

Review on Rabies: Neglected but Dangerous

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Abstract: Rabies has been recognized as a zoonotic viral disease of all warm-blooded animals affecting the central nervous system and transmitted by the saliva of a biting mammal. The disease is dominant in Asia and Africa. In Nigeria, lack of accurate data on human and animal rabies which has been reported due to misdiagnosis, under-reporting, inadequate rabies diagnostic units, poor knowledge on the mode of transmission and prevention of the disease, cultural beliefs and lack of national surveillance system. There is a need for the Nigeria Government to address the issue of rabies virus infection and other striking infections. Vaccination campaigns should be nationally coordinated employing a free door-to-door vaccination approach for effectiveness; free vaccination of adult dogs throughout the nation can provide herd immunity. Eradication also requires responsible pet ownership, stray animal management, leash law amendments, human population curtailment, animal importation, translocation and quarantine regulations, schedules for early pre-exposure vaccination of companion animals and rational post-exposure prophylaxis of humans which include proper wound care, administration of rabies vaccine and rabies immunoglobulin; exposed unvaccinated animals should be euthanized. This review focuses on the old and current situation of rabies, the predicaments in the complete eradication of rabies disease and effectively combating its menace in Nigeria.

Key words: Rabies • Herd Immunity • Vaccination • Immunoglobulin • Dogs • Exposure Prophylaxis • Status

INTRODUCTION

The pandemic outbreak of viral diseases such as Ebola and Coronavirus (COVID-19) in recent times has put a thick veil on many other old, neglected killer viral diseases. One of these neglected, but deadly viral diseases include, but not limited to rabies virus, oncoviruses, herpes simplex virus and Human Immunodeficiency virus (HIV). Rabies virus has been recognized since 1912 as a zoonotic viral disease of all warm-blooded animals affecting the central nervous system and transmitted by the saliva of a biting mammal such as cats, bats, raccoons, foxes and skunks which are

in abundance in the United States and Canada. Dogs are the main vectors worldwide as about 99% cases are dog mediated [1]. Some countries like Australia, New Zealand, Antarctica and scanty island territories are considered free of rabies [2, 3]. Rabies has been reported to cause about 59,000 to 60,000 human deaths annually. About 15 million people receive rabies post exposure prophylaxis (PEP) annually while over 95% mortality rate has been reported in Asia and Africa [1, 4, 5]. In developing countries such as Nigeria, lack of accurate data on human and animal rabies which has been reportedly owed to misdiagnosis, under-reporting, inadequate rabies diagnostic units, poor knowledge on the mode of

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transmission and prevention of the disease, cultural beliefs and lack of national surveillance system has been a major factor in eliciting the true incidence and mortality rate of the disease [6-8]. Furthermore, routine vaccination of pets such as dogs, cats and monkeys in Africa including Nigeria is ridiculously low and rabies control programs have failed woefully. The estimate of human cases with those officially reported do not correlate as rabies cases such as non-bite exposure including inhalation of virus aerosol, open wounds, mucus membranes laden with rabies antigen saliva or with infectious material like brain tissue from a rabid animal which can also occur may not be reported [8]. Human rabies fatalities occur frequently in individuals who have no access to proper health care or have no financial capacity for treatment [9]. This review aimed at highlighting the old and current situation of rabies, the predicaments in the complete eradication of rabies disease and effectively combating its menace in Africa especially Nigeria.

History of Rabies: Rabies virus got its name from a Latin word derived from Sanskrit “rabhas” or “rabere” meaning “to do violence” or “to be mad” and it is recognized as one of the typical zoonosis that is well known for about 4300 years, first recognized in Egypt around 2300 B.C and in ancient Greece where it was described by Aristotle [3, 5]. Early Roman writers described the infectious material as poison from which the Latin word “virus” emanated upon recognition of the infectivity of saliva of rabid dogs by Zinke in 1804 [3, 5]. There was no protective or remedial treatment in animals until 1885 when Louis Pasteur discovered and administered a rabies vaccine to a man named Joseph Meister who was bitten by a rabid dog after he demonstrated the neurotropism of the virus in 1881. This first-ever vaccination became the milestone in modern science in the area of infectious diseases targeted towards the control and prevention of diseases [5]. The first rabies oral vaccination campaign for wildlife was conducted in Switzerland in 1978 and other European countries subsequently. A three field trial of three oral vaccination campaigns and mandatory vaccinations to dogs in the outbreak area was initiated using SAD B19 bait in 1988; Finland was declared rabies-free country in 1991 [5].

Aetiology of Rabies and Classification of Rabies Virus: Rabies virus has been described as a rod- or bullet-shaped, enveloped, single stranded, negative-strand RNA virus of about 75-180nm in size with

projections and helical nucleocapsid belonging to the order *Mononegavirales*, family *Rhabdoviridae* and genus *Lyssavirus*. The *Lyssavirus* genus is grouped into seven (7) genotypes based on their antigenic characterization: The classical *Rabies* virus (RABV; genotype 1), *Lagos* bat virus (LBV; genotype 2), *Mokolavirus* (MOKV; genotype 3), *Duvenhagevirus* (genotype 4), European bat lyssavirus (EBLV-1; genotype 5), European bat lyssavirus (EBLV-2; genotype 6) and the Australian bat lyssavirus (ABLV; genotype 7) [3, 5]. Based on the analysis of the genotype (G) gene, sequences of representative virus isolates, immunogenicity and virulent properties, the genus *Lyssavirus* further subdivided into two phylogroups namely: Phylogroup I comprising genotypes 1, 4, 5, 7, ARAV, KHUV and IRKV while phylogroup II comprise genotype 2 and 3 respectively. All except *Mokolabat* virus (MOKV) were isolated from bat [1, 3].

Other emerging Lyssaviruses have been identified in Eurasia and they include: Aravian (ARAV), Khujand (KHUV), Irkut (IRKV) and the West Caucasian bat virus (WCVB) while Rochambeau virus (RBUV) was included as putative specie but there is no phylogenetic relationship to the Lyssaviruses [3]. The Lyssavirus genotype rabies virus (RABV) negative-strand RNA consists of about 12 kb coding for five different proteins which are: Viral nucleocapsid protein (N), Envelope matrix protein (M), Phosphoprotein (P), Glycoprotein (G) and RNA polymerase (L) [3, 7, 10]. The Polymerase, Nucleoprotein and the Phosphoprotein form a genome complex giving rise to an inner nucleocapsid; the matrix protein forms the inner layer of the bi-layered lipid envelope while the glycoprotein forms the outer layer as well as the spike-like projections which are a target of virus-neutralizing antibody [3].

Epidemiology of Rabies in Asia and Africa: Rabies virus has been reported to be endemic in Asia and Africa as many other continents had succeeded in curtailing the disease [3, 11]. In Asia, reports showed that rabies is characterized by a high rate of human mortalities with an estimated mortality rate at 39,000 persons annually and contributing to 56% human death cases of rabies worldwide [11]. However, countries such as Japan, Singapore, Malaysia, Taiwan, Hong Kong and South Korea have successfully eradicated canine rabies through mass dog vaccination and stray dog control programs [11]. Meanwhile, Thailand, Sri Lanka and Vietnam reported a slight reduction through mass dog vaccination, intensified post-exposure prophylaxis and awareness education [12, 13]. South Asia comprising of eight

countries including India, Bangladesh, Bhutan, Pakistan, Maldives, Nepal, Afghanistan and Sri Lanka are experiencing rabies endemic with the exception of Maldives, Timor Leste and some island countries of India [11, 14]. India experience 97% dog bites as the principal source of rabies, which is followed by 2% bites from cats and 1% bite from wildlife such as jackal and mongoose with an annual estimate of 17million animal bites resulting into 20, 000 human deaths which accounts for about 29% of all global deaths [11]. Additionally, rabies is not a notifiable disease in India and even in the face of high human mortality rate, surveillance rate is still poor. Although, the Government of India approved intradermal vaccination after the discontinuation nerve tissue vaccine and cell culture vaccines; there is no national rabies control program while organizations that initiate rabies control programs are confined to small urban areas with minimal inter-sectoral coordination [11]. Bangladesh, Nepal, Cambodia and Pakistan shared a similar experience with India where stray dogs and wild animals are the principal sources of rabies coupled with no rabies control program, less effective vaccines and cultural sentiments. Afghanistan and Bhutan have no proper epidemiological data and the disease is endemic in these areas. Even though both countries identified rabies as a notifiable disease, there are cases of occasional re-emergence in Bhutan [11]. Rabies disease became epidemic in Thailand due to previously low coverage of dog vaccination making Thailand the third ranking country in Asia with human rabies deaths. However, two regulations for rabies control in the Rabies Act B.E 2535 (1991) were employed: all dogs from two months of age must be vaccinated and tagged else all dogs that are not properly tagged will be caught and destroyed five days after except contact is received from the owner [11]. Furthermore, program strategies such as accessibility to post exposure prophylaxis (PEP) using intradermal (ID) rabies vaccination, mass dog vaccination, increasing educational awareness programs and sterilization programs were employed to ensure gradual reduction in rabies epidemic in Thailand while Philippines achieved significant level of rabies reduction through the aforementioned programs including dog registration, a method also employed by the Republic of China [11]. In 2017, Zafar *et al.* [15] identified animal bite or exposure to animals among others as a major risk factor for rabies infection in Asia and dog bites affect more males than their female counterparts which is associated with pet dogs. Exposure of livestock farmers to rabies infection is associated with handling animal placenta during delivery

and abortion cases with naked hands; milking and consuming unpasteurized animal product. In their study, they identified other risk factors which include: knowledge factor as many are unaware of zoonotic diseases while some that are aware do not put their knowledge into practice; traditional factor; socioeconomic factor; and poor prevention practice [15]. In African countries such as Kenya, rabies was first confirmed in 1912 and rabies problem was reported to be the highest in Machakos district where rabies persisted for more than forty (40) years [10]. However, in a six (6) year study in Kenya, animal bite incidents mostly dog bites was estimated to be 289 per 100,000 persons and this was highest in Kilifi at 302 per 100,000 persons while lowest in Machakos at 121 per 100,000 persons [16]. Cases of rabies infection in less than 15 years were reported to be highest in Kitui, Machakos and Nandi counties while males' victims are more than female victims. In Mozambique, a four (months) rabies study reported in Maputo and Matola cities showed dog bite as a major source of contracting the rabies infection; males are more affected and bite to the head poses a quick central nervous system attack; children under the age of fifteen years are highly predisposed to the infection as 12 out of 14 rabies cases in their study were in this category [17]. Failure to properly diagnose the condition contributed to poor surveillance and under-reporting while seeking traditional healers for medical care results in a higher mortality rate [17]. Factors contributing significantly to the low level of canine immunization in Mozambique include: lack of adequate public health laws on dog ownership and immunization; poor implementation of existing legislation on dog ownership and immunization; limited access to veterinary services for canine immunization and irregular implementation of canine immunization campaigns [17].

Epidemiology of Rabies in Nigeria: Annual reports on rabies incidence have not been properly documented as the accuracy of statistical data of both human and animal rabies is not consistent with the actual incidence rate [7]. In 1995, 380 laboratory-confirmed cases of rabies and 1,540 cases were clinically confirmed and reported and all cases were dog mediated [1]. Rabies infection by dog bites accounts for about 99% while cats, monkeys and other mammals account for 1% in Nigeria and human deaths due to rabies reported from 10 states between 1980 and 2014 showed 78 deaths which is far below the actual mortality rate; all of which were not laboratory confirmed cases but by symptoms [8]. Factors responsible for these inconsistencies include under-reporting due to

knowledge, attitude and practice of people; socio-economic factors are also associated with non-dog vaccination [1].

Vaccination, Vaccination Problems and Rabies Epidemic in Nigeria: Like other Asian and African countries, Nigeria is not exempted from the rabies epidemic as many incidents reported are mainly dog related amongst other animals. Dog-to-dog, dog-to-livestock and dog to-human transmissions have been identified [4, 18]. Detection of rabies in three (3) months old puppies makes the matter worse and children who are lovers of puppies are at high risk of rabies infection [18]. Failure of control policies on dog vaccination, registration, licensing and stray dog elimination as well as human vaccination campaigns sponsored by certain arms of government have been reported to be expensive and inadequate in terms of coverage which contributed to the menace of rabies in Nigeria [4]. Kehinde *et al.* [4] reported a total number of 12 cases in a 10 year retrospective study (1997-2007) with the highest number of cases in 2004; 75% cases occurred in children under the age of 12 years; nine (9) cases in animals with 8 (88.9%) in dogs and one (1) case in goat (11.0%). Also, seasonal occurrence which is high during the rainy season associated with dogs and low during dry season associated with goats, has been reported [4]. Furthermore, Kolesho [19] reported prevalence of rabies in dogs, cats and primates in Lagos State over a ten (10) year period between 1986 and 1995. In the study, it was observed that 3,715 dogs, 74 cats and 4 primates were vaccinated; an indication that rabies is grossly under reported and vaccination in pet animals is very poor in Nigeria. Other limitations include: poor documentation of animal sex, breed, age and date vaccinated, pre and post exposure vaccination; and inability of the ministry to supply animal records according to zones [4, 19]. In the same Lagos State, Hambolu *et al.* [20] reported the record of dog bites cases from private and government owned veterinary clinics where 196 dog bites cases were recorded from 2006 to 2011; 116 male rabid dogs and 76 females bit 69 children, 109 adults and 18 unknown victims. One hundred and fifty six (156) dogs were vaccinated and 40 unvaccinated and only 7 offending dogs were quarantined and 189 dogs were not quarantined because bites were provoked by victims [20]. In another place in Nigeria, Audu *et al.* [21] reported two cases of rabies-related death because the victims had no access to post exposure prophylaxis due to its unavailability, long distance to health facility (95.8km), sought alternative (traditional) treatment and high

financial cost. These indicate that rabies was severely under-reported and no curative measures were adequately administered. The problems of rabies elimination with vaccination in Nigeria is multifactorial and some of these problems were identified by Adedeji *et al.* and Tekki *et al.* [1, 22] to include but not limited to: failure to seek treatment at health facilities which is a reflection of financial incapacitations, failure to execute laboratory diagnosis, human factors such as increased traveling to rabies endemic areas, lack of communication on the part of the government, lack of knowledge and information, lack of adequate public awareness, lack of good laboratory and proper surveillance, lack of appropriate control methods, lack of motivation, inappropriate management of the disease, dog owner's attitude towards vaccination, political instability, cultural and religious beliefs, ignorance, government's negligence, governments policies, increasing demand for meat, hunting with dogs and poor road network. Animal factors include increase in host population, migration of dogs and stray animals, consumption of animal brains. Vaccination factors include low vaccination coverage, vaccine failure, unavailability of Rabies Immunoglobulin (RIG) as prescribed by World Health Organization (WHO), use of low potency vaccine, safety issues, failure of animals to show adequate antibody titre, high cost of pre exposure prophylaxis (PEP), lack of delivery systems and resources, challenges in the testing of vaccine efficacy, long incubation period, inconsistent vaccination, inferior vaccine quality and vaccine shortage [1].

Effective Eradication of Rabies Infection in Nigeria: The Way Forward: The success of a vaccine is dependent not only on its product but also the design [23] and there are five conceptual frameworks in consideration which are: Basic reproduction number (R_0) which is the number of secondary cases arising from a primary case in the absence of constraint in the spread of the infection; Vaccine impact (Q), a parameter that infuses the fraction of vaccinated hosts which become protected and the ratio of average protection to average host life expectancy; Herd immunity; Repeat vaccination especially where they have low impact and or low duration of protection as this provides herd immunity against infection with high R_0 ; and Maternal protection [23]. A comprehensive domestic animal program also requires responsible pet ownership, stray animal management, leash law amendments, human population curtailment, animal importation, translocation and quarantine regulations, schedules for early pre-exposure

vaccination of companion animals and rational post-exposure prophylaxis of humans which include proper wound care, administration of rabies vaccine and rabies immunoglobulin; euthanasia of exposed unvaccinated animals [10].

Vaccination campaigns should be nationally coordinated employing a free door-to-door vaccination approach for effectiveness. Free vaccination of adult dogs throughout the nation can provide herd immunity [7, 23]. There should be a veterinarian to coordinate zonal activities and this should be the same at state and national levels in conjunction with the federal ministries of health and information; every veterinary faculty to have rabies diagnostic laboratories, intensified public awareness even though many educated folks are aware of the rabies, many village people need more awareness [23, 24] Additionally, there is the need for detailed epidemiological studies where there is proper recording of rabies incidents, accurate collection and laboratory analysis; enforcement of compulsory vaccination and revaccination of all pets especially dogs; eradication of stray dogs, cost reduction of pre and post-exposure prophylaxis treatment as well as adequate production of potent anti-rabies vaccines in the country and adequate supply for human and animals.

CONCLUSION

Rabies is still endemic in Nigeria and cases are 100% fatal. Dogs are large reservoirs for the virus and are responsible for about 99% infection cases in Nigeria; while rabies cases are grossly under-reported as the reported cases are not the true representative of rabies situation in Nigeria as well as some African countries, lack of consistency in creating awareness; knowledge and attitude of victims to seek clinical treatment; the attitude of clinicians to properly diagnose the condition and proper documentation of rabies cases; lack of surveillance systems; lack of access to pre and post exposure prophylaxis (PEP) due to poor financial conditions, distance and bad road networks; unavailability of rabies vaccines; irresponsible pet ownership; as well as regular vaccination campaign abandonment by the government are major factors that contributed to the increasing menace and difficulty in the proper eradication of rabies in Nigeria. In order to properly control rabies infection and its menace, a free door-to-door mass dog vaccination is mandatory as dogs irrespective of their ages are the major reservoir for the disease. This should be followed by enacting the Rabies Act to include free dog registration and a cheap annual vaccination of all pet animals; and

eradication of stray dogs. Public awareness and education of clinical and laboratory personnel should be intensified; proper documentation and reporting to relevant quarters should be intensified and emphasized; creation of rabies laboratories and PEP centers throughout the nation especially in rural areas for easy and low cost accessibility.

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