originated the terms virus and vaccination (in honor of Jenner, British scientist) and developed the scientific basis for experimental approach to vaccination and well known historical achievement in the field of vaccination [24].

Through adaptation of street (wild-type) rabies virus to laboratory animals, he was able to change virus properties which can change virulence and incubation period over several passages. After adaptation to laboratory animals and cell lines, the virus was known to lose its virulence other than intra cerebral root of inoculation and increase expression of G-protein to the host cells resulting in high immune responses [25].

In 1885 Louis Pasteur develops the first RABV vaccine from the spinal cord of rabbits infected with rabies that was air-dried for inactivation. As the vaccine used by Pasteur was virtually a mixture of inactivated and live RABV, although occasional failures were happened, Pasteur's vaccine was doomed to be subject to criticism [26]. To solve these safety issues, the Semple rabies vaccine was developed by adding phenol to partially or completely inactivated live viruses in Pasteur's vaccine [27]. Unfortunately, both Pasteur's vaccine and the Semple rabies vaccine are derived from nerve tissue and the presence of the myelin component and other potential allergic materials in infected brains restricted the application of these vaccines, due to severe adverse effects. Subsequently, it was found that

Table 1: Rabies Pre-exposure Prophylaxis recommendation.

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus present continuously and often in high concentrations. Specific exposures likely to go unrecognized. Any way of exposure.	Rabies research laboratory workers; rabies biologics production workers.	Serologic testing every 6 months; booster vaccination if antibody titer is below acceptable level.
Frequent	Exposure usually episodic, with source recognized, but exposure also might be unrecognized. Any rout of exposure.	Rabies diagnostic laboratory workers, cavers, veterinarians and staff, and animal-control and wildlife workers in areas where rabies is enzootic. A person frequently handle bats.	Serologic testing every 2 years; booster vaccination if antibody titer is below acceptable level
Infrequent	Exposure nearly always episodic with source recognized.	Worker with terrestrial animals in where rabies is uncommon to rare. Veterinary students. Visitor areas where rabies is enzootic. A person frequently handle bats.	No serologic testing or booster vaccination.
Rare	Exposure always episodic with source recognized.	Most population in areas where rabies is epizootic	No vaccination is necessary.

these issues could be circumvented by producing vaccines from the brain tissue of newborn suckling mice, as the substances responsible for these side effects were largely absent in embryonic and newborn animal nerve tissues. The rabies vaccine was thereby developed using this technique [28].

However, the vaccine was not fully free of brain tissue components such as myelin, and severe adverse reactions were still reported [29]. An alternative approach to overcome these issues employed embryonated eggs, such as chick or duck embryos, as the media to produce rabies vaccines. Collectively, although these approaches slightly improved the quality of vaccines, they failed to thoroughly resolve the safety issues and were generally less efficacious with poor immunogenicity, which significantly hampered the generalization of these vaccines, and therefore lead to their discontinuation in most areas of the world [26].

The recent advance of modern cell cultivation techniques has made it feasible to produce high-quality rabies vaccines from cell culture. An important development was that, although RABV is highly neurotropic, it can lose its tissue tropism and adapt to *in vitro* cultured cells, a feature that can be utilized to propagate RABV in many different cell types, in order to achieve high virus yields. The first licensed human rabies vaccine developed from cell culture was the primary hamster kidney cell vaccine, which was created by cultivating viruses in primary hamster kidney cells [30]. Subsequently, fixed RABV was adapted to the human diploid cell strain, initially using the lung-derived cell line WI-38, but subsequently switched to the fetal lung cell strain MRC-5, to produce the human diploid cell vaccine [31,32].

As the first purified, concentrated, and lyophilized rabies vaccine, the human diploid cell vaccine elicited significantly higher immunogenicity and caused much fewer adverse effects compared to other rabies vaccines, and was therefore recommended as the gold standard reference vaccine by the WHO. However, the lower virus yields and higher production costs make the human diploid cell vaccine difficult to scale up and can be generally unaffordable to most developing countries, where the majority of human deaths from rabies occur. As an alternative, other cell culture vaccines, such as the purified duck/chick embryo cell vaccine, were developed and proved to be as effective as human diploid cell vaccine, and are now commonly used for human rabies prevention worldwide [33]. Nevertheless, as the primary culture cells inherently have a limited capacity to divide, they are technically difficult to adapt to large-scale industrial cultivation for vaccine manufacturing. For this reason, the Vero cell line was used to produce purified Vero cell rabies vaccine [34]. Vero cell cultivation can easily be scaled up and the virus titers produced in Vero cells are generally higher than those in primary culture cells. Importantly, the Vero cell line has a long history of being used in vaccines without safety concerns [35].

These advantages of Vero cells significantly reduce the costs of rabies vaccine production and make rabies vaccines affordable to most developing countries. Undoubtedly, Vero cells will continue to be one of the most common and popular media for human rabies vaccine production in the future. Over the years, several types of anti-rabies vaccines have been developed, produced and used for protection of man and animal against rabies. Pasteur's basic approach to vaccine development such as attenuation and inactivation are still key pillars of vaccinology. In modern technology however, purification of target microbial components, genetic engineering and enhanced knowledge of immune defense to enable creation of attenuated mutants, expression of vaccine proteins and polysaccharide [36]. Development of recombinant rabies vaccines has been proposed through the application of reverse genetics to generate rabies viruses with modified properties [37]. Ideally, to generate more robust memory responses, vaccine preparations could involve live attenuated virus to elicit a strong memory response, although use as either a pre-exposure or post-exposure option requires extensive development [38]. Most progress in this area has been made with post-exposure treatment of experimental rabies in animals, rather than post exposure prophylaxis in the manner of licensed vaccines. Prominent among these new prototype vaccines that may be licensed in the future for treating rabies is the so-called Tri GAS construct that contains three copies of the glycoprotein gene [39]. Over expression of the glycoprotein gene by this construct stimulates a strong immune response and simultaneously seems to attenuate the infection [40].

The vaccine effectiveness

Rabies is a public health problem, approximately 50,000 humans' worldwide die from the disease annually [41]. Most of the peoples at risk live in 90 countries with a population of approximately 2.4 billion, where the rabies reservoir is the dog and more than 95 percent of human rabies cases are transmitted by dogs [42]. In Ethiopia, 94.01 percent of rabies cases are caused due to the bite of rabid dogs and the rest cases incriminate domestic and wild animals [43].

Table 2: Type of contact, exposure and recommended post-exposure.

Category	Type of contact	Type of exposure	Recommended post exposure prophylaxis
I	Touching or feeding animals	None	None, if reliable case history is available
II	Lick on intact skin Nibbling of uncovered skin Minor scratches or abrasions without bleeding	Minor	Administer vaccine Immediately, Stop treatment if animal remains healthy after confirm, and observation period of 10-14 days.
III	Single or multiple trans dermal bites, scratches, licks on broken skin mucous member	Sever	Administer RIG and vaccine immediately Stop treatment if animal remains healthy after confirm, observation period of 10-14 days.

Since the first rabies vaccination in 1885 by Louis Pasteur, significant progress has been made in improving the pre and post exposure treatment of human rabies [42]. Several types of anti-rabies vaccines are used for pre and post exposure treatment, which include live attenuated which is live virus after several passage, inactivated (killed), DNA-based and vector vaccines [43].

Rabies can be a vaccine-preventable disease, provided that Post-Exposure Prophylaxis (PEP) is given promptly and correctly. Protection against rabies correlates with the presence of rabies specific Virus Neutralizing Antibodies (VNAs). From WHO, VNA titers greater than 0.5 international units per ml serum can reliably provide protection to humans and animal? As main source is dog, vaccinating dogs has been shown to be the most cost-effective strategy for preventing rabies in humans. As reported by the WHO, vaccination coverage of 70% of the canine population can efficiently reduce virus transmission and prevent human rabies .even if efficacious vaccines are readily available; rabies still has a high death rate, mainly due to the cost and accessibility of proper PEP treatment, the current PEP schedule not only requires multiple injections but also time-consuming problem that is even more pronounced due to the fact that RAV specific immunoglobulin (RIG), which is both expensive and often in short supply, is required to treat severe exposure [44].

Vaccine immunogenicity is a key factor in judging the effectiveness of vaccines and usually reflects both the antigen content of a particular batch and the titer of antibody induced following inoculation. The key parameter measured in humans or animals, is the titer of neutralizing antibody induced following vaccination [45].

Rabies vaccines produced in mammalian neural tissues have the disadvantage of causing severe adverse reactions, at a rate estimated as 0.3-0.8 per thousand treated patients [11]. The vaccines recommended by WHO include those produced in Vero cells, available since the 1980s. Unfortunately, the cell culture rabies vaccines are expensive and not readily available to individuals living in developing countries where rabies is endemic in dogs [46].

Rabies vaccine types based on time of administration

Uniquely among vaccines, those for rabies can be given both pre- and post-exposure to virus. Pre-exposure vaccination is appropriate for travelers to RAV-endemic regions, veterinarians and researchers working with the virus and source animal with most transmitter animal. Post-exposure vaccination is possible because the exposure event, usually a bite, is easily identifiable and the incubation period is of sufficient length for vaccination to induce a protective immune response. This is principally through the development of neutralizing antibodies. Post-exposure vaccination is usually accompanied by injection of anti-rabies immunoglobulin of either human (HRIG) or equine (ERIG) origin, and is referred to collectively as Post-Exposure Prophylaxis (PEP). Whether PEP is given can be decided by the level of exposure on (Table 2) which, despite the extreme consequences of developing disease, is a factor in resource-poor areas of the world Pre exposure recommendation on (Table 1) indicate when and for whom is given [47].

Pre-exposure vaccination consists of an intramuscular injection of 1 ml vaccine on days 0, 7, 21 and 28. Depending on the vaccine manufacturer, boosting is recommended at 3-5-year intervals. This has been borne out by recent cohort studies of UK bat workers who are required to be vaccinated against rabies prior to licensing to work with bats [47].

Post-exposure vaccination is given typically as an intramuscular injection on days 0, 3, 7, 14 and 30. HRIG is given on day 0, unless the recipient has received previous vaccination against rabies. One innovation has been the replacement of intramuscular inoculation with intradermal injection of vaccine [48].

Pre exposure prophylaxis vaccine in animal: A regular rabies vaccination schedule before is critical to protect animals against recognized and unrecognized rabies exposures. Parenteral animal rabies vaccines should be administered only by or under the direct supervision of a licensed veterinarian on premises. Rabies vaccines may be administered under the supervision of a licensed veterinarian to animals held in animal shelters before release. The veterinarian signing a rabies vaccination certificate must ensure that the person who administered the vaccine is identified on the certificate and has been appropriately trained in vaccine storage, handling, and administration and in the management of adverse events. This ensures that a qualified and responsible person can be held accountable for properly vaccinating the animal [49].

Pre-exposure immunization has been used on domesticated and wild populations. In many jurisdictions, domestic dogs, cats, ferrets, and rabbits are required to be vaccinated. Dog aside from vaccinating humans, another approach was also developed by vaccinating dogs to prevent the spread of the virus [50]. Researcher in different time and place produced developed a dog vaccine that gave three-year immunity from rabies. The development of the vaccine resulted in the elimination of rabies in many parts of the Visayas and Mindanao Islands. The successful program in the Philippines was later used as a model by other countries, such as Ecuador and the Yucatan State of Mexico, in their fight against rabies conducted in collaboration with the World Health Organization [51].

Cell culture-derived vaccines can be used for the parenteral vaccination of companion animals and livestock, and have also been used to develop oral vaccines for wildlife immunization [52]. The combination of high titres of attenuated strains of RABV with an oral bait attractive to wildlife vectors such as the red fox (Vulpes vulpes)

have been highly effective at eliminating rabies from western Europe and remain in use throughout eastern Europe and Turkey [53,54].

In Tunisia a rabies control program was initiated to give dog owners free vaccination to promote mass vaccination which was sponsored by their government. The vaccine is known as Rabisin (Mérial), which is a cell based rabies vaccine only used countrywide. Vaccinations are often administered when owners take in their dogs for check-ups and visits at the veterinarian [55].

Wild animal also vaccination in pellet form which can be left out for wild animals to produce a herd immunity effect [56]. Baits are distributed by airplanes in rural areas and by hand in urban and suburban areas. The idea of wildlife vaccination was conceived during the 1960s, and modified-live rabies viruses were used for the experimental oral vaccination of carnivores by the 1970s. The development of safe and effective rabies virus vaccines applied in attractive baits resulted in the first field trials in Switzerland in 1978 to immunize red foxes [14]. ORV programs have seen success in preventing the westward spread of raccoon variant rabies in the United States and even eradicating rabies in red foxes in Switzerland [57].

Imrab is an example of a veterinary rabies vaccine containing the Pasteur strain of killed rabies virus. Several different types of Imrab exist, including Imrab, Imrab 3, and Imrab Large Animal. Imrab 3 has been approved for ferrets and, in some areas, pet skunks [58].

Multiple vaccines are licensed for use in domestic animal species. Vaccines available include inactivated (killed) and modified-live virus vectored products, products for IM and SC administration, products with durations of immunity for periods of 1 to 3 years, and products with various minimum ages of vaccination. Rabies vaccines should be administered under the supervision of a licensed veterinarian to animals held in animal shelters before release. Within 28 days after initial vaccination, a peak rabies virus antibody titer is expected, and the animal can be considered immunized [59]. The use of Oral Rabies Vaccines (ORV) for the mass vaccination of free-ranging wildlife should be considered in selected situations [21,60].

Oral vaccination with attenuated strains is common place in Europe although often, the cause of attenuation has not been deduced, and as such reversion to virulence is a concern. Molecular manipulation of vaccine strains with reverse genetics enables the mechanisms of attenuation to be investigated, which can then be applied to safely attenuate RAV, preventing possible reversion to virulence [61].

Post exposure prophylaxis treatment in animal: Any animal potentially exposed to rabies virus (Rabies Exposure) by a wild Carnivorous mammal or a bat that is not available for testing should be regarded as having been exposed to rabies. Unvaccinated dogs, cats, and ferrets exposed to a rabid animal should be euthanatized immediately. If the owner is unwilling to have this done, the animal should be placed in strict isolation for 6 months and vaccinated one month before being released. Protocols for the post exposure vaccination of previously unvaccinated domestic animals have not been validated, and there is evidence that the use of vaccine alone will not prevent the disease [62].

Currently, there are no licensed products or nationally established protocols for rabies PEP of naïve rabies-exposed animals, including domestic dogs. However, the knowledge and biologics for potential PEP of such animals exist. In a few studies, dogs were protected against rabies when treated in accordance with a protocol that emulated rabies PEP in humans with regard to biologics and schedule of administration. However HRIG is in critically short supply on a global basis [63]. The limited availability and subsequent high cost of HRIG limits its use for PEP of humans in developing countries.

Pre exposure prophylaxis vaccine in human: Pre exposure vaccination is indicated for persons whose occupation, travel, or recreational activities place them at higher risk of exposure to rabies. Occupational groups include veterinarians, veterinary technicians, animal control officers, bat researchers, wildlife workers, and animal disease laboratory workers. International travelers are recommended to receive pre-exposure vaccination if they are likely to come in contact with animals in countries where canine or other animal rabies is prevalent, and immediate access to appropriate medical care, including rabies vaccine and immune globulin, might be limited [20].

Pre-exposure prophylaxis is given for two reasons: To provide protection against unrecognized or unapparent exposures to rabies and to simplify Post-Exposure Prophylaxis (PEP) by eliminating the need for Rabies Immune Globulin (RIG) and by decreasing the number of required vaccine doses when an exposure occurs. Pre-exposure immunization does not eliminate the need for prompt post-exposure prophylaxis following a recognized exposure; it only reduces the PEP regimen. Anyone who receives the pre exposure prophylaxis series is considered immunologically primed against future rabies exposure. Therefore, if they are exposed to a rabid animal, they simply require PEP for a person previously vaccinated (i.e., days 0 and 3 vaccination) it explained on table1 below [20].

Post exposure prophylaxis treatment in human: The essential components of rabies post-exposure prophylaxis are wound treatment and, for one previously unvaccinated persons, the administration of both human Rabies Immune Globulin (RIG) and vaccine are present [64].

Local treatment of wounds, thorough washing and flushing (for about 15 minutes, if possible) with soap or a cleansing agent and copious amounts of water of all bite wounds and scratches should be done immediately or as early as possible. Where available, an iodine-containing, or similarly veridical, topical preparation should be applied to the wound, Tetanus prophylaxis and measures to control bacterial infection should be given as indicated [10].

Specific treatment, the immediate treatment is started after exposure, is the better. Post-exposure antirabies vaccination should always include administration of both passive antibody and vaccine, with the exception of persons who have ever previously received complete vaccination regimens (pre-exposure or post-exposure) with a cell culture vaccine or persons who have been vaccinated with other types of vaccines and have previously had a documented rabies virus neutralizing antibody titer. These persons should receive only vaccine, when get pre exposure before. The combination of RIG and vaccine is recommended for both bite and non-bite exposures reported by persons who have never been previously vaccinated for

rabies, regardless of the interval between exposure and initiation of prophylaxis. If post-exposure prophylaxis has been initiated and appropriate laboratory diagnostic testing (FAT) indicates that the exposing animal was not rabid, post-exposure prophylaxis can be discontinue [64]. Post exposure vaccination is usually accompanied by injection of anti-rabies immunoglobulin of either human (HRIG) or equine (ERIG) origin, and is referred to collectively as PEP [65].

Source: [48].

Rabies Immune Globulin (RIG), a recombinant monoclonal antibody targeting a specific epitope of the G protein, is highly effective in neutralizing RABV *in vitro* or before the virus enters the CNS [66]. It is an essential component of PEP, since it delivers passive immunity which is particularly important at early stages, before the host develops active immunity to the vaccine. However, once the virus accesses the CNS, these antibodies are restricted to crossing the immune-privileged BBB to neutralize virus infection. Although, in theory, the antibody could be given intracerebrally, it is definitely not a practical therapy. On the other hand, it has been firmly established that enhancement of BBB permeability is required to allow the passage of VNAs into the CNS of activated B cells, in order to cross the BBB and release antibodies in situ for RABV clearance [67,68,69].

RIG is also an important component of post-exposure prophylaxis to inhibit viral spread in the interval before sufficient immunity is developed in response to vaccination. It should be injected into and around the wound site, ideally on the day of exposure or up to 7 days after the initial dose of vaccine [70].

Twenty IU/kg on day zero in conjunction with the first vaccine one dose. If possible, the full calculated dose of RIG should be used to infiltrate the wound. If it is two not possible to do so, any remaining portion of the dose should be administered intramuscularly at a site different from the site used to administer the vaccine. Because, the antibody response following the recommended vaccination regimen with HDCV has been satisfactory, routine post-vaccination serologic testing is not recommended. Serologic testing is indicated in unusual circumstances, as when the patient is known to be immune suppressed [64].

Application of rabies vaccines

As dog is the main source of rabies in humans, principal method of dog rabies control is mass vaccination, and has been successfully used to eliminate human dog-mediated rabies in countries like Malaysia, Philippines, Tunisia, Western Europe and North America among others. According to the World Organization for Animal Health (OIE) and the WHO recommendations, the critical percentage of dogs to be vaccinated to prevent rabies cases should be at least 70% [11]. This target coverage has been supported by empirical evidence and theoretical observations worldwide investigating the relationship between vaccination coverage and reduction in rabies incidence. A study conducted in Tunisia indicates 70% dog vaccination coverage through parenteral vaccination in most regions of the country resulting in elimination of the disease [71].

Most developing countries, especially those in Asia, Africa, Latin America and the Middle East, 70%-95% of their population rely on traditional medicines for treatment of different diseases [72]. Herbal medicines include medicinal products of plant roots, leaves, barks, seeds, berries or flowers that can be used to promote health and treat diseases in humans and animals [73]. The beneficial medicinal effects of folk drugs typically result from combinations of secondary products present in the plant which used as sources of medicines throughout history and continued to serve as the basis for many pharmaceuticals used today [74]. However, their potential as the source of drugs is still unexplored [75].

In Ethiopia people have clear understanding on the danger of the disease but believe to cure with different traditional and religious treatment rather than seeking effective post exposure prophylaxis. Most people use wide variety of traditional treatment in cases of bite by animals (mostly dogs) believed to be rabid. The significance of the disease is evident from the continued existence of traditional specialists in rabies treatment within the community [76].

It is widely believed in Ethiopia that the skill of traditional health practitioners is 'given by God' and knowledge on traditional medicines is passed orally from father to a favorite child, usually a son or is acquired by some spiritual procedures. Traditional Healing knowledge is guarded by certain families or social groups [77].

The widespread use of traditional medicine among urban and rural population of Ethiopia could be attributed to cultural acceptability, physical accessibility and economic affordability as compared to modern medicine. Healing in Ethiopian traditional medicine is not only concerned with curing of diseases but also with the protection and promotion of human physical, spiritual, social, mental and material wellbeing [78]. Individuals who are exposed to rabies virus often see traditional healers for the diagnosis and treatment of the disease. These widespread traditional practices of handling rabies cases are believed to interfere with timely seeking of (PEP) [79].

The application of traditional medicine to veterinary medicine has been termed as ethno veterinary medicine. It is mainly concerned with beliefs, knowledge, skills, methods and practices which are used in the healthcare of animals [80]. Most people use wide variety of traditional treatment in cases of bite by animals (mostly dogs) believed to be rabid [81] and Traditional Medicine (TM) includes folk drugs composed of herbs, herbal materials, herbal preparations and finished herbal products (Contain as active ingredients of plant parts, or other plant materials) [82]. The effectiveness of and safety of these traditionally used antirabies folk drugs in the country was not well demonstrate and understood [78].

Advantage and disadvantage of rabies vaccine

Dog vaccination status is of higher importance; it minimizes or eliminates further economic impact. In contrast, unvaccinated dogs, or dogs whose vaccination status is unknown, represent a pathway to further economic impacts. If the vaccination status of a dog can be readily determined, the initial cost of vaccination negates any further downstream impacts, but when humans and livestock are exposed to a dog that might have rabies, or whose vaccination status is unknown, further costs may be necessary. Livestock vaccination also represents an up-front cost, without further impacts, while unvaccinated, exposed animals will either not become infected, or will die from rabies. Similarly, there are two pathways following human exposure: the individual both seeks medical treatment and is given PEP, incurring direct and indirect costs [83].

A vaccine, like any medicine, is capable of causing serious problems, such as severe allergic reactions. Serious problems from rabies vaccine are very rare. Mild problems include inflammation sign on administration site, soreness, redness, swelling, or itching where the shot was given including headache, nausea, abdominal pain, muscle aches, dizziness. Moderate problems hives, pain in the joints, fever. Other nervous system disorders, such as Guillain- Barré Syndrome (GBS), have been reported after vaccination, but this happens so rarely that it is not known whether they are related to the vaccine. Several brands of rabies vaccine are available in the United States, and reactions may vary between brands, provider can give you more information about a particular brand. If reaction occurs, signs of a severe allergic reaction, very high fever, behavior changes, hives, swelling of the face and throat, difficulty breathing, a fast heartbeat, dizziness, and weakness. These would start a few minutes to a few hours after the vaccination [84].

Current rabies vaccine and vaccination status in Ethiopia

According to Ethiopian Health And Nutritional Research Institute (EHNRI) laboratory data from 1990-2010, out of 6,739 animal brain tissue samples examined by direct Fluorescent Antibody Test (FAT), 4,939 (73.4%) were positive for rabies virus of which dogs represent 91.1% with the incidence rate of 89% and the remaining percent accounted by other domestic animals (Cats, cattle, sheep, goats and equines). Similarly, 97.3% of human rabies were due to dog bites and the remaining 0.2% and 2.5% were contributed by other domestic animals rather than dogs and wild animals, respectively [85].

Ethiopia's current population is estimated at 1,100 million and above. The fatal human cases in 2001-2009 were 386 humans with annual range of 35 to 58 percent and different animals with different ratio also exposed, in the ten years a minimum of 6,263 and a maximum of 21, 832 doses of the human rabies vaccine were produced and distributed every year [86]. There are a number of challenges in the prevention and control of rabies in Ethiopia. One is inadequate laboratory capacity and lack of diagnosis centers at different sites for effective surveillance and response, diagnosis of rabid animals at one center, at Ethiopian Public Health Institute. There is also inadequate sharing of surveillance data between human and animal health care sectors at both local and national levels, resulting in loss of opportunities to prevent human rabies, early detection and timely response to rabies outbreak. Studies showed, lack of sufficient awareness about the disease management and high reliance on traditional treatment that interfere with timely post exposure management account for a major human cases [86].

The Fermi type adult sheep brain nervous tissue vaccine produced at the Ethiopian Public Health Institute (EPHI) since 1940's. The country is still producing and using this long time WHO banned Fermi type anti-rabies vaccine for post exposure treatment. Regardless of its quality, there is limited supply of rabies vaccine and also lack of adequate, safe and effective PET and PEP biologics in public health. Whereas high quality vaccine may be available in some private facilities, the cost is prohibitive and cannot be afforded by public at large. The possibility of producing rabies vaccines locally have been explored during the last some years and currently produced from Pasteur Virus (PV) and Evinyl Rokitnki Abelseth (ERA) rabies virus strains, and pre-clinical trial completed [87].

Modern cell culture anti-rabies vaccine production for animal use has been transferred to National Veterinary Institute from the Ethiopian Public Health Institute for mass production. For human purpose, the effort to replace Fermi type with modern cell culture vaccine is in progress at EPHI and currently preclinical trials were finalized. In the coming few years, it is assumed to replace Fermi vaccine which is expected to contribute to the control and elimination of the disease in Ethiopia [88].

At present some ongoing efforts of rabies survey put by EHNRI and fragmented rabies prevention and control by distributing Fermi type nerve tissue vaccine to few health centers are also practiced .Although the usage of nerve tissue vaccine recommended to be discontinued by WHO starting from 1984.it was produced and still used in Ethiopia for treatment of rabies owing to the expensive cost of modern cell culture vaccine than Fermi type produce at EHNRI. Ethiopian cell culture vaccine named as ETHIORAB has been produced by EHNRI and is of its clinical trial phase in dog [85].

Conclusion and Recommendations

Since rabies frequently occurring and the disease is life threatening, affects all warm blooded mammals, and its occurs is worldwide mostly in developing country Asia and Africa more death recorded. In Ethiopia, the disease is endemic and a threat to both urban and rural community due to large numbers of stray dogs and varieties of wild carnivores. Rabies is a major public health problem in most parts of the country, where the dogs play a principal role as a reservoir and transmitters of the diseases to humans. Rabies has a vaccine but not treatment, so prevention by pre exposure vaccine is best for source animal and high risk population. mass vaccination of dog population have greater role so, should be carried out as much as possible in the world mostly in developed country. However, rabies remains endemic to many parts of the developing world where the resources of appropriate PEP are limited, the infrastructure and facility are inadequate, and, most importantly, awareness about rabies is lacking. In these cases, inexpensive, safe, and effective vaccines are urgently needed. This situation is even more pronounced given the fact that the most important and probably the only practical way to control rabies globally is the mass vaccination of dogs as well as wildlife reservoirs. The vaccine is given as pre exposure and post exposure with or without rabies immunoglobulin and it have no contraindication for pregnant but for immune suppressed. Generally, mass vaccination of dogs, proper post exposure management, appropriate surveillance system, and increasing the awareness of the community about the disease needs special attention for prevention and control of the disease, vaccination as prevention is better than curing especially for rabies due to its fatality.

By keeping in view the rabies with its vaccine importance to prevention and control option, the following recommendations are forwarded:

- Creating awareness about its fatality and not only vaccine importance but also vaccination for rabies reduction followed elimination by vaccine and vaccination for all source or carrier individuals is important.
- Post exposure treatment should be given after immediately exposure to bite or scratch by rabid animals.

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