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Review
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RABIES, THE ADMINISTRATION OF VACCINES AND PUBLIC HEALTH CONCERN, NEGLECTED CHALLENGES AND HISTORICAL PERSPECTIVE IN CHINA

Mohamad Hesam SHAHRAJABIAN[1]*, Wenli SUN[1]

[1]*Chinese Academy of Agricultural Sciences, Biotechnology Research Institute, National Key Laboratory of Agricultural Microbiology, Beijing, China*

Abstract: Rabies virus is transmitted via contact of saliva of a rabid animal with a persons' mucosa or a skin lesion. It is a fatal encephalomyelitis caused by members of expanding *Lyssavirus* genus, and the genus included 17 species. The aim of this literature review is to survey on rabies and vaccination in China, threats and challenges to eliminate it, especially in China. The information provided is obtained from randomized control experiments, review articles, and analytical observations and studies which were gathered from various literature sources such as Scopus, Google Scholar, PubMed, and Science Direct. Rabies virus is a bullet shaped enveloped virion, and the classical rabies virus and its field strains are discovered worldwide and induces to rabies in animals and humans. In recent years, China has made wonderful and significant achievements in rabies prevention and control, and currently, the mortality and incidence rate of human infection with rabies have decreased to the minimum level historically, which has caused a notable foundation for the ultimate elimination of human rabies. Generally, five proteins are available in mature rabies virus (RABV) particles, phosphoprotein, nucleoprotein, glycoprotein, matrix protein, and RNA-dependent RNA polymerase. The main carriers of rabies in China are dogs which are accountable for most of the human rabies deaths in China. Most common way of entry of rabies virus into the body is both via infected neural tissue through open cuts in the skin and salvia. Rabies remain a public health problem and continue to present health risks for both animals and human; It is important to improve access to post-exposure prophylaxis (PEP) in endemic countries where human rabies deaths still happen, but the big problem is its costs that should be curtailed and surveillance strengthened for controlling and eliminating it.

Keywords: Dogs, Glycoprotein, Lyssavirus, Post-exposure prophylaxis, Rabies virus

***Corresponding author:** Chinese Academy of Agricultural Sciences, Biotechnology Research Institute, National Key Laboratory of Agricultural Microbiology, Beijing, China
E mail: hesamshahrajabian@gmail.com (M. H. SHAHRAJABIAN)
Mohamad Hesam SHAHRAJABIAN https://orcid.org/0000-0002-8638-1312
Wenli SUN https://orcid.org/0000-0002-3855-3992

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1. Introduction

Rabies is a deadly disease present since ancient times induce by rabies virus that is neurotropic *lyssavirus* causing acute lethal encephalitis (Zhang et al., 2015; Khan et al., 2019; Cui et al., 2023; Shahrajabian and Sun, 2023a,b,c). The virus infection causes encephalomyelitis in humans with a roughly 100% case mortality rate (Jochmans and Neyts, 2019). Rabies cause over 95% of the deaths happening in African and Asian countries (Knobel et al., 2005). It is also considered as a neglected tropical disease that principally influences poor and vulnerable individuals from poverty-stricken countries (Wang et al., 2019). Li et al. (2019) reported around 35,000 human deaths from rabies in Asia every year. The most significant symptoms and signs are aerophobia, hydrophobia, and mental disorders (Wang et al., 2013). The dog, red fox, and raccoon dog are known to have a considerable function in the global epidemiology of rabies (Cliquet et al., 2008). Vaccines have shown important functions in rabies prevention both as companion animals, and also as inactivated vaccines to protect humans, and as reduced live vaccines utilized for oral vaccination in feral and wildlife dogs. Improved vaccination strategies, continuing development of diagnostic tools, and better understanding of the virus-host relationships which affect infection results will all can have roles to future progress of rabies control techniques (Nandin-Davis, 2023). Some of the most important rabies cases reported in wildlife from different families are: (1) *Phyllostomidae*: Common vampire bat (*Desmodus rotundus*), and Great fruit-eating bat (*Artibus lituratus*), (2) *Molossidae*: Brazilian free-tailed bat (*Tadarida brasiliensis*), (3) *Vespertilionidae*: Brazilian brown bat (*Eptesicus brasiliensis incognita/unidentified*), (4) *Canidae*: South American gray fox Hoary fox (*Lycalopex griseus*, *Lycalopex vetulus*, *Lycalopex* spp.), and Crab-eating fox (*Cerdocyon thous*), and Red fox (*Vulpes vulpes*), (5) *Procyonidae*: Kikanjou (*Potus flavus*), Coati (*Nasua nasua*), (6) *Cebidae*: Guianan squirrel monkey (*Saimiri sciureus*), (7) *Callitrichidae*, (8) *Camelidae*, (9) *Cervidae*, and (10) *Leporidae*: *Lepus* spp. (Meske et al., 2021). Vaccines suited for post-exposure prophylaxis

(PEP) are adjuvanted rabies vaccines, protein vaccines, genetically modified and inactivated rabies virus (Ertl, 2019). Clinical symptoms of rabies in animals just can be utilized for presumptive diagnosis due to various types of clinical rabies such as paralytic and furious, which have symptoms that are very similar to other diseases and change between individuals (Ward and Brookes, 2021). The aim of this manuscript is survey on rabies and vaccination in China, threats and challenges to eliminate it, especially in China.

2. Rabies Historical View

The word rabies comes from the Sanskrit word rabbahs which means to do violence, it refers to the Vedic period of India 93th century BC, when the God of Death was represented being presented by a dog, his constant companion and the emissary of death (Fu, 1997; Coertse et al., 2023). Rabies in an always deadly viral disease of global significant, and wildlife has an important function as reservoirs and sources of rabies to domestic humans and animals (Shoemaker et al., 2023). Woldehiwet (2002) also reported that the current English name, rabies, is obtained directly from Latin, meaning raging, savage, furious, or madness, whereas the Greek term hydrophobia is not precisely used for rabies in human.

Table 1. Rabies historical overview

Ancient Greek	Galen, Democritus, Celsus, and Aristotle had warned people of the dangers related to the bite of a mad dog.
First Century AD	The famous Roman writer Cardanus surveyed saliva to be the carrier of the infectious factor.
1804 AD	George Gottfried Zinke who experimentally showed the infectivity of rabid dog salvia by inoculating a healthy dog with the suspected salvia.
Few decades after 1840 AD	French scholar, Viktor Galtier showed that rabbits could serve for both study and diagnosis of rabies.
Few decades after 1840 AD	Louis Pasteur indicated they infective parameter resides in the nervous tissue of the rabid animal.
1884 AD	Pasteur and his colleagues proved their first publication entitled new communication on rabies.
At the beginning of the twentieth century	Dr. Paul Ambroise Remlinger, a Pasteurian scientist showed the capability of infective agent to pass through a Berkfeld filter.

The recorded history of rabies goes back to 2300 BC, when a dog owner in ancient Babylon was charged for a death induced by a dog bite; ancient Greek philosophers like Aristotle, Democritus, and Celsus as well as the famous physician Galen, had warned people of the dangers connected with the bite of a mad dog, indicating that the infectivity of the animal was suspected some 2000 years ago (Wiktor, 1985; Cai et al., 2021; Johnson et al., 2021). Rabies historical overview is shown in Table 1.

3. Rabies Reservoirs, Rabies virus and *Lyssavirus* Genus

The most notable global rabies reservoirs are cats, dogs, foxes, skunks, raccoons, coyotes, bats, and mongooses. The main source of exposure along with being the primary vector for rabies in humans are domestic dogs (Sultan and Khan, 2013; Khan et al., 2019). The main global rabies reservoirs are shown in Table 2. *Lyssavirus* is a genus of RNA viruses include the rabies virus traditional related to the disease. The etiologic agents of rabies encephalitis belong to the *Mononegavirales* order, *Rhabdoviridae* family and *Lyssavirus* genus. *Lyssaviruses* have a 12 kg-long non-segmented RNA genome of negative polarity encoding five viral proteins: nucleoprotein N, phosphoprotein P, matrix protein M, glycoprotein G and polymerase L. The *lyssavirus* genus is shown in Table 3.

Table 2. Predominant global rabies reservoirs (Fu, 1997)

Dogs	Major vector of rabies throughout the world, particularly Asia, Africa, and Latin America.
Foxes	Arctic, Europe, and North America
Raccoons	Eastern United States
Skunks	Midwestern United States, Western Canada
Coyotes	Africa, Asia, and North America
Mongooses	Yellow mongoose in Africa, and Asia; Indian mongoose in the Caribbean Islands
Bats	Vampire bat from Northern Mexico to Argentina, insectivorous bats in North American and Europe.

The Ribonucleoprotein (RNP) core in connection with the matrix protein is condensed into the ordinary bullet-shaped particle that is trait of rhabdoviruses. A lipid bilayer envelope in which the surface trimeric glycoprotein spikes are anchored surrounds the RNP-M structure. The membrane tail shows the trailing piece of envelope that is often observed attached to the virus as it buds from the plasma membrane of the infected cell when viewed under the electron microscope (Wunner, 2007). *Desmodus rotundus* is the major bat species, among vampire bats, which is accountable for frequent cases of rabies in different parts of the world (Oliveira et al., 2022).

Table 3. The *lyssavirus* genus (Warrell, 2010)

Genotype	Reservoir species (potential vectors)[a]	Known distribution
Phylogroup I		
1 - Rabies virus	Dog, fox, raccoon, skunk, bats etc.	Widespread; bats in Americas only
4 – Duvenhage	Insectivorous bat (*Nycteris thebaica*)	South Africa, Zimbabwe, Kenya
5 - European bat *lyssavirus*		
Type 1a	Insectivorous bats (Sheep, cats)	Northern and Eastern Europe
Type 1b	Insectivorous bats	Western Europe
6 - European bat *lyssavirus*		
Type 2a	Myotis dasycneme bats	Netherlands, Germany
	Myotis daubentonii bats	UK
Type 2b	Myotis daubentonii bat	Switzerland, Finland
7 - Australian bat *lyssavirus*	Flying foxes (fruit bats) Insectivorous bats	Australia
Phylogroup II		
3 – Mokola	Shrew, rodents (cats, dogs)	South Africa, Nigeria, Cameroon, Ethiopia
2 - Lagos bat virus	Bats (cats, dog, water mongoose)	Zimbabwe, South Africa, Kenya
	Has NOT been detected in man	

a= mammals infected by reservoir species may become vectors.

The nucleoprotein (N), matrix protein (M), phosphoprotein (P), glycoprotein (G), and large RNA-polymerase protein (L) genes (orange) are separated by intergenic nucleotide sequences and the pseudogene (ψ) sequence and flanked by the leader (Le) RNA and trailer (Tr) RNA sequences (green) at the 3′ and 5′ termini, respectively (Wunner, 2007). Virus enters the cell following attachment via coated pits (viropexis) or through cell surface receptors, mediated by the viral glycoprotein (G) fusing with the cellular membrane (endocytosis). After internalization, the viral G mediates low pH-dependent fusion with the endosomal membrane and the virus is uncoated, releasing the helical nucleocapsid (NC) of the ribonucleoprotein (RNP) core. The five structural genes (N, P, M, G, and L) of the genome RNA in the NC are transcribed into five positive (+) strand monocistronic messenger RNAs and a full-length (+) strand (antigenome) replicative intermediate RNA. The antigenome RNA serves as the template for replication of progeny genome (-) strand RNA. The proteins (N, P, M, and L) are synthesized from their respective mRNAs on the free ribosomes in the cytoplasm and G is synthesized from the G-mRNA on membrane-bound ribosomes (rough endoplasmic reticulum). Some of them N-P molecular complexes produce cytoplasmic inclusion bodies (Negri bodies) in vivo and some N-P complexes encapsidate the (+) strand and (-) strand viral RNAs. After progeny genome RNA is encapsidated by the N-P protein complex, and L protein is incorporated from progeny RNP (both shorter defective and full-length standard) structures the M protein binds to the RNP and condenses the RNP into the skeleton structures. The skeleton structures interact with the trimeric G protein structures anchored in the plasma membrane and assemble into virus particles that bud from the plasma membrane of the infected cell into adjacent extracellular or interstitial space (Wunner 2007).

4. Rabies Diagnostic and Vaccination

It is difficult to establish a definitive clinical diagnosis of human rabies, and it may need the availability of cardinal symptoms in the encephalitic form, and sometimes problem and delay of diagnosis in developed countries is possibly connected to the lack of a clear bite history (Hemachudha et al., 2002). Deubelbeiss et al. (2013) also found that it is difficult to recognize human rabies when a history of exposure is not present. Rabies virus (RABV) is a member of *Lyssavirus* family, *Rhabdoviridae*, and has five structural proteins: nucleoprotein (N), matrix protein (M), phosphoprotein (P), glycoprotein (G), and an RNA dependent RNA polymerase (L) (Wunner et al., 1988; Wang et al., 2014). The rabies virus G protein, which is a trimer of about 67 kDa, is the main antigen accountable for inducing the production of virus-neutralizing antibodies (VNAs), and for conferring immunity against lethal rabies virus infection (Cruz et al., 2008). The G gene was the first RABV gene to be cloned and sequenced. From the nucleotide sequence, a poly peptide (524 amino acids long) was gathered, which included a signal sequence of 19 amino acids (Cruz et al., 2008). Understanding of why and where risks exist are needed to reduce zoonotic disease threats (Muller et al., 2015; Abutarbush et al., 2022; Tierradentro-Garcia et al., 2022). Pfaff et al. (2019) also concluded that fatal disease is basically connected to rabies virus (RABV), a neurotropic single-stranded RNA virus of the family *Rhabdoviridae* in the genus *Lyssavirus* within the order *Mononegavirales*. It is the main antigen protein to be utilized as a good candidate to designed modern anti-rabies DNA vaccines (Perrin et al., 2000; Diogo et al., 2001; Gholami et al., 2014). The frequently used rabies vaccine is a type of inactivated viral vaccine is propagated in cell culture, and usually applied for pre-exposure or post-exposure when combined with rabies immunoglobulin (RIG) to avoid or prevent most rabid

dog bite tragedies (McGettigan, 2010). Wang et al. (2019) noted that the development of novel inexpensive, effective, and safe vaccines has become a prime concern for rabies control worldwide, and the chimpanzee adenovirus-vectored rabies vaccine ChAd68-Gp warrants extensive test for clinical application. Anothaisintawee et al. (2019) showed that mass dog vaccination and post-exposure prophylaxis (PEP) is one of the main appropriate control technique, effectual rabies elimination has yet to be understood. The post-exposure prophylaxis should be grouped as an emergency medical service, and it should be part of the hospital medical emergency, and mass dog vaccination against rabies should be increased to decrease the risk of potential bite of pet dogs and roaming dogs in communities (Gongal et al., 2022). The characteristics of various methods to gain monoclonal antibodies are hybridoma technique, antibody library technique, and B cells immortalization technique (Fan et al., 2022). Quiambao et al. (2022) concluded that 1-week pre-exposure prophylaxis with Vero cell rabies vaccines and human diploid cell vaccine can induce effective priming in 2-64-year-olds, and it has achieved more than 99% seroconversion. In Greece, it has been reported that the main goal and current extensive attempts should be to prevent spread particularly in the domestic and wild animal populations (Tsiodras et al., 2014). He et al. (2006) reported that the recombinant maltose binding protein (MBP)-N fusion protein can be isolated and expressed simply, and it can be appropriate and safe source of antigen to analyze seropositivity in vaccinated canines. Disinfection and cleaning are important to prevent cross-contamination of samples in the laboratory environment, and the effectual disinfection protocol should be considered carefully validated to guarantee reliability of results, and staff safety (Aiello et al., 2016). The criteria and use for choosing different assays change on the basis of the sample analyzed and the goal of the diagnosis, which will also change on the basis of the setting in non-endemic and endemic (Rudd et al., 2005; Duong et al., 2016). Liu et al. (2010a) concluded that it was potentially appropriate for the more development of easily handled, highly sensitive and relatively rapid detection tools/kits for rabies surveillance in those regions of China where rabies is endemic. Undurraga et al. (2020) reported that the elimination programs of dog rabies usually depend on parenteral vaccination, capture-vaccine-release and mobile static point significantly boosted free-roaming dog coverage, and oral vaccination, and door-to-door parentral vaccination was the most cost-effective program. Definition of categories of exposure is presented in Table 4.

Servat et al. (2019) believed that the quality of rabies-inactivated (Rabisin, Boehringer-Ingelheim) vaccines for veterinary use is of greatest importance to change the cross-protection of pets against phylogroup I bat *lyssaviruses* occurring in Europe. Nishizono et al. (2012) showed that Rapid Neutralizing Antibody detection test (RAPINA) is a rapid and easy technique for measuring the level of rabies virus-neutralizing antibody (VNA) levels after and before immunization with the rabies vaccine and it does not require a special skill level nor advanced tools. The Enzyme Linked Immunosorbent Assay (ELISA) method which is characterized the immunogenic from the glycoprotein formulated in vaccines seems to be relevant and is a promising candidate to be standardized the quality of vaccine batches before release (Gibert et al., 2013). Parameter which can limit canine rabies vaccination program are diminished community education and outreach, limited laboratory-based surveillance, underestimation of the population at risk, irregular vaccine applications in time and space, exclusion or puppies, cold chain failure, inaccessible naïve free-ranging dogs, translocation of cases, competing priorities, effect of other species such as wildlife and livestock, lack of adequate resources, accessibility to remote hotspots, cultural disparities, impact of poverty on responsible social ownership and common animal health care, less than appropriate cooperation between human health and veterinary services, sisyphean fatigue, staff burn-out and frustration (Rupprecht et al., 2019). Marosi et al. (2019) found that inhibitors of detrimental host reaction to rabies together with antibodies can be considered among the probable therapeutic and post-exposure choices in human rabies cases. Shi et al. (2018) revealed that adjuvants can be applied as an enhancer in rabies vaccination, and non-sized aluminum maybe a candidate adjuvant for the development of more effective rabies vaccines. Laager et al. (2019) indicated that dog rabies vaccination is an efficacious way of preventing rabies in the dog population and to subsequently decline human exposure. Zhang et al. (2016a,b) noted that PIKA which is a new adjuvant, is an effectual and safe vaccine which has the potential to develop next-generation rabies vaccine and encourage the start of more clinical researches.

Table 4. Definition of categories of exposure (Lee, 2004; Linscott, 2012)

Category	Exposure criteria	Biologic recommendation
I	Touching, feeding of animals or licks on intact skin	No exposure, therefore no treatment (if history is reliable)
II	Minor scratches or abrasions without bleeding or licks on broken and nibbling of uncovered skin	use vaccine alone
III	Single or multiple transdermal bites, scratches or contamination of mucous membrane saliva (i.e., licks)	Use immunoglobulin plus vaccine

Table 5. Rabies vaccines and immunoglobulins

Pasteur (Paris) virus strains (PV, for Pasteur virus) of rabbit fixed rabies virus; also adapted to Vero cells
PV-12 strain of Pasteur rabbit fixed rabies virus; also adapted to BHK-21 cells
Pitman-Moore (PM) strain of fixed rabies virus, adapted to human diploid, primary dog kidney and Vero cells
CVS (challenge virus strain)-11 Kissling strain, adapted to BHK-21 cells
LEP (low egg passage) (40-50 passages) Flury chick embryo-adapted rabies virus, also adapted to primary chick embryo cells and to BHK-21 cells
HEP (high egg passage) (227-230 passages) Flury chick embryo-adapted rabies virus; also adapted to primary chick embryo cells
Kelev (100 passages) chick embryo-adapted rabies virus
ERA (Evelyn Rokitniki Abelseth) strain of Street-Alabama-Dufferin (SAD) virus, adapted to porcine kidney cells; also adapted to BHK-21 cells (in Canada)
Different SAD variants are ERA virus adapted to BHK-21 cells (in Europe)

Luo et al. (2019) showed that the artemisinin derivative ART boosted immune response of inactivated rabies vaccine when used as an adjuvant; in the experiment, the artesunate could be used as a new candidate adjuvant for rabies vaccination. Shafiur Rahaman (2017) noted that sustainable application of programs to manage dog population, dog bite management and awareness raising population can bring out fruitful results, but vaccinating dogs is the most effective plan suggested by researchers. Moghadami et al. (2017) also proved that the vaccination of dogs and cats is important by preventing dogs from being exposed to humans. Rabies vaccines and immunoglobulins is presented in Table 5.

5. Post-Exposure Prophylaxis (PEP)

The progress of human rabies vaccine has evolved dramatically from the first crude nerve tissue vaccine produced them conducted in the presence of Louis Pasterur in 1885 (Tarantola et al., 2019; Saffar et al., 2023). Prophylaxis of animal rabies is important for breaking the transmission cycle and preventing the spread of rabies to humans (Costa et al. 2007; Hu et al., 2007). Rabies in humans can be prevented via appropriate and timely post-exposure prophylaxis (PEP) (Li et al., 2019; Rysava et al., 2019). Appropriate and timely administration of PEP is important to prevent rabies, and even though general public with high risk immunosuppression and exposures can develop rabies despite adherence to core practices, this occurrence remains significantly rare (Whitehouse et al., 2023). Zhai et al. (2022) reported that highly protective potency, the broad-spectrum neutralization activities, and rapid onset of action can make ormutivimab an effectual substitute for human rabies PEP. Rabies vaccine is a main component of modern post-exposure prophylaxis, which included wound care and the infiltration of rabies immunoglobulin, when PEP is timely and properly administrated, expected survivorship approaches 100% (Recuenco et al., 2017). PEP is not effectual after beginning of symptoms and attempts to develop a treatment for clinical rabies have been failed (Rogee et al. 2019). The cost of post-exposure prophylaxis (PEP) is both related to the direct cost of rabies biological and tools and also related to indirect costs that patients experience as a result of travel, loss of work time, and accommodation over the period of time that a PEP regimen requires to be completed (Tarantola et al., 2019). Wambura et al. (2019) also claimed that adoption of the dose-saving intradermal route for PEP administration, reduction of PEP costs to patients, and placing rabies vaccines with the standard vaccines supply and logistics system would significantly improve PEP accessibility and availability to those who are at risk, is a condemnatory step to achieving elimination of human deaths from rabies. They have highlighted that sharing information on practices of PEP more widely among countries may help in programs to increase access to life-saving treatment. PEPE induces antibodies against rabies (Wijaya et al., 2017). Rabies PEP consists of wound washing, immediate rabies vaccination following the possible exposure, and in some cases, rabies immunoglobulin (RIG). Lankester et al., (2014) showed that an important assumption of controlling and eradicating rabies at source through mass dog vaccination is that the public health sector through reduced rabies risk and therefore reduced expenditure on PEP. Changalucha et al. (2019) noted that PEP access could be improved and rabies death reduced through ring-fenced procurement, changing to dose-sparing ID regimens and free provision of PEP. But, PEP is costly and costs can be a major barrier to both bite victims and to low- and middle-income countries (Hampson et al. 2008; Sambo et al. 2013). Currently, only cell-culture or embryonated egg-based rabies vaccines (CCEEVs) are recommended by the World Health Organization (WHO); the original nerve-tissue based vaccine (NTBV) has not been suggested since 1980s (Abela-Ridder et al., 2016). Koraka et al. (2014) found that its native trimeric configuration of rabies virus (RABV-tG) applied in combination with Matrix-M™ is a promising vaccine candidate which overcomes the limitations of currently used vaccines; presently accessible vaccines are expensive, cumbersome to produce and also need intensive immunization and booster schemes to induce and keep protective immunity. Koraka et al. (2019) confirmed that some inflammatory responses may be involved in the pathogenesis of serious disease and the

results proved the effectual intervention included inhibition of virus and host response. The indication and procedure for PEP replies on the type of contact with the suspected rabid animal and immunization status of the patient. For category I exposures, no PEP is needed; for group II, immediate vaccination is suggested; for category III, immediate vaccination is recommended, and application of RIG, in indicated. For categories II and III, through flushing and washing with soap or detergent and copious amounts of water of all bite scratches and wounds should be done instantly, depending on the characteristics of the wound, antibiotics, analgesics and a tetanus vaccination maybe indicated. Beyene et al. (2018) recommended increasing awareness about its fatality and not just vaccine importance but also vaccination for rabies decrease followed eradication by vaccine and vaccination for all source or carrier individuals, and also post exposure treatment should be given after quickly exposure to bite or scratch by rabid animals. Fooks et al. (2019) noted that next generation human rabies vaccines are required to lessen cost and number of doses for PrEP and PEP, and it could be important to develop various vaccine platforms with unique requirement for optimally protective immune responses. They have introduced PrEP vaccines that induce long-lived rabies virus neutralizing antibody and sustained memory B cell responses after a single dose would be needed and replication-defective adenoviral vectors may obtain these requirements. Echevarria et al. (2019) highlighted the need for a comprehensive pan-lysaavirus rabies vaccine, which able to prevent human rabies in all situations. Rabies pre-exposure prophylaxis recommendation is shown in Table 6.

6. DNA Residue

Chinese vaccine products not only secure disease control and prevention domestically, but also provide the needs for international public health (Xu et al., 2015; Deidda et al., 2018; Zhao et al., 2018). Quality control plans account for significant portion of a laboratory budget which should be effectual (Shen et al., 2018; Won et al., 2019). There are two kinds of anti-rabies vaccines; the non-nerve tissue vaccine, and the nerve tissue-based vaccine (Mengesha et al., 2014). Mengesha et al. (2014) reported that the presently available non-nerve tissue vaccines are Purified Chick Embryo Cell (PCEC) vaccines, Human Diploid Cell Vaccine (HDCV), Purified Vero Cell Vaccine (PVRV), and Purified Duck Embryo Vaccine (PDEV). In rabies virus (RV), the viral genome (3′/N-P-M-G-L5′/) encodes a nucleoprotein (N0, a phosphoprotein (P), a glycoprotein (G), a matrix protein (M), and a RNA-dependant RNA polymerase (L) (Wunner, 2007; Osinubi et al., 2009; Luo et al., 2013). The G is closely associated with pathogenicity, and is a basic contributor to protective immunity (Cox et al., 1977; Morimoto et al., 2001). Because the G is the best surface-exposed viral coat protein, it is avle of eliciting the production of virus neutralizing antibodies (VNA), and also accountable for host cell receptor recognition and membrane fusion (Osinubi et al., 2009). G protein is a type I membrane glycoprotein including 505 amino acids in the native form, and it is the mediator of both entry into host cells and binding to cellular receptors (Anilionis and Wunner, 1981; Seif et al., 1985; Coll, 1995).

Table 6. Rabies pre-exposure prophylaxis recommendation (Beyene et al., 2018)

Risk category	Nature of risk	Typical populations	Pre-exposure recommendations
Continuous	Virus presents continuously and often in high concentrations. Specific exposures likely to go unrecognized. Anyways 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.

It contains a transmembrane domain, a cytoplasmatic domain, and an ectodomain exposed domain, a transmembrane domain, and an ectodomain exposed as trimer (3 × 65 kDa) on the virus surface (Gaudin et al., 1992; Rath et al., 2005). Also the G protein induces the production of cell-mediated immunity by cytotoxic T lymphocytes and T helper cells (Macfarlan et al., 1986; Celis et al., 1988). Bassi (2008) found that the glycoprotein (G) of rabies virus (RV) is principal for virus infectivity and induction of the protective immunity. Li et al. (2010) stated that the rabies virus (RV) glycoprotein (G protein) leads to neutralizing antibodies, which are important in protection against rabies. The M protein is the smallest and most abundant protein in the virion, forming a layer between the protein G in the outer membrane and the ribonucleoprotein (RNP) core (Mebatsion et al., 1999), and the M protein is a multi-functional protein vital for virus maturation and budding and of course regulates the expression of both viral and host proteins (Wu et al., 2013). The M protein is active in viral assembly and budding, regulation of the viral genome and mRNA syntheses (Finke et al., 2003). The G and N proteins have been identified as viral antigens (Yang et al., 2013). The N protein is the main antigen that induces T cell immunity (Goto et al., 2000). Protein P has multiple performances at different stages of the viral cycle, forming a complex with the nascent nucleoprotein that prevents the association of the latter with hose-cell RNA and forming a two-subunits viral RNA polymerase complex with protein L (Gerard et al., 2009). Ashraf et al. (2005) claimed that plant-derived G protein induced complete protective immunity in mice against intracerebral lethal challenge with live rabies virus. Zhao et al. (2020) suggested that by replacing the signal peptide, the expression level of the G protein with native conformation could be significantly improved, as G protein from the rabies virus plays an important role in the binding of virus to target cells. Different and various types of vaccine with numerous platforms have been analyzed both clinically and preclinically for rabies PEP or Pre-P, and the most important and promising for PEP are vaccines on the basis of traditional rabies vaccines which have been supplemented with a potential adjuvant, inactivated genetically modified protein vaccines and rabies virus, whereas for Pre-P recombinant vaccines according to replication-defective adenoviruses may provide an affordable substitute to currently utilized vaccines (Ito et al., 2021; Atici and Oguzoglu, 2022; Itakura et al., 2022; Abedi et al., 2023; Challhua et al., 2023; Izumi et al., 2023; Scrima et al., 2023). Both an animal and human health perspective, current rabies vaccines seem able to protect against *lyssaviruses* categorized within phylogroup I. However, no protection is afforded against phylogroup II viruses or other more divergent viruses (Evans et al., 2012). Evan et al. (2012) also recommended that the development of novel vaccines that stimulate a pan-*lyssavirus* neutralizing immune response is of importance to those at occupational risk from infection.

7. Rabies in China and New Studies

The risk of rabies had been significantly decreased to a persistently low level in China, and the constant high-risk regions for rabies in China were Guangxi, Guizhou, Hainan, and Hunan (Li et al., 2023: Sun et al., 2021; Sun et al., 2022). Human rabies was first reported in China in around 556 BC, and has persisted for more than 2500 years (Zhang et al., 2011). In ancient Chinese medicine, rabies was very well described and recognized, and people gained enough awareness and knowledge about it (Miao et al., 2021). Rabies virus has a 12-kb non-segmented negative sense RNA genome encoding five viral proteins (3/ to 5/): phosphoprotein (P), nucleoprotein (N), Glycoprotein (G), matrix protein (M), and RNA-dependent RNA polymerase (L) (Tao et al., 2021). It has a long history in China for more than 2000 years and it was first known in 556BC, and there have been three main epidemics in China since the 1950s, and the third and the current epidemic started in 1997 (Zhang et al., 2009a,b; Huang et al., 2010; Shahrajabian et al., 2020a,b; Shahrajabian et al., 2021). Li et al. (2023) reported that re-emerging high-risk provinces were Anhui and Yunnan in China, and the important point is priority animal vaccination in those identified high-risk provinces. It has been also reported that although, the occurrence of rabies has been decreased significantly in the past decade, it still remains the second most important cause of death from zoonotic infectious diseases in Chinese adolescents and children (Dong et al., 2020; Langguth et al., 2021; Li et al., 2021; Das et al., 2022). On the basis of the data of Chinese Center for Disease Control and Prevention, there were a total of 25,700 rabies deaths from 2004 to 2018 in mainland China, and the cases were basically caused by dog bites (Qian et al., 2019; Qiao et al., 2021). Without extensive education, forced vaccination, and strict administration, dog rabies has spread to ferret badgers (*Melogale moschata*, FBs) in Southeast of China, and the virus presently independently circulates in this animal population (Zhang et al., 2009; Liu et al., 2010b).

The world's top producer and user of rabies vaccine is China which represented around 84% of all rabies vaccine vials needed in 2020 (Li et al., 2023). The cost of rabies control and prevention in China is high, however the result is still not acceptable, and according to the official data, China administers nearly 12-15 million doses of vaccines every year, which is around one billion but has the second highest occurrence after in India (Nadal et al., 2022). China should to boost the animal surveillance and registration system, particularly in regions with high rabies risk, and to do more trials on large-scale dog vaccination (Nadal et al., 2022), to gain the goal of eliminating dog-mediated rabies by 2030 (Yin et al., 2013). Currently, three types of rabies immunoglobulin (RIG) factors are utilized in passive immune treatment: equine rabies immunoglobulin, human rabies immunoglobulin, and high-purity f (ab) 2 fragment created by equine immunoglobulin (Li et al.,

2020). Ormutivimab is the first recombinant human anti-rabies monoclonal antibody which was developed and approved in 2022, and it is an antibody of IgG1 subtype, manufactured by Chinese hamster ovary (CHO) cells, and it can precisely neutralize the linear neutralizing antigen epitope in situ point I of rabies virus glycoprotein (Li et al., 2020). In different parts of China the rabies virus associated with dogs, isolates can be categorized into six genetic lineages (China I-VI), and among these lineages, China I has become the principle epidemic type transmitted and hosted by dogs, and this lineage has replaced the wildlife and dog-associated China II lineage in the past years (Ming et al., 2018). In Inner Mongolia Autonomous Region which is a boundary province located in northern China, human rabies cases boosted from 2005 to 2007, and reduced during 2008-2011, and up until 2014, many rabid animals are reported included raccoon dogs, dogs, cows, red foxes, sheep, cows and camels (Zhu et al., 2015). Zhang et al. (2014) and Xing et al. (2014) reported that high rate of rabies virus carried by domestic dogs possibly was the main reason for current rabies epidemic in China. Zhang et al. (2006a,b,c) reported that phylogenetic analysis showed that all the rabies epidemics of Chinese isolates have a close connection with viruses circulating in Asian canine population in comparison with rabies viruses isolated previously. In Guangdong, which has the third highest human rabies cases among 31 provinces in China, at least 18.2% caused by stray dogs, due to a large number of dogs, both stray and domestic, and vaccination has been found more effective than culling (Hou et al., 2012). On the basis of the results, it has been proved that the rabies viruses in China and Southeast Asia share a common ancestor and form 2 clades with each being further grouped into 3 lineages, and the viruses circulating in Southeast Asia probably derived from China (Gong et al., 2010). It is also important to understand the temporal and spatial patterns of rabies in humans for risk assessment and develop targeted interventions (Guo et al., 2013; Ruan, 2017; Huang et al., 2019), specially for India and China which have the maximum and second highest reported number of rabies, respectively (Ren et al. 2015; Wolelaw et al., 2022). Wang et al. (2022) reported that rabies vaccination after pre-exposure prophylaxis (PEP) could lead to the body to produce enough sufficient RVNA, and rabies vaccination after PEP has indicated comparatively an appropriate immune efficacy and acceptable safety for preventing human rabies. Ding et al. (2020) reported that SYN023, which is a mixture of two anti-rabies humanized monoclonal antibodies (mAbs), namely, CTB012 and CTB011, at 0.3 mg/kg is relatively effectual and safe and can be selected for more clinical researches in Chinese subjects.

The phylogeographic structure showed Chinese rabies viruses have been transmitted extra-provincially and intra-provincially because of human-related characteristics (Meng et al., 2010). Ming et al. (2009) reported that phylogenetic experiment utilizing either partial or complete genomic sequence of HN10 showed that this isolate is most closely connected with viruses previously shown to circulate in Hunan and Guangxi provinces. Taxitiemuer et al. (2017) reported that wild fox bite is a main risk parameter of rabies infection in Xinjiang Province of China. It has been showed that rabies virus isolated from Guangxi have a close genetic connection and topographical distribution (Liu et al., 2007). Liu et al. (2012) proved that botanical polysaccharide preparations from *Echinacea*, *Astragalus*, kelp, and wolfberry could be applied in rabies vaccine formulations for persistent and early prophylaxis. Human rabies virus vaccine strain CTN181 from China was sequenced, and its overall length of the genome was 11,923 nucleotides (nt), including a leader sequence of 58 nt, phosphoprotein (P) gene of 894nt, nucleoprotein (N) gene of 1353nt, glycoprotein (G) gene of 1575nt, matrix protein (M) gene of 609nt, a trailer region of 70nt, and RNA-dependent RNA polymerase (RdRp, L) gene of 6387nt (Du et al., 2008). Li et al. (2013) reported that Sanofi Pasteur has improved a next generation rabies vaccine (PVRV-NG), and it was at least as immunogenic as Verorab and was well tolerates and it presents an appropriate substitute for the prophylaxis of rabies. Liu et al. (2023) reported that vaccine+ormutivimab can protect those who are above 18 years old with category III suspected rabies exposure as a component of postexposure prophylaxis, and ormutivimab has a weaker impact on the immunity response of rabies vaccines. Meng et al. (2011) concluded that although dog rabies viruses comprise six main clades, namely, Africa 2, Africa 3, Arctic-related, Cosmopolitan, Indian and Asian subcontinent clades, the last three clades circulate widely in Asia, with the Arctic-related clade circulating in a large region spreading from central Asia to eastern Asia, and countries such as Nepal, Russia, northeastern Iran, Pakistan, Korea, and the north of India. In some studies, it has been reported that incomplete postexposure prophylaxis and not quick seeking postexposure prophylaxis are usual in rural China and may cause to PEP failure and rabies deaths (Wang et al., 2018; Chen et al., 2019a,b), and people should be well educated on how to treat dog bites and seek quick, and proper PEP, and not use other unapproved methods (Zhao et al., 2019). There are two kinds of oral rabies vaccination which are currently being under commercial licence for the vaccination of different wildlife species, vector-based vaccines (VBVs), and modified live vaccines (MLVs); VBVs are designed by inserting antigenic glycoprotein encoding genetic material from the rabies virus into other vector viruses, and the active component of MLVs is replication-component, live rabies virus which has been modified so that it can induce the body ،s natural immune response (Yale et al., 2022). The main goal of rabies vaccines are providing appropriate amounts of rabies glycoprotein to locations, rich in antigen presenting cell to lead to production of enough rabies virus neutralizing antibodies, as well as memory T and B

cells, for prevention of rabies (Moore, 2021). Different clinical experiments have proved sufficient data to support a decrease in the number of doses, a shorter timeline needed for PEP, and the approval of the intradermal route of application for PEP and pre-exposure prophylaxis (PreP) (Briggs and Moore, 2021). Song et al. (2009) reported that the following suggestions and recommendations should be considered for prevention and treatment of rabies in China, (1) establishing national animal rabies surveillance network is important, (2) strict control of free-ranging dogs and obligatory rabies vaccination should be done, (3) the cost of PEP should be free or reduces, particularly in rural areas, (4) education of the public and health care staff should be increased, and (5) PEP should be decided to withhold or start on the basis of postmortem diagnosis of the biting animal. Chen et al. (2023) concluded that the clinical application of Ormutivimab, boosts post-exposure prophylaxis of rabies in China, and decreases infection rate. Li et al. (2021) observed that after 2011, the rate of negative reaction to rabies vaccine in China has significantly declined, and the rate of negative reaction to rabies vaccine in the midwestern states is higher than the counterpart in the eastern parts.

8. Conclusion

Rabies is the main fatal zoonosis induced by the rabies virus, which infects wild animals, humans, and livestock. Its virus belongs to the *lyssavirus* genus, which also consists of other *lyssavirus* species that cause rabies-like diseases and can be carried by domestic animals, wild carnivores and many bat species. The rabies virus is the only pathogen accountable for the large majority of rabies cases in humans. Rabies virus infects the peripheral nerves and then migrates into the central nervous system of the brain through the spinal cord, causing fatal encephalitis and myelitis and resulting the death of the infected subjects. Basic rabies reservoirs are dogs in major vector of rabies throughout the world, particularly Asia, Latin American and Africa; foxes, in Europe, North American, and Arctic; Raccoons in Eastern United States; skunks in Modwestern United States, Western Canada; coyotes in Africa, Asia, and North America, mongooses in yellow mongoose in Africa, and Asia, Indian mongoose in the Caribbean Islands, and bats in North American Europe, South and Center America. The genomic RNA of the classic rabies virus (RAVB) encodes five structural proteins: nucleoprotein (N), phosphoprotein (P), matrix protein (M), glycoprotein (G0), and large protein (L). The G protein is the only protein on the surface of mature virus and acts an essential role in virus infection. Also, the G protein is a major antigenic stimulus of the host immune system during infection and vaccination. There are three categories of exposure, (I) touching, feeding of animals or licks on intact skin, (II) Minor scratches or abrasions without bleeding or licks on broken and nibbling of uncovered skin which needs immediate vaccination and administration of rabies immunoglobulin, (III) single or multiple transdermal bites, scratches or vaccine contamination of mucous membrane saliva which needs local wound treatment. Vaccination against rabies is of primary importance in control of infection in both humans and animals. WHO also recommended only vaccines of high quality and efficacy. Rabies is preventable through prompt administration of post-exposure prophylaxis (PEP) to exposed persons, but PEP access is limited in many rabies-endemic countries. The death toll can be significantly reduced through access to post-exposure prophylaxis (PEP), consisting of wound cleaning, rabies immunoglobulin (RIG) and vaccination. Access to PEP is limited in many developing and under-developed countries with endemic rabies and PEP is often only available from health facilities in mega cities. Patients also need to pay for PEP and the costs are reported as a major obstacle for many victims. Rabies have been reported in all over the China, especially Hunan, Sichuan, Guangdong, Guangxi, Hubei, Guizhou, Jiangxi, Shandong, Anhui, Henan, Jiangsu, Fujian, Hebei, Yunnan, and Liaoning. In China, rabies remains is still a public health issue and the techniques to control and prevent human rabies should be included public education and awareness about rabies, elimination of stray animals, pet vaccination programs, and enhanced post-exposure management. Domestic dogs are the primary vector and reservoir of rabies transmission in China, although RAVB has been isolated and identified in other animal species, such as ferret badger, cat, fox, cattle, pig, and donkey. Unsuccessful control of rabies and inadequate PEP of cases may be the principle factors inducing to the serious human rabies epidemic in China. It is widely approved that rabies elimination requires an integrated approach by human and animal related services. There is an urgent need to have public health management which may improve effectiveness and sustainability of rabies eliminating programs. China needs to focus on prevention, strengthen multi-agency coordination mechanism, boost the quality of public health services in the years to come.

Author Contributions

The percentage of the author(s) contributions is presented below. All authors reviewed and approved the final version of the manuscript.

	M.H.S.	W.S.
C	50	50
D	50	50
S	50	50
DCP	50	50
L	50	50
W	50	50
CR	50	50
SR	50	50
PM	50	50
FA	50	50

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding accustion.

Conflict of Interest

The authors declare that there is no conflict of interest.

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