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Rabies Virus at the Beginning of 21st Century

Edited by Sergey Tkachev



Rabies Virus at the Beginning of 21st Century

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Rabies Virus at the Beginning of 21st Century
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Edited by Sergey Tkachev

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IntechOpen Book Series

Veterinary Medicine and Science

Volume 9

Aims and Scope of the Series

Paralleling similar advances in the medical field, astounding advances occurred in Veterinary Medicine and Science in recent decades. These advances have helped foster better support for animal health, more humane animal production, and a better understanding of the physiology of endangered species to improve the assisted reproductive technologies or the pathogenesis of certain diseases, where animals can be used as models for human diseases (like cancer, degenerative diseases or fertility), and even as a guarantee of public health. Bridging Human, Animal, and Environmental health, the holistic and integrative “One Health” concept intimately associates the developments within those fields, projecting its advancements into practice. This book series aims to tackle various animal-related medicine and sciences fields, providing thematic volumes consisting of high-quality significant research directed to researchers and postgraduates. It aims to give us a glimpse into the new accomplishments in the Veterinary Medicine and Science field. By addressing hot topics in veterinary sciences, we aim to gather authoritative texts within each issue of this series, providing in-depth overviews and analysis for graduates, academics, and practitioners and foreseeing a deeper understanding of the subject. Forthcoming texts, written and edited by experienced researchers from both industry and academia, will also discuss scientific challenges faced today in Veterinary Medicine and Science. In brief, we hope that books in this series will provide accessible references for those interested or working in this field and encourage learning in a range of different topics.

Meet the Series Editor



Rita Payan Carreira earned her Veterinary Degree from the Faculty of Veterinary Medicine in Lisbon, Portugal, in 1985. She obtained her Ph.D. in Veterinary Sciences from the University of Trás-os-Montes e Alto Douro, Portugal. After almost 32 years of teaching at the University of Trás-os-Montes and Alto Douro, she recently moved to the University of Évora, Department of Veterinary Medicine, where she teaches in the field of Animal Reproduction and Clinics. Her primary research areas include the molecular markers of the endometrial cycle and the embryo–maternal interaction, including oxidative stress and the reproductive physiology and disorders of sexual development, besides the molecular determinants of male and female fertility. She often supervises students preparing their master’s or doctoral theses. She is also a frequent referee for various journals.

Meet the Volume Editor



Dr. Sergey Tkachev is a senior research scientist at the Institute of Fundamental Medicine and Biology, Kazan Federal University, Russia, and at the Institute of Chemical Biology and Fundamental Medicine SB RAS, Novosibirsk, Russia. He received his Ph.D. in Molecular Biology with his thesis “Genetic variability of the tick-borne encephalitis virus in natural foci of Novosibirsk city and its suburbs.” His primary field is molecular virology with research emphasis on vector-borne viruses, especially tick-borne encephalitis virus, Kemerovo virus and Omsk hemorrhagic fever virus, rabies virus, molecular genetics, biology, and epidemiology of virus pathogens.

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Preface

Rabies is a zoonotic viral disease that is fatal once clinical manifestations develop. Its agent, the rabies virus (RABV), is a (-)ssRNA virus belonging to the order *Mononegavirales*, the family *Rhabdoviridae* (from the Latin word “rhabdos”, meaning “rod,” because representatives of this family have rod-shaped virions), and the genus *Lyssavirus* (from the name “Lyssa,” an ancient Greek goddess, the personification of rabies).

Despite significant progress in fighting rabies worldwide and successful eradication programs in Western Europe, rabies remains an important public health concern, causing approximately 50,000 human cases per year. Rabies is present on every continent except Antarctica and Australia, with 95% of human deaths occurring in Asia and Africa. In almost 99% of cases, the transmission of RABV to humans occurs from domestic dogs. However, rabies can affect both domestic and wild animals and can be transmitted to humans through bites or scratches, usually through saliva.

This book summarizes current knowledge regarding RABV, its prevalence and genetic diversity, and modern approaches to its diagnosis, prevention, and treatment. It is a useful resource for scientists, doctors, and students studying the problem of rabies, conducting research, carrying out preventive measures, and providing medical care to patients.

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Section 1

Common Issues
of the Rabies Virus

Introductory Chapter: Rabies in the 21st Century

Sergey Tkachev

1. Introduction

Rabies is known as a fatal viral infection that is most commonly spread to humans and pets through the bites, scratches, or contamination of mucous membranes with the infected saliva of an infected animal. In an infected organism, an acute progressive encephalomyelitis/encephalitis develops ultimately resulting in death.

The infection is caused by a neurotropic zoonotic virus belonging to the *Lyssavirus* genus (named after *Lyssa*, an ancient Greek goddess, the personification of rabies) of the *Rhabdoviridae* family (from the Latin *rhabdos*, meaning “rod”, because the members of this family have rod-shaped virions). Currently, the *Lyssavirus* genus contains 18 virus species (<https://talk.ictvonline.org/>), and between them, the rabies virus is the most important one concerning its impact on public health.

2. Molecular biology of rabies virus

The rabies virus (RABV) is enveloped, bullet-shaped viruses, 180 nm in length and 75 nm wide (**Figure 1**). Virions are composed of two structural units: an

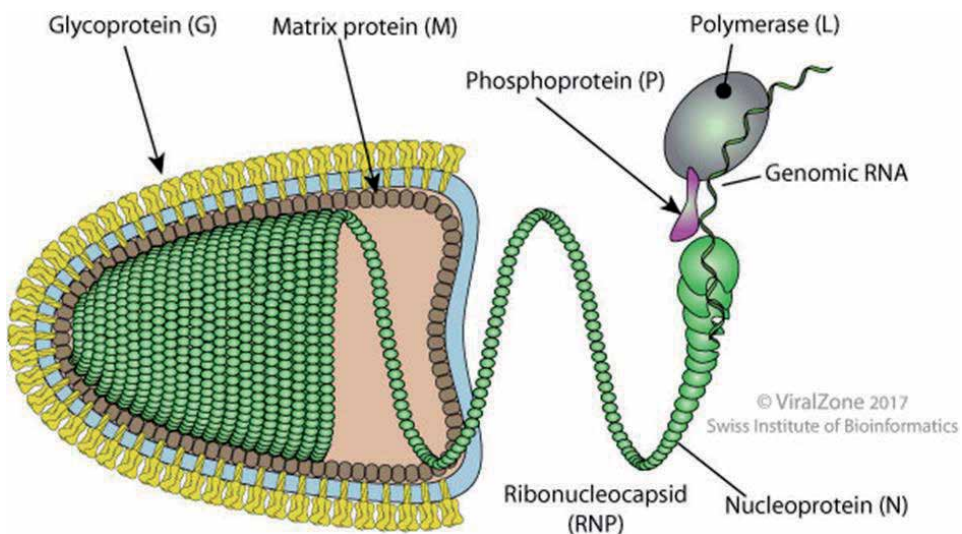


Figure 1.
The structure of the rabies virus (<https://viralzone.expasy.org/22>).

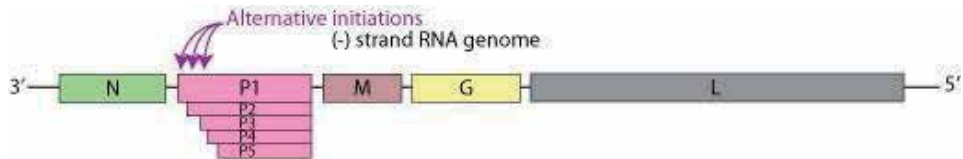


Figure 2.
Genome structure of the rabies virus (<https://viralzone.expasy.org/22>).

internal helical nucleocapsid (consisting of nucleoprotein N and viral genome RNA), and a lipid envelope derived from the host cytoplasmic membrane during virus budding.

RABV contains a negative-sense ssRNA genome 11.9–12.3 kb in length, encoding five protein-coding genes: N, P, M, G, and L, which are separated by intergenic regions of variable length (**Figure 2**) [1]. P gene has alternative initiation points that lead to translation of P protein and at least four additional shorter gene products [2]. At 3'- and 5'- ends of RABV genome 58 nt leader sequence, and 57–70 nt trailer is located, subsequently [3].

3. Genetic diversity of rabies virus

Currently, phylogenetic analysis of RABV is commonly based on the N gene [4]. Previously, it was demonstrated that RABV genetic diversity has a strong geographic pattern throughout the world, which possibly results from the recent virus spread [5, 6]. Based on data received, all currently known RABV genetic variants can be divided globally into seven major groups [6]. Within these major groups, smaller genetic groups could be distinguished; thus, within the Cosmopolitan, and the Arctic/Arctic-like major groups, circulating in the Russian Federation six smaller groups were described in Russia: Arctic rabies (northern parts of Siberia), Arctic-like rabies (Khabarovsk Krai, Transbaikal region), Steppe rabies (Eurasian Steppe), Central European Russian rabies, Northeast European Rabies, and Caucasian rabies [6–8].

4. Rabies distribution

Currently, RABV is distributed globally and rabies infection is registered on all continents except Antarctica and, possibly, Australia. According to CDC data (<https://www.cdc.gov/rabies/>), the most (more than 90%) of all animal cases of rabies reported occur in wild animals; before 1960, most were in domestic animals. According to current data, the principal rabies hosts are wild carnivores and bats. Despite significant progress in the prevention and prophylaxis of rabies worldwide [9], rabies remains an important public health concern, especially in developing countries within Africa and Asia where rabies virus causes approximately 50,000 lethal cases per year [10]. Also, the official statistical data could be greatly underestimated due to the lack of systematic surveillance in some countries.

5. Rabies pathogenesis, prevention, and prophylaxis

Delivered into a wound through the bite or wound contamination with virus-containing biological liquids, the virus can replicate at the inoculation site [11].

After that, RABV reaches the sensory or motor neurons and then propagates up to the central nervous system by following neuronal connections. Such pathways through nervous tissue shield the virus from the host immune system, resulting in absence of early antibody response [12]. Being delivered to the central nervous system, the virus disseminates rapidly, and nearly all regions of the central nervous system may be affected. Nevertheless, the duration of the asymptomatic incubation period can be long-standing (two months on average), while the symptomatic period with clinical signs is rapid and severe (about one week).

Although rabies has the highest case fatality rate (100%), fortunately, it is a preventable disease. Postexposure prophylaxis consisting of rabies immune globulin or/and rabies vaccine is very effective in preventing the disease development when administered promptly after virus exposure has occurred. Also, very important measures to reduce the risk of RABV transmission to humans are vaccination of domestic animals against rabies and stray animal control programs.

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The Early Development of the Vaccinia–Rabies Recombinant Vaccine Raboral®

Richard Lathe and Marie Paule Kieny

Abstract

The recombinant vaccinia–rabies vaccine, now known as Raboral®, has been widely used in Europe and North America to control/eliminate rabies in the principal wildlife vectors, and thus prevent human transmission. The origins of this vaccine are sometimes forgotten, although the formulation has not changed substantially in almost four decades. This groundbreaking vaccine was assembled by a team at a very young (at that time) genetic engineering company, Transgène, in Strasbourg, France. The joint leaders of the rabies vaccine team reflect, 36 years later, on the trials and tribulations that went hand in hand with the construction of the vaccine.

Keywords: Alsace, glycoprotein, Pasteur, rabies, Raboral, vaccine, vaccinia virus, wildlife

1. Introduction

Rabies is a devastating disease that is inexorably fatal, unless – as Louis Pasteur demonstrated [1] – it is rapidly treated by immunization. Even so, the vaccination regimen that Pasteur recommended is punishing, and brought its own risks of hyperinflammation. In the mid-20th century rabies was widespread among wildlife (principally foxes in Europe and raccoons in North America), and even in developed countries the bite of an infected animal was a death warrant if not immediately and intensively treated.

With the advent of genetic engineering (GE) technologies in the 1980s, the renowned Institut Mérieux in Lyon, France – established in 1897 by Marcel Mérieux, one of Louis Pasteur’s assistants – brought a new task to the newly established GE company Transgène in Strasbourg: make a rabies vaccine. This chore was handed down to ourselves, two young postdoctoral scientists in the company.

Transgène, founded by Pierre Chambon and Philippe Kourilsky in 1979/1980, although being allocated half a floor in Pierre Chambon’s institute at the University of Strasbourg (**Figure 1**), was not quite ready: all available resources, at the very beginning, were allocated to setting up all the essential GE ingredients – oligonucleotide synthesis, DNA sequencing (done manually on thin polyacrylamide gels using radiophosphorus), basic sequence analysis, simple expression vectors in bacteria, yeast, and mammalian cells, even making our own restriction enzymes. Other GE companies were well ahead, and had cloned and expressed key molecules such as growth hormone, interferons, and hepatitis B surface antigen. We were both over-optimistic and underweight.



Figure 1. *Transgène and the Wistar Institute. (Left) The Laboratoire de Génétique Moléculaire des Eukaryotes (LGME) under Pierre Chambon at the Faculty of Medicine, University of Strasbourg (founded 1538), France, where Transgène was housed (6th floor) during the development of the rabies vaccine (1980s). The building was constructed in 1964 and was demolished in 2011 [https://www.archi-wiki.org/Adresse:Facult%C3%A9_de_m%C3%A9decine_(Strasbourg)]. (Right) Wistar Institute of Anatomy, Philadelphia, USA. The Wistar was founded in 1892, and the Wistar Institute Building was opened in 1894. Image courtesy Jeffrey M. Vinocur 2006. Images are reproduced under Wikipedia Creative Commons Attribution-ShareAlike License.*

2. Construction of the Vaccine

But we set to. The Scientific Director of Transgène, Jean-Pierre Lecocq, established a collaboration with researchers at the Wistar Institute (**Figure 1**) under Hilary Koprowski (Philadelphia) who had obtained, for the first time, a cDNA copy of rabies virus glycoprotein at the end of 1981 [2, 3] – the key antigenic determinant of this virus. Beginning in early 1982, we expressed the cDNA in *E. coli*, *B. subtilis*, yeast, mammalian cells (reviewed in [4]). The pressure was on, we worked 7 days a week, so did our key technical staff; we were fuelled by Martha Argerich interpreting J.S. Bach on the tape player until long after the sun set over the Vosges hills (**Box 1**). The extracts were sent to the rabies expert in Philadelphia, Tadeusz Wiktor. He systematically vaccinated lab animals (mostly mice and hamsters) with the extracts, and then challenged them with street rabies virus. None survived.

We were dismayed, and ready to give up. Two developments changed everything. First, at a chance meeting with Peter Curtis (Wistar) he advised that there was a possible problem with his cDNA sequence – there appeared to be a mutation. Second, we were impressed by the growing achievements of recombinant vaccinia virus (the basis of the smallpox vaccine), inspired by Enzo Paoletti in 1983 [5], in eliciting immunity beyond what could be obtained with bacteria, yeasts, or even mammalian cells.

The mutation in the rabies glycoprotein cDNA was indeed suspect – a Pro to Leu mutation near the beginning of the mature protein sequence at a position that (to our minds) seemed to resemble known mutations at the beginning of the

It is singularly appropriate that the recombinant rabies vaccine should have been developed in Strasbourg, the central town of the province of Alsace, France. Louis Pasteur, famed for the first rabies vaccine, was born in the Jura hills (the southern extension of the Vosges – the hills of Alsace) and was Professor of Chemistry at Strasbourg University (formerly known as the Université Louis Pasteur) from 1849 to 1854, where he married Marie (also known as Louise) Laurent (the daughter of the Rector of the University), who for many years acted as his scientific assistant. The first patient to be treated against rabies, Joseph Meister (9 years old), traveled from Alsace to Pasteur's laboratory (then in Paris) for treatment [1]. The first fox to be inoculated with the new recombinant vaccine was in Malzéville, over the Vosges hills just 100 km from Strasbourg.

Box 1.
Rabies, Pasteur, and Alsace.

oncoprotein RAS (Gly to Asp, or Gly to Val) that entirely transform the structure and activity of the protein. The first thing we did was to correct the mutation. Something we had never done before, and this took months. In the key *Nature* paper

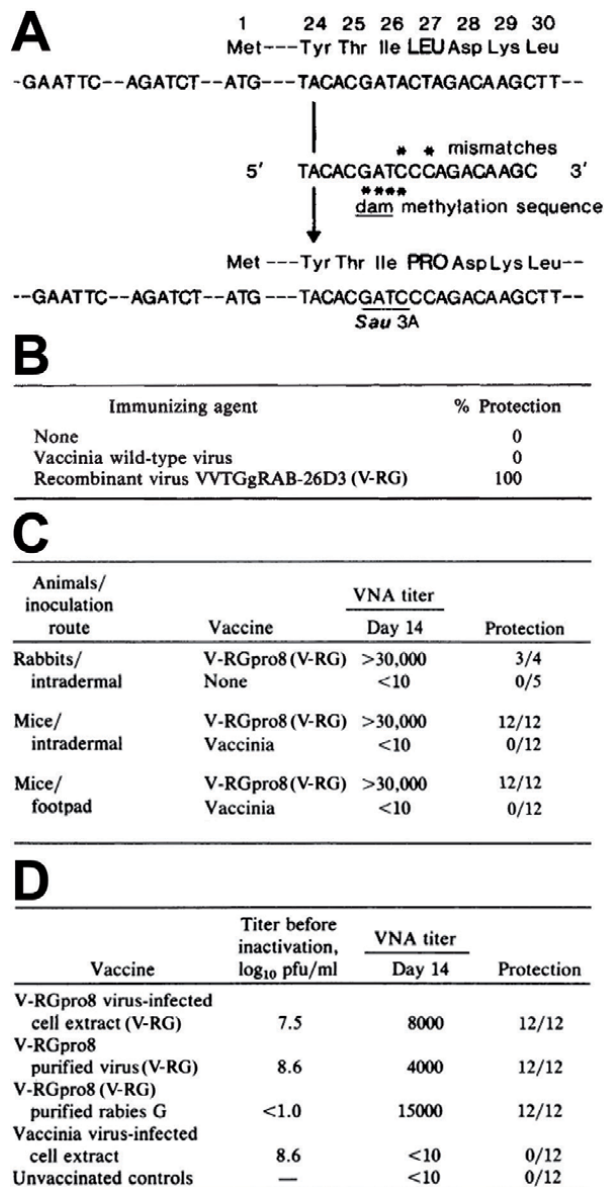


Figure 2.

Construction and Activity of the Vaccinia-Based Recombinant Rabies Virus Raboral® VR-G. The recombinant was variously known as VR-G, VVTGgRAB-26D3, and VR-Gpro8. (A) Correction of a mutation in the N-terminus of the rabies glycoprotein coding sequence. Panel adapted, with permission, from [6]. (B) Protection from rabies using the live recombinant vaccine [6]. Mice were inoculated (intradermal) with 5×10^5 PFU of VR-G or wild-type vaccinia, and challenged on day 15 by intracerebral inoculation of CDC culture-adapted street rabies virus (2400 LD₅₀ units). All vaccinated animals survived. Panel adapted, with permission, from [6]. (C). Protection of rabbits and mice: inoculation was with 2×10^8 PFU (intradermal) or 5×10^7 (footpad) of VR-G; intracerebral challenge at day 14 was with 2400 (mice) or 24 000 (rabbits) mouse LD₅₀ units of MD5951 street rabies virus. Panel adapted, with permission, from [7]. (D) Protection using inactivated VR-G. Vaccines were inactivated with β -propiolactone before intraperitoneal administration into mice. Challenge at day 14 was with 240 LD₅₀ units of MD5951. Panel adapted, with permission, from [7].

the reader will see that, because our techniques were challenged, we took advantage of an artificial site for Dam methylase (that governs mismatch repair in *E. coli*) site to tip the balance in our favor (unheard of today) (**Figure 2A**). But it worked! We wonder how many rabies glycoprotein sequences circulating in the GE world today bear that same signature alteration.

The second thing we did was to get vaccinia up and running as a vehicle. We got into collaboration with Robert Drillien and Danièle Spehner at the Institut de Virologie on the same campus, and they supplied us with a microgram of vaccinia virus DNA. The key thymidine kinase gene – required for recombinational exchange with the vaccinia genome – had already been cloned by Robert, but we lacked a promoter to drive expression. We wanted the 7.5 K gene promoter, that had been worked up by researchers in the USA, but starting with only 1 microgram of DNA (the vaccinia genome is ~190 kb in length), given the state of the technology, cloning was near to impossible. In the event we turned to calculations of insert size, vector size, and absolute concentrations based on the physicochemistry of ligation [8, 9], and brewed up an optimum ligase mix. Only four clones were obtained. Two were 7.5 K in one orientation, and two were the same promoter in the other orientation! Were we lucky? No, in retrospect we would have got nothing had we not used the mathematics of the ligation reaction to get what we needed.

From there it moved quite rapidly. Ligate the promoter to the modified rabies G coding sequence, insert the construct into the vaccinia TK gene on a plasmid – then transfect the recombinant (TK-negative) plasmid into vaccinia virus-infected cells, and select chemically using bromodeoxyuridine (that kills TK-positive viruses). And we had our first vaccinia–rabies recombinant ('26D3').

This sped off to Tad Wiktor in Philadelphia. We waited what seems like an eternity, but he reported quickly back with his preliminary results: 'this is the best rabies vaccine I have ever seen' – it protected mice against severe rabies challenge (**Figure 2B–D**) better than any other rabies vaccine. And so it turned out – first published in September 1984 ([6, 7]; reviewed in [10–12]).

What lessons can be drawn, if any? Our first thought is that we worked as a team, there was no academic infighting, no bickering about authorships that is too common today, and we all worked day and night to see the project through. Even technical staff were there late in the evening and at weekends. Second, collaboration is essential: we could not have done this project without the participation of scientists both near (Robert Drillien and Danièle Spehner) and far {Tadeusz Wiktor (**Figure 3A**)},

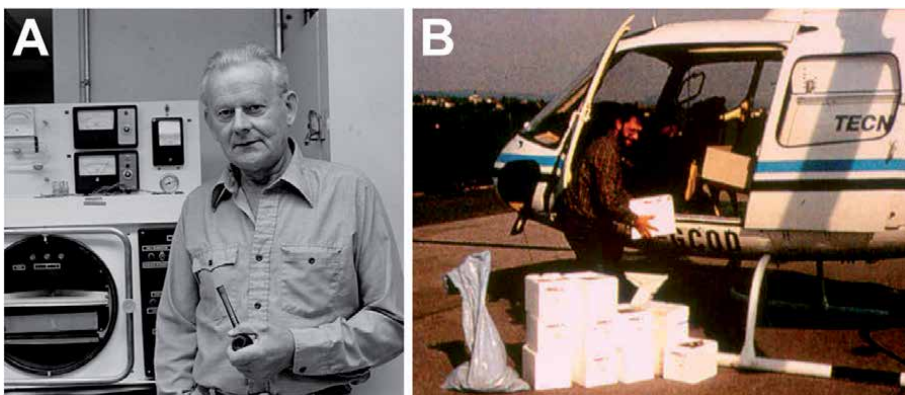


Figure 3. *Pioneering Rabies Vaccination. (A) Tadeusz J. Wiktor (1920–1985), rabies expert, Wistar Institute, who first tested the recombinant for efficacy. Photo courtesy of the Wistar Institute. (B) Loading vaccine baits into a helicopter during the first wildlife vaccination campaigns (Belgium, ca 1988; image collection M.P.K.).*

Peter Curtis, and Hilary Koprowski}. Third, we wonder whether Martha Argerich and J.S. Bach played a role. In this day of *P* values, we would need to run the entire project again with a different musical background.

3. Vaccination of Wildlife

The vaccine was originally envisaged for human use, and steps were taken in this direction in collaboration with the Institut Mérieux. However, there was reluctance



Figure 4.
Experimental vaccination of foxes, Malzéville, France, ca 1986 (image collection M.P.K.).

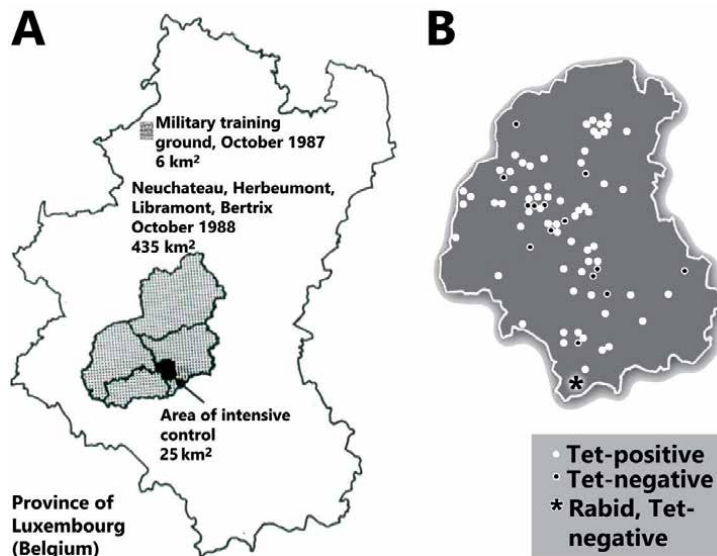


Figure 5.
First wildlife vaccination campaigns. Baits containing VRG were prepared from fish oil and protein. (A) Test areas in Belgium, 1987–1988. Vaccines were distributed at 15–50 baits per km²; uptake ranged from 27% at day 4 to 94% at day 223 (image collection M.P.K.). (B) Larger-scale field trial in a 2200 km² area of Belgium; distribution was at 15 baits per km²; the area was vaccinated three times (1990–1991). Baits contained a tetracycline biomarker, and uptake determined from the presence of tetracycline (Tet; UV fluorescence in jaw) was 81% after the third phase. The single rabid fox detected after the campaign, at the periphery of the baited area, was Tet-negative. Image adapted, with permission, from [17].

to introduce a new vaccinia-based vaccine for human use because smallpox, the original target of vaccinia, had recently been declared eradicated by the World Health Organization (WHO) [13]. A committee of international experts including WHO representatives, who met in Bethesda, MD, in November 1984, did not envisage early human use [14]. However, because rabies is transmitted to humans principally from domestic dogs – that themselves acquire the infection from foxes (in Europe), and from raccoons and coyotes (in North America) – the next step was to try the new vaccine out for efficacy in animals. With support from Philippe Desmettre at the Institut Mérieux, Transgène was in touch with Pierre-Paul Pastoret in Belgium and colleagues at the French Ministry of Agriculture Rabies Research Station in Malzéville close to Nancy, and this was soon followed by the

| Europe (including Russia) | |
|----------------------------------|--|
| Austria | Eliminated (2006) |
| Belgium | Eliminated (1999) |
| Bulgaria | Reduction in seeded areas |
| Czech Republic | Eliminated (2002) |
| Estonia | Eliminated (2009) |
| France | Eliminated (1998) |
| Germany | Eliminated (2006) |
| Hungary | Reduction in seeded areas |
| Italy | Eliminated (1986/1995); then reduction |
| Latvia | Reduction in seeded areas |
| Lithuania | Reduction in seeded areas |
| Luxembourg | Eliminated (1999) |
| Poland | Reduction in seeded areas |
| Kaliningrad (Russia) | Reduction in seeded areas |
| Russia | Experimental |
| Slovakia | Eliminated (2006) |
| Slovenia | Reduction |
| Switzerland | Eliminated (1996) |
| Ukraine | Reduction |
| North America | |
| Canada | Reduction in seeded areas |
| United States | Reduction in seeded areas |
| Middle and Far East | |
| Israel | Reduction in seeded areas |
| Tunisia | Experimental |
| India | Experimental |
| China | Experimental |

**In many cases Raboral® was used in conjunction with conventional attenuated viruses, although Raboral® is the only vaccine licensed for use in the USA (<http://www.raboral.com/about-rabies/raboral-v-rg>). Data: key reviews are by Freuling et al. [18] and Maki et al. [19].*

Table 1.
Wildlife Vaccination Campaigns Using Raboral®.*

demonstration that oral administration of the vaccine (10^8 pfu) to foxes (**Figure 4**) gave complete protection against lethal challenge, and almost complete protection following administration in home-made bait [15], quickly followed by oral protection of raccoons in the USA by colleagues at the Wistar Institute [16].

This was expanded to small-trials followed by large-scale campaigns to eradicate sylvatic rabies in Europe and North America by dropping baits (e.g., chicken heads or artificial baits) seeded with live recombinant virus from helicopters (**Figure 3B**) according to a carefully planned routine (taking in mind the number of wildlife species per square kilometer, and the transmission factor R – what percentage of animals do we need to vaccinate to block propagation? – of current interest given the COVID pandemic). It worked. The first trials (**Figure 5**) demonstrated wide uptake by foxes and downturn of rabies cases. Using this vaccine, rabies has now been widely eliminated in many European countries; substantial reductions in rates of rabies in wildlife have been achieved in several areas of Eastern USA and Canada (**Table 1**) where active vaccination campaigns are ongoing (<http://www.raboral.com/about-rabies/raboral-v-rg>). Over 250 million doses of Raboral® have been distributed worldwide [19]. Although highly successful in Europe [18], campaigns in the USA and Canada are constrained because of rabies re-emergence through long-distance movements of carrier species such as arctic foxes [19].

4. Vaccinia-based vaccines for human use

The vaccinia–rabies recombinant has never been approved for human use, even though vaccinia virus has been used widely across the world in our populations to eradicate smallpox, and the vaccinia–rabies recombinant is very much attenuated compared to standard strains of vaccinia. Notwithstanding, intense efforts have been made to develop vaccinia as an anticancer agent for direct prophylactic or curative use in human [20–23], but for recombinants expressing viral antigens few clinical trials have been carried out (with some exceptions; e.g., [24]). Efforts in the 1990s were invested into the development of viral vectors based on vaccinia derivatives such as modified virus Ankara (MVA) [25], or fowlpox or canarypox [26]. More recently, high levels of protective antibodies have been obtained against SARS coronavirus using vaccinia recombinants in experimental animals (e.g., [27–29]), and, given the threat of COVID-19, MVA-based recombinants are being actively explored in California [30] and Germany (<https://www.vfa.de/de/englische-inhalte/vaccines-to-protect-against-covid-19>) as potential vaccines against SARS-COV-2, the etiologic agent of COVID-19.

One potential way to circumvent safety concerns may be to employ inactivated recombinant vaccinia virions that display viral antigens at their surface: very substantial levels of protection were observed with chemically inactivated recombinant vaccinia–rabies virus [7], and this might afford an entry route for new human vaccines based on vaccinia – perhaps even at some stage including Raboral® or further attenuated derivatives, given that rabies in human remains a major concern in several regions such as India [31].

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Disclaimer

The views expressed herein are solely those of the authors and do not reflect the views of the WHO, Transgène SA, the INSERM, or of any other institution with which the authors are or have been associated.

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The Diagnosis, Clinical Course, Treatment, and Prevention of the Rabies Virus

Jaida Hopkins, Samantha Sweck and Sean Richards

Abstract

Rabies, despite available vaccines, causes approximately 55,000 deaths every year. Diagnosing relies on noting physical behaviors such as hydrophobia, vomiting, fever, behavior changes, paralysis, and consciousness, as well as, using several methodologies to molecularly detect the presence of the virus. RABV often enters through a bite wound given that it is transmissible through saliva. Infection spreads from muscle fibers into the peripheral nervous system traveling to the central nervous system. Infection of the central nervous system can lead to encephalitis (furious rabies) or acute flaccid paralysis (paralytic rabies). Treatment relies heavily on the time of exposure. If the patient is diagnosed prior to being symptomatic, post-exposure prophylaxis (PEP) can be administered. However, once the patient has begun displaying symptoms, therapy success rates sharply decline. Prevention includes vaccinating during both pre- and post-exposures, as well as utilizing Stepwise Approach towards Rabies Elimination (SARE) to aid impoverished countries in declining their rabies mortality rates.

Keywords: rabies virus, RABV, diagnosis, treatment, prevention

1. Introduction

Rabies, an RNA virus from the genus *Lyssavirus*, also known as RABV, is a lethal pathogen to several species [1]. The evolutionary history of the virus suggests that its most recent ancestor likely diverged into two descendants, one infecting bats, the other infecting dogs. Once domesticated dogs became infected in the Old World, humans became the next target. Evolutionary biology tells us that rabies likely did not exist in the New World prior to the settlement of Europeans but was common throughout Europe, Asia, and Africa well before the discovery of the Americas [2].

RABV is transmitted through the saliva of an infected individual into the bloodstream of a healthy individual, typically via a bite, but possible through other wounds or ocular route. Upon infection, there are two ways the virus may manifest: furious and paralytic. Furious rabies often presents itself with bouts of anxiety, irritability, phobias, and many other symptoms that will later be discussed. Paralytic rabies has some common symptoms with furious rabies, however, paralysis is the most notable symptom just prior to death [3].

According to the CDC in 2015, nearly 60,000 human deaths occurred on average each year. Statistically, this can be interpreted as 1 human death every nine

minutes [4]. Despite its large impact globally, the virus is relatively diminutive. The rabies virus has evolutionarily reduced its single-stranded RNA genome to only five genes. These genes encode five proteins, three of which make up the ribonucleoprotein (RNP) complex; the other two form the virus's envelope [5].

While the rabies virus has been heavily researched, lives continue to be lost. There is a great understanding of the epidemiology of the virus, however little is understood about the pathogenesis. Herein, the findings regarding the diagnosis, clinical course, treatment, and prevention of the rabies virus are summarized as well as data gaps in research and understanding of this pathogen.

2. Diagnostics

Once the patient has become infected, the incubation period can be as short as 5 days or as long as 2 years. However, it is common for symptoms to occur 20–90 days after initial exposure [6]. Nevertheless, there are several techniques for diagnosing a patient during and after the incubation period.

2.1 Physical symptoms

As mentioned previously, the two ways the rabies virus may present itself is paralytic and furious symptoms. A patient with paralytic rabies will show progressive paralysis until death. If infection occurred due to a bite, the paralysis typically starts around the wounded area, spreading outwards. It is also common for patients to have a fever, vomiting, weakness in muscles, and myalgia prior to the paralysis [7].

Furious rabies often presents itself with more obvious symptoms. The infected individual commonly displays mood swings, unregulated consciousness, phobias, especially hydrophobia, as well as spasms of the respiratory system [1, 8]. Other symptoms may include a cough, psychosis, delirium, and difficulties swallowing [9].

2.2 Neuroimaging

For both furious and paralytic rabies, magnetic resonance imaging (MRI) will produce the same key diagnostic images. When symptoms first arise in the prodromal phase, progression in hypersignal T2 changes can be seen around the brachial plexus and the spinal nerve roots associated with the extremity of infection origin. The main MRI feature is increased T2 signal (seen on T2 and FLAIR sequences) in the affected parts of the brain and spinal cord, with a predilection for grey matter structures including basal ganglia, thalami, hypothalami, limbic system, and brainstem. The abnormal hypersignal T2 changes will continue to progress as the patient enters a coma. Once in the comatose phase, the contrast will enhance around the spinal cord, nerve roots located at the sine and cranial region, deep grey matter, brain stem, limbic structures, and thalamus (**Figure 1**) [8].

Another study noted that lesions could be seen throughout different areas of the neuroaxis. They, too, found that paralytic and furious rabies present the same MRI indications, however, they are more noticeable in the paralytic form. The blood–brain barrier often shows no sign of damage until the patient reaches the comatose state. Imaging of the blood–brain barrier has greatly improved as new techniques such as diffusion-weighted and diffusion tensor imaging can capture objective and subjective data [11].

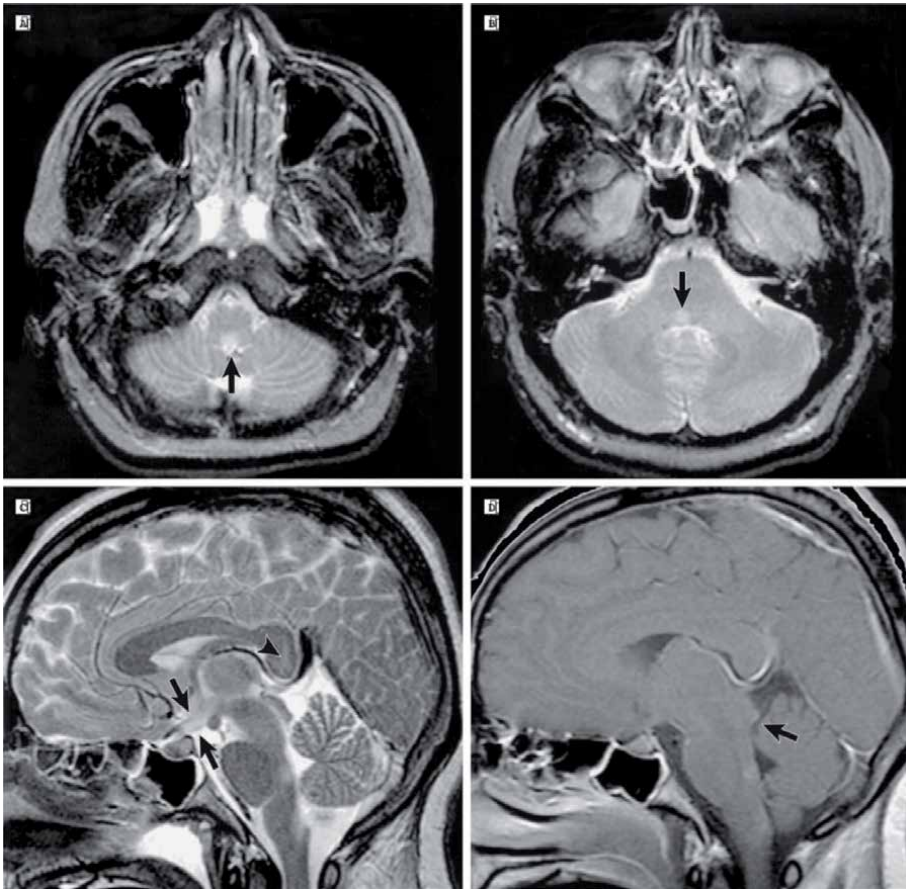


Figure 1. Magnetic resonance images with arrows pointing to high focal areas (A. dorsal medulla, B. pons, C. hypothalamus, and D. splenium of corpus callosum) of an infected patient with furious rabies [10].

2.3 Testing techniques

There are several techniques used to diagnose a patient with a rabies infection; including reverse transcription polymerase chain reaction (rtPCR) analysis, fluorescent antibody test (FAT), tissue culturing, and viral antibody neutralization [12, 13]. The FAT assay has long been a microbiological standard for diagnosing rabies (and other viral infections). Fluorescent antibody virus neutralisation (FAVN) test is also used to diagnose rabies [13]. The CDC recommends a direct form of FAT to detect the rabies virus in animals ante-mortem, however, the animal is usually euthanized after detection and brain tissue samples taken to solidify the diagnosis post-mortem. However, diagnosis in humans requires several different types of methods such as direct rapid immunohistochemistry testing, the use of electron microscopy, and reverse transcriptase-polymerase chain reactions on biological samples (**Figure 2**) [15].

Another test utilizing immunohistochemistry, known as the direct rapid immunohistochemistry test (dRIT) is a specific form of histology because it employs antibodies unique to RABV. While this testing method can give a reliable result in less than an hour, retrieving brain samples is very invasive [16].

Samples can also be viewed using electron microscopy. When Negri bodies are located in samples, electron microscopy can give a clear depiction of the bullet-shaped

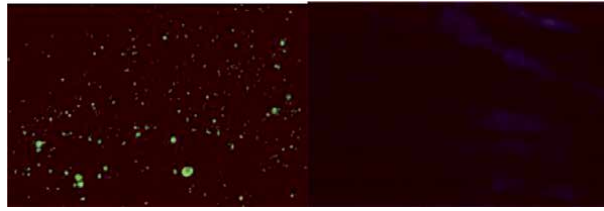


Figure 2.

These images show the comparison of a positive direct FAT result (left) and a negative direct FAT result (right) [14].

rabies virus being produced. A colloid can be used to compare the virus size to further interpret the image, however shape and size alone are not enough to identify with confidence [17].

Saliva and skin samples can be used for identifying the presence of RABV. rtPCR can be used to confirm or oppose the results of FAT test results. Because RABV is a single-stranded RNA virus, rtPCR can help transform RNA into DNA through amplification for analysis of a complement to a rabies-specific primer. This is often achieved by inoculating suckling mice and retrieving brain or kidney samples after death [15, 18].

2.4 Patients with psychiatric disorders

Given that the rabies virus significantly impacts the central nervous system, it is not uncommon for hallucinations, manic episodes, anxiety, and bouts of paranoia to be present in an infected patient [19, 20]. However, these are also common symptoms of psychiatric disorders such as schizophrenia. While it is rare, it is possible that correct RABV diagnosis may be complicated by a previous diagnosis of psychiatric disorders. Patients suffering from hypochondriasis could elicit pseudorabies [20]. In several case studies with reports of hypochondriasis, patients did not respond to therapies and often attempt suicide multiple times [20, 21]. While these situations are rare, they should be noted when diagnosing patients with certainty.

3. Clinical course

3.1 Pathophysiology

The most common entry point for RABV is through the bite of an infected individual as rabies resides in saliva [22]. However, transmission from organ transplants and aerosol droplets have also been recorded [23–25]. Upon entry, an incubation period often takes place in the myocytes, and rarely fibrocytes, where the virus attaches to the G-protein of the cells, enters through pinocytosis or fusion, and replicates in the cytoplasm of the cells [5, 24]. Virions will replicate with little to no immune response until the virus interacts with and infects a nerve cell. The rabies virus gains access to the nervous system by binding to the nicotinic acetylcholine receptors on the postsynaptic membrane at the neuromuscular junction [26]. From the point of nerve cell infection, the virus will travel via axon transport through the nervous system, eventually reaching the brainstem to give rise to either encephalitis or acute flaccid paralysis [7, 27]. The incubation periods are highly variable depending on the dosage of the virus. However, in humans, the incubation period is often >1–3 months. Canine incubation periods are most commonly less than 60 days [26, 28].

Once infection is recognized by the immune system, cytokine, IgM, and IgG antibody production increases [5]. Specific cytokines, Interleukin-1 β (IL-1 β) and TNF α , are thought to be the reason inflammation of the central nervous system occurs post-exposure [29]. The presence of these cytokines initiate a cascade reaction, upregulating proteins necessary for the inflammatory response such as the major histocompatibility complex and adhesion molecules. These proteins then interact with leukocytes to allow the blood brain barrier to become more permeable, thus causing an immune response leading to encephalitis [30]. As for the natural defense against rabies, RABV signals a series of molecular cascades that initiates type I interferon responses that have antiviral properties, decreasing the pathogenicity of rabies [31]. However, to artificially aid the natural response, there is heavy research on the potential to activate dendritic cells which subsequently enhance the activity of interleukin proteins and high mobility group box 1 (HMBG1) to enhance immunogenicity [32, 33].

4. Treatment

Although the rabies disease has been documented for thousands of years, it is still largely considered incurable after the onset of symptoms [34]. This is due to the small window of time during which aggressive treatment is practical and effective. With that knowledge, most often treatment resolves to be mostly palliative with aggressive treatment proving to be essentially ineffective after RABV is established in the patient.

4.1 Aggressive approach

If a patient presents for treatment early in the process of the clinical disease, the choice may be made to apply an aggressive approach. At this point, the patient must be immediately admitted to an intensive care hospital and post-exposure prophylaxis (PEP) should be administered [26]. PEP consists of immediate washing of the wound with soap and water, a post-exposure vaccination, and injection of an anti-rabies immunoglobulin (RIG) directly into the wound [35].

Active immunization has evolved greatly since the first rabies vaccine was developed and administered in 1885 [36, 37]. Louis Pasteur is credited with this first vaccine that consisted of injecting the patient with homogenates of RABV-infected rabbit spinal cord multiple times over a period of days. The initial injection was believed to be fully inactivated after an extended desiccation period, and each subsequent inoculation was increasingly more virulent as the desiccation period was decreased. While this was found to be somewhat effective, two major issues presented themselves. First, the inactivation of the RABV was inconsistent which led to some patients becoming infected after receiving the vaccine. Second, there was an inequity in the supply of the RABV-infected rabbits and the demand of the human population. These were rectified with the introduction of RABV-infected sheep and goat brain vaccines [36, 37]. These new vaccines were inactivated via chemical agents such as phenol; this proved to be much more consistent. However, soon it was understood that vaccines produced from mature brain material contained an excess of myelin which caused sensitization and ultimately killed the patients [38]. From this discovery emerged the current methodology by which rabies vaccines are created. Chick embryos served the same role as the previous tissues, but they have markedly less myelin due to the young age [39]. The same can be said of the lines of human diploid cells infected with fixed RABV for vaccines [36, 37]. In the United States, there are two CDC-approved vaccines: the human diploid cell culture vaccine (HDCV) and the purified chick embryo cell culture vaccine (PCECV) [15].

The post-exposure vaccine is primarily an intramuscular vaccine that ought to be given on day 0, 3, 7, 14, and 30 [36]. An intradermal vaccine has recently been developed in an attempt to decrease the amount of vaccine needed per injection [40]. While the decreased cost of the vaccine is an attractive option, intradermal injections are generally considered more difficult which could decrease the effectiveness of the vaccine due to improper injections. The World Health Organization (WHO) strongly recommends purified cell culture and embryonated egg-based vaccines [41].

Although the vaccines have been proven to stimulate an appropriate immune response to RABV, this immune response is often too delayed to prevent the virus from entering the nerves [42]. With this knowledge, passive immunization is recommended for all patients that have no previous history with the disease or a pre-exposure vaccination. At this time, two types of rabies immunoglobulin are available – human rabies immunoglobulin (HRIG) and equine rabies immunoglobulin (ERIG). These have been used since the 1970's to temporarily increase the concentration of rabies virus neutralizing antibodies (RVNA) specifically at the site of exposure [43]. If the patient has multiple bites or wounds, the RIG needs to be applied at each site to be effective [44]. HRIG is to be administered at a dosage of 20 IU/kg while the recommended dosage for ERIG is 40 IU/kg [42, 44]. Due to higher odds of sensitization as well as quicker elimination of the RVNA, HRIG is generally the most preferred option for passive immunization. However, it is approximately five times more expensive than ERIG. This results in a major deficiency in many of the countries most in need of rabies treatment [44].

Because the available RIGs are generally inaccessible to developing countries, WHO encouraged researchers to pursue synthetization of a human monoclonal antibodies (mAbs) cocktail that can be used to treat rabies [45]. At this time, there are a number of rabies mAbs products in clinical trials, but none have been approved by the US Food and Drug Administration [46]. In 2018, WHO officially adjusted their recommendations for treatment of rabies to include mAbs products in place of RIG if available [46].

A protocol known as the Milwaukee Protocol was presented as a potential cure in the late 20th century, but it has since been proven to be inconsistent and generally ineffective in reverting or curing the patient of the disease [47–49]. This protocol consisted of an induced coma and one or more antivirals. The coma was soon determined to be ineffective. It is now recommended that sedation should be limited to prevent the use of ventilatory support if possible [48, 49].

Antivirals could serve an important role in the treatment of the rabies virus as they act as inhibitors of viral replication. An effective antiviral could slow the progression of the rabies virus enough for the patient's innate immune response to develop and react appropriately. However, at this time, there are few antivirals supported for the treatment of RABV. Ribavirin is a purine analogue that acts as an RNA mutagen and has shown to be clinically effective for multiple viruses including Hepatitis C and Lassa fever virus [50, 51]. Despite its inclusion in the sporadically effective Milwaukee Protocol, it has repeatedly proven to be ineffective against the rabies virus. Interferon- α (IFN- α) is a signaling protein used to trigger an immune response which has been shown to limit RABV spreading in mice trials [50, 51]. However, additional trials in which primates were administered intramuscular and intrathecal IFN- α determined the effects of immediate inoculation to be incomplete while the effects of delayed inoculation were nonexistent [52, 53]. Six human patients have been treated with IFN- α on two different dosage schedules and despite evidence of increased IFN in serum and CSF, there was no evidence of a beneficial effect on the disease itself [54]. Another therapy previously included in the Milwaukee Protocol is ketamine [50, 51]. At low concentrations, approximately

1 μM , ketamine works as a non-competitive antagonist of the N-methyl-D-aspartate (NMDA) receptor which causes a state of dissociative anesthesia. A study from 1991 showed that a high concentration of ketamine could induce inhibitory effects on the RABV genome transcription [55]. Since that time, multiple other trials using neuron cultures and infected mice have produced evidence that ketamine is generally ineffective against the disease [56]. With that knowledge, it is believed that ketamine should not be used for treatment of the rabies virus until further studies produce more promising results. Amantadine is the third and final antiviral that was considered in the Milwaukee Protocol [47, 51]. It is a synthetic inhibitor of viral replication by impeding the release of viral genetic material into the host cell. Although amantadine demonstrated some interference in cellular trials, it failed in animal trials [57]. Minocycline, a broad spectrum antimicrobial, was considered for RABV treatment as it has proven benefits for multiple other viruses [58]. However, when applied to rabies-infected animals, Minocycline caused a number of harmful effects causing an increase in mortality [59].

More recently, researchers have addressed the use of favipiravir in treatment of rabies [50]. Available for influenza treatment in some countries, favipiravir has shown some activity against the rabies virus in mice trials [60]. Continued studies are needed to assess the future of this and other antivirals. It ought to be noted that despite variations in the effectiveness of these antivirals, all have shown that an early start of treatment greatly improves the efficacy of these therapies.

4.2 Palliative care

As previously mentioned, there is a small window of effectiveness for an aggressive treatment of RABV; after that window has passed, the focus of treatment is purely one of comfort for the patient. Many patients develop phobias that will likely require seclusion in a calm, quiet room. Although there is little to no evidence of human-to-human transmission, visitors and medical professionals need to be cautious of potential contamination via the patient's secretion [61]. Dehydration is a major concern as paralytic rabies often inhibits the patient's ability to swallow and furious rabies can cause intense hydrophobia. Treatment for the dehydration is typically a secured intravenous line. If additional nutrients are needed, they can be administered through the same line.

Rabies typically causes a generalized inflammation that induces a fever, but it can also trigger a neurogenic (central) fever as well [62]. Many antipyretics, such as acetaminophen and ibuprofen, have been successfully used to treat the generalized fever. However, those are generally ineffective towards the central fever. There is some evidence to support the use of baclofen, bromocriptine, chlorpromazine, and morphine in the treatment of a central fever [63]. However, these have not been studied specifically for a rabies-induced central fever and so practitioners should be mindful of potential side effects. Additionally, these drugs are rarely available in the developing countries where RABV is most prevalent [61]. In this case, external, physical means of cooling the patient can be used as needed.

The majority of patients infected with furious RABV develop intense agitation and fear. A variety of sedatives and tranquilizers are used to calm these symptoms. Because benzodiazepines are included on the WHO's list of essential medicines, they are commonly used to treat rabies-induced agitation as well as many other forms [61]. They can be administered intramuscularly, intravenously, or intrarectally as needed. However, as previously mentioned, it is important to administer any sedative slowly to ensure the patient retains consciousness and does not lose respiratory function [64].

Lastly, clinicians will likely need to address the patient's pain level. This can be accomplished using opioids such as morphine or other highly effective analgesics. These can be delivered intravenously, intramuscularly, intrarectally, or even transdermally as needed [61]. Although many of these methods of treatment are expensive and generally unlikely to cure a patient once rabies symptoms are present, palliative care is a responsibility of caretakers and clinicians.

5. Prevention

Due to the general ineffectiveness of post-exposure treatment, the rabies virus has a remarkably high mortality rate despite the availability of vaccines that have shown a near perfect success rate when administered prior to infection. This indicates that the main issue with prevention is the lack of accessibility in the impoverished countries of Asia and Africa. In 2015, the World Health Organization (WHO) and the World Organization for Animal Health (OIE) with the help of the Food and Agriculture Organization of the United Nations (FAO) set a goal to rid the world of dog-mediated rabies by 2030 (Zero by 30) [65]. After assessing cost and general accessibility, it was decided that the best way to eliminate dog-mediated rabies is to vaccinate dogs rather than humans. Vaccinating at least 70% of dogs should effectively break the cycle of rabies transmission.

To reach this goal, WHO, OIE, FAO and many smaller agencies collaborated to create the Stepwise Approach towards Rabies Elimination (SARE) [66, 67]. A similar stepwise approach proved successful in the elimination of fox RABV from Europe [68]. SARE consists of five stages for each country to work through. Stage 0 is simply the lack of information and data on RABV cases in a country where rabies is believed to be present. Stage 1 is an assessment phase in which data are gathered to determine the extent to which RABV pervades the country of interest. During this phase, the government assesses the current guidelines or structures in place as well as collects and analyzes all available data on previous or existing RABV cases. The beginning of an action plan is usually concocted in Stage 1. Evolution of this plan happens in Stage 2; it is important to develop an understanding of the available funding at this point as that has been the biggest limitation for developing countries in the past. Stage 3 is the implementation of the country's rabies control strategy. During this phase, the plan will likely need to be adapted to address any challenges that arise; these may include the exposure of wildlife reservoirs of RABV such as the fox rabies previously found in Europe. When reported human cases have decreased to zero, the country will shift into Stage 4 – elimination of dog RABV. This requires the maintenance of the reduced dog-to-human rabies transmission as well as continued implementation of the action plan to continue to reduce dog rabies cases. Lastly, in Stage 5, the country must develop a post-elimination strategy to maintain the freedom from human and dog rabies.

While the SARE tool has been developed to be adaptable enough to succeed worldwide, there are likely to be some setbacks in the different landscapes. Specifically, areas of poverty will be constrained by the financial resources they can acquire. Many parts of Asia have political instability that will greatly challenge the need for nation-wide commitment to this goal. Similarly, Africa's linguistic and cultural complexity will oppose the need for excellent communication and tracking [66]. Ultimately, it will take a dedicated and educated global population to eliminate rabies as a whole; until then, vaccinating animals and at-risk populations is the most efficient means of prevention.

6. Conclusion

This chapter served to outline the diagnosis, clinical course, treatment, and prevention of the RNA virus RABV. A swift rabies's diagnosis is imperative to ensure the patient's greatest chance of survival. Clinicians may utilize many techniques such as MRI, rtPCR, FAT, FAVN, dRIT, and electron microscopy to diagnose patients before physical symptoms arise. The same methods can be used to confirm a diagnosis after the patient presents with symptoms if needed. Rabies can present in patients in the furious or paralytic form. Although these cause very different physical symptoms, the pathophysiology is very similar. Generally initiated by a bite or other wound, the virus will incubate in the myocytes nearest the entry point and replicate undetected for an average of 1–3 months. Eventually, the virus will infect a nerve cell and travel through axon transport to the CNS at which point it will cause encephalitis or paralysis. Once the virus has infiltrated the CNS, it is essentially incurable. However, if detected early, patients can receive PEP - a combination of active and passive immunization most frequently in the form of a cell culture vaccine and a dose of RIG. At this time, there are no antivirals considered to be effective for treating RABV. If the virus becomes established in the patient, the treatment plan is adjusted to ensure the most comfort for the patient and their loved ones. This most often consists of a variety of sedatives, pain management, antipyretics, and fluids. Due to the great lethality of RABV in humans, multiple global organizations have banded together to attempt to eradicate the modern world of the rabies virus. The Zero by 30 movement strives to implement a stepwise method to eliminate dog-mediated rabies cases worldwide by 2030. This is believed to be possible if 70% or more of the dog population is vaccinated against rabies. In combination with the vaccination goal, Zero by 30 also encourages countries to implement educational standards on rabies, bite prevention, and responsible pet ownership.

At this time, the community of RABV researchers need to be working to improve current treatment options in order to decrease the number of RABV-related deaths. This might be done by developing a mAb alternative to the too-expensive RIG options or finding an effective antiviral either currently on the market or newly developed. The release of additional rabies vaccines for humans would also help to lower the price and improve the accessibility in a way that would benefit the highly affected countries.

Conflict of interest

The authors declare no conflict of interest.

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Section 2

Epidemiology of the Rabies
Virus - Practical Experience

Occurrence of Dog Bites and Rabies within Humans in Srinagar, Kashmir

Namera Thahaby, Afzal Hoque Akand, Abdul Hai Bhat, Shabeer Ahmed Hamdani and Mudasir Ali Rather

Abstract

Open garbage dumps and dog bites are major public health problems in the Kashmir region. In Srinagar city, there are more than 91,000 dogs, or about one dog for every 12 citizens. The mounting street dog population is leading to increasing fright in the city due to the fear of rabies. Although treatable, rabies can be deadly without access to vaccines and treatment. Unfortunately, Kashmir is experiencing a shortage of the anti-rabies vaccine. More than 80,000 dog bites and 20 deaths due to rabies were reported in the Kashmir valley in the period 2008–2012. We conducted our study of dog bites in Srinagar, which has a large stray dog population, perhaps due to mismanagement of garbage. We obtained our data from Shri Maharaja Hari Singh (SMHS) Hospital. We found that most dog bite victims were males aged 30–40 years presenting with category 3 bites to the legs. The majority of victims were bitten in the evening and reported to the hospital the same day. Most victims received immunoglobulin treatment. We suggest that proper garbage control can help to curb the stray dog population in the area and thus reduce the incidence of rabies.

Keywords: rabies, dog bites, Srinagar, Kashmir

1. Introduction

Open garbage dumps and dog bites are major public health problems in the Kashmir region. In Srinagar city, there are more than 91,000 dogs [1], or about one dog for every 12 citizens. More than 80,000 dog bites and 20 deaths due to rabies were reported in the Kashmir valley in the period 2008–2012 [2]. The area's Anti-Rabies Clinic (ARC), Shri Maharaja Hari Singh (SMHS) Hospital, depleted its stock of vaccine fourfold in a ten-month period [3]. The overwhelming majority of dog bite cases (9514) occurred in Srinagar [4]. Of these cases, 80% occurred in urban spaces and 20% occurred in rural areas.

2. Research methodology

The present study was conducted in the Srinagar district in Kashmir, which has a large stray dog population, perhaps due to mismanagement of garbage. We obtained data on dog bites and victims from SMHS.

| Wards | North zone (9 wards) | South zone (9 wards) | East zone (8 wards) | West zone (8 wards) |
|-------|------------------------------|--------------------------------------|---|------------------------------|
| 1 | Tarbal, JamiaMasjid, Kawdara | Malroo, Lawaypora | Harwan, Nishat | SafaKadal, IddGah |
| 2 | Zadibal, Madeen Sahib | BeminaKhumaniChowk | Dalgate, Lalchowk | Palpora |
| 3 | Lal Bazaar, Umer Colony | AllochiBagh, MagermalBagh | Dud Dal, Locut dal | Nawab Bazaar, Ali Kadal |
| 4 | Hazratbal, Tailbal | Rajbagh, JawaharNagar, WazirBagh | JogiLankar, Zindashah Sahib | Syed Ali Akbar, Islam Yarbal |
| 5 | New Theed, Alusteng | Mahjoor Nagar, Natipora, Chanapora | Ganpatyar, Barbarshah | Shaheed Gung, Karan Nagar |
| 6 | Zakoora | BaghatBarzallua, Rawalpora | BanaMohalla, Chinkral Mohalla, S.R.Gung | Qamarwari, Chattabal |
| 7 | Ahmad Nagar | Humhama | Akil Mir Khanyar, Khaja Bazar | Bemina East, BeminaWest |
| 8 | Soura, Buchpora | PanthaChowk, Khanmoh | Hasna Abad, Makhdoom Sahib | Parimpورا, Zainakote |
| 9 | Nowshahra, Zoonimar | S.D.colony Batamaloo Nundrash colony | | |

Table 1.
Srinagar Municipal Corporation zones and wards.

We categorized the incidents into zones as per the Srinagar Municipal Corporation, as shown in **Table 1**. This was done to determine which zone recorded the greatest number of cases.

3. Results

Table 2 shows the distribution of dog bite victims according to gender and zones (**Figure 1**). Overwhelmingly, the majority of victims in each zone are male. In the east zone, 82.23% of victims were males and 17.76% of victims were females. In the west zone, 71.90% of victims were males and 28.09% of victims were females. In the north zone, 72.94% of victims were males and 27.05% of victims were females. In the south zone, 73.06% of victims were males and 26.93% of victims were females. Statistically, there is a nonsignificant difference concerning gender for

| Gender | Zones | | | |
|--------|-------------|-------------|-------------|-------------|
| | East | West | North | South |
| Male | 162 (82.23) | 238 (71.90) | 213 (72.94) | 236 (73.06) |
| Female | 35 (17.76) | 93 (28.09) | 79 (27.05) | 87 (26.93) |
| Pooled | 197 | 331 | 292 | 323 |

$$\chi^2 = 8.023, p = 0.045$$

Figures in parentheses indicate percentage.

**indicates difference at 5% level of significance.*

Table 2.
Distribution of victims according to gender and zone.

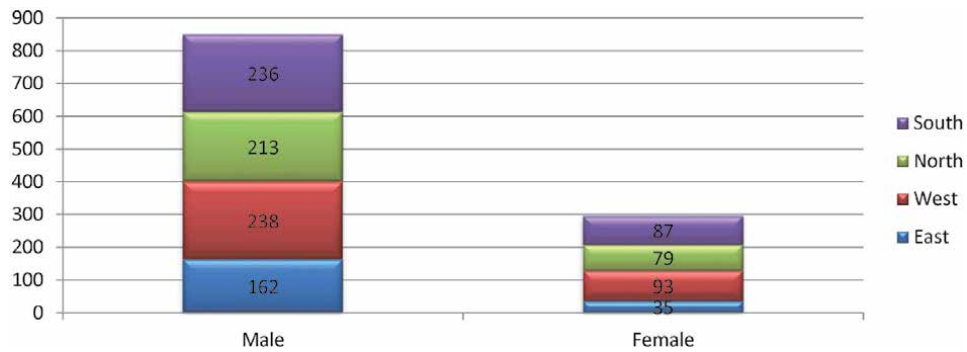


Figure 1.
 Distribution of dog bite victims according to gender and zone.

different zones. **Table 3** shows the distribution of victim age according to zones. In the east zone, 24.87% of victims were aged 30–40 years, 19.28% of victims were aged 20–30 years, 14.72% were aged 10–20 years, 12.89% were aged 40–50 years, 12.69% were aged 1–10 years, 9.64% were aged 50–60 years, and the remaining 6.59% of victims were aged 60 years and older.

The same pattern was observed for the west, north, and south zones. Statistically, there is a nonsignificant difference concerning age for different zones. **Table 4** shows the date of reporting according to different zones. In the east zone, 67.51% of victims reported on the same day, 25.88% reported after a day or more, and the remaining 6.59% reported after a week. The same pattern was observed among the other zones. Statistically, there was a nonsignificant difference concerning the date of reporting for different zones. **Table 5** depicts the distribution of victims according to the time of exposure for different zones. In the east zone, 53.80% of victims were bitten by dogs in the evening, 29.44% were bitten in the morning, 8.62% were bitten in the daytime, and 8.12% were bitten in the nighttime. The same pattern was again seen in the other zones. Statistically, there was a nonsignificant difference concerning the time of exposure for different zones. **Table 6** depicts victims according to the time of reporting for different zones. In the

| Age | Zones | | | |
|--------------------|-------------|-------------|------------|-------------|
| | East | West | North | South |
| 1–10 years | 25 (12.69) | 33 (9.96) | 33 (11.30) | 39 (12.07) |
| 10–20 years | 29 (14.72) | 43 (12.29) | 43 (14.72) | 58 (17.95) |
| 20–30 years | 38 (19.28) | 63 (19.03) | 58 (19.86) | 64 (19.81) |
| 30–40 years | 49 (24.87) | 102 (30.81) | 84 (28.76) | 70 (21.69) |
| 40–50 years | 24 (12.18) | 44 (13.29) | 32 (10.95) | 45 (13.93) |
| 50–60 years | 19 (9.64) | 31 (9.36) | 22 (7.53) | 22 (6.81) |
| 60 years and older | 13 (6.59) | 15 (4.53) | 20 (6.84) | 25 (7.73) |
| Pooled | 197 | 331 | 292 | 323 |
| Mean SD | 33.91 17.49 | 47.28 28.22 | 41.7 22.6 | 46.14 18.75 |

$\chi^2 = 15.726, p = 0.611$

Figures in parentheses indicate percentage.
 *indicates difference at 5% level of significance.

Table 3.
 Distribution of dog bite victims according to age and zone.

| Date of reporting | Zones | | | |
|------------------------------|-------------|-------------|-------------|-------------|
| | East | West | North | South |
| Same day | 133 (67.51) | 255 (77.03) | 221 (75.68) | 261 (80.80) |
| After one day or more | 51 (25.88) | 63 (19.03) | 55 (18.83) | 45 (13.93) |
| After a week | 13 (6.59) | 13 (3.92) | 16 (5.47) | 17 (5.26) |
| Pooled | 197 | 331 | 292 | 323 |
| $\chi^2 = 14.103, p = 0.028$ | | | | |

*Figures in parentheses indicate percentage.
indicates difference at 5% level of significance.

Table 4.
Distribution of dog bite victims according to date of reporting and zone.

| Time of exposure | Zones | | | |
|-----------------------------|-------------|-------------|-------------|-------------|
| | East | West | North | South |
| Morning | 58 (29.44) | 86 (25.98) | 63 (21.57) | 55 (17.02) |
| Daytime | 17 (8.62) | 28 (8.45) | 29 (9.93) | 29 (8.97) |
| Evening | 106 (53.80) | 203 (61.32) | 183 (62.67) | 227 (70.27) |
| Night | 16 (8.12) | 14 (4.22) | 17 (5.82) | 12 (3.71) |
| Pooled | 197 | 331 | 292 | 323 |
| $\chi^2 = 21.524, p = 0.01$ | | | | |

*Figures in parentheses indicate percentage.
indicates difference at 5% level of significance.

Table 5.
Distribution of dog bite victims according to time of exposure and zone.

| Time of reporting | Zones | | | |
|-----------------------------|------------|-------------|-------------|-------------|
| | East | West | North | South |
| Morning | 72 (36.54) | 98 (29.60) | 85 (29.10) | 83 (25.69) |
| Day | 28 (14.21) | 54 (16.31) | 44 (15.06) | 46 (14.24) |
| Evening | 84 (42.63) | 165 (49.84) | 153 (52.39) | 179 (55.41) |
| Night | 13 (6.59) | 14 (4.22) | 10 (3.42) | 15 (4.64) |
| Pooled | 197 | 331 | 292 | 323 |
| $\chi^2 = 12.34, p = 0.194$ | | | | |

*Figures in parentheses indicate percentage.
indicates difference at 5% level of significance.

Table 6.
Distribution of dog bite victims according to time of reporting and zone.

east zone, 42.63% victims reported in the evening, 36.54% reported in the morning, 14.21% reported in the daytime, and 6.59% reported in the nighttime. **Table 7** depicts victims according to the site of the bite. In the east zone, 63.45% of victims had bites on the legs, 13.19% had bites on the hands, arms, and shoulders, 7.01% had bites on the buttocks, 13.19% had bites on the knees and thighs, 1.01% had bites on the face, and 2.03% had bites on the abdomen and back. Likewise, the other zones

| Site of bite | Zones | | | |
|--------------------------|-------------|-------------|-------------|-------------|
| | East | West | North | South |
| Face | 2 (1.01) | 7 (2.11) | 3 (1.02) | 7 (2.16) |
| Hands, arms, & shoulders | 26 (13.19) | 75 (22.65) | 65 (22.26) | 70 (21.67) |
| Legs | 125 (63.45) | 173 (52.26) | 159 (54.45) | 190 (58.82) |
| Knees, thighs | 26 (13.19) | 31 (9.36) | 25 (8.56) | 22 (6.81) |
| Buttocks | 14 (7.10) | 36 (10.87) | 33 (11.30) | 30 (9.28) |
| Abdomen & back | 4 (2.03) | 9 (2.71) | 7 (2.39) | 4 (1.23) |
| Pooled | 197 | 331 | 292 | 323 |

$\chi^2 = 21.899, p = 0.11$

Figures in parentheses indicate percentage.
 *indicates difference at 5% level of significance.

Table 7.
 Distribution of dog bite victims according to site of bite and zone.

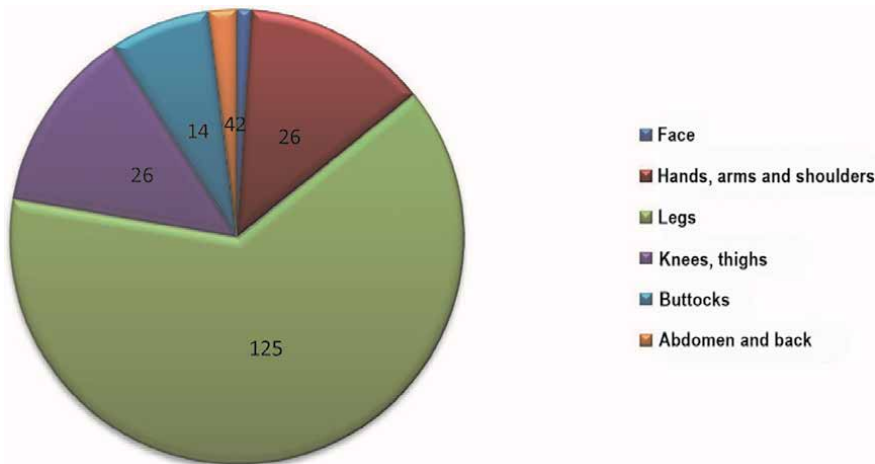


Figure 2.
 Site of bite.

| Category of bite | Zones | | | |
|------------------|-------------|-------------|-------------|-------------|
| | East | West | North | South |
| 1 | 0 (0.00) | 0 (0.00) | 0 (0.00) | 0 (0.00) |
| 2 | 47 (23.85) | 114 (34.44) | 92 (31.50) | 88 (27.24) |
| 3 | 150 (76.14) | 217 (65.55) | 200 (68.49) | 235 (72.75) |
| Pooled | 197 | 331 | 292 | 323 |

Fisher exact test = 0.04*

Figures in parentheses indicate percentage.
 *indicates difference at 5% level of significance.

Table 8.
 Distribution of dog bite victims according to category of bite and zone.

| Immunoglobulin | Zones | | | |
|----------------|-------------|-------------|-------------|-------------|
| | East | West | North | South |
| Received | 153 (77.66) | 266 (80.36) | 246 (84.24) | 282 (87.30) |
| Didn't receive | 44 (22.33) | 65 (19.63) | 46 (15.75) | 41 (12.69) |
| Pooled | 197 | 331 | 292 | 323 |

$\chi^2 = 10.085, p = 0.017$

*Figures in parentheses indicate percentage.
indicates difference at 5% level of significance.

Table 9.
Distribution of dog bite victims who received immunoglobulin treatment according to zone.

showed a similar trend. Statistically, there was a nonsignificant difference concerning the site of bite for different zones (**Figure 2**). **Table 8** depicts victims according to the category of bite. In the east zone, 76.14% of victims had category 3 bites, while 23.85% had category 2 bites. A similar pattern was observed for the other zones. **Table 9** depicts victims according to those who received immunoglobulin treatment. In the east zone, 87.30% of victims received immunoglobulin, while 12.69% did not. The other zones showed a similar distribution. Statistically, there was a nonsignificant difference in receiving immunoglobulin for different zones.

4. Discussion

Rabies is a deadly disease if not treated promptly and properly. In our study, we collected data on dog bite victims and patterns in different zones in Srinagar, Kashmir. We found that males were bitten more than females, which is likely due to the fact that men in the area venture out of their homes to go to work more often than the women do. Most victims are 30 to 40 years old, which conforms with the findings of Mohammadzadeh et al. [5] and Agarvval and Reddaiah [6]. Due to fear of rabies, most victims reported to the hospital on the same day they were bitten. The highest number of cases was seen in the evening when people usually return from work and school. The site of the bite is important, as the rabies virus has broad tissue tropism. The majority of dog bites were to the legs, which other studies by Ain et al. [4], Acharya et al. [7], Chopra et al. [8], and Agarvval and Reddaiah [6] have also confirmed. When a dog threatens a person, it typically bites the lower extremities. Conversely, when a person threatens a dog, the dog is more prone to biting the upper extremities. Although only some of the bites were to the face and head, we observed that children aged younger than 10 years were more prone to being bitten on the head compared to older victims. Typically, children display offensive acts toward dogs, and the head of a child is closer to the mouth of a dog. Most of the bites were category 3, which means the bites penetrated the skin and caused deep wounds. Victims of category 3 bites received immunoglobulin treatment. The west zone of the city experienced the greatest number of dog bite incidents. This might be because the area is crowded and has many open garbage dumps, which attract stray dogs and increase the risk of rabies transmission. The west zone is a downtown area where streets are densely inhabited and where people regularly throw food into the streets. The accessibility of food in the garbage not only augments fertility in dogs but also makes them more prone to attack humans whom they may view as competition for food.

5. Conclusion

Open garbage dumps are a public health problem and they have led to an increased stray dog population in Srinagar, Kashmir, and thus an increased incident of dog bites and rabies cases. We suggest that proper garbage control can help to curb the stray dog population in the area and thus reduce the incidence of rabies.

Abbreviations

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Rabies Virus Infection in Livestock

Abdelmalik I. Khalafalla and Yahia H. Ali

Abstract

Rabies is a lethal zoonotic encephalomyelitis and a major challenge to public and animal health. Livestock are affected by rabies mostly through bites of rapid dogs or wildlife carnivore's species. They are considered as 'dead-end' hosts that do not transmit the virus. Rabies in livestock has been endemic in many developing countries for many years and diagnosed through clinical signs and dog-biting history. An introduction on rabies situation in farm animals will be given then subchapters including `rabies in bovines, rabies in small ruminants, rabies in swine and rabies in camelids. In each subchapter we shall discuss, epidemiology, modes of transmission, diagnosis and prevention and control measures.

Keywords: rabies, old world camelids, new world camelids, epidemiology, diagnosis, spread

1. Introduction

Rabies is the oldest known zoonotic fatal viral disease that affects only warm-blooded mammals. The rabies virus (RABV) infects the central nervous system transmitted through direct contact (such as through broken skin or mucous membranes in the eyes, nose, or mouth) with saliva or brain/nervous system tissue by an infected animal.

RABV almost exclusively infects neurons and eventually causing disease in the brain and death. The virus particle binds cell-surface receptors and follows the endosomal pathway. The virus's life cycle then advances, and following several days or months, the virus enters the peripheral nerves (**Figure 1**). It is then transported to the central nervous system by retrograde flow in the axons [1].

People usually get rabies from the bite of a rabid animal. Around 99% of human cases of rabies are due to dog bites or rarely from non-bite exposures, which include scratches, abrasions, or open wounds. RABV can infect any mammal. However, animal species reported to be involved in the transmission of rabies to domestic farm animals are dogs, foxes, wolves, jackals, and vampire bats (**Figure 2**).

The species of livestock and the carnivores that transmit RABV to them vary from geographical area to another. For instance, according to Kasem et al. (2019), camels, sheep and goats are the most affected species among farm animals by rabies (21.5%, 16.5%, and 16.5%, respectively) and foxes and wolves (11.4% and 2.5%, respectively) are the most common wild animals infected with rabies in Saudi Arabia (**Figure 3**). **Table 1** show reported animal rabies cases according to the reviewed articles in some Asian, African, European, and Latin American countries.

The circulation of rabies virus among livestock has extraordinarily influenced endeavors to control the disease in humans as these animals are in regular contact

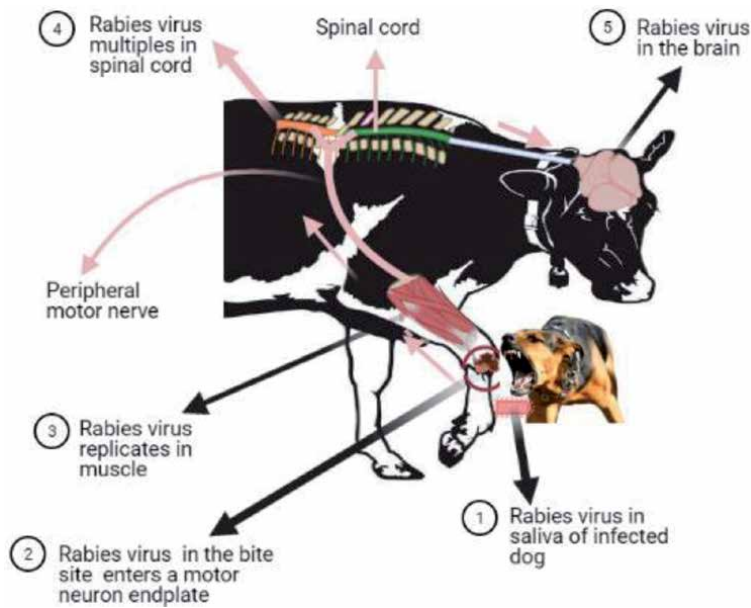


Figure 1.
Pathogenesis and spread of rabies virus in animals from the bite site to the central nervous system.

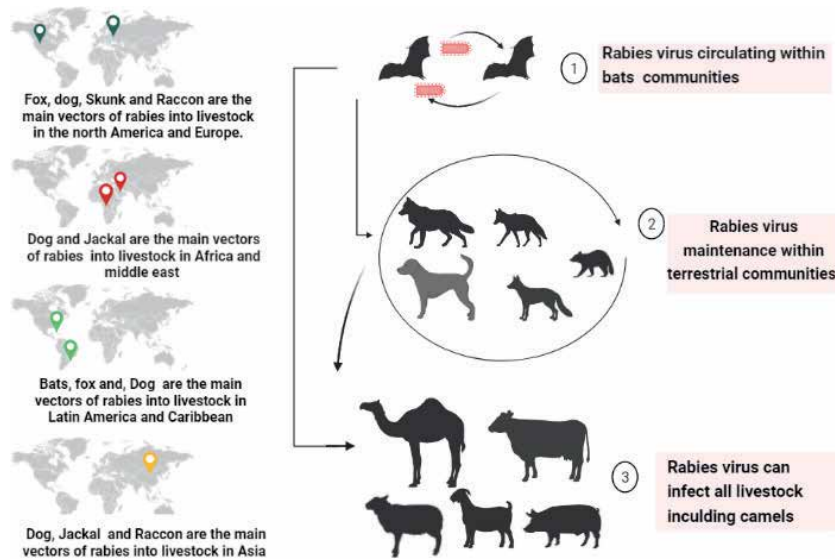


Figure 2.
Rabies virus transmission cycle in bats, terrestrial animals, and livestock.

with individuals. Additionally, affected livestock pose a potential risk to veterinarians and farmers, which underline the importance of applying rabies control measures to humans [15]. Rabies is a transmissible disease among animals causing economic losses directly or indirectly on the local and national economy. Due to their total reliance on livestock for their livelihoods, the losses due to rabies are relatively high for pastoral peoples in rural areas of the world due to their total dependence on livestock. Nevertheless, rabies in livestock remains underreported in developing countries because most of these countries lack adequate and efficient reporting systems and only clinical diagnosis is accessible.

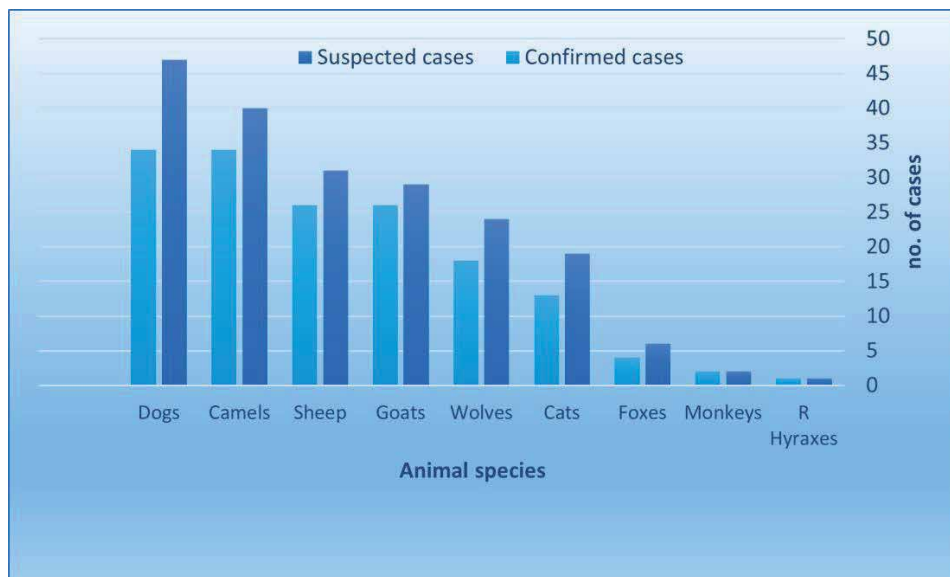


Figure 3. Suspected and confirmed cases of rabies in animals in Saudi Arabia recorded between 2010 and 2017 (modified from Table 1 in Kaseem et al. [15]).

2. Economic impact of rabies in livestock

Hampson et al. [38] estimated the economic costs of canine rabies to be 8.6 billion USD, mainly due to loss of productivity due to premature deaths, costs of post-exposure prophylaxis (PEP), and income loss for seeking PEP. Costs of Livestock deaths were 512 million USD per year, especially in livestock-dependent African economies (e.g., Sudan, Ethiopia, and Tanzania) and Asia (China, India, Bangladesh, and Pakistan). In Bhutan, rabies results in loss of cattle and their production, thus causing direct economic losses to the farmers besides a cost to the government due to managing outbreaks and provision of mass rabies PEP [39]. Most rabies human deaths were in Asia and Africa. Estimated rabies human deaths worldwide annually are 55,000, about 31,000 in Asia and 24,000 in Africa. In Bangladesh, dogs bit nearly 100,000 people, with at least 2,000 rabies deaths in 2009 [40].

Besides its public health significance, the occurrence of rabies in domestic animals (cattle, sheep, and goats), which are the source of food and income to the poor rural people, had raised its economic importance. The authors reviewed a report stating that the incidence of rabies in livestock is re-emerging disease reported in rabies endemic and free countries [29].

3. Laboratory diagnosis of rabies in livestock

During the eclipse phase after infection, the rabies virus replicates in non-nervous tissue such as muscle. After several days or months, the virus enters the peripheral nerves and is transported to the central nervous system and then disseminated within the CNS and the highly innervated tissues, resulting in clinical signs. Most of the virus is found in nervous tissue, salivary glands, saliva, and cerebrospinal fluid (CSF), which should all be handled with extreme caution. As there are neither gross pathognomonic lesions nor specific and constant

| Country | Animal species | | | | | | | Reference | |
|------------------|----------------|--------|------|-------|-------------|-------|-----|-----------|------------------------------|
| | Dog | Cattle | Goat | Sheep | Equidae | Camel | Pig | | Fox |
| Bangladesh | 10 | 1 | 1 | 1 | 1 (Horse) | | | | Uddin et al. [2] |
| | 384 | 290 | 355 | | | | | | Islam et al. [3] |
| India | | | | | | 1 | | | Kumar and Jindal [4] |
| | | | | | | | 3 | | Preethi et al. [5] |
| Sri Lanka | 6788 | 915 | 233 | 13 | | | | | Pushpakumara et al. [6] |
| China | | | | | | | 20 | | Jiang et al. [7] |
| | | 21 | | | | 15 | | | Liu et al. [8] |
| | | | | 36 | | | | | Zhu et al. [9] |
| Nepal | 374 | 442 | 122 | 60 | 14 (Horses) | | 21 | | Devleeschauwer et al. (2016) |
| Iran | | 6 | | | | | | | Simani et al. [10] |
| | | | | | | 12 | | | Mohammadpour et al. [11] |
| Jordan | | | | | | 8 | | | Al-Rawashdeh et al. [12] |
| Oman | 2 | | 312* | | | 40 | | 47 | Al-Abaidani et al. (2015) |
| | | | | | | 22 | | | Ahmed et al. [13] |
| Indonesia (Bali) | 7114 | 8 | 1 | | | | 1 | | Putra [14] |
| Saudi Arabia | 34 | | 26 | 26 | | 34 | | 18 | Kasem et al. [15] |
| Uganda | 15 | 6 | 4 | | | | | 1 | Ormodo et al. [16] |

| Country | Animal species | | | | | | | Reference | |
|----------|----------------|--------|--------------------------|-------|---------------------------------|-------|-----|-----------|------------------------|
| | Dog | Cattle | Goat | Sheep | Equidae | Camel | Pig | | Fox |
| Sudan | | | | | | 83 | | | Ali et al. (2004) |
| | 1158 | 172 | 501 | 82 | 33(Horses), 467 (Donkeys) | 79 | | | Ali, et al. [17] |
| | 708 | 76 | 184 | 111 | 12 (Horses), 277 (Donkeys) | 60 | | | Ali, et al. (2009) |
| | 64 | 53 | 34 | 28 | 26 (Horses) | 11 | | | Baraa et al. [18], |
| | | | | | | 5 | | | Abbas and Omer [19], |
| | | 1 | 1 | | | 6 | | | Ahmed et al. [20], |
| Ethiopia | 4 | 1 | 1 | | 4 (Donkeys) | | | | Ali [21] |
| | 1951 | | | | | | | | Nibret [22] |
| | 1434 | | | | | | | | Reta, et al. [23] |
| | 1724 | 37 | | | 13 (Horses), 19 Donkey | | | | Oyda and Megersa [24] |
| Kenya | | 28 | 12 | 5 | 3 (Horses) | | | | Multugeta et al. [25] |
| | 2796 | 1192 | 280 (sheep & goat) | | 113 | 1 | | 17 | Bitek et al. [26] |
| | | | | | | | | | |
| Morocco | 2458 | 2390 | 331(sheep & goat) | | 1455 (Horses) | 9 | | | Darkaoui et al. [27] |
| Algeria | 667 | 98 | | | | | | | Matter et al. (2015) |
| Nigeria | | | | | | | | | Kaltungo et al. (2018) |
| | | 1 | | | | | | | Ibrahim et al. [28] |
| | | 5 | 1 | 1 | | | | | Tekki et al. [29] |

| Country | Animal species | | | | | | | Reference | |
|--------------------|----------------|--------|-----------------|-------|-------------|-------|-----|-----------|----------------------------|
| | Dog | Cattle | Goat | Sheep | Equidae | Camel | Pig | | Fox |
| Sierra Leone | | 9 | | | | | | | Suluktu et al. [30] |
| Ghana | | | | | | | 3 | | Tasiame et al. (2016) |
| Namibia | 644 | 592 | 131 | | | | | | Hikufe et al. (2019) |
| USA | 62 | 36 | 11 [*] | | 13 (Horses) | | | 314 | Xiaoyue et al. (2018) |
| Brazil | | | | | | | 2 | | Pessoa et al. [31] |
| | | | 6 | | | | | | Moreira et al. [32] |
| Mexico | | 1037 | | | | | | | Bárceñas-Reyes et al. [33] |
| Guatemala | | 154 | | | | | | | Gilbert et al. [34] |
| Russian Federation | 3731 | 6740 | | | | | | 4347 | Botvinkin and Kosenko [35] |
| Belarus | 215 | 129 | | | | | | 734 | Botvinkin and Kosenko [35] |
| Latvia | 566 | | | | | | | 2281 | Westerling et al. [36] |
| Lithuania | 183 | 638 | | | | | | 802 | Westerling et al. [36] |
| Estonia | 131 | 81 | | | | | | 566 | Westerling et al. [36] |
| Ukraine | 78 | 7 | 1 | | 2 | | | 226 | Polupan et al. [37] |

^{*}Both sheep and goats.

Table 1. Reported animal rabies cases according to the reviewed articles in some Asian, African, European, and Latin American countries.

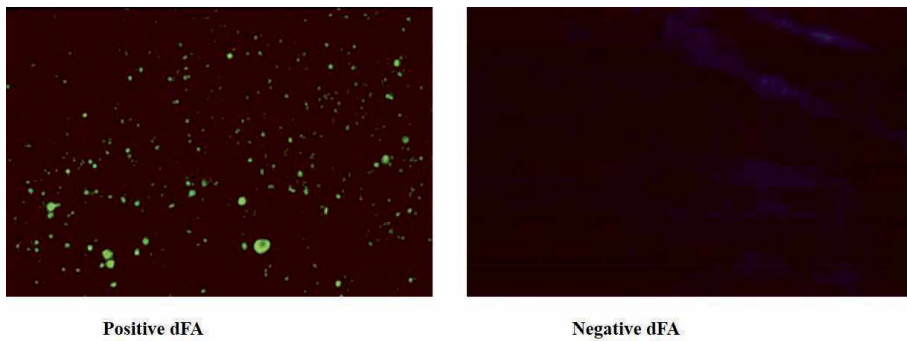


Figure 4. Direct fluorescent antibody test (dFA), brain impression smears (source: Centers for Disease Control and Prevention (CDC)).

clinical signs for rabies, confirmatory laboratory diagnosis must be performed [41]. Laboratory diagnosis of rabies is based on the direct detection of rabies viral antigen using different histopathological and serological techniques with the dominance of fluorescent antibody test (FAT) (**Figure 4**). RABV infection induces the formation of cytosolic protein aggregates called Negri Bodies (NBs) detected by histopathology. However, this test is no longer recommended for diagnosis [41]. Brain samples are tested using the rapid immuno-chromatographic and direct Fluorescent Antibody assay in Nigeria [28, 29]. In China, FAT and RT/PCR are used for diagnosing rabies [8]. Real-time PCR is used as well in different laboratories [30]. Diagnosis of rabies is performed in Ethiopia by animal inoculation, cell cultures, serological tests, histological examination, molecular methods, and immunohistochemistry [42].

In Iran, laboratory diagnosis of rabies is practiced using different techniques, antigen in saliva using mouse inoculation test (MIT), fluorescence antibody test (FAT) and rapid tissue cell inoculation test (RTCIT). Antibodies against rabies in serum and cerebrospinal fluid (CSF) using mouse neutralization test (MNT) [10].

4. Prevention and control measures

It is important to remember that in developed countries, where canine rabies is eliminated, the virus may circulate in wildlife. In contrast, in most developing countries, the principal reservoir is dogs. The major rabies control strategies are vaccination of susceptible animals, mainly dogs and cats, elimination or control of stray dogs, and pre- and post-exposure vaccination of humans at risk. For rabies vaccination in animals, inactivated virus (for companion animals and livestock), live attenuated virus (for wildlife and free-roaming dogs), or recombinant vaccines (for wildlife, cats, and dogs) are used [41]. In China, local rabies vaccines have been used for emergency immunization of beef and dairy cattle and Bactrian (two-humped) camels [8]. In Ukraine, vaccination of domestic dogs and cats, besides oral vaccination of wild animals, mainly foxes, is adopted to control rabies [37]. In Latin America, due to attacks of bats, rabies is a significant problem, especially in cattle; many countries tend to vaccinate cattle but with an inadequate response from owners. In Guatemala, cattle vaccination coverage was estimated to be 11% [34]. In Latin America (e.g., Guatemala), vampire bat control activities (poisoning or culling) are used to control rabies in cattle, besides vaccination of cattle, although it is not widely used due to high cost [34]. In Morocco, free annual rabies vaccination campaigns for dogs are practiced; nevertheless, only around 6%

vaccination coverage rate is achieved. Elimination of stray dogs is done by shooting or using strychnine poison [43]. In Algeria, a mean of 131 positive dog rabies cases were reported annually; this is considered extremely high compared to neighboring Tunisia and Morocco. Elimination of stray dogs and vaccination of canines are the main control measures adopted [44].

Vaccination of livestock in affected areas was implemented in 2012 in Bela Vista city, Arkansas state, USA, where a rabies outbreak was reported. More than 200 cattle were vaccinated with two doses of the vaccine to prevent the disease in bovine, equine, goat, and sheep (reviewed by [29]).

5. Rabies in cattle

Cattle, like other warm-blooded animals, are susceptible to rabies infection. The incidence of rabies in cattle is variable according to the management system.

5.1 Epidemiology

The incidence of rabies in cattle is continuously reported worldwide. In India and Bangladesh, cattle were found to be the most affected domestic animals with rabies [2]. Cattle were the first most likely livestock tested positive for rabies in Mongolia [45]. Rabies was considered one of the most common infectious diseases affecting cattle and is most reported in cattle in Bhutan [39]. In Sri Lanka, cattle were the second most clinically diagnosed species with rabies during 2005–2014 [6]. In China, during 2004–2018, results of a rabies survey showed that cattle were the second most (12.5%) affected species according to rabies laboratory-confirmed cases [46]. In India, rabies' prevalence was 61.4% in cattle and buffalo [47]. In Nepal, cattle and buffalo appeared to be the most affected species even than dogs [48]. According to Bárcenas-Reyes et al. (2019), there is an increase in rabies cases in humans and cattle in Latin America and the Caribbean. Taghreed and Asmaa [49] reviewed some published rabies reports in Oman, Saudi Arabia, Egypt, Algeria, Iraq, and Yemen. Dogs were the main rabies reservoir, and the disease was found in camels, foxes, cattle, sheep, and goats. Dogs, cattle, and humans are the most common hosts for rabies in Ethiopia. Cattle come second to dogs [24]. Out of 48 animal deaths of rabies, cattle (28) were more affected than other animal species [25]. The same picture was reported in Nigeria [29]. In Kenya, cattle were found to be the second most rabies-affected species.

Within samples submitted for rabies diagnosis, those of cattle, goats, sheep, and horses showed a higher percentage of positivity than dog and cat ones [26]. In Namibia, cattle rabies cases are second to dogs during 2011–2017 [50], also in Uganda during 2011–2013 [16]. In South Africa, rabies has been mainly diagnosed in dogs (52%), followed by (34%) cattle [51]. In a review about rabies in Morocco, most of the reviewed reports showed that cattle were found to be the second most affected animal after dogs [27, 52].

In Euro-Asia and Europe, until 2001, cattle were the first rabies affected species in the Russian Federation, second in Belarus [35], the first one in Lithuania, the second one in Latvia, and the third after dogs and cats in Estonia [36]. In Guatemala, 154 cattle rabies due to vampire bat bites were reported (reviewed by [34]). In the United States, Canada, and Mexico, few cases were reported in cattle [53]. The same situation showing a very few reported rabies cases in cattle in Ukraine during 2012–2016 was reported [37].

5.2 Clinical signs

The paralytic form of rabies is the main sign in cattle, but some animals also show depression and excitation [54]. Foaming, bellowing, hitting and biting any object, hazing at humans and other cows were reported in Sierra Leone [30]. In Peru, abortive rabies cases were reported, rabies virus neutralizing antibodies were detected in 11% of cattle in areas of vampire bats, no deaths were observed in those animals within two years [55]. The observed clinical signs of rabies in cattle in two localities in India and Bangladesh were aggression, mania, profuse salivation, frenzy, and restlessness [2].

5.3 Transmission

Rabies virus is transmitted mainly through bites from rabid dogs, which accounts for over 90% of confirmed rabies cases [29]. However, according to Acha [56], rabies affecting bovines is primarily a problem of the southern area of the Hemisphere where vampire bats transmit it. In Africa, domestic dogs are the essential reservoir and transmitter of rabies to humans and other domestic animals [22, 57]. However, according to Warrell [58], jackals are the reservoir species in Botswana, Namibia, Zimbabwe, and bat-eared foxes in northern South Africa.

Rabies is transmitted to cattle mainly by the bite of rabid dogs in Bhutan [39]. In China, dogs are the primary transmitters, while in border areas, wild foxes are [46]; camels and wild foxes were reported to transmit rabies to cattle [8]. In Saudi Arabia, the main reservoirs of rabies are reported to be foxes and wild dogs [15].

In Europe, the increase in rabies cases in domestic animals like cattle, sheep, horses, cats, and dogs is associated with increased disease incidence in red foxes. Wild animals are reported as a cause for more than 90% of the animal rabies cases in the U.S. and Canada in 2010 [59]. Foxes are the main affected animals and the source of rabies infection in Ukraine [37]. In Latin America and the Caribbean, the main transmitter of rabies is the blood-sucking bat [33, 54]. In Colombia, the major transmitters, reservoirs, and vectors of the rabies are insectivorous, frugivorous and hematophagous bats; Vampire bat, which appeared as the main rabies reservoir from Mexico to South America [60].

Cattle can transmit rabies to humans as well as other animals. In Iran, a case of human rabies due to contact with the saliva of rabid cattle was reported [10].

6. Rabies in goats

6.1 Epidemiology

In Ethiopia, of 48 animal deaths of rabies, 12 were goats which were the second more affected animal species [25]. In Sudan, a review on rabies showed that goats were the most rabies-affected species after dogs, as clear from previous reports [17, 18, 61, 62]. In Kenya, the third most rabies-affected species were sheep and goats [26]. The same situation was reported in Morocco [27] and Namibia [50]. In South Africa, rabies-diagnosed cases in goats were the third-highest figures after dogs and cattle [51]. The same situation was reported in Uganda during 2011–2013 [16].

Reported dog bite in goats was higher than in cattle in Bangladesh [3]. The reported prevalence of rabies in goats in India was 48.7% [47]. Sheep and goats showed the third-highest positivity reported for rabies diagnosis in Oman [63]. In Saudi Arabia during 2010–2017, confirmed rabies cases in goats were the

third-highest number following dogs and camels [15]. In Sri Lanka, goats were the third most species that clinically rabies diagnosed during 2005–2014 [6]. In Nepal, goats were the fourth most affected species [48]. However, Uddin et al. (2015) reported that goats showed a low level of rabies prevalence (0.5%) in Bangladesh.

Compared to other species, a low number of cases were reported in goats in United States, Canada, and Mexico [53]. A very few rabies cases in goats in Ukraine were reported during 2012–2016 [37]. Rabies virus neutralizing antibodies were detected in 5% of goats in areas of vampire bats in Peru, seropositive animals remained healthy for further two years suggesting abortive rabies infection [55].

6.2 Clinical signs

Uddin et al. (2015) reported that in Bangladesh, profuse salivation and restlessness were the only observed clinical signs of rabies in goats. The authors reviewed other reports describing salivation (16%) and restlessness (3%), others reporting 100% for salivation, behavioral change, or mania, 70% for aggression or hyperesthesia. In Nigeria, Restlessness, agitation, and aggression were observed in rabies-affected goats [29]. A paralytic form of rabies was reported in goats in Brazil [54]. The same picture was reported in Brazil, where six goats bitten by bats showed apathy, isolation from the herd, sternal and lateral recumbency. Previously reported clinical signs showed that the furious form of rabies is more commonly appears in goats, aggressiveness occurs in 83%, excessive bleating in 72%, salivation in 29%, and paralysis in 17% of cases (**Figure 5**) [32]. In Nigeria, a case of rabies in goat was presented with nibbling on the metal fence, foamy salivation, excessive bloating, and inability to eat or drink [64].

6.3 Transmission

Dogs are the primary rabies transmitter to goats; rabies reservoirs are variable in different countries. Canine rabies is dominant in Africa, Asia, the Middle East, and Latin America, where bats play an increasing role in the latter. In North America and Europe, canine rabies has been greatly eliminated; rabies is maintained in wildlife, as reviewed by Tilahun et al. [65]. In Bali, dogs are the primary source of rabies infection to human and domestic animals [14]. Most reported rabies cases in goats were due to dog attacks, especially in African and Asian countries [3, 16, 18, 21, 47]. Sheep and goats accounted for a meager percentage as a source of rabies infection for humans in Ethiopia [23].



Figure 5. Rabid Saanen buck presenting depression, somnolence and abnormal standing position (source: [32]).

7. Rabies in sheep

7.1 Epidemiology

In Kenya, sheep and goats were the third most rabies-affected species [26]. The same situation was reported in Morocco [27] and Namibia [50]. In South Africa, rabies diagnosed in sheep were the fourth-highest figures after dogs, cattle, and goats [51]. In Oman, sheep and goats showed the third-highest positivity reported for rabies diagnosis [63]. During 2004–2018 in China, it was noticed that sheep were the third most (9.7%) affected species [46]. Confirmed rabies in sheep was the third-highest number following dogs and camels in Saudi Arabia during 2010–2017 [15]. Within the affected species, a low number of cases was reported in sheep in United States, Canada, and Mexico [53].

7.2 Clinical signs

In sheep, attacking people and other animals besides other abnormal behavior was seen in Nigeria [29]. In Nigeria, observed clinical signs in a rabid ewe were aggressiveness, restlessness, corneal opacity, muscular tremor, hydrophobia, and salivation [57]. In an outbreak of rabies in sheep in China, clinical signs observed were arched back, tremors, and a swimming movement of all four limbs, followed by paralysis and death [9]. A paralytic form of rabies was reported in sheep in Brazil [54]. In another study in Brazil, clinical signs observed were abnormal gait, trembling, lateral recumbency, convulsion, opisthotonos, and fever [66]. Abortive rabies cases were reported in sheep in Peru, rabies virus neutralizing antibodies were detected in 3.6% of sheep that were healthy for two years later [55].

7.3 Transmission

The main transmitter of rabies to sheep is dogs. In Africa, the source of most rabies reported cases in sheep was the dog [29, 57, 62]. In China, dogs are the main rabies transmitters, while in border areas, wild foxes are [46]; wild foxes were reported to transmit rabies to sheep [8]. An increase in rabies cases in sheep is associated with a rise in the disease incidence in red foxes in Europe [59]. Rabies transmission from sheep to human was reported; three patients got rabies from direct contact with their sheep which a wolf had attacked in Iran [10].

8. Rabies in camelids

8.1 Epidemiology

Camelids are susceptible to rabies. However, most of the publications described clinical rabies in dromedary camels (*Camelus dromedarius*), with few reports in Bactrian camels (*Camelus bactrianus*) [8, 46] and the New World camelids [67]. From 2006 to 2013 in Oman, foxes reported the highest positivity rate (70.1%), camels accounted for the second higher positivity (59.7%) for rabies diagnosis [63]. Camels were the second most likely livestock after cattle to test positive for rabies in Mongolia from 1970 to 2005 [45]. Camels were the fourth (4.2%) mainly rabies tested positive animals during 2004–2018 in China [46]. In China, rabies infection in camels was reported [8]. According to the confirmed rabies cases in Saudi Arabia during 2010–2017 [15], Dogs and dromedary camels were the most affected

species. In Iran, a review on zoonotic diseases published articles [11] revealed that camels are one of the essential sources as well as carriers of infection for humans, livestock, and wildlife in Iran and worldwide. Rabies is highly endemic in Iran; it is circulated easily in wildlife and livestock. The authors reviewed reported camel rabies cases in Iran, 3 cases during 1996–2006; an outbreak of camel rabies was reported for the first time in 2008 in central Iran. A rabid wolf attacked 8 camels; another camel rabies in the east was reported in 2012 [11]. In Jordan, Rabies in 8 camels was described [12]. In India, a report of clinical signs of rabies in she-camel was described [4].

Reports of rabies in dromedary camels from Morocco, Mauritania, Sudan, Yemen, Saudi Arabia, UAE, Niger, Jordan, India, Israel, and Iran were reviewed by Abbas and Omer [19]. Ali et al. (2004) reviewed dromedary camel rabies in Sudan; the first confirmed rabies cases were in 1926, then laboratory-confirmed cases continued to be reported, 17 cases from 1927 to 1939, 21 from 1940 to 1970. Other cases were reported in different parts of the country, 21 in the north and 16 in the Western States. Camel population in Sudan is about 4.8 million; the reported rabies cases are very few compared to the population, which is mainly due to under-reporting. Other cases in camels were reported as well in Sudan [20].

In a review about camel diseases, many rabies cases have been reported in Mauritania, Saudi Arabia, Iran, and Pakistan; infection is usually due to rabid dog bites [68]. In Niger, an outbreak of rabies in the camel herd due to feral dog bites was reported [69].

Rabies outbreak in camels in Iran was described [70]. An outbreak of dog rabies in the camel herd was reported in Sudan in 1998, and it resulted in the death of 19 camels [71]. Antibodies against rabies were detected in non-vaccinated camels imported for slaughtering in Nigeria, which may indicate subclinical rabies infection [72]. Very few suspected rabies cases in camels were reported in Morocco during 1991–2015 [27].

8.2 Clinical signs

Camels with furious rabies form show restlessness, anxiety, salivation, and attacking and biting form followed by terminal paralysis, lateral recumbency (**Figure 6**) and a characteristic flexion of four limbs, reviewed by Abbas and Omer [19]. Mohammadpour et al. (2020) reviewed a report stating that a furious form of rabies is seen in most of cases in camels.

Rabies clinical signs observed in Bactrian camels were reduced appetite, excessive activity and agitation, cessation of rumination, lip twitching, hypersalivation, tachypnea and howling, paralysis [8]. Some reports described the occurrence of rabies dumb form more frequently. Most rabies cases (67%) in camels in Oman were



Figure 6.
A case of rabies in a dromedary camel showing lateral recumbency and excessive salivation.

of the dumb form; observed clinical signs were restlessness, salivation, head and neck rotation in all directions, paralysis, recumbency, and death [73]. Clinical signs seen in rabid camels were hyperesthesia, profuse salivation, anorexia, and paralysis [12]. In India, clinical signs of rabies in the camel described the appearance of hyperexcitability, bellowing, aimless running, salivation, convulsions, swaying of the hindquarters and recumbency, biting tendency to the owner and wooden objects [4]. Noticed rabies clinical signs in camels were unusual behavior including aggression, pica, ptyalism, and terminal paralysis [69]. During an outbreak of rabies in camels, reported clinical signs were high sensitivity, ferocity, biting faces of other camels, bloat, restlessness, limb paralysis, and yawning [70]. In a rabies outbreak, clinical signs noticed in most of the affected camels were restlessness, irritability with very harsh and loud sounds. Later excitement became noticeable. There were then rubbing incoordination (staggering gait), tenesmus, abnormal sexual behavior: (she-camels mounting each other), raising of tails, and slight salivation, terminated by paralysis of the hindquarter, recumbency, and death of 19 camels [71]. In Khartoum, two camel rabies cases in 1996, 1997 showed off food, salivation, nervous signs followed by biting fence and their forelimbs and abdomen, then recumbency, hind limbs paralysis, and death [74]. An almost similar picture was previously reported by Afzal et al. [75], which were hyper-excitability, salivation, attacking inanimate objects, biting of its forelimbs, sternal recumbency, paralysis of hind legs, and death.

8.3 Transmission

Transmission of rabies to camels is mainly through dog bites, except in some countries where wild animals like foxes and wolves are involved. In China, the main rabies transmitters are dogs; meanwhile, in border areas, the wild fox is [46]; camels were reported to be rabies-infected by dogs and wild foxes [8]. In Iran, a rabid wolf was reported to transmit the infection to camels [11]. In Oman, the main animals involved in rabies transmission are foxes [63]. In another study in Oman, it was noticed that most rabid camels were bitten by foxes, which confirmed the major role of foxes in rabies transmission [13]. In Saudi Arabia, the majority (70%) of camel rabies cases were due to wild dog bite, while wild foxes accounted for about 17% of cases [73]. Almost in all reported camel rabies cases in Sudan, dogs were the source of infection [18, 62, 71, 74]. The same finding was reported in other African as well as Asian countries, Niger [69], Mauritania, Saudi Arabia, Iran, and Pakistan [68], China [8] Saudi Arabia [15].

9. Rabies in pigs

9.1 Epidemiology

Pig rabies is not commonly reported; information about rabies in pigs is scarce. Tasiame et al. (2016) described an outbreak of dog-originated pig rabies in a herd of 23 pigs in Ghana with 13% mortality. In China, the first report for rabies cases in pigs was documented [7]. In China during 2011, an outbreak of pig rabies resulted in 14 deaths was reported [76]. In the USA, DuVernoy et al. [77], was the first to describe the clinical picture of a wild animal's originated pig rabies. During 2004–2018 in China, it was noticed that pigs were the least rabies-affected species (1.4%) compared to sheep, cattle, camels, and foxes [46]. In Brazil, Pessoa et al. (2011) reported the occurrence of pig rabies presented with neurological signs; it was attacked by a bat; there are several reports of detection of rabies virus in swine

in Brazil. Preethi et al. (2020) reported the occurrence of pig rabies for the first time in South India; three pigs in a herd of 25 pigs were attacked by a stray dog. Osiyemi et al. [78] reported rabies cases in pigs in Nigeria.

9.2 Clinical signs

Observed clinical signs in pigs are anorexia, hyperexcitation, constipation, twitching of the head, and foaming [79]. Jiang et al. (2008) described clinical signs of rabies in pigs, the furious form was seen in almost all infected pigs, and it included hyperexcitation, roaring, and attacks on other pigs. In India, clinical signs in rabid pigs were aggressiveness, inability to stand with violent grunting, paralysis, lateral recumbency, convulsions, rapid chewing, head twitching, hyperexcitation, and profuse salivation, change in vocalization. Out of 25 pigs, mortality was 12% [5]. In the USA, rabies clinical signs that appeared in pigs were fever, restlessness, salivation, aggression, anorexia, head rubbing, depression, vocalization, and progressive paralysis (DuVernoy et al., 2008). In Brazil, two pig rabies cases were reported: one with flaccid paralysis of the pelvic limbs; the other showed nervous signs, anorexia, and paresis, then pelvic limbs and tail paralysis. Generally, observed clinical signs were exclusive of the paralytic form [31].

9.3 Rabies transmission in pigs

Like other species, the transmission of rabies in pigs is mainly through dog bites and wild animals, especially in Latin America. In Brazil, Pessoa et al. (2011) reported the occurrence of bat-originated pig rabies. In the USA, DuVernoy et al. (2008) reported pig rabies caused by wild animals. In China, the first report for rabies cases in pigs was associated with dog bite [7]. In China during 2011, an outbreak of pig rabies was reported to be dog originated [76]. Tasiame et al. (2016) described an outbreak of dog-originated pig rabies in Ghana.

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Rabies Virus in Sierra Leone: Challenges and Recommended Solutions for Elimination by 2030

Roland Suluku, Emikpe Benjamin Obukowho, Abu Macavoray and Moinina Nelphson Kallon

Abstract

The objective of this write-up is to find possible solution control canine rabies virus in Sierra Leone and other low-income countries in the world. Rabies is a viral disease affecting both humans and animals in Sierra Leone. The country has no policy on dog ownership and management, two veterinarians, limited access to rabies vaccines and human immunoglobulin, and a lack of information about the disease in the country despite increasing dog bite cases and death. There is no wildlife specialist to initiate wildlife vaccination. Continuous vaccination increased awareness, trained personnel in veterinary and wildlife, development of policies on responsible dog ownership and by-laws and increase financial support from the government and private sector will help Sierra Leone eliminate rabies in the first half of the twenty-first century.

Keywords: Rabies, Dog, Vaccination, Eradicate, Virus

1. Introduction

Rabies Virus is an acute, progressive, and fatal anthrozoönotic infection of the central nervous system belonging to the genus lyssavirus and family Rhabdoviridae that causes rabies [1]. History of rabies date back to work done by various contributors, such as Democritus (460–370 BC), Aristotle (384–322 BC), Pliny the Elder (23–79 AD), Galen (130–200 AD), Celsus (25 BC–50 AD), Rufus of Ephesus (80–150 AD), Oribasius (320–400 AD), and Aetius of Amida (502–575 AD) [2]. Records obtained from ancient Mesopotamian civilization approximately 4,000 years old associate rabies to bites by a mad or vicious dog [3, 4]. In the 16th century, Girolamo Fracastoro reported that when an animal bites and break into the skin it introduces the rabies virus [5]. In 1885, Louis Pasteur developed the first successful rabies vaccine [6]. Yet, rabies remains a threat to both humans and dogs in the 21st century [7, 8].

Rabies had been in Sierra Leone since antiquity but was isolated from the brain of the rabid dog at the Teko Central Veterinary Laboratory in Makeni, northern Sierra Leone in 1949 [9]. Rabies also existed in Kenema, Blama, and other parts of the country later found to be endemic with the virus.

Lack of veterinary staff prevented the government from developing policies on dog ownership and management, undertaking large-scale research and

awareness-raising on rabies [10] resulting in dogs receiving limited attention from their owners. Some could not feed their dogs, provide treatment nor pay for a rabies vaccine. With this obvious gap, rabies continues to take its toll on both humans and dogs. To combat this menace, the government focused on vaccinating dogs in major cities and outbreak communities providing high-cost rabies vaccines for affluent dog owners, while leaving dogs from low-income earners and the public unvaccinated. Liberia and other parts of sub-Saharan AFRICA reported a similar situation [11].

The death of thirteen people from 1968 to 1973 warranted government to vaccinate 4700 dogs in 1974 [12] which in turn gave prominence to control of rabies through a national vaccination of dogs which was short-lived due to the hosting of the Organization of African Unity (OAU) conference in the 1980s. The Government diverted meager resources to the hosting leaving most government departments unable to discharge their normal duties and service. Funding allocations to government departments dwindled and development in the veterinary sector diminished hence the inability to provide basic veterinary infrastructure and vaccination exercise for dogs and cats. No doubt, the difficulties, and hardship after the hosting of the OAU conference followed by political injustices brought resentment to governmental policies among the population.

Animal welfare occupied a lower primordial position on the list of national priority and family. This is also true across Africa where there is a lack of coordination and collaboration regarding dog ownership management, rabies control, and elimination activities, both within and across countries [12]. Most homes could no longer afford three meals a day and dogs have to cater for their daily survival. People focus their energies on their survival rather than dogs (Suluku et al. 2007). Dogs migrate with their owners during the war, which led to an increase in dog population in the capital city of Freetown and other district headquarter towns [13].

The bloody civil war (1991–2002) which brought untold suffering on the people of Sierra Leone was advantageous to dogs with many migrating to major cities and towns. The migration led to the increased urban population, congestion, and uncoordinated waste disposal in the city, the district headquarters towns, and refugee camps. In neighboring Liberia, the Lancet report 2014 reported a similar situation with a lack of electricity supply in large areas of the country especially after the rebel war from 1989 to 2003 and the devastating Ebola outbreak in 2014–2015. After the war, the crime rate increased and the need for dogs as guard dogs becomes inevitable for most people and families. Stray dogs do find food in garbage dumpsites, which enhanced survival and increased dog population, with a corresponding increase in dog bite cases. There is also no organized network of rabies actors to combat the escalating rabies cases in the country and at the regional level. However, some Africa regional groups such as Pan-African Rabies Control Network (PARACON) were established in 2015 to provide a forum to share information and provide available tools and knowledge to eliminate dog-mediated human rabies in Sub-Saharan Africa by 2030 [14].

2. Challenges of canine rabies virus control in Sierra Leone and other developing countries

2.1 Policies

Policies on dog ownership and management existed during the colonial era but were abandoned after independence. People and their dogs in the past received an annual rabies vaccine. The Government trained and empowered Police officers

often called dog police, to impound, and penalized dogs' owners who failed to comply. The license and vaccination of dogs gradually disappear and dog owners no longer vaccinate their dogs against the rabies virus. Compounding the situation further is the complete lack of rabies vaccine in the country in the recent past and the prolonged civil war. Vaccinations of dogs are mostly done on an ad-hoc basis and only a few people especially children vaccinate their dogs. In most countries in Africa, people vaccinate their dogs on World Rabies day. Such spurious vaccination exercise will not eliminate rabies in the continent. The lack of effective policies on how people should own and manage dogs also tends to increase rabies outbreaks in the country. In China, for example, the national policy requires the availability of PPE (Personal protection equipment) in clinics in remote areas. Unfortunately, there was no information regarding the availability of PPE in remote communities in Sierra Leone [15]. Government across the African continent faces many challenges to effectively coordinate multifaceted programs of implementing the animal-human interface in the ecosystem in which they live [16]. The coordination of such structures is lacking in Africa and most countries have little or no public information concerning policies and strategies to eliminate rabies on the continent.

In the past decade, resource-poor countries in Africa are making some progress in rabies control and have increased their efforts due to a shift in policy by the tripartite group comprising FAO, WHO, and OIE to eliminate canine rabies by 2030 in African countries [17]. Despite this shift in policy towards canine rabies elimination, there is little public information concerning policies and strategies addressing canine rabies elimination for the whole continent.

2.2 Lack of veterinary personnel

Sierra Leone has only two veterinary officers employed by the government and three are lecturers at Njala University. The mandate of the Government veterinary doctors relates to the welfare of all animals in the country however, those deployed in the capital city are saddled with the administrative matter. With a higher rate of dog bites often reported every week by WHO, saddled administrative duties prevent them to do a follow-up on people bitten by dogs.

The lack of organized outreach programs by the government veterinary doctors and routine vaccination exercises for dogs make canine rabies control and elimination in Sierra Leone extremely difficult [18, 19]. This problem is not only affecting Sierra Leone but also other countries in sub-Saharan countries such as Angola, Botswana, Cameroon, Ethiopia, Kenya, Nigeria, Namibia, South Africa, Tanzania, Zambia, and Zimbabwe [20] where ethnoveterinary practices are commonly used to control of rabies.

2.3 Lack of information on rabies

The livestock division in the Ministry of Agriculture and Forestry from antiquity lacks veterinary personnel and other support staff to provide adequate information and services to animals and pets owners in the country. People do not know where to go when bitten by a rabid dog, nor is the vaccine available to treat both dogs and humans. Often human medical personnel refers dog bite victims to the veterinary doctor or clinics which implied that the knowledge of rabies and its treatment plan is low among medical personnel, especially in rural communities. The perception of the disease among the people is also poor as death associated with rabies is often attributed to witchcraft. Many countries in Africa have in one way or the other established a network to control rabies (40/54) however, there is still a lack of epidemiology data on rabies control and prevention [21] in both humans and other

domestic animals [22]. In a review of dog control in West and Central Africa, it was reported that half of the countries in the two regions do not have reliable figures on dog population nor reported cases of rabies [23].

This obvious gap necessitates the need for research on the perception and knowledge of rural and urban dwellers on rabies and how best to handle dogs that bite people, this approach will help eradicate the disease in countries where 70% live in rural communities by 2030.

On the provision of vaccines, there is only one veterinary pharmacy located in the capital city of Freetown where animal owners and dog bite victims do patronize for rabies vaccines. To increase awareness of rabies and the need for antirabies vaccination, the Animal Health Club initiated a rabies campaign between 2008 and 2013. With this effort, people became aware of rabies but lack vaccine to initiate large-scale vaccination exercises in the country hamper this laudable move to control the dreaded disease (Unpublished World rabies day report 2013).

2.4 Lack of wildlife specialist to engage in wildlife rabies vaccination

In Sierra Leone, the wildlife department in the Ministry of Agriculture and Forestry is responsible for all wildlife activities in the country. However, there had not been any anti-rabies campaign, especially for wildlife. Since the reservoirs of rabies are wildlife, vaccinating dogs against rabies without vaccinating wildlife is a fruitless endeavor, particularly when over 95% of dogs roam freely. This untamed or stray dog makes rabies eradication in Sierra Leone to be a herculean task to achieve by 2030. Currently, the wildlife unit is not adequately prepared for antirabies vaccination of the wildlife even though Njala university trains and graduates wildlife specialists every year.

2.5 Lack of follow-up on dog bite victims

After the establishment of the National Livestock and Animal Welfare Rabies Control Task Force (NLAWRCT) and the One Health Platform, the World Health Organization and the livestock officers, and community animal Health established animal bites (including dogs) surveillance across the country. WHO reports animal bites in a weekly meeting as shown in tables and figures 3.1, 3.2, and 3.3 respectively. Livestock officers including community animal health workers report to the Epidemiological unit in the ministry of agriculture which also share such information during weekly meetings with development partners but there was no strict follow-up by both partners and the government officers on the rabies status of the dog and the persons bitten by the dogs. The lack of reliable data on death due to rabies to inform government makes it impossible to allocate resources to rabies control. This pattern is consistent with most African countries where the level of the estimate of rabies burden is grossly lacking and insufficient to warrant investment [24].

3. Method to control and eliminate canine rabies by 2030

3.1 Formulation of by-laws

Since By-laws are rules or laws established by an organization or community to regulate itself, hence authorities and community members may establish and enforced by-laws to own and manage dogs [25]. Such acts and regulations should be enforced by the state veterinary services, and statutory animal welfare standing advisory committee should be in place to advise the government. These Established by-laws will help reduce rabies in communities, as was the case in the city of Craig in 1965.

In Sierra Leone, the Animal Health Club encouraged Villages around Njala University to formulate animal rearing by-laws. The club trained the villagers to wash and fed their dogs, the Animal Health Club provided groundnuts, seed rice, and cassava as an incentive for the children to care for their dogs in 2010. With this approach, communities have not reported any rabies incidents (Animal Health Club unpublished report 2010).

3.2 Responsible dog ownership

The concept of responsible dog ownership is a multifaceted social phenomenon intended to shape daily animal-human interaction [26]. Animals are increasingly becoming integrated into the human family in such a way that necessitates increasing attention and control [27]. It is therefore the moral responsibility of the owner to train the dogs in such a way that it conforms to the dictates of society. Dog owners are often to blame for the behavior of their dogs [28]. By providing sleeping places for dogs, feeding them at the appropriate time, providing water and treatment do make dogs behave responsibly, and reduce the chances of contracting rabies. Where such care is not in place, such dogs do scavenge for food in the nearest garbage, dumpsites, and neighborhoods. Such dogs around garbage dumpsites are often termed stray dogs, but most often are owned but unsupervised. Stray or unsupervised dogs often contract rabies through exposure to rabies virus from other street dogs and wildlife, which are a reservoir of rabies.

3.3 Continuous vaccination of both domestic and wildlife animals

Human beings have striven to eradicate pathogens of public health importance. Routine vaccination of diseases such as measles, polio, and diarrhea has saved over 10 million lives between 2010 and 2015 [29]. Successes of these magnitudes have convinced the World Health Organization (WHO), World Organization for Animal Health (OIE), the Food and Agricultural Organization (FAO) of the United Nations, and the Global Alliance for Rabies Control (GARC) to plan Canine rabies elimination by 2030. Their main elimination strategy is the continuous vaccination of both domestic dogs and wildlife animals. Domestic dogs present the greatest threat to public health particularly in poor countries where dog ownership and management policies are weak or non-existence such as Sierra Leone [30, 31].

Developed nations have successfully eliminated canine rabies through continuous vaccination of domestic dogs and wildlife, good dog ownership, and management followed by strongly enforced welfare policies [32].

In low-income countries including Sierra Leone, continuous vaccination of domestic dogs alone will not eliminate canine rabies because large-scale, dog vaccination campaigns should include vaccination of wildlife host species to effectively control or eliminate dog rabies [33]. Such a rabies vaccination campaign should utilize the One Health Approach to raise awareness. It should also be backed with strong bylaws, or animal welfare policies, effective dog population management, and strong political backing to eliminate canine rabies by 2030.

3.4 Training of canine and wildlife specialist in third-world countries

The reservoir of the rabies virus is mostly wildlife animals, but that which helps to transfer rabies to humans is a dog, ‘man’s best friend” Developing countries or low-income countries lack specialists in the area of canine and wildlife practice. In Sierra Leone and by extension West Africa need to train canine and wildlife specialists with a focus on rabies and other zoonotic disease control.

3.5 Development of the seven freedoms of animal welfare for developing countries

The five freedom of animal welfare originated from intensively kept animals often referred to as the golden standard developed by Professor Brambell and his team [34]. These five freedoms include Freedom from hunger and thirst, freedom from discomfort, freedom from pain, injury, and disease, Freedom to express normal and natural behavior, and Freedom from fear and distress. High-income countries like the United States of America, Europe, and South America have used this to eradicate and control the rabies virus.

The five freedoms do not apply to low-income countries where dogs scavenge in garbage dumpsites, feed through the hunting of rodents and wildlife animals they often roaming freely in the neighborhood and bushes during hunting.

Continuous vaccination of these dogs will not prevent rabies as they continuously interact with wildlife hence the need to complement the seven freedoms of animal welfare in low-income countries including Sierra Leone.

4. Tables and figures

The above data shows the number of and cats dog, cats bite cases, and people who have died of dogs and Cat bite cases in Sierra Leone from 2018 to 2020. The number of dog bite cases in 2018 was 1,354 cases resulting in 10 deaths while in 2019, the number of bite cases increased to 1, 544, but the number of death remains the same at 10. In 2020, 1,301 dog bites cases was resulting in 6 death. A personal interview with the Laboratory personnel of the National Central Veterinary Laboratory in Makeni reported that out of 10 dog bite cases reported about 90% are positive for rabies. Thus indicating the presence of rabies in the country. Out of 270 blood samples collected from dogs in the north, south, and east of the country, 24% show positive rabies antibodies in unvaccinated dogs (Unpublished PhD thesis, 2020). Sierra Leone is therefore far from rabies control if the above solutions are not properly taken into consideration (**Figures 1–3** and **Tables 1–3**).

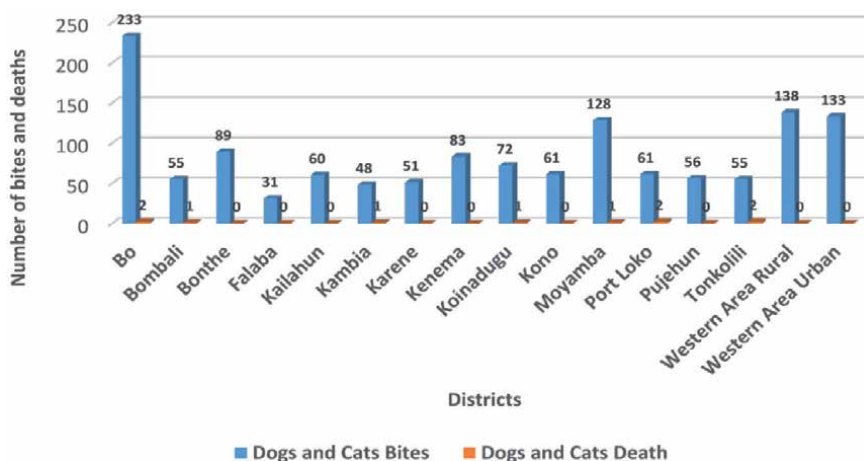


Figure 1.
Graph showing dogs, cats bites and deaths 2018.

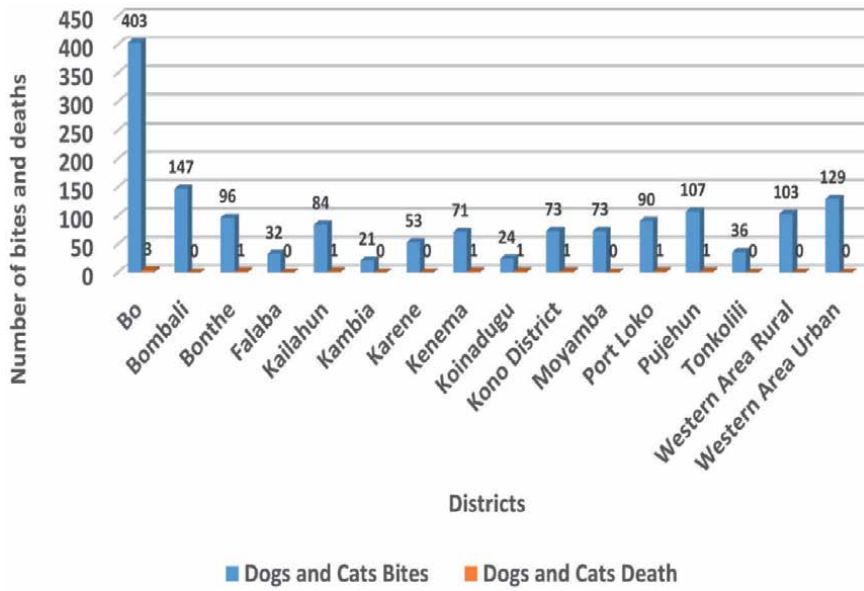


Figure 2.
 Graph showing dogs, cats bites and deaths 2018.

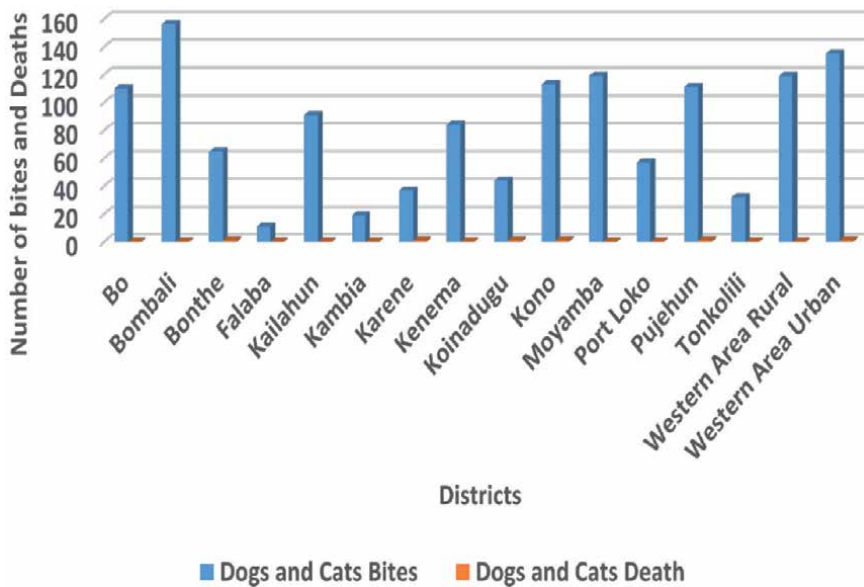


Figure 3.
 Graph showing dogs, cats bites and deaths 2018.

| Dog, Cats bites and Death 2018 | | |
|--------------------------------|---------------------|---------------------|
| District | Dogs and Cats Bites | Dogs and Cats Death |
| Bo | 233 | 2 |
| Bombali | 55 | 1 |
| Bonthe | 89 | 0 |

| Dog, Cats bites and Death 2018 | | |
|---------------------------------------|----------------------------|----------------------------|
| District | Dogs and Cats Bites | Dogs and Cats Death |
| Bo | 233 | 0 |
| Bombali | 55 | 1 |
| Bonthe | 89 | 0 |
| Fallaba | 31 | 0 |
| Kailahun | 60 | 0 |
| Kambia | 48 | 1 |
| Kerena | 51 | 0 |
| Kenema | 83 | 0 |
| Koinadugu | 72 | 1 |
| Kono | 61 | 0 |
| Moyamba | 128 | 1 |
| Port Loko | 61 | 2 |
| Pujehun | 56 | 0 |
| Tonkolili | 55 | 2 |
| Western Area Rural | 138 | 0 |
| Western Area Rural | 133 | 0 |

Source: Ministry of Health and Sanitation 2021.

Table 1.
Dog and cat bites and deaths 2018.

| Dog, Cats bites and Death 2019 | | |
|---------------------------------------|----------------------------|----------------------------|
| District | Dogs and Cats Bites | Dogs and Cats Death |
| Bo | 403 | 3 |
| Bombali | 147 | 0 |
| Bonthe | 98 | 1 |
| Fallaba | 32 | 0 |
| Kailahun | 84 | 1 |
| Kambia | 21 | 0 |
| Kerena | 53 | 0 |
| Kenema | 71 | 1 |
| Koinadugu | 24 | 1 |
| Kono | 73 | 1 |
| Moyamba | 73 | 0 |
| Port Loko | 90 | 1 |
| Pujehun | 107 | 1 |
| Tonkolili | 36 | 0 |
| Western Area Rural | 103 | 0 |
| Western Area Urban | 129 | 0 |

Source: Ministry of Health and Sanitation 2021.

Table 2.
Dog and cat bites and deaths 2019.

| Dog, Cats bites and Death 2020 | | |
|---------------------------------------|----------------------------|----------------------------|
| District | Dogs and Cats Bites | Dogs and Cats Death |
| Bo | 110 | 0 |
| Bombali | 156 | 0 |
| Bonthe | 65 | 1 |
| Fallaba | 11 | 0 |
| Kailahun | 91 | 0 |
| Kambia | 19 | 0 |
| Kerena | 37 | 1 |
| Kenema | 84 | 0 |
| Koinadugu | 44 | 1 |
| Kono | 113 | 1 |
| Moyamba | 119 | 0 |
| Port Loko | 57 | 0 |
| Pujehun | 111 | 1 |
| Tonkolili | 32 | 0 |
| Western Area Rural | 119 | 0 |
| Western Area Urban | 135 | 1 |

Source: Ministry of Health and Sanitation 2021.

Table 3.
Dog and cat bites and deaths 2020.

5. Recommendations for the control of canine rabies in Sierra Leone

Rabies virus control in Sierra Leone and other developing countries requires awareness-raising using the Animal Health Club, One Health Strategy, vaccination of dogs (roaming and owned) and wildlife animals, formulation of by-laws for owning and managing dogs followed by the development of seven freedoms of animal welfare for developing countries.

- a. Raise awareness using the Animal Health Club Strategy. Animal Health Club is an organization established to care for the health and well-being of both humans and animals (domestic and wildlife) living in a healthy environment. This club helps to raise awareness on diseases affecting both animals and humans using the One Health Approach [35]. In the case of the rabies virus, the club will work with the country's governance structure to raise awareness on the disease at the national, district, chiefdom, section, and town or village level. At National, the club contacts the appropriate ministries involved in rabies control, which include the Ministry of Agriculture, Health and Sanitation and Environment. Other Ministries include Education, Internal affairs, and Trade while the club will interact with Market women, traders, drivers, bike riders, Local artists, Paramount Chiefs, Town chiefs, and community elders (AHC Unpublished Report, 2012) to implement its activities on rabies and other zoonotic diseases.

At the district level, the club work with Directors, of the respective ministries to identify stakeholders involved in rabies and engages them in raising awareness on the disease at the district level. These involved District Medical officers, Agricultural Officers, Livestock officers, Health Education officers, environmental officers, Police Local Unit Commander and Military officers, Districts council officers, Mayors of cities. Principals and Head Teachers of secondary and primary schools, University lecturers and students, Local artists, Drivers' union, bike riders (often called OKADA), Petty traders, market women, and village town criers. Quiz, Drama, and debate competitions should be organized in schools, while local artists compose songs and act plays in their local dialects and 'Okada' or motorcycle riders drop rabies flyers, leaflets, and blow their horns to draw the attention of the public.

The club uses these and other media to raise awareness and sensitize people on rabies. Other media include Radio discussion and Phone-In programs, Jingles, distribution of flyers, handbills, and posters, composing songs in local dialects. Important personalities in the communities will commence the vaccination exercise as a show of commitment by the government, and other dignitaries in society.

- b. Formulate dog ownership and management by-laws. The Animal Health Club engages the community, towns, or villages in a focus group discussion to understand challenges and constraints in owning and managing dogs, the consequences of rabies on dogs, people, and the community. Animal Health Club members help to edit the by-laws in simple English and read to the entire community, town, or village. Accepted by-laws are reprinted and distributed in Churches, mosques, schools and read to the audience. If the authorities did not receive any complaint, the by-law becomes binding. This approach was adopted in Njala University and surrounding communities to control rabies.
- c. Conduct regular vaccinations of owned and unsupervised dogs. Such regular vaccination will drastically eliminate canine rabies in the community. Although sylvatic rabies exists in Sierra Leone, the continuous vaccination exercise in developing countries will contain the virus to a low ebb in low-income countries such as Sierra Leone. Vaccination of over 70% of dogs confers immunity against rabies in a community [36]. This statement holds for communities where they vaccinate both roaming and owned dogs and responsible pet ownership is strongly observed. However, if these dogs interact with animals in the wild, they are likely to contract rabies. These explain why rabies had not been successfully controlling or eliminate in these communities.
- d. Established rehoming centers for unowned/unsupervised dogs.

In Sierra Leone, most people in rural communities do exchange items such as rice, chicken, ducks, and farm labor to obtain a dog. To reduce the stray dog population, there is a need to establish a rehoming center that will help to redistribute captured stray and unsupervised healthy dogs to communities and homes that desire to care for dogs. In this center, stray dogs that are terminally ill can be euthanized while healthy stray dogs can be treated, fed, and distributed to communities or people that desire to own dogs. Rehoming is a good strategy to control the stray dog population and reduce canine rabies infection. Sierra Leone has not established rehoming center, but plans are underway to establish such by the one-health platform. The rehoming centers also train new dog owners on how to cater to dogs.

- e. Training of para vets or veterinarians to provide services to dog owners in countries where such personnel and veterinary services are limited such as Liberia, Sierra Leone, and The Gambia.

6. Conclusion

Rabies disease elimination requires concerted effort to control especially in low-income countries. The efforts should include the availability of the antirabies vaccine, sound policies on rabies virus control, a sufficient number of veterinary personnel, wildlife specialists, and adequate information on rabies with follow-up on dog bites. Adopting the Animal health club model, Formulation of animal rearing by-laws, enforcing responsible dog ownership, continuous vaccination of stray and owned dogs and wildlife animals, training of wildlife specialists and veterinarians with the development of the seven freedoms of animal welfare will help eradicate canine rabies virus in low-income countries including Sierra Leone before 2030.

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Conflict of interest

The authors declare no conflict of interest

Research interest

Control of Zoonotic disease in rural communities through awareness-raising using the One Health Approach.

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Despite significant worldwide progress in fighting rabies, a zoonotic viral disease, it remains an important public health concern, causing approximately 50,000 human cases per year. This book summarizes current knowledge regarding rabies, the prevalence and genetic diversity of the rabies virus, and modern approaches to rabies diagnosis, prevention, and treatment. It is a useful resource for scientists, doctors, and students.

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