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Review Article

Rabies virus : A Descriptive Review for its Epidemiology, Etiology ,pathophysiology, Transmission and prevention mechanism

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Abstract:

Rabies is a deadly viral disease that affects the nervous system of both humans and animals. The causative agent belongs to the family of *Rhabdoviridae* and is most commonly transmitted through the saliva of infected animals, such as dogs, cats, foxes, and bats, via bites or scratches. Human-to-human transmission is extremely rare but may occur under specific circumstances. The disease manifests in two clinical forms: the furious form, characterized by aggression, excessive salivation, and hydrophobia, and the dumb [paralytic] form, where paralysis gradually develops. Transmission occurs primarily through bites or open wounds exposed to infected saliva and, less commonly, via contact with mucous membranes during handling of infected animals. Diagnosis in advanced stages relies on clinical signs, but definitive confirmation is achieved through post-mortem examination of brain tissue. Laboratory testing can also be performed on saliva or other tissue samples. Currently, there is no effective treatment once clinical symptoms appear, making prevention through vaccination the most effective strategy. Mass vaccination campaigns for animals are crucial in controlling rabies, particularly in rural areas, alongside public education programs to raise awareness about the risks of contact with potentially infected animals. The purpose of studying rabies in humans and animals is to emphasize the importance of understanding its transmission, pathogenesis, and preventive measures, given that rabies remains a fatal viral disease that can be transmitted from animals to humans.

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Introduction

Rabies is “zoonotic , fatal and progressive neurological infection caused by rabies virus of the genus *Lyssavirus* and family *Rhabdoviridae”* It affects all “warm-blooded animals” and This disease is widespread globally and endemic in numerous nations [1]. Approximately “15 million” people receive rabies “post-exposure prophylaxis” [PEP] each year, while over 60,000 people die from rabies each year. Wildlife such as “raccoons, skunks, bats, and foxes” are major rabies reservoirs, and the primary means of transmission are the bites of rabid animals, particularly dogs, and the saliva of an infected host. the virus travels along neurons to the central nervous system [CNS] [2]. Incubation period ranges from “2 to 8 weeks” However, it can last anywhere from ten days to eight months and sometimes even years. The further the bite is from the “CNS” the longer the incubation period [3]. Neuropathological lesions are comparatively mild, “despite severe neurologic symptoms” and a fatal outcome. the disease is known as hydrophobic “ lyssa” , rage, tollway the disease “Hydrophobia” “fear of water” . in which attempts to drink water or swallow lead to painful spasms of the muscles of the throat or larynx -causes increase in saliva production. This helps to Increase the likelihood of transmission [4]. severity of rabies infection is related to immunity [5]. The rabies virus uses a number of strategies to avoid the host's immune system. Since it is a major zoonosis, early treatment and successful prevention and control measures depend on an accurate and timely diagnosis [6]. In “1804” Zinke recognized that the saliva of infected dogs was contagious. Prior to the discovery of Pasteur in “1885” there was no effective treatment for either prevention or cure in animals. Pasteur proved the virus' neurotropism in 1881 [7,9]. “Pasteur” discovered and administered a “rabies vaccine” “prior to the structure and properties of RABV were understood. In the same year, first time he administered the rabies vaccine to Joseph Meister, who was attacked worsely by rabies-affected animal. That day was the milestone for the beginning of the modern science in the area of infectious diseases targeting “control and prevention of diseases”[8,10].

Etiology

The most dreaded and ancient disease that affects both humans and animals is rabies. It has been around for a very long time [7,11]. Rabies; alternatively, "rabere" [which means "to be mad" in Latin] Since the beginning of civilization, the disease has been recognized. In 23rd “century BC” the first written record of rabies was found in the Babylonian Eshmuna code. But Louis Pasteur was the first to identify a virus as the disease's cause in the 1880s [8,12].

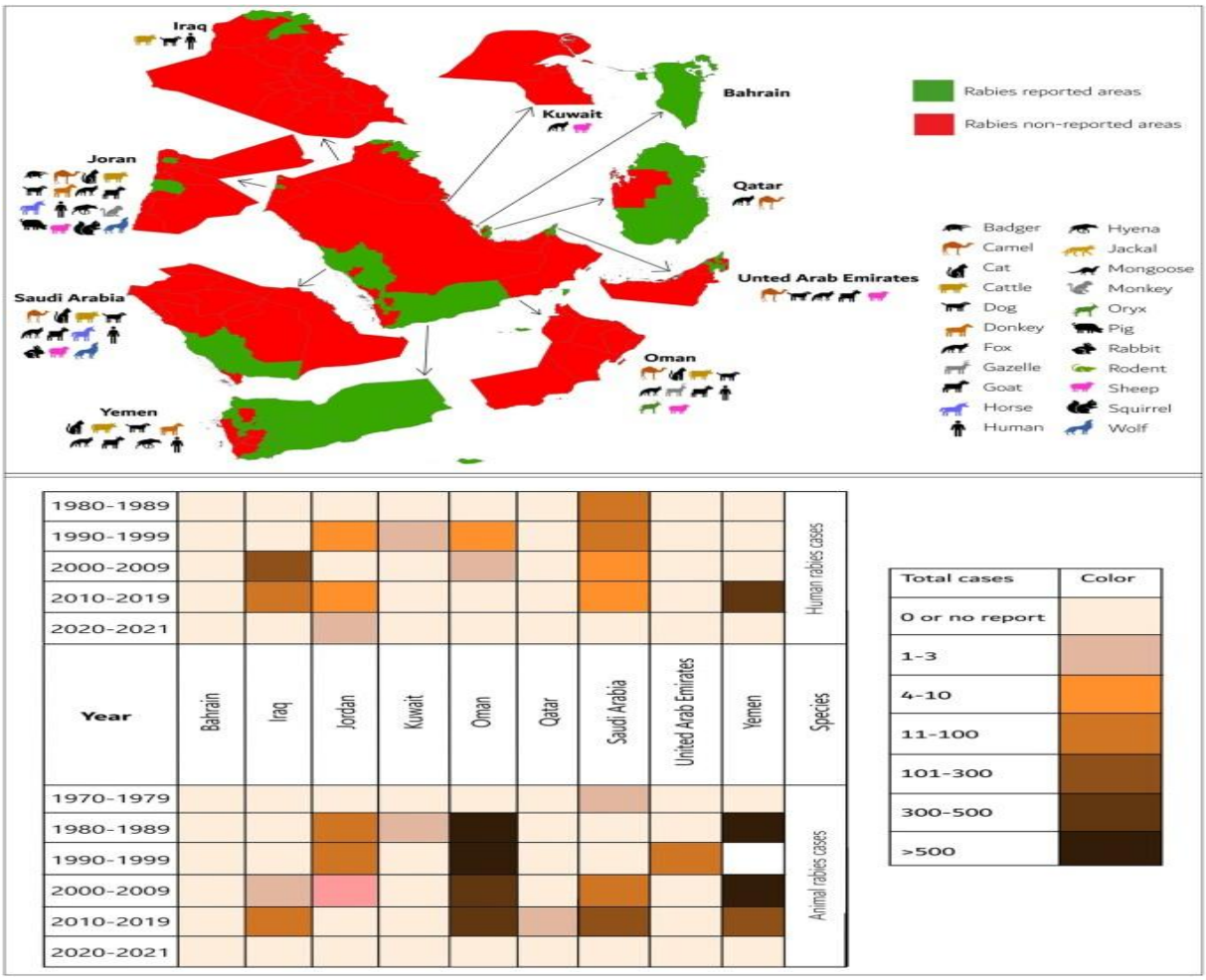
A “bullet-shaped” enveloped infectious particle, the rabies virion is a member of the Lyssavirus genus within the Rhabdoviridae family and Mononegavirale order. Its genome is 12 Kb of negative sense single-stranded RNA. Heat, desiccation, and sunlight can all inactivate “RABV” which is “not viable outside of the host”. Seven different RABV genotypes are known to exist in nature, according to sequence and phylogenetic analyses [13].

The classical “RABV , RV-genotype1” and its field strains are known world over and cause rabies in majority of the cases in humans and animals. Rabies-related viruses [RRVs], namely Lagos bat virus [genotype 2], Mokola virus [genotype 3] and Duvenhage virus “genotype 4” are widely distributed in “Africa, while “European” bat Lyssavirus “EBLs 1 and 2; genotype 5 and 6, respectively are limited to western and eastern Europe. Australian bat Lyssavirus “ABLV”, new “7th genotype” has been identified [14].

Epidemiology of Rabies

Rabies is distinct from other viral diseases in that it can infect a broad spectrum of people, including all warm-blooded animals. With the exception of islands, rabies is common everywhere in the world. With the exception of Australia and Antarctica, rabies is endemic in many of the nations [15]. Rabies is estimated to cause 59000 human deaths annually in over “150 countries” with 95% of cases occurring in “Africa and Asia” . Due to widespread underreporting and uncertain estimates, it is likely that this number is a gross underestimate of the true burden of disease [2,16].

The “99 % of rabies” cases are dog mediated and the burden of disease is disproportionally borne by rural poor populations, Dog-mediated rabies has been eliminated from “Western Europe, Canada, the United States of America, Japan and some Latin American countries”. Australia and many Pacific island nations have always been free from dog mediated rabies. These countries may still report imported cases and incur costs for maintaining disease freedom or surveillance of endemic transmission in wildlife [16]. If we consider status of rabies in Asia it is clear that majority of the developing nations of this subcontinent are the fatal sufferer of rabies. As per the “WHO global vaccines research forum”, over “3 billion” people are affected with dog rabies and more than “30,000 deaths” occur annually in Asian continent means every 15 min, mortality of one Asian. But the painful fact is that among the rabies induced mortality in human , 15% of mortality occurred in children under 15 years of age [17]. In most cases, officially reported human rabies cases do not match the true incidence of rabies cases. This typically occurs in the majority of developing nations, particularly in Africa. It is a more serious public health issue in WHO South East Asian Region [SEAR] member countries, where it accounts for approximately 99% of global human mortality [18].Bahrain is the only country free from both human and animal rabies. Kuwait, Qatar, and the UAE have not reported natural human rabies cases, while Yemen, KSA, and Iraq are considered endemic for human rabies [Fig. 1] [19] Historically, Yemen has reported the highest number of human rabies cases [$n = 439$], followed by Iraq [$n = 249$], KSA [$n = 91$], Jordan [$n = 14$], and Oman [$n = 9$], with Jordan averaging two cases annually [20]



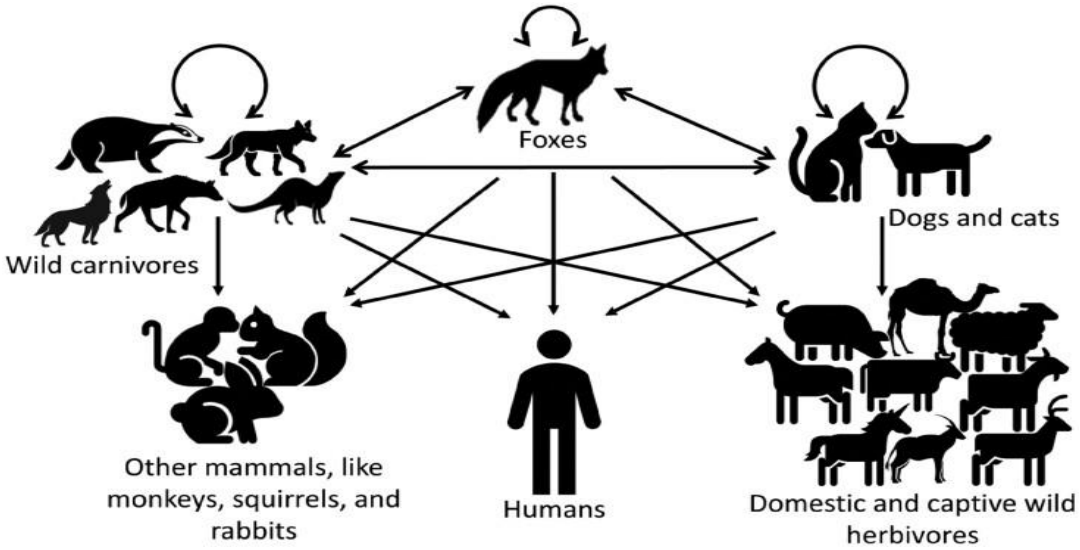
Spatial [top] and temporal [bottom] distribution of natural rabies cases at the human–animal interface in the history of Arabian Peninsula. Animal species icons in the top figure represent species previously reported in this region

Mode of Transmission

The RABV travels through cranial nerves [facial and glossopharyngeal nerves] from the central nervous system to the salivary glands, where it is expelled in saliva that is prepared for transmission to a new host. The most frequent method of rabies transmission [90%] is through the bite of an infected animal, such as a dog or cat, due to their close contact with humans [19]. 85% to 95% of human rabies cases are caused by dog bites in the majority of countries worldwide, especially in Asia and Africa. Usually, the victims suffer from both physical and psychological trauma [20]. RABV typically enters the body through cuts or wounds rather than through healthy skin. Therefore, RABV must be deposited into bite wounds, open skin cuts, and mucous membranes from saliva or infected neural tissue in order to spread [21].

The risk of rabies infection by bite is “5%–80%” which is approximately “50 times” more than by a licks or scratches, occurrence of which is “0.1%–1%” Mortality in RABV infection depends on the severity of infection, location of the bite wound and sufficient amount of virus in the saliva [22]. Percutaneous infections most likely happen as a result of superficial bites, scratches, and undetected skin contact. Human non-bite exposures have been rare over the past half-century [23].

In the last “50 years” few non bite exposure have been documented in human. But the number of cases of rabies not being transmitted by animal bite is less , The non-bite exposure includes inhalation of aerosolized RABV into the body system at higher concentration, organ and cornea transplants, and contamination of open wounds, abrasions, mucous membranes with rabies antigen laden saliva or with infectious material such as “brain tissue from a rabid animal” [24].



Physiopathology of Rabies

The RABV causes relatively slow but progressive disease without initial clinical signs which turns fatal after onset of clinical signs. The virus at the injected site remains hidden “eclipse” for variable time “a threshold must exceed to cause disease”. The incubation or eclipse period is highly variable from “2 weeks to 6 years” “avg. 2–3 months”, which entirely depends on the concentration of the virus inoculated, inoculation site and density of innervations [25]. Bites on the hands, neck, face, and head are a major risk factor; primarily, bleeding causes the incubation period to shorten because the length and number of neurons are reduced. Since RABV typically remains in the muscle for a long time, there may be an opportunity for post-exposure therapy and host immune system clearance of RABV [26].

The lyssavirus enters the body through direct contact with mucosal membranes or through abrasions. It cannot penetrate the most intact skin. After replicating within the bitten muscle tissue, the rabies virus enters the central nervous system. The virions are transported in carrying vesicles and enter the central nervous system [CNS] entirely through fast retrograde transport next to motor axons without being absorbed by sympathetic or sensory endings [2] .

The entrance of virus inside tissues The lesion is formed in the form of Negril bodies in nerve cells, and the bodies are 2_8 mm in size, micro-shaped, surrounded by a clear Halo [27]. The virus attaches itself to the target cells [myocytes, local sensory and motor neurons] via G-protein coupled receptors, multiplies in muscle cells and macrophages, and then ascends centripetally along the nerves via sensory nerve spindles or motor nerve neuromuscular junctions to reach the central nervous system [28]. The incubation period varies from 5 days to

several years [usually 2–3 months, rarely more than 1 year], depending on the amount of virus in the inoculum, the density of motor endplates at the wound site and the proximity of virus entry to the central nervous system [29]. Due to the presence of large inoculums at the site of bite, the virus may also enter in blood. Despite tremendous progress in rabies diagnosis, prevention, and control, its pathogenesis remains unclear, particularly when it comes to rodents using fixed strains [30].

Rabies Sign and Symptoms

The average time for symptoms to appear after being exposed to the virus is 1 to 12 weeks, but they can appear anywhere from a few days to more than a year later. The amount of time required is determined by how long it takes the virus to move from the site of the wound to the brain, where symptoms appear. This depends on a number of variables, such as the patient's or animal's size, the amount of virus that entered the body, and the distance from the brain where the infection occurred [31]. Early symptoms can include anxiety, restlessness, anorexia or increased appetite, vomiting, diarrhea, a mild fever, pupil dilatation, hyperreactivity to stimuli, and excessive salivation. These symptoms are frequently nonspecific [32].

Signs of Rabies in Animals

Once the virus has entered the host , it enters peripheral nerves and transports to neurons in the central nervous system central nervous system through retrograde axonal transport. Once in “CNS” the virus replicates causing the development of clinical disease as it spreads via the brain. Behavioral changes are the result of this replication with two main outcomes of disease are distinguished in animals according to predominant neurological symptoms : “furious rabies” is characterized by agitation, aggression, sexual stimulation, roaming behavior, excess salivation and drooling. The paralytic rabies : or dumb rabies: is marked by lethargy and paralysis Fear and inability to drink water so I called hydrophobia [33].Although, the late stage of the disease may differ in either case, heart failure is typically thought to be the cause of death, even though brain replication can result in the failure of multiple organ systems. Rabies virus must reach the brain after an exposure before it can start to cause symptoms. “The incubation period”, which may extend for “weeks or months” is the interval between exposure and the onset of symptoms [34]. Animal rabies is even harder to diagnose without laboratory testing because symptoms can differ greatly from case to case. There is no question that once symptoms appear, rabies will always lead to death [35].

Sign of Rabies In Human

Human rabies can present as either paralytic [dumb] or encephalitic [furious], with the brainstem being implicated in both clinical manifestations. In contrast to “furious rabies” which is characterized by “irritability, agitation, hyperaesthesia, autonomic disturbances, and the pathognomonic symptom of hydrophobia” which is caused by a triad of inspiratory muscle spasm, painful laryngospasm, terror [fear of swallowing], and generalized flaccid paralysis prodromal symptoms of rabies include “itching, pain, or parasthesia at the bite wound site, as well as gastrointestinal distress” [36].

The first symptoms of rabies may be “like the flu” including “weakness or discomfort, fever, or headache”. There also may be “discomfort, prickling, or an itching sensation at the site of the bite”. These symptoms may last for “several days”. Usually; severe disease appears within two weeks of the first symptoms, when the rabies virus causes brain dysfunction. Common signs include anxiety, confusion, agitation, and

hallucinations [37]. It is important to note however, that rabies symptoms can vary greatly, meaning that not every person will demonstrate all "or even many" of the typical symptoms [38].

Immunopathology of Rabies

The fatal outcome of rabies under normal circumstances is likely caused by neuronal dysfunction and an intriguingly near total "lack of an inflammatory response" within the central nervous system, rather than neuronal death [39]. In addition to their protective function, immune mechanisms frequently have pathological repercussions based on the severity of the infection when immune effectors are activated, particularly in the nervous system. Since nervous tissue is typically concealed from the immune system, RABV's neurotropic nature is what causes this process [40]. Antibodies that neutralize RABV target its glycoprotein. Extensive immune-mediated damage to the "CNS tissues" has been observed as a result of an inappropriate and widespread immune response against rabies in central nervous system [41]. The virus may be transported by infected immune cells from weakly to strongly innervated regions, such as lymph nodes and the central nervous system, which could explain how RABV can enter the central nervous system through organ transplantation [42]. RABV is presented to T cells by astrocytes and microglia, and cytokines are used for signaling, especially when mononuclear cells infiltrate the central nervous system [43].

The RABV-infected activated T cells release IFN-γ, which in turn triggers the expression of "class I and class II major histocompatibility complex" [MHC] antigens by microglia and astrocytes, as well as sensitizing these "MHC" antigens for subsequent cytokine production. Intracerebral inflammatory and immunological responses may be initiated and developed as a result of microglia and astrocyte stimulation [40, 44].

Diagnosis of Rabies

A preliminary diagnosis can be made based on some common clinical signs in dogs and other animals. Animals exhibiting unusual behavior should be segregated and prohibited from biting people for ten days. The prodromal stage of rabies is characterized by noticeable behavioral changes [45]. In its early stages, rabies can be mistaken for other illnesses or even for a "simple aggressive temperament", making diagnosis challenging [46].

The World Health Organization [WHO] recommends the direct fluorescent antibody test [dFAT], an immunohistochemistry procedure, as the reference method for diagnosing rabies [47,48]. The OIE and WHO both recommend "dFAT as the gold standard test" for diagnosing rabies in fresh dog brain tissues [49,50]. Using fluorescent microscopy techniques, the FAT depends on a detector molecule "typically fluorescein isothiocyanate" and a rabies specific antibody forming a conjugate that can bind to and visualize the rabies antigen [50].

"Particularly in decomposed samples or archival specimens", RT PCR [Reverse Transcription Polymers Chan reaction] assays have shown themselves to be a "sensitive and specific tool" for routine diagnostic purposes. Brain samples obtained after death are reliable for the diagnosis. Samples of saliva, urine, and cerebrospinal fluid can also be used to make the diagnosis [51].

The Cerebral inclusion bodies; called "Negri bodies" are "100% diagnostic for rabies infection but are found in only about 80% of cases". If possible, "the animal from which the bite was received should also be examined for rabies"[52]. Certain "light microscopy" methods can also detect rabies at a tenth of

the price of “conventional fluorescence microscopy” methods, making the disease detectable in less developed nations [53].

Pre-exposure vaccination and management

Animal management is now the cornerstone of rabies prevention and control. Animal rabies control primarily consists of vaccinating “dogs and cats” removing stray animals, educating the public about health issues [54]. Although there are minor variations in the rabies vaccination of horses, it is impossible to overstate the importance of rabies vaccination for companion animals, including horses. Horses have an equal risk of contracting rabies as dogs and cats, which usually supports rabies vaccination as a preventative measure [55]. Unfortunately, because there aren't many clinical cases of equine rabies, rabies vaccination for horses is frequently disregarded. Veterinarians and horse owners should seriously consider rabies vaccination for horses due to the disease's deadly nature and importance to human health [56].

The WHO recommends that all employees who handle materials that are suspected or infected get a preventive vaccination. The immunization regimen consists of three injections at 0, 7, and 28 days. One to three weeks following the last vaccination, a serological assessment of antibodies should be conducted [57].

“Re-examination should be done in every “6 months” for persons working in laboratory or every 2 years for other diagnosticians. Even if the titre goes below 0.5 International Units [IU] per ml, booster vaccination is recommended for sure. When serological monitoring is not available, booster vaccination is recommended at “1 year” followed by vaccination” at every “1–3 years” [58].

Live attenuated virus is used in rabies vaccines for animals. or recombinant vaccines and physically inactivated viruses [59]. The use of injectable vaccine preparations has limitations, particularly when it comes to wildlife and carnivores. Therefore, efforts to formulate oral vaccines have been ongoing, with notable outcomes in both laboratory and field trials [60].

Post-exposure management.

Any animal that comes into contact with a confirmed or suspected rabid animal must be placed under strict quarantine for six months. Vaccination against rabies should be administered at the time of isolation or one month prior to release [61]. Following exposure, a 45-day observation period must be followed by an immediate revaccination. Livestock that have not received vaccinations must be closely monitored for six months. Animals that exhibit symptoms of rabies should be put down, and their heads need to be sent for testing [62,63]. Of all the vaccines , the rabies vaccine can be given in a special way both before and after viral exposure. Pre-exposure vaccination is suitable for travelers, veterinarians, and researchers, particularly in areas where the disease is naturally endemic [64].

Therapeutic approach

Rabies is almost without exception “lethal disease” and once Central Nervous System signs appear, the mortality reaches up to 100% in spite of administration of” post-exposure prophylaxis “PEP” [47,65]. Rabies “PEP” consists of wound washing, a dose of human rabies immune globulin “HRIG” and rabies vaccine given at the time of your first medical visit, and a dose of vaccine given again on days” “3- 7”and “14 after the first dose” [66]. “The Human Rabies Immune Globulin “HRIG” is administered only once at the beginning of the “PEP course” and only to previously unvaccinated persons. This will provide immediate antibodies until the body can respond to the vaccine by actively

producing antibodies of its own" [66,67].

There is NO effective therapy that is effective for patients who develop rabies encephalomyelitis , combined with administration of rabies immune globulin, is the only approved effective method for post exposure prophylaxis against rabies [68] Rabies-infected mice treated with "recombinant human interferon alpha" "rhIFN α-2A" showed significantly lower levels of "TNF-α and IL-6" expression in both the "pre-exposure and post-exposure groups" as well as delayed mortality [69].

Prevention and Control

Wildlife rabies is becoming a bigger problem in Middle Eastern countries like "Saudi Arabia, Iran, and Turkey". In addition to carnivore species, which are the traditional focus of control efforts, bats serve as wildlife reservoirs. Rabies is 100% preventable and nearly always results in death in humans. The current lack of coordination and communication between public health and veterinary officials makes rabies control in developing nations even more difficult [70]. "The first and foremost part of rabies control program is to define case by identification of the rabid animal after diagnosis by a qualified laboratory. Confirmation in the laboratory should be done by dFAT"[50,71]. "Rabies prevention and control program require enhanced surveillance based on laboratory and variant typing". "For this accurate and timely information and reporting are necessary to determine the" "management of potentially exposed animals aiding in emerging pathogen discovery" [72].

The following actions are part of a prompt and comprehensive response for effective disease control and eradication.

1. Regional reference laboratory, national, and international characterization of the RABV.
2. Determining and managing the virus's point of entry
3. Strengthening laboratory-based monitoring for both "domestic and wild animals"
4. A higher percentage of animals are being vaccinated against rabies.
5. Control of vector population is required.
6. Provision for education and outreach to the public and professionals.
7. Instruction on avoiding contact with questionable animals The most economical, humane, and sustainable way to eradicate regional rabies virus variants in a One Health setting is through integrated veterinary management of local animal populations, which includes mass dog vaccinations and community education about responsible pet ownership [72].

Conclusion

The rabies is a viral disease which is fatal in nature, among unvaccinated human as well in animals. It can be controlled by proper awareness and immunization against the lyssavirus in both farm animals as well as pets. Rabies can be prevented by avoiding direct contact with the rabid animal, its mucous membranes, and wounds and by giving proper training to wildlife workers, veterinarians, animal handlers and laboratory workers because prevention is better than cure.

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