

Update on lyssaviruses and rabies: will past progress play as prologue in the near term towards future elimination?

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Abstract

Rabies is an ancient, much-feared, and neglected infectious disease. Caused by pathogens in the family Rhabdoviridae, genus *Lyssavirus*, and distributed globally, this viral zoonosis results in tens of thousands of human fatalities and millions of exposures annually. All mammals are believed susceptible, but only certain taxa act as reservoirs. Dependence upon direct routing to, replication within, and passage from the central nervous system serves as a basic viral strategy for perpetuation. By a combination of stealth and subversion, lyssaviruses are quintessential neurotropic agents and cause an acute, progressive encephalitis. No treatment exists, so prevention is the key. Although not a disease considered for eradication, something of a modern rebirth has been occurring within the field as of late with regard to detection, prevention, and management as well as applied research. For example, within the past decade, new lyssaviruses have been characterized; sensitive and specific diagnostics have been optimized; pure, potent, safe, and efficacious human biologics have improved human prophylaxis; regional efforts have controlled canine rabies by mass immunization; wildlife rabies has been controlled by oral rabies vaccination over large geographic areas in Europe and North America; and debate has resumed over the controversial topic of therapy. Based upon such progress to date, there are certain expectations for the next 10 years. These include pathogen discovery, to uncover additional lyssaviruses in the Old World; laboratory-based surveillance enhancement by simplified, rapid testing; anti-viral drug appearance, based upon an improved appreciation of viral pathobiology and host response; and improvements to canine rabies elimination regionally throughout Africa, Asia, and the Americas by application of the best technical, organizational, economic, and socio-political practices. Significantly, anticipated Gavi support will enable improved access of human rabies vaccines in lesser developed countries at a national level, with integrated bite management, dose-sparing regimens, and a 1 week vaccination schedule.

Keywords

Disease, Elimination, Encephalitis, Lyssavirus, Rabies, Vaccine, Virus, Zoonosis, Rabies

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Introduction

As reflected by the recent emergence of the novel coronavirus, SARS-CoV-2, such pathogens continue to pose substantial yet somewhat predictable concerns to human health and welfare at a global level. In contrast to more newly appreciated threats, rabies is one of the oldest described infectious diseases, likely with a more ancient pedigree, pre-dating most historical accounts¹. Rabies and related lyssaviruses continue to cause major mortality in countless mammalian species, including *Homo sapiens*, domestic animals, and wildlife². Although lyssavirus-related mortalities remain uncommon in humans within developed countries, these viruses, and the burden posed in lesser developed countries (LDCs), have captured the attention of scientific, agricultural, and public health communities because of their extreme fatality rate, the highest for any conventional agents, with an estimated human death every 10–15 minutes³. Having the capacity to cause severe disease with serious health and economic implications, without efficient treatment yet available, rabies is considered a major neglected viral zoonosis. As a vaccine-preventable disease, the Food and Agriculture Organization (FAO), the World Organization for Animal Health (OIE), and the World Health Organization (WHO) have focused upon an ambitious plan for the global elimination of human rabies mediated via dogs (GEHRD) or ‘Zero by Thirty’ (ZBT) by 2030 (<https://www.who.int/news-room/detail/28-09-2019-united-against-rabies-collaboration-celebrates-one-year-of-progress-towards-zero-human-rabies-deaths-by-2030>). This plan was perhaps the singular galvanizing event of the early 21st century, in a sea of other notable examples over the past 10 years,

that has reset the underpinnings for challenges and success in the field, as currently appreciated^{4–19} (Table 1). The objective of this brief commentary is to provide an update on the recent progress and extant dilemmas related to rabies and to highlight evidence-based opinions on the evolving scenarios forecast to arise over the next “ZBT decade”, illustrated objectively by data provided through the contemporary, peer-reviewed literature, exemplified primarily during the last few years^{1–201}.

Viral characteristics

Taxonomically, the etiological agents reside in the order Mononegavirales, family Rhabdovirus, genus *Lyssavirus*. Rabies virus is the type-species and most important member of this mono-phyletic genus. Since the 1950s, at least 17 other recognized and proposed lyssavirus species have been described from Africa, Australia, and Eurasia, all of which can be differentiated antigenically and genetically yet cause a clinically indistinguishable encephalitis and not a so-called ‘rabies-like’ disease (https://talk.ictvonline.org/ictv-reports/ictv_online_report/negative-sense-rna-viruses/mononegavirales/w/rhabdoviridae/795/genus-lyssavirus).

The basic viral structure consists of a characteristic bullet-shape and helical symmetry by transmission electron microscopy (<https://apps.who.int/iris/bitstream/handle/10665/310836/9789241515153-eng.pdf?ua=1>). Ultrastructurally, lyssaviruses may be distinguished from other rhabdoviruses, but not from one another. Virions have a length of about 180 nm (130–300 nm) and a diameter ranging from 45 to 100 nm

Table 1. Highly notable events in the applied rabies field related to detection, prevention, and control over the past decade.

Item	Reference
Discovery of new lyssavirus species	4
Suggestion of rabies virus adaptation beyond carnivores and bats to other mammals, such as non-human primates	5
Greater appreciation of wildlife reservoirs in previously considered “rabies-free” areas	6
Recognition of additional antigen detection, serological, and molecular tests for very sensitive and specific lyssavirus diagnosis	7
Recognizable shifts from animal culling to mass dog vaccination as a proven management strategy	8
Planning for the global elimination of human rabies mediated via dogs by 2030	9
Greater focus upon local infiltration of wounds with scarce rabies immunoglobulins	10
Availability of human monoclonal antibodies as an alternative to polyclonal rabies immunoglobulin	11
Recommendations on dose-sparing and shorter 1 week human prophylaxis regimens	12
Expansion of the distribution of vampire bats and rabies virus spread	13,197
Support for pre-exposure vaccination for those in remote settings, such as children in communities with a high exposure rate to canine rabies virus and those at risk of vampire bat depredation	14
<i>In vitro</i> alternatives to animal testing in the determination of vaccine potency	15
Demonstration of compounds with repeatable <i>in vitro</i> anti-rabies virus activity	16
Renewal of interest for the oral vaccination of free-ranging dogs against rabies	17
Elimination of canine rabies in Mexico	18
Expectations of Gavi support for human rabies vaccination	19

(with one rounded and a flattened end). The bacilliform or rod-like particles appear hemi-spherical at both ends when mature. Lyssavirus plane projection imagery reveals surface spicules, a host cell-derived envelope, and a nucleocapsid with helical symmetry. This thin fringe of spicules, about 8 nm thick, does not cover the surface of the plane end of the virus. The genome, approximately 12 kb in size, is composed of a negative-sense, single-stranded, non-segmented RNA and contains five transcription units encoding five viral structural proteins (3'-N-P-M-G-L-5'), separated by short noncoding introns, except for a longer, noncoding intergenic G-L region (<https://apps.who.int/iris/bitstream/handle/10665/310837/9789241515306-eng.pdf?ua=1>). The viral structural proteins include the nucleoprotein (N, ~400 aa), the phosphoprotein (P, ~300 aa, as a cofactor of the polymerase), the matrix protein (M, ~200 aa), the outer surface glycoprotein (G, ~500 aa), and the RNA-dependent RNA polymerase (L, ~2,000 aa). Besides their classically recognized role in structure, receptor binding, membrane fusion, endosome formation, uncoating, encapsidation, transcription, translation, replication, assembly, and release, the viral proteins are also involved in subtle immune evasion and overt disease progression^{20,21}. Improving upon much earlier ultrastructural accounts, recent studies using high-resolution imaging, cryo-electron microscopy, crystal structural and functional analyses, proteomic profiling, and molecular modeling have provided unique insights into a finer understanding of dynamic viral and host protein interactions, neurotropism, the underlying regulation of replication and transcription, intracellular transport, and the future development of more rapid diagnostics, novel biologics, and rational anti-viral drug design²²⁻³².

Pathogenesis

In a rabid animal, virions are shed intermittently in the saliva, usually transmitted via a bite and deposited deeply within a wound, eventually access the peripheral nervous system, travel in retrograde fashion, replicate primarily in the central nervous system, and transit gradually to the salivary glands and other tissues, in a well-known, generalizable productive infectious cycle model³³. Lyssaviruses display a high degree of neurotropism, with a preference for neurons, but non-neuronal cells may also be targeted³⁴. For entry, the viral G protein can recognize not just one but several host cell receptors that are highly conserved among a diversity of avian, marsupial, and placental species, albeit at apparently different relative efficiencies and outcomes. For example, the wide-ranging ability to infect neuronal, muscle, and epithelial cells and fibroblasts suggests a rather ubiquitous expression of entry receptors in different tissues³³. In contrast to some other rhabdoviruses, lyssaviruses are not lymphotropic. Besides neurons, some lyssaviruses can infect specialized neuro-epithelial cells³⁵. Nevertheless, viral dissemination within the infected host is facilitated primarily via attachment to, transport by, and replication within neurons³³. As a quintessential neurotropic pathogen, rabies virus continues to be used experimentally as an anatomical transneuronal tracer, to better understand connectivity within the nervous system¹⁸⁹.

Viral replication and assembly occur in compartmentalized, sequestered intracytoplasmic “factories”, historically termed

Negri bodies, a histopathological hallmark of infection for over a century, although not always detected readily, which limited their diagnostic utility in the face of improved tests²⁹. Despite the virulence of rabies, gross and microscopic injuries may appear rather minor and principle pathogenic mechanisms remain unclear. For example, lyssavirus infection of neurons may result in mitochondrial dysfunction, producing oxidative stress and acute degenerative changes of neuronal processes³⁶. In addition, one potential host-mediated response implicates a role for the *SARM1* gene in axonal “self-destruction”, impeding viral spread but also with subsequent pathological impacts of neuronal and dendritic cell loss³⁷.

Operationally, exposure is defined as transdermal or mucosal contamination with saliva, brain tissue, or other virus-containing substances². Human cases continue to be documented following exposure via these well-recognized routes³⁸⁻⁴⁰. Incubation periods range from less than a week to greater than a year (i.e. typically shorter, after bites to the head and neck), with most cases presenting within 4–6 weeks of exposure⁴¹. The few documented occurrences of exceptionally long incubation periods (i.e. exceeding several years) remain poorly understood regarding mechanism, localization, recognition, etc., or whether much delayed prophylaxis would be effective after the initial infection process². Initial illness is characterized by non-specific onset, including fever, headache, dizziness, vomiting, and myalgia. Later, subjects may experience severe encephalitis, including hydrophobia, aerophobia, and photophobia. Patients succumb from cardio-pulmonary dysfunction and complications related to multiple organ failure⁴². Delayed innate immune responses may contribute to pathology⁴³. The very few survivors from infection frequently have long-term neurological sequelae^{44,190}. Clinical suspicion is heightened after documentation of rabid animal exposure and the onset of compatible signs, but conflicts in adequate laboratory confirmation may confound interpretations⁴⁵.

Immune responses

Innate immunity plays a critical first-line role in anti-viral host defense and modulation of infection after lyssavirus exposure. Toll-like receptors (TLRs), cytoplasmic ds-RNA, and triphosphate-RNA sensors (among others) are part of the host pattern recognition system, activated after sensing of viral RNA post-infection^{186,187}. Activation of TLR3, TLR7, etc., results in a cascade of events, including the production of interferons (IFNs) and interleukins and the induction of initial adaptive immune responses, including the recruitment of B cells and facilitation of germinal center formation⁴⁶. If, after inoculation into a peripheral lesion, local lyssavirus infection is followed by the production of viral RNA, sensed by TLRs and other pathways, leading to the activation of IFN-stimulated genes, induction of IFN, and the incitement of subsequent anti-viral signaling, then how does a productive infection actually ensue? Suppression of anti-viral defense signals, such as for IFN production, could lead to a promotion of viral spread by disrupting both innate and adaptive immunity. Several mechanisms have been described in which viral structural proteins were found to be involved in the blocking of cytokine signaling pathways⁴⁷. In addition,

lyssaviruses may restrict G protein expression and reduce its incorporation into mature virions, subverting the activation of antigen-presenting dendritic cells⁴⁸. Such mechanisms constitute a combined viral immune evasion and suppression strategy, supporting overall a more efficient host invasion. Although somewhat ignored, immunity as defined by the induction of virus-neutralizing antibodies (VNAs) against lyssaviruses can be operative and protective in naïve (i.e. unvaccinated human or other animal) hosts⁴⁹. Administration of attenuated, recombinant, and adjuvanted veterinary biologics or high-potency, multi-dose, prime-boosting applications of inactivated human vaccines promote both innate and humoral immunity via antigen-presenting cells, T cell differentiation, the induction of VNA-secreting plasma cells, and long-lived memory B cells⁵⁰.

Diagnostic applications

Often overlooked, rabies diagnosis has undergone a seeming renaissance of late^{2,7,51-53}. Infection is confirmed by the finding of viral antigens, antibodies, amplicons, nucleic acids, or biomarkers in subjects with signs compatible with an encephalitis. When a case of rabies is suspected, management decisions are made that run the gamut from an individual, exposed patient to a programmatic intervention⁵⁴. Hence, laboratory evaluation is critical. Although most testing occurs postmortem in animals, the diagnosis of rabies in humans prior to death (i.e. antemortem) provides definitive diagnosis for infection control, closure for families, identification of others who may have been exposed to the same source, appropriate patient palliation or rare hope, and the opportunity to attempt experimental therapeutic approaches⁵⁵. Prior traditional methods for antemortem and postmortem rabies diagnosis had multiple limitations. Advances in “best fit” technology and understanding of basic viral pathobiology have led to the improvement or design of many more diagnostic options, beyond the 20th century detection of Negri bodies. Such newer assays, augmented by traditional methods, have begun to revolutionize lyssavirus diagnosis across the global landscape. Unfortunately, while there are antemortem methods for confirmation concomitant with encephalitis, there are still no sensible diagnostic tests available for lyssavirus detection prior to onset of clinical disease. Moreover, assay choice, sample selection, protocol adherence, and post-analytical interpretation issues are not unique to lyssavirus diagnostic challenges, as described in detail in the latest WHO monograph of laboratory methods⁷.

Historically, conventional testing included (1) direct microscopic detection of intracytoplasmic inclusions (i.e. Negri bodies) in infected neurons (no longer recommended for routine primary diagnosis); (2) direct fluorescent microscopy (direct fluorescent antibody [DFA]) during postmortem diagnosis (i.e. widely used in animals and humans as a standard test), with direct staining of viral antigens in touch impressions of brain tissues, including portions of the brainstem (i.e. needed for a definitive diagnosis), the cerebellum, or the hippocampus; (3) virus isolation (i.e. usually reserved in research settings or for confirmatory diagnosis when the DFA test gives a weak or uncertain result) with two primary tests being the mouse inoculation test and the rapid tissue culture infection test in MNA cells;

(4) rapid rabies enzyme immune diagnosis, an enzyme-linked immunosorbent assay (ELISA)-based technique which detects the viral N antigen; (5) antibody demonstration in the serum (in the absence of a history of vaccination) or in CSF, offering indirect evidence of infection by demonstration of anti-N antibodies or anti-G VNA (i.e. via virus neutralization), including the mouse neutralization test (no longer recommended), the rapid fluorescent focus inhibition test (RFFIT), and the fluorescent antibody virus neutralization test (FAVN).

Over the past decade, a variety of molecular methods, many based on PCR modalities, are increasingly applied to various sample types for human antemortem diagnosis and as a confirmatory test for other samples⁷. Likewise, immunohistochemical methods traditionally applied for rabies diagnosis of fixed, paraffin-embedded tissues are now being leveraged as tools explore for more rapid applications. These tests, many now automated, include (1) the direct rapid immunohistochemical test (dRIT), which is an approximately 1 hour test based on detecting viral N protein in brain tissue; (2) the indirect rapid immunohistochemistry test (iRIT), offering the detection and differentiation of virus variants via traditional light microscopy; (3) the reverse transcriptase polymerase chain reaction (RT-PCR) assay, the most frequently employed molecular method that seeks to detect rabies virus and related lyssavirus RNA; (4) the qPCR-based assays (with varying chemistry and detection kits), allowing for the “real-time” detection and quantification of genome copies, with the advantage of a closed-tube assay for a significant reduction in cross contamination; (5) the Qiagen QIASymphony SP/AS, in conjunction with quantitative reverse transcription-PCR (qRT-PCR); (6) the rapid immunodiagnostic test (RIDT), detecting antigens from postmortem samples and utilized without the need for more sophisticated laboratory equipment, which is based on a lateral flow strip assay in a one-step test that facilitates low-cost, rapid identification of viral antigens; (7) nucleic acid sequence-based amplification (NASBA), which allows the utilization of three enzymes to produce multiple copies of RNA in isothermal conditions; (8) and several other updated assays (e.g. Platelia Rabies II ELISA, a rapid antibody detection test (RAPINA) based on immunochromatography, latex agglutination tests for rabies virus-specific antibodies, proteomics, metabolomics, etc.). These provide multiple options for laboratorians in both developed countries and LDCs.

One additional method, the LN34 pan-lyssavirus RT-PCR assay, represents an idealized candidate test for postmortem diagnostics, owing to its ability to detect RNA across the diversity of the viral genus, high sensitivity, potential for use with deteriorated tissues, and user-friendly design⁵⁶. Providing data from a multi-site evaluation of the LN34 assay in 14 laboratories using 2,978 samples (1,049 DFA-positive) from Africa, the Americas, Eurasia, and the Middle East, high diagnostic specificity (i.e. 99.7%) and sensitivity (i.e. 99.9%) were shown when compared to the DFA test (i.e. no DFA-positive samples were negative by the LN34). The LN34 assay exhibited low variability in repeatability and reproducibility studies, suggesting a new gold standard for centralized laboratories. Once quality control is optimized, utilization of more directed, improved point-of-care diagnostics

should range from enhanced surveillance activities in the field to better assessment of exposed patients in the clinic under more real-time conditions in support of better understanding of the underlying disease epidemiology for timely responses^{2,7,57,58}.

Epizootiological insights

As a representative disease of nature, any presumption that rabies is “rare” is a simple fallacy, dependent upon epidemiological context and the public/professional reference frame (<http://outbreaknewstoday.com/rabies-signs-and-symptoms-exposure-transmission-and-diagnostics-81094/>). As lyssaviruses are RNA viruses, an expectation of reasonably high mutation rates in the face of strong purifying selection is the rule for anticipated fixation, adaptation, emergence, and extinctions in the short term and over longer historical periods. Lyssaviruses exist as “ecological ensembles”, metapopulations of distinct species and variants, residing within multi-reservoir mammalian communities in often rapidly changing environments⁵⁹. Such host population–viral assemblages are perpetuated in ecologically diverse urban, rural, and wilderness ecosystems, from the Tropics to the Arctic^{60–64}. Despite this broad host spectrum and wide geographic distribution, from a public health perspective, based upon laboratory-based surveillance and epidemiological analyses, today the overwhelming number of human fatalities are still due to rabid domestic dogs, primarily in LDCs^{65,66}. By comparison, transmission to humans by rabid wildlife, in both developed countries and LDCs, is much less common^{67–76} (Table 2).

Evolutionarily, bats are recognized as the ultimate reservoir of the lyssaviruses^{1,2,77}. Despite more than 17 conspecific members, rabies virus appears to be the only lyssavirus with clear reservoir representation among multiple orders of mammals^{1,2,78}. Unique to the region, independent rabies virus lineages may be found among multiple bat species throughout the Americas^{64,79–81}. Host shifts from engagement of bat rabies viruses to other mammals are suggested by derived variants in raccoons, skunks,

and marmosets in the New World^{1,2,5,82,83}. Additionally, multiple mesocarnivore variants (much more distantly descended originally from ancestral bat rabies viruses) are now represented by dogs, other wild canids, mustelids, mongoose, etc. in both the Old and the New Worlds⁸⁴. Although most rabies virus variant transmission patterns are intrinsically intraspecific (e.g. dog-to-dog, bat-to-bat, etc.), interspecific spillover infection may occur to practically any bitten mammal, from a veritable alphabet soup of armadillos to zebras⁸⁵. While some spillovers may be amplified by short transmission chains, the majority of these are ultimately dead-end infections, such as to domestic or wild hooved stock. Perhaps the most extreme example of the latter is the case of dog-jackal-kudu rabies in southern Africa⁸⁶. Transmission of rabies viruses from domestic animals or wildlife to humans is almost always a single term event (i.e. the person dies without a secondary case), except for the rarity of human-to-human infection from tissue/organ transplants⁸⁷. Such instances are examples of the devastating amplifying consequences when rabies is unsuspected, ignored, or mis-diagnosed.

Early to end-stage clinical manifestations of encephalitis are generally recognized as key supportive factors in viral transmission, along the lines of mania⁸⁸. However, even “normal”, daily social behaviors, involving mucosal or transdermal exposures, may also be operative towards routine perpetuation, as viral excretion in the saliva occurs days before the onset of abnormal signs. Morphologically, mammalian heterodont teeth have several different shapes and multiple functions, to bite, rip, grind, crush, groom, nip, shear, stab, suckle, etc. Beyond primary use in prey capture, killing, and feeding or for established specialized behaviors, the effectiveness of mammalian transmission of lyssaviruses via a bite may be better appreciated by cursorial examination of such teeth from a representative canid (Figure 1A), felid (Figure 1B), vampire bat (Figure 1C), and insectivorous bat (Figure 1D), designed for many different functions but secondarily repurposed as highly effective “pathogen delivery devices” into peripheral tissues. This feature is enhanced by inter-related characteristics, such as local muscular strength, bite force, physical dexterity, chewing capacities, etc., as basic life history attributes of most predators, in stark contrast to the feeding apparatus of a typical mammalian herbivore (Figure 1E). Such ultimate outcomes for highly successful intraspecific viral perpetuation appear obvious (e.g. rabid fox to fox, raccoon to raccoon, bat to bat, etc.), as well as for spillover opportunities to different species (e.g. rabid fox to deer, raccoon to woodchuck, bat to cow, etc.), with relevant public health, agricultural, and environmental ramifications^{89–91}. For example, some of the highest case fatalities have occurred after human exposure to rabid wolves (likely infected originally by interactions with rabid dogs), given the risk for severe cranio-facial bites⁹². Also, while felids do not serve as typical reservoirs, they are highly efficient predators/vectors, presumably infected primarily during aggressive encounters with a bat, or via another mesocarnivore, such as a rabid dog, fox, raccoon, skunk, mongoose, ferret badger, etc., before a human or other species encounter⁹³. In contrast to carnivores, vampire bats, as obligate vertebrate parasites, are the only mammals involved in natural viral exposures

Table 2. Documented examples of recent reports of human rabies cases transmitted by wildlife.

Mammal	Locality	Reference
Insectivorous bat	USA	67
Vampire bats	Latin America	68
Wolf	Russian Federation	69
Fox	China	70
Jackals	Bangladesh	41
Raccoon dogs	South Korea	71
Ferret badgers	China	72
Skunk	Mexico	73
Raccoon (or spillover to cat?)	USA	74
Mongoose	Puerto Rico	75
Non-human primates	India	76

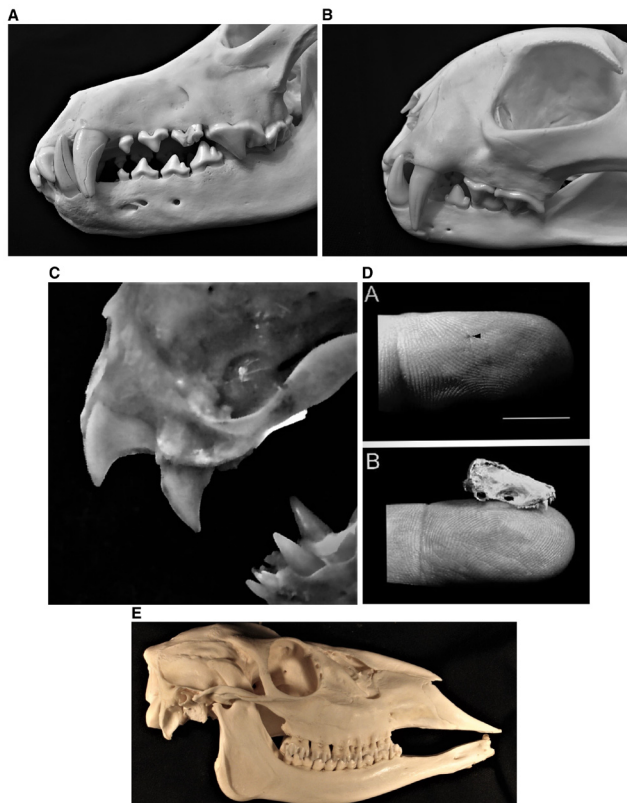


Figure 1. Lyssavirus virions are effectively transmitted transdermally via the saliva into peripheral tissues of a prospective host by the bites of infected mammals, as exemplified by representative mesocarnivores and bats (and in contrast to herbivores). **1A.** Close-up of the canines and carnassial teeth of a canid apex predator, the North American gray wolf, *Canis lupus*. **1B.** Close up of the canines and carnassial teeth of the most common rabid wild felid diagnosed within North America, the bobcat, *Lynx rufus*. **1C.** Close up of the specialized incisors and canines of the common vampire bat, *Desmodus rotundus*. **1D.** Example of an insectivorous bat bite. A. Demonstration of a typical small lesion to a finger from an insectivorous bat (bar inset approximately 1 cm). B. Comparison of the skull of an insectivorous bat to a human digit. This figure was reprinted with permission from Elsevier (Jackson AC, Fenton MB. Human rabies and bat bites. *The Lancet*. 2001. 357:1714)²⁰¹. **1E.** Lateral view of the skull of a representative mammalian herbivore, demonstrating the distinct operational differences in the dentition (i.e. incisors, canines, and cheek teeth) between those taxa serving largely as “dead-end rabies victims” in contrast to typical lyssavirus reservoirs and vectors, depicted in **1A–D** (This figure was adapted from Smalette, specimen 12092010, Wikimedia Commons, the free media repository, licensed under the terms of Creative Commons Attribution-Share Alike 3.0 Unported license https://commons.wikimedia.org/wiki/File:12092010_Right_View.JPG#filelinks).

to other taxa directly because of their hematophagous nature, due to preying upon much larger livestock, humans, or other mammals⁹⁴. For nearly all other, non-vampire bat–human encounters, individuals may not receive prophylaxis because of ignorance of the risk or because they may not realize they were exposed⁹⁵. Although human infections with bat lyssaviruses

have been documented on all continents, outside the Americas and Europe, this risk may not be appreciated more widely in Africa and Asia, where few human cases receive laboratory confirmation or characterization and the current epidemiological introspection is well focused upon the task of canine rabies remediation^{1,2,4,77}.

Fundamentally, as nearly all rabies cases occur after a bite, applied epidemiological data collection on the incidence of animal bite by age, sex, season, locality, species, etc., can be highly informative to public health policy creation in mitigating risks of disease occurrence by preventing and responding to exposures^{2,41,58,74,86,91,92,95,191}. Applied appropriately with mass dog vaccination and human prophylaxis in a local, national, or regional One Health context saves lives and healthcare costs^{2,96}. For example, one multi-variate regression study in seven Latin American countries from 1995–2005 found that an increase in dog vaccinations decreased canine rabies cases, reported human exposures, and human deaths⁸. Within the Middle East, research incorporating proven epidemiological methods with phylogeographic approaches has shown the impact of environmental factors upon canine rabies virus dispersal⁹⁷. Such anthropogenic facets have undoubtedly played a critical part since canine domestication to the present, given historical interdependence, translocations, and close animal–human bonds^{1,2,84}. This increasing integration of classical epidemiological methodology with modern diagnostics, molecular techniques, health economics, or modeling approaches has provided key insights into applied rabies dynamics, improved prophylaxis, cost-effective prevention, and multi-species control strategies^{2,59,98–110} (Table 3).

Modern strategies to prevent, control, and selectively eliminate rabies

Before the 20th century, most global rabies prevention and control efforts focused upon a gamut of responses, including denial, avoiding exposures, quackery, quarantine, isolation, dog killing, collaring or muzzling, and wildlife culling, with varying levels of success. Thereafter, although some of these earlier strategies are still employed, a century of development has now resulted in pure, potent, safe, and effective rabies vaccines for administration to humans, domestic animals, and wildlife^{2,111–113}. Somewhat unique for viral diseases, these vaccines may be used routinely for either pre-exposure prophylaxis (PrEP) or post-exposure prophylaxis (PEP) to minimize the opportunity for a productive lyssavirus infection (Table 4). Updated recommendations for human prophylaxis have been forthcoming, built upon epidemiological insights and clinical studies of biologics first licensed during the latter part of the 20th century, focused upon greater dose-sparing use of the intradermal route of vaccine administration, shorter regimens, infiltration of rabies immunoglobulins (RIGs) or monoclonal antibodies, and relevant applications of PrEP to those at risk^{2,10–12,14,19,98,114}. Greater harmonization of these guidelines is expected to follow suit in both LDCs and developed countries¹¹⁵. Unfortunately, despite highly effective PrEP and PEP, humans will still succumb to rabies because they receive no prophylaxis, a lack of RIGs or infiltration, inadequate vaccination, or a delay in PEP of several days or more, especially after a severe exposure. Historical

Table 3. Selective illustration of a diversity of recent epidemiological applications in humans, domestic animals, and wildlife for improved detection, prevention, and control on a global basis.

Example	Citations
Informatics for policy making on human prophylaxis recommendations at a global level	98
Predictive modeling of potential spatial spread in a canine rabies-free continent	99
Annual animal rabies laboratory-based surveillance summary for North America	74
Emergency department syndrome-based surveillance	100
Meta-analysis of animal bite statistics in Iran	92
Using ecological insights to overcome barriers for improved canine vaccination	101
Geographic information system use for wildlife rabies outbreak response	102
Health economics comparison of canine rabies control demonstration sites in Africa and Asia	103
Public health investigation of mass human exposure events from bats in the USA	104
Cohort assessment of the risk of rabies in biting Haitian dogs	105
Retrospective, multi-hospital analysis of the relative adequacy of rabies immunoglobulin administration to patients	106
Prospective, spatiotemporal study of human exposure risk factors in Ethiopia	107
Cross-sectional household survey on dog populations, bite incidence, and rabies knowledge in an African community at risk	108
Case series of rare human rabies survivors in India	109
Human case report, after substantial patient contact with bats in the home, but without prophylaxis, demonstrating the need for continued education	110

Table 4. Use of prophylaxis before or after lyssavirus exposure in humans, domestic animals, and wildlife^{2,11,112}.

Group	Pre-exposure prophylaxis	Post-exposure prophylaxis
Humans	Parenteral vaccine doses administered to any persons at risk of viral exposure, with serological surveillance of certain occupational groups (i.e. laboratory workers, veterinarians, etc.) for determination of a routine booster when immunity wanes, based upon virus neutralization antibody detection	Thorough wound cleansing, infiltration of rabies immunoglobulin into wounds, and parenteral administration of several doses of rabies vaccine (for the previously vaccinated person, only rabies vaccine is administered)
Domestic animals	Ideally, all domestic animals (but especially dogs and cats) at risk of exposure should receive a single parenteral vaccine at around 3 months of age, a booster at about 1 year of age, and periodic annual or triennial boosters dependent upon label indications and local regulations	Immediate, single, parenteral re-vaccination upon known exposure to invoke an anamnestic response
Wildlife	Mesocarnivore reservoirs (e.g. coyotes, ferret badgers, foxes, jackals, mongoose, raccoons, raccoon dogs, etc.) may be targeted for oral vaccination by well-designed programs for which vaccine safety and efficacy have been determined (in addition, parenteral vaccination may occur for mammals maintained in zoological collections or by trap-vaccinate-release of free-ranging wild mammals)	Primarily occurs naturally when a previously vaccinated animal develops an anamnestic response upon consumption of another dose of oral vaccine

and recent work highlights the importance of humoral immune responses and the role of VNAs directed against the viral G protein¹¹³. Although the development of new biologics is ongoing and the scrutiny to obtain vaccines directed against disparate lyssaviruses continues, the only approved products on the market are directed against rabies virus. Several new vaccine development concepts have been studied in animal models, including novel adjuvants, virus-like particles, and nucleic acid-, chimeric rabies

virus-, simian adenovirus-, and epitope-based vaccines^{50,192,193}. These approaches could expand the spectrum of coverage and may require even fewer vaccine doses or less-expensive applications for either human PrEP or PEP. Regardless of future innovations, rabies virus is the predominant lyssavirus of importance. As such, human survival is virtually assured by the prompt and proper use of today’s biologics after rabies virus exposure.

Equally impressive to the progress in the use of human prophylaxis is the success also demonstrated for animals¹¹⁶⁻¹²⁴ (Table 5). All developed countries eliminated canine rabies. Increasingly, LDCs repeated the model, starting with the regional program in the Latin American countries, despite large numbers of free-ranging dogs in urban centers and rural communities. While the GEHRD can be accomplished via the combination of human prophylaxis and domestic animal control by vaccination, without the elimination of canine rabies virus circulation, the long-term effectiveness of such a strategy equates to the “incurable wound”. Rather, by removing the underlying problem, a primary rationale for most of the more-costly human prophylaxis is minimized. Such a vision is feasible, as the accumulated data from disease modeling studies indicate that the basic reproduction number, R_0 , is less than 2, control through mass canine vaccination is highly effective in reducing cases in dogs and subsequently in humans owing to a reduced animal burden, and ~70% annual coverage is a sound target for prevention^{125,126}. Concerns about the estimated population of dogs to vaccinate, actual determination of vaccine coverage, relative density, age and birth rates, levels needed to prevent re-establishment from endemic areas, and more efficient methods of reaching free-ranging animals are identified as some of the crucial factors influencing the effectiveness of such interventions^{125-128,194}.

Beyond prevention in humans and domestic animals, rabies is the only zoonosis in which wildlife vaccination, using attenuated or recombinant biologics, has risen from an academic

concept to a safe, effective, and economical long-term practice on a grand scale¹²⁹⁻¹³³. For example, after the multi-year use of oral rabies vaccine (ORV) distributed in edible baits, western Europe and large parts of southern Ontario became free of fox rabies^{124,134}. Within the Republic of Korea, ORV was used for the elimination of rabies virus in raccoon dogs¹³². In the USA, ORV for raccoons began during 1990 and programs to date have prevented raccoon rabies spread beyond the eastern states as plans are formulated for elimination¹³⁵. Locally, within the state of Texas, large outbreaks in coyotes and gray foxes occurred during the late 1980s and research began to evaluate the utility of ORV for these wild canids¹³⁶. By the mid-1990s, large-scale ORV began in west-central Texas for gray foxes and southern Texas for coyotes (Figure 2). To date, tens of millions of baits have been distributed in the state over tens of millions of square kilometers. The last case of coyote rabies virus variant was detected during 2004 and the last case of gray fox rabies virus variant was diagnosed during 2013 (in an infected cow)⁷⁴. Gray fox vaccination has ceased, with the elimination of that rabies virus variant, but, as a precaution, annual ORV maintenance occurs in southern Texas because of the threat of the re-emergence of coyote rabies. In concept, ORV programs could be expanded, based upon enhanced surveillance, particularly within Mexico and border locations¹³⁷. Around the globe, additional species and biologics are under evaluation for ORV application¹³⁸⁻¹⁴⁴. Moreover, given the success of ORV in rabies suppression, other diseases are also being explored for prevention and control in wildlife¹⁴⁵⁻¹⁴⁸. Operational studies in different taxa will continue to uncover

Table 5. Evidence of global progress in applied rabies prevention, control, and elimination.

Locality	Interval	Item	Reference
India	2012–2016	Gradual estimated declines in human rabies cases within seven states (primarily because of human prophylaxis), with a need for improved surveillance at a national level	116
China	2007–2017	Decrease in estimated human cases from 3,300 to 516 (primarily because of human prophylaxis) at a national level, based on passive surveillance	117
Republic of Korea	1998 to date	Classified as a notifiable disease since 1961, with a decrease of 68 animal rabies cases to 0 by 2014, primarily by domestic animal vaccination and oral vaccination of wildlife	118
Thailand	1980–2015	Human rabies cases decreased from ~370 to ~5, concomitant with decline in animal cases	119
Vietnam	1992–2017	Reduced human-reported deaths from 404 to 74	120
Sri Lanka	1973–2015	With a national plan for elimination, human deaths declined from 377 to 24, while dog vaccinations increased from <300,000 to >1.4 million	121
KwaZulu-Natal, South Africa	2007–2014	Using a combination of methods, including increased public education, human prophylaxis, and dog vaccination, canine cases fell from 473 to 37 and human cases were reduced from approximately 9 to 0	122
Americas (21 Latin American and Caribbean countries)	1998–2014	Consistent decline in human and canine rabies case incidence, approaching 0	123
Europe	1978–2016	Based upon the European rabies surveillance data base, only 3,982 total animal cases were reported (an approximately 4.3-fold decrease) and at least 12 countries self-declared rabies freedom, primarily because of oral vaccination of wildlife	124

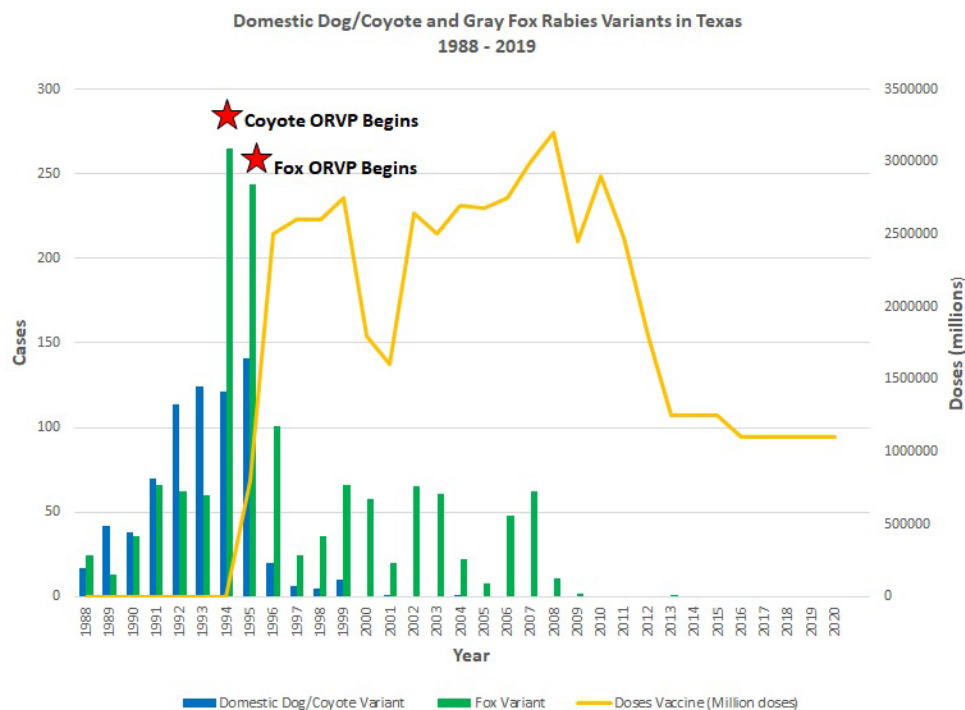


Figure 2. Demonstration of the impact of the Texas oral rabies vaccination program (ORVP) in response to coyote and gray fox rabies outbreaks. Comparison of laboratory-diagnosed cases of coyote and gray fox rabies virus variants to the combined number of oral rabies vaccine doses distributed over time in west-central and southern Texas, leading to elimination.

basic pathobiological and immunological mechanisms to improve upon the next generation of ORV¹⁴⁹. Such advances stand as a legacy to those researchers from the 1960s who grappled with pragmatic ideas of how to approach the problem of wildlife reservoirs once canine rabies was prevented, controlled, or eliminated.

Experimental treatment options

In comparison to rabies vaccines and antibodies for humans, anti-viral strategies have also been under development, with renewed fervor post-2004 and documentation of the first survivor without a history of vaccination, yet with much less discernable clinical progress, in part because of the obstacle of safe and effective delivery of compounds to the central nervous system^{55,150,151}. Fundamentally, unlike the former focus on biologics, designed to prevent a productive infection, the latter efforts wrestle primarily with the “post-infection treatment” dilemma when routine public health interventions fail, and a clinical case develops. Recent investigations demonstrate that nucleoside inhibitors and their analogs, previously identified to inhibit other RNA viruses, are also capable of limiting lyssavirus replication. These could present potential broader-spectrum anti-viral candidates for future concentration. For example, a recent study demonstrated that favipiravir (T-705), a viral RNA-dependent RNA polymerase inhibitor that acts as a purine analog (shown previously to protect against filovirus infection), can limit lyssavirus infection *in vitro*¹⁶. Not surprisingly,

observations of several such drug effects are not easily extrapolatable to *in vivo* data^{152,153}. The likelihood of finding a lyssavirus-specific modality is predictably low, compared to the potential finesse of broader approaches for other “high-stakes” RNA virus targets among the Mononegavirales¹⁵⁴. In the interim, this highly controversial aspect of the field will see-saw between an empirical, research-based *in vitro/in vivo* side and an emergency “hit-or-miss best guess” slant to clinical treatment of lyssavirus encephalitis, in which, among others, patient families, hospital administrators, multiple medical specialties, national regulators, ethicists, viral diagnosticians, and developers of novel biologics, as well as fit-for-purpose anti-viral drugs, will all play a part^{2,42,55,150–155}. In addition, one part of the dilemma is the absence of relevant animal models to consider for actual clinical rabies treatment, particularly in a manner similar to the management of human encephalitis. However, there is no shortage of domestic animals that are euthanized after rabies virus exposure or the onset of compatible illness. Rather than euthanasia as the only current tool, perhaps these naturally occurring animal cases might be better utilized under more ideal circumstances. For example, as veterinarians receive PrEP, institutional intensive care facilities are available to isolate and sedate suspects safely, and academic teaching hospitals are renown for their biomedical research, greater progress in the field overall might ensue if the profession embarked upon the more routine clinical care and experimental treatment of rabid domestic animal patients, based upon current insights.

Remaining issues

Given the palpable enthusiasm and actual progress generated by the GEHRD concept to date, candor and objectivity in the context of current pandemic events help to color expectations with the approach and passage of a ZBT world. What might this entail? As reflected in daily headlines, interconnected competing priorities will remain a reality, in contrast to “just rabies”. These include recognizable emergent communicable viral diseases (e.g. COVID-19 and zoonoses due to henipaviruses, hemorrhagic filoviruses, etc.), longstanding agricultural concerns over high-value commodities (e.g. ASF, FMDV, H1N1, etc.), devastating natural calamities, particularly associated with climate change (e.g. drought, fire, floods, etc.), and strong differing expert opinions about the “best way” to spend limited global funds in LDCs¹⁵⁶. Even under ideal circumstances, a sustainable ZBT business plan remains elusive given wandering variables (i.e. the number of dogs at risk, the quantity of vaccine doses needed, the determination of producers to meet rising demands, the opportunity costs of local vs. regional sources of biologics, long-term sources of support, etc.), as do other unresolved topics^{1,157,194,195}. Nevertheless, these are just anticipated nuances of a plan well in motion, and, as finer-grained program plans for GEHRD evolve, countries will grapple with these and other broader debates, such as a dependence upon external sources of modern biologics vs. a very clear need for self-sustainability (<https://www.dawn.com/news/1526311/pakistan-to-become-self-sufficient-in-four-antiseras-by-june>).

One way to envision the landscape post-ZBT may be ascertained in part by scenarios whence this goal has already been achieved locally, nationally, or regionally¹⁵⁸. Within this forum, some may toy with the somewhat unimaginable concept of “eradication” (i.e. quite dependent upon flexible terminology but in stark contrast to the obviousness patterned by the definition as pertinent to smallpox and rinderpest). Concomitant with such freedom is the flaunting by others of long-standing rules related to vaccination and the improper movement of adopted animals from LDCs that, not surprisingly, introduce rabies to previously canine rabies-free territories^{159,160}. Similarly, a primary focus upon the threat of canine rabies translocation is warranted from enzootic to “free” areas, but ignoring the reality of wildlife rabies altogether seems an object legend for appreciation and disaster, using the experience of Taiwan alone¹⁶¹. Canine rabies deserves to be at the forefront, while wildlife rabies remains lurking prominently in the background. Understandably, while reservoirs such as foxes, mongooses, raccoons, and skunks have been recognized historically for many decades to centuries, such is not the case for ferret badgers, non-human primates, or other potential candidate hosts, especially in localities where lyssavirus surveillance is much less than ideal¹⁶².

As may be obvious from a cursorial examination of the more specialized aspects of the inarguable progress in rabies diagnostics and biologics, there is a certain skewedness towards technical approaches in disease problem-solving, with much less of a focus on more anthropological, economic, political, or societal concerns for introspection^{163,195}. Without the inclusion of these arenas beyond mere “lip service”, transdisciplinary boundaries

persist, preventing an ultimate understanding of why a given program may fail¹⁶⁴. Additionally, “vaccine hesitancy” has crept even into the rabies field, both human and veterinary, despite an abundance of need, safety data, and epidemiological modeling (<https://www.avma.org/javma-news/2020-03-01/vaccine-hesitancy>). Unplanned exclusionary practices by discipline can undermine otherwise sophisticated solutions to long-term disease control, prevention, and elimination, unless there is a concerted effort to appreciate bias, conflict, distrust, xenophobia, polarization, and related administrative, community, cultural, and religious concerns¹⁶⁵. In some situations, suppression of actionable healthcare priorities may not only be ignored but intentionally suppressed¹⁶⁶. Besides public and political disparities, there are similar disconnects on continuing education needs and maintaining expertise among healthcare workers, veterinary staff, and often-overlooked wildlife professionals^{167,168}. Also, the expressed routine needs of the applied user and the academic provider approach to trendy, fundable high-tech solutions does appear in need of remedy (as opposed to the simple, practical, available, and inexpensive, e.g. cell-phone technology, locally produced coolers to maintain the cold-chain, etc.)^{169,188,196}.

One expectation of collateral damage from an unrelenting supply of naïve, unsupported, and alternative “facts” about nearly everything during the new internet age arises in part from the coverage and communications about rabies survivors and the misuse of simple terms, such as “treatment”. Clearly, rabies is a vaccine-preventable disease but is not treatable, *per se*⁵⁴. One suggested downside may be a public misunderstanding of the ability to receive an outdated misnomer of “post-exposure treatment” after the onset of illness and thus being somewhat cavalier in reception to an accepted biomedical notion of prompt and proper PEP. While it is one thing having a true shortage in supply of biologics, living far from healthcare, or being poor in the pocket in the affordability of what should be otherwise provided for free as a life-saving intervention, it is yet quite another to be the receiver of exaggerated, misinterpreted, or false news about rabies. Similarly, a perceived long “event horizon” towards the recognition of an actual documented therapy coupled with the ongoing tragedy of human rabies that will continue for the foreseeable future underscore serious discussions over patient rights and individual options for euthanasia and a dignified death in the face of an obviously fatal outcome, unless more attractive alternatives beckon (https://timesofindia.indiatimes.com/india/can-rabies-patients-opt-for-euthanasia/articleshow/73164110.cms?utm_source=contentofinterest&utm_medium=text&utm_campaign=cppst).

Conclusions and future directions

Lyssaviruses seem to attract special concentration compared to other members in the Rhabdoviridae, not the least of which is because these agents possess a zoonotic risk associated with the highest case fatality rate documented for any infectious disease. Besides stealth by modulation of replication locally and within the nervous system, lyssavirus proteins can effectively interact with host innate immunity and disable the establishment of otherwise resilient anti-viral responses. A fundamental understanding of this basic host-pathogen relationship at both the

molecular and the cellular levels in multiple species and elucidating how non-traditional laboratory hosts, such as bats, might efficiently modulate lyssavirus infection under natural circumstances represent exciting challenges for future research. Such insights may open new avenues in the development of novel biologics and anti-viral strategies. These studies should lead to human and animal clinical trials, allowing the generation of new licensed vaccines, antibodies, drugs, and delivery systems that are even more efficient in the prevention or treatment of lyssavirus infection. Enhanced laboratory-based surveillance is key for human prophylaxis, domestic animal vaccination, wildlife management, program monitoring, and border controls. Otherwise, viral phenotypic plasticity combined with the broad distribution of known and suspected wild reservoirs, especially among mesocarnivores and bats, together with the likelihood of spillover to domestic animals, particularly dogs, raise the strong probability of enzootic perpetuation, epizootic spread, and translocation to “rabies-free” areas.

Over the past 10 years, substantial progress has occurred on a global level regarding pathogen discovery, diagnostics,

prophylaxis, and engagement of professionals in academia, government, industry, and international non-governmental organizations. Further success requires maintaining this transdisciplinary philosophy, with collaboration among virologists, immunologists, epidemiologists, veterinarians, physicians, producers, regulators, economists, and social scientists within an updated One Health approach in a common endeavor to better understand, communicate, detect, prevent, control, and eliminate lyssavirus infections in the next decade^{170–183} (Table 6). Supporting focus, enthusiasm, and momentum, based upon the evidence at hand, is critical but will not be simple, overly rapid, or inexpensive (https://www.who.int/neglected_diseases/news/WHO-EB-commend-progress-against-NTDs-and-calls-road-map-2021-2030/en/). These timely critical lessons learned about surveillance, diagnosis, and management, with best practices applied from one pathogen more than millennia-old in the making, should also be applicable to many of tomorrow’s emerging zoonoses. In this regard, the ensuing pandemic of SARS-CoV-2 presents a much-told cautionary tale as to a legacy related not only to rabies but also to other neglected tropical diseases as well (Table 7)^{199,200}.

Table 6. Predictive scenarios for the rabies field over the next decade.

Likely events	Supportive citations
Broadened surveillance for new lyssavirus species among bats and other mammals	170
Prediction and documentation of associated mammalian species reservoir status for unresolved lyssaviruses (e.g. Mokola, Shimoni, etc.)	171
Better appreciation of bat reservoirs in suggestive “rabies-free” areas, such as islands	172
Refinement of linear flow and related assays for improved “point of care” use in the rapid diagnosis of lyssaviruses	173
Movement beyond pilot projects towards actual national canine rabies elimination in Asia	120
Demonstration of regional elimination of human rabies mediated via dogs in Africa	174
Clinical trials of new biologics to reduce or replace the use of rabies immunoglobulins	175
Expansion of human monoclonal antibodies breadth against divergent lyssaviruses	176
Licensing of purified, serum-free rabies vaccines, with updated label claims for intradermal use	177
Considerations on the use of oral rabies vaccines for other species, such as bats	178
Use of a single vaccine dose for pre-exposure vaccination in remote communities at risk	179
Abandonment of animal testing in the determination of vaccine potency	180,198
Evidence in support of anti-viral drug use based upon insight to viral targets	30
Programmatic use of oral vaccination of dogs for control among free-ranging animals	181
Elimination of canine rabies in Latin America and better “south-south” engagements for repetition of best practices beyond technology	182
“ <i>In situ</i> genomic surveillance” expansion within lesser developed countries	183
Protection of “free regions” by expansive elimination of canine rabies in enzootic areas	184
Utilization of Gavi support for human rabies vaccination into national health programs	185

Table 7. Potential impacts of the COVID-19 pandemic upon rabies activities.

Benefits	Limitations
Greater appreciation for diseases of nature and viral zoonoses specifically, such as rabies	Lessons lost, due to pandemic fatigue
Enhanced laboratory-based surveillance for lyssaviruses	Pathogen discovery focused primarily upon coronaviruses alone
Additional scrutiny to better understand how bat populations deal with lyssavirus burden	Unnecessary backlash against bat populations in general
Broader consideration of dogs now as pets, rather than livestock for consumption, closure of wildlife markets, and halting use of bats as bushmeat	Unpopular consumptive activities driven ever more underground
Shelter-in-place, limiting human exposure to rabid animals	Mass unemployment drives even greater community shifts and increases individual movements for resources
More animals vaccinated in aftermath of best practices, including use of drive-up clinics	Veterinary services not viewed as an essential activity compared to public health
New vaccine approaches provide insights for novel human prophylaxis	Unfulfilled promises and adverse events sour demand for novel products
Anti-viral strategies reap extension against other RNA viruses, such as in the Mononegavirales	No major cross-reactivity to rhabdoviruses
Broader One Health adoptive strategies	Anti-public health sentiments due to presumption of civil liberties lost
Global elimination of human rabies mediated via dogs (GEHRD) achieved before 2030 owing to greater preventive focus	GEHRD setback for decades owing to economic global repercussions


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Disclaimer

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