ABSTRACT Rabies is a classical zoonosis that has been known to man for ages. The disease can be caused by several viral species in the Lyssavirus genus, but the type species, rabies virus (RABV), is far the most important from a zoonosis perspective. The extreme neurotropism of RABV and the evolutionarily conserved elements and structures of the mammalian brain suggest that this virus evolved an ultimate niche for replication, simultaneously exploiting classical social behavior of a wide diversity of hosts among the chiropters and carnivores. Substantial evidence indicates that RABV originated in bats and later switched hosts to yield globally disseminated canine rabies. Following the revolutionary work of Louis Pasteur, control and elimination of dog rabies was achieved in Europe, but widespread colonial introduction of European strains of dog RABV to other parts of the world occurred. Thus, dog rabies spread rapidly in the 1900s, and today the vast majority of the tens of thousands of annual human rabies cases stem from dog rabies, which has become endemic in the entire developing world. The fact that human rabies is preventable, through control in the dog reservoir on one hand and through effective prophylaxis in cases of exposure on the other hand, is an indictment of public health strategies and practices. This article discusses some of the drivers that have contributed to the recurrent neglect of rabies in the modern world, as well as evolving One Health-based rabies control partnerships and initiatives that have been progressive, productive, and promising of true global benefits.

INTRODUCTION
Rabies is a classical zoonosis that has been known to man for ages. The disease can be caused by several viral species in the Lyssavirus genus, but the original lyssavirus, the rabies virus (RABV) itself, is far the most important from a zoonosis perspective. The extreme neurotropism of RABV and the evolutionarily conserved elements and structures of the mammalian brain suggest that this virus evolved an ultimate niche for replication, simultaneously exploiting classical social behavior of a wide diversity of hosts among the chiropters and carnivores. Substantial evidence indicates that RABV originated in bats and later switched hosts to yield globally disseminated canine rabies. Following the revolutionary work of Louis Pasteur, control and elimination of dog rabies was achieved in Europe, but widespread colonial introduction of European strains of dog RABV to other parts of the world occurred. Thus, dog rabies spread rapidly in the 1900s, and today the vast majority of the tens of thousands of annual human rabies cases stem from dog rabies, which has become endemic in the entire developing world. The fact that human rabies is preventable, through control in the dog reservoir on one hand and through effective prophylaxis in cases of exposure on the other hand, is an indictment of public health strategies and practices. This article discusses some of the drivers that have contributed to the recurrent neglect of rabies in the modern world, as well as evolving One Health-based rabies control partnerships and initiatives that have been progressive, productive, and promising of true global benefits.

RHABDOVIRUSES
The majority of all viruses, in particular those that are zoonotic and hence relevant within the One Health context, are RNA viruses. Among RNA virus families,
most animal viruses possess membranes (envelopes) (Fig. 1) acquired during their exit from infected cells, which then also facilitate entry into new host cells. In contrast, the vast majority of plant viruses do not have lipid membranes, given the architecture of plant cells, but there are two important exceptions. One is the Bunyaviridae (Rift Valley fever virus, Crimean Congo hemorrhagic fever virus, etc.), while the other is the Rhabdoviridae. There are a vast number of different rhabdoviruses that infect an astonishing array of hosts within the insect, plant, fish, and mammalian orders (1). However, not only are the rhabdoviruses of insects the most numerous within the family, but those rhabdoviruses of hosts other than insects are mostly transmitted by insects. A peculiar exception to insect transmissibility is the topic of this article, the lyssaviruses, of which RABV is the type species. Rabies, together with its unique transmission mechanism, is a classical zoonosis that has horrified humans for ages (2).

## LYSSAVIRUS DIVERSITY

The Lyssavirus genus comprises 12 species, many of which have been discovered in recent years (Table 1). With the discovery of new viruses came the realization of the extensive diversity within the genus and the likelihood that more species remain to be discovered. However, it is the original lyssavirus, RABV, that is by far the most important from a zoonosis perspective (3–5).

### THE EMERGENCE AND EVOLUTION OF RABV

Canine rabies has in all likelihood existed since antiquity, with ancient documents describing a disease transmissible from dogs to man with epidemiological and clinical features that closely resemble rabies (6). More recently, with the advancement of sequence analysis and modeling, the principle of RABV host switching from chiropters to carnivores was demonstrated with the use of molecular clocks (7). The interpretation of molecular clocks in RNA virus evolution requires much care, considering the propensity of RNA viruses to mutate rapidly, the formation of quasispecies, and the subsequent positive or adaptive selection (8). Nevertheless, the approach is useful in determining ancestral links and pathways of divergence, although attempts to precisely date such events may be less dependable.

With the exception of the African Mokola virus (9, 10), all lyssavirus species are exclusively viruses of bats or, in the case of RABV, occur in bats and terrestrial mammals. For one recently discovered lyssavirus, Ikoma, only one case is known to date (civet cat, Tanzania), and it is not possible to conclude on the likely reservoir species (11). As far as the bat lyssaviruses are concerned, most recent insights suggest a propensity for specific RABV variants to most efficiently spill over to bat species that are phylogenetically close to the parental host species, regardless of spatial and other ecological factors (12). Furthermore, those lyssaviruses of bats occurring in tropical and subtropical climates (as op

**FIGURE 1** Genome type and membrane presence of the major families of animal RNA viruses. dsDNA, double-stranded DNA. doi:10.1128/microbiolspec.OH-0006-2012.f1
posed to temperate regions of the world) evolve at a significantly faster rate, probably due to more sustained yearlong bat activity (13). This factor is likely to have been a key contributor to the diversity of lyssaviruses found in the tropical and subtropical regions of Africa (14, 15). Considering the above and given the genetic diversity of the bat lyssaviruses, as opposed to the relatively closely related assemblage of terrestrial RABV, the evidence for the spillover from bats to yield globally disseminated canine rabies is substantial. In the modern day, such events are well documented. A decade-long record of the spillovers of a bat variant of RABV into skunks and foxes, with subsequent propagation within the spillover host species, provides one of the best showcases of the natural frequency of such events (16).

**RABIES VIRUS: AN OPPORTUNIST PAR EXCELLENCE**

The extreme neurotropism of RABV and the evolutionarily conserved elements and structures of the mammalian brain suggest that this virus evolved an ultimate niche for replication. To reach this niche, furtive evasion of immune responses is achieved while transport within immune-privileged neuronal systems is rapid and uninterrupted (17). After utilizing the neuronal tissues of the brain for extensive replication, the virus transports to the salivary glands (primarily, but also to other locations). Here efficient replication is followed by viral passage into the oral cavity, with high numbers of infectious virions accumulating in saliva. Thus, efficient transmission is guaranteed should saliva and virus be exposed to mucosal tissues or breach the dermal protection of a new host in another way. In dogs and other carnivores, this is in fact often achieved through the ability of the virus, during neurovirulent infection of the brain, to render the infected animal aggressive, warranting biting events that allow virus entry into new hosts. Given the transmission mechanism, it is evident that RABV very efficiently exploits the classical social behavior of mammals. Such reservoir species belong in particular, but not exclusively, to the Carnivora and the Chiroptera orders (3, 18, 19). The entire process, inclusive of neurotropism, neurovirulence, evasion/exploitation of host immunity, glandular passage, and direct-contact transmission, is highly efficient (Fig. 2).

**PATHOGENICITY AND IMMUNE EVASION OR AMBIVALENCE AND THE BLOOD-BRAIN BARRIER**

Following a transmission event, i.e., passage of virus through the dermis or otherwise into cellular tissues of a susceptible host, it is possible, but still undetermined, that virus may replicate in nonneuronal cells after receptor-mediated entry. One likely receptor for such purpose is nicotinic acetylcholine (20). Nicotinic acetylcholine, followed by viral passage into the oral cavity, with high numbers of infectious virions accumulating in saliva. Thus, efficient transmission is guaranteed should saliva and virus be exposed to mucosal tissues or breach the dermal protection of a new host in another way. In dogs and other carnivores, this is in fact often achieved through the ability of the virus, during neurovirulent infection of the brain, to render the infected animal aggressive, warranting biting events that allow virus entry into new hosts. Given the transmission mechanism, it is evident that RABV very efficiently exploits the classical social behavior of mammals. Such reservoir species belong in particular, but not exclusively, to the Carnivora and the Chiroptera orders (3, 18, 19). The entire process, inclusive of neurotropism, neurovirulence, evasion/exploitation of host immunity, glandular passage, and direct-contact transmission, is highly efficient (Fig. 2).

**PATHOGENICITY AND IMMUNE EVASION OR AMBIVALENCE AND THE BLOOD-BRAIN BARRIER**

Following a transmission event, i.e., passage of virus through the dermis or otherwise into cellular tissues of a susceptible host, it is possible, but still undetermined, that virus may replicate in nonneuronal cells after receptor-mediated entry. One likely receptor for such purpose is nicotinic acetylcholine (20). Nicotinic acetylcholine,
given its postsynaptic location, is unlikely to serve for entry into motor neurons, but enriches RABV at the neuromuscular junction and could be used to infect muscle cells. Another good receptor candidate is p75 neurotrophin (p75NTR), which is widespread on neuronal as well as nonneuronal cells, including muscles (21). p75NTR expression renders resistant cells permissive, but on the other hand, there is no difference in disease progression in p75NTR-deficient and wild-type mice (22). One study has shown that RABV and European bat lyssavirus-I bind to p75NTR, while other bat lyssaviruses do not (23). It is also understood that dog RABV strains are highly specific for neurons while bat strains can also infect astrocytes, but much remains to be clarified with regard to the disease progression of bat lyssaviruses in their respective reservoirs. For RABV, perhaps the most likely receptor for neuronal entry is neuronal cell adhesion molecule (NCAM) (24). This molecule is widespread on all peptide hormone-producing cells and neurons, where its presynaptic location renders it an ideal receptor candidate for RABV. The expression of NCAM renders virus-resistant cells permissive, providing some experimental evidence. In NCAM-deleted transgenic mice, animals remain susceptible to RABV infection, but the disease is markedly delayed, indicating a role for NCAM, albeit not essential (24). It thus appears that RABV receptors may be ubiquitous and that different receptors and coreceptors

**FIGURE 2** The rabies cycle. Lyssaviruses are uniquely adapted to effectively exploit the ecological and anatomical characteristics of their primary mammalian hosts and vectors. CNS, central nervous system. doi:10.1128/microbiolspec.OH-0006-2012.f2
are involved, depending on RABV strain and lyssavirus species. These aspects are not well understood and are likely to play a major role in the puzzling differences in tropism, pathogenicity, and infection outcomes of different lyssavirus species and RABV variants.

Once the synaptic cleft has been bridged, RABV moves from the axon terminal toward the neuron cell body (site of virus replication and subsequent crossing of the synaptic cleft to reach the next-in-line neuron). The mode of transport, in this retrograde direction, was thought to be enabled by interaction of viral proteins with the dynein light chain 8 (25, 26), but later findings disputed this concept, suggesting that the light chain 8 instead impacts on a transcriptional level (27). Nevertheless, axonal travel directed toward the brain is fast (50 to 100 mm/day), and the strict unidirectional traverse has also made RABV an ideal tool as a tracer in studies of neuronal networks and anatomy (28).

Replication of lyssaviruses involves the synthesis of five subgenomic mRNAs, one for each of the viral proteins (3′-N-P-M-G-L-5′). The order of genes on the RNA genome determines the corresponding number of transcripts, with the rate of transcription gradually declining from the 3′ to the 5′ end of the genome (14). The relative copy numbers of individual proteins are thus well regulated and important in maintaining viral phenotype. For example, changing the position or copy numbers of the G gene on the viral RNA with corresponding higher rates of G transcription has been shown to have an attenuating effect on the virus phenotype (28, 29). However, although it has been shown that pathogenicity could correlate inversely with the rate of G expression in some studies (29, 30), other recent findings discredited this concept, illustrating the fact that the factors that influence lyssavirus virulence are multiple and complex (31). While the influence of G copy numbers on virus pathogenicity may be in doubt, various studies have demonstrated that G is likely to be a major determinant of pathogenicity. For example, Ito et al. (32) demonstrated that a nonpathogenic RABV is converted into a pathogenic virus through three mutations within the G gene and that these mutations affect pathogenicity through their impact on virus cell-cell spread in the CNS. Classically, a single mutation at Arg-333 in RABV G has been associated with attenuation, playing a major role in vaccine development (33, 34). It has become clear that various proteins, inclusive of G, P, and M, can be determinants of pathogenicity and that the importance of single amino acid changes should be considered within a larger and cooperative context of the entire viral genotype.

Apart from the role of individual proteins and domains on these proteins, there is substantial evidence that RABV pathogenicity correlates inversely with the rate of replication and the capacity to induce neuronal apoptosis. Among others, RABV uniquely evades host innate immunity by selective targeting of interferon-activated signal transduction and activator of transcription (STAT) proteins by the viral phosphoprotein (P). STAT signaling is inhibited in various ways (17). It appears that such unique mechanisms of immune evasion are conserved among all lyssaviruses (35). There seems to be an ambivalent role for the innate immune response to RABV pathogenesis (36). Transgenic mice that overexpress LGP2 (a regulator of RIG1-mediated innate immunity) and thus have an impairment of innate immunity have improved survival from rabies. Such intervention actually favors RABV elimination from the brain. Thus, RABV appears to exploit innate immunity to develop an immunoevasive strategy. The mouse blood-brain barrier (BBB) remains firmly closed in the case of infection with a virulent RABV strain, while the BBB opens when infection is with an attenuated RABV strain (37). This loss of BBB integrity is more extensive in the cerebellum than the cerebral cortex, and with the possible exception of CD8, immune effectors for virus clearance more commonly target the cerebellum. The observation that attenuated RABV infection promotes RABV-specific antibody entry into CNS tissues, and that passively administered RABV-specific antibodies can cross the BBB under certain conditions, has specific relevance for future rabies therapy (38).

**CONTROL OF DOG RABIES AND EMERGENCE OF WILDLIFE RABIES IN THE DEVELOPED WORLD**

The establishment of rabies cycles in dogs became an important public health concern in the New World starting in the 1800s. Following the revolutionary work of Louis Pasteur, subsequent developments in rabies vaccinology allowed for the eradication of New World dog rabies—first in the United Kingdom and Western Europe and later in North America (39, 40). However, an important caveat was to follow: the emergence of wildlife rabies. In Europe, it was the red fox that became the principal rabies vector and reservoir, while raccoons, skunks, various fox species and coyotes, and other species became important reservoirs in North America (39, 41, 42). Extensive vaccination and breakthroughs in oral vaccination allowed for the eradication of fox rabies in Western Europe, but wildlife rabies persists in North
Emergence of Dog Rabies in the Developing World and the Burden of Human Rabies

At the time when control and elimination of dog rabies was achieved in the New World, widespread colonial introduction of European strains of dog RABV to other parts of the world occurred (45). Thus, dog rabies spread rapidly in the 1900s, and today the vast majority of the tens of thousands of annual human rabies cases stem from dog rabies, which has become endemic in the entire developing world. In Africa, several hundred million people are estimated to be at risk of endemic dog rabies, with more than 30,000 human deaths annually. In Asia, current estimates indicate as many as 40,000 human deaths annually (46). The fact that human rabies is entirely preventable, through control in the dog reservoir on the one hand and through effective prophylaxis in cases of exposure on the other hand, is a major indictment of public health strategies and practices in the developing world.

Factors Impacting the Control of Rabies

Why then has a highly fatal but preventable zoonosis progressively established itself as a neglected disease throughout Africa and Asia? Many factors contribute, but the lack of priority is perhaps most strongly driven by institutional juggling of the responsibility for rabies control and poor awareness or appreciation of the public health impact of rabies. Considering classical priorities in the developing world, it is worth reflecting that rabies is not associated with any agricultural importance. The impetus for effective control would likely be greater if rabies had a major economic impact. To an extent this is the case in some countries where the laboratory-confirmed rabies cases in cattle (incidental, spillover hosts) regularly outnumber those cases confirmed in dogs and other carnivores (rabies reservoirs) (14, 47). The veterinary neglect of dogs is exacerbated by the fact that dogs are typically unrestricted and free roaming in areas of Asia, Africa, and Latin America where dog rabies is endemic. These animals are excluded from classical health care systems, as only a small minority of owned and restricted dogs are of interest to private veterinarians and veterinary services (48). The resources needed for primary health care of large, free-roaming dog populations are significant and may not seem warranted for a disease that is seen as an issue of public health. On the public health side, misdiagnosis is common (49, 50), as rabies frequently presents with a variety of nonspecific clinical symptoms, including paralysis, which occurs in as many as one-third of cases (51, 52, 72). Apart from overlapping symptoms, the degree of professional ignorance of rabies in some areas where dog rabies is endemic is often puzzling (49, 53). It is also true that rabies primarily affects rural community types, characterized by poverty, remote location, poor infrastructure, and negligible health care. Collectively, poor surveillance and diagnosis in the animal reservoir and misdiagnosis, ignorance, and insufficient services on the medical side combine to fuel the circle of neglect (Fig. 3), allowing for the progression of rabies. Estimates published as long ago as 2005 indicated that the disease threatened more than 3 billion people in Asia and Africa and in more than 150 countries and territories (54).

On the global health agenda, a loss of newsworthiness and geopolitical issues may well have influenced advocacy and disease priority. Dog rabies, although spectacularly persistent and opportunistic, is prevalent only in the developing world and does not necessarily demand the same attention as some new diseases with pandemic potential, such as those associated with novel strains of influenza or coronaviruses. In reality, mortality due to rabies, which occurs mostly in children and without any other health risk factors, outstrips many other infectious diseases that are perceived to be more important (54, 55), and rabies also has the highest case-fatality ratio of all infectious diseases of humans (52). Thus the World Health Organization (WHO) recognizes rabies as notifiable. Unfortunately, a few countries where rabies is particularly prevalent—such as India—do not (56), and structures for publication of rabies statistics by the WHO were not well supported by many member countries. The World Organisation for Animal Health (Office International des Epizooties, or OIE) also regards rabies as notifiable, with publication of statistics on the World Animal Health Information Database (WAHID) (57), but statistics from countries where dog rabies is endemic generally do not correlate with even the most conservative estimates (46, 58).

The inevitable neglect of a disease associated with poverty and for which the primary reservoir is not livestock is perhaps predictable, and thus rabies is a classic example of a disease for which any hope of future control is dependent on the unconditional execution and instruction of the “One Health” paradigm on global, regional, and national levels.
ASPIRATIONS FOR A RABIES-FREE WORLD AND EVOLUTION OF NEW PARTNERSHIPS

A number of diverse groups and organizations that are independent from broader United Nations bodies or reference organizations such as the WHO or the OIE focus on rabies activities in different parts of the world. For example, the Latin-America National Rabies Directors Network (REDIPRA, established in 1983) is an important coalition for the region. The Rabies in the Americas Association was formed in 1990 and among others hosts an annual Rabies in the Americas (RITA) meeting, the largest annual rabies conference that consistently attracts a global audience. In Europe, Rabies in Eurasia meetings took place under the auspices of the OIE in Kiev (2003) and Paris (2007), but more recently the Middle East and Central Eastern Europe Rabies Expert Bureau (MEEREB, 2010) was also formed. Focusing on the problem of rabies in Asia, the Rabies in Asia Foundation (RIA, 2006) and the Asia Rabies Expert Bureau (AREB, 2004) are also new initiatives. The Southern and Eastern African Rabies Group (SEARG) was formed in 1992 as a coalition of anglophone countries of the continent. In francophone Africa, the Africa Rabies Expert Bureau (AFROREB, 2008), driven by Sanofi Pasteur, was more recently established. While these organizations epitomize the effort of rabies champions, experts, and interest groups, more is needed to curb dog rabies and thus prevent human rabies. For the parts of the world where dog rabies is endemic, only REDIPRA and the Pan American Health Organization in Latin America can claim tangible successes in rabies control through a One Health approach. There is no pan-Asian or pan-African approach to rabies control, underlining these parts of the world as the problem areas where almost all cases of human rabies occur. Since rabies is so effectively controlled in the developed world, but a serious problem across the entire continents of Africa and Asia, it is clear that a global approach is needed to promote and address the realities of the persistent progression of dog rabies among the world’s poor.
The Alliance for Rabies Control was formed in Scotland in 2006 and became the Global Alliance for Rabies Control (GARC) in 2007, in that year also launching as one of its first major initiatives the inaugural World Rabies Day (WRD). WRD, sanctioned by the United Nations, falls on September 28 (the anniversary of Louis Pasteur’s death) and has been remarkably successful in promoting rabies initiatives across the world. Since the inaugural event, participatory activities and the numbers of countries involved in subsequent WRD initiatives have consistently increased in leaps and bounds from year to year, clearly illustrating the need for such messages in communities across the world (59).

The principal objective and achievement of WRD remains advocacy and the generation of widespread awareness of rabies and its true burden—the key first step toward the quest for and implementation of any (or better) disease control measures. Indeed, 2007 also saw the launching of a GARC rabies control program in Bohol, Philippines, that in due course proved to be quite successful and led the way for other similar initiatives. GARC also established the Partners for Rabies Prevention (PRP) in 2008, as a widely representative group of rabies stakeholders and experts who endeavor to support leading public-private rabies control activities across the world. In essence, PRP provides a uniquely uniting enterprise that allows for collective strategic thinking and generation of ideas and plans through the utility of diverse skills, experiences, and capabilities of the global spectrum of partners. As one of the first undertakings, PRP developed and launched a blueprint for rabies elimination and control, in a quest to meaningfully assist in potential or existing national and international rabies interventions. This blueprint is essentially a novel and dynamic operational toolkit for rabies elimination that is entirely built on the principles of the One Health concept (60).

New vigor and global partnering to address the neglect of dog rabies in the developing world gradually resulted in several projects that have the core objective of demonstrating human rabies prevention through dog rabies control and eventual elimination. Three such large-scale demonstration projects are supported and partially funded by the Bill & Melinda Gates Foundation and administered by the WHO and represent a significant step in raising the profile of rabies in the developing world (61, 62). The project sites are located in Asia (Philippines, Visayas Islands) and Africa (southeastern Tanzania and KwaZulu-Natal Province, South Africa). These programs will serve as a platform for generating information on the unique challenges and solutions facing each site, with a view to extending these projects to neighboring regions. It is estimated that eliminating rabies in these three areas will save in excess of 50 million people from the constant fear of rabies (62).

The selection and establishment of these programs was based on detailed plans that promised success in demonstrating effective control and elimination of dog rabies. Apart from dog rabies endemicity, other criteria included (i) a good record of rabies surveillance; (ii) disease burden in dogs and humans well supported by laboratory diagnosis; (iii) a general understanding of the epidemiology of rabies in the region; (iv) potential to benefit other countries in the region, based on demographic and geographic similarities; and (v) proven, government-driven efforts or commitment to control the disease in dogs (see, for example, references 63–65).

Rabies is a complex disease, and the components of programs to control the disease are therefore equally multifaceted. Thus, one of the intentions of these demonstration projects has been the development or implementation of research into new technologies and biologics to improve strategies for dog rabies control. For these programs, typical research activities include, among others aspects of vaccinology, epidemiology, diagnostics, animal primary health, human health, dog ecology, dog population management, and knowledge, attitudes, and practices of the affected communities. Generally, the benefits gained from international interest, participation, and contributions to these control programs were evident from early on (63), and success in one of the fundamental goals of the Gates Foundation/WHO programs, i.e., human rabies prevention, has already been reported (58, 73). The aim of these projects is to demonstrate and enable a paradigm shift toward an ideal One Health approach in dealing with rabies. Clearly, maintaining isolated rabies-free regions in Africa or Asia will be nearly impossible and pan-continental strategies, grown from successful regions/projects, will be necessary for sustained control. Such a lofty ideal will be incredibly challenging to fulfill. However, the largest hurdle to the elimination of dog and human rabies remains the lack of political priority or will and not the lack of methodology, biologics, or funding.

As catalysts for national and global approaches to dog rabies control and human rabies prevention, demonstration or pilot programs are essential. Thus, apart from the Gates Foundation/WHO programs, several other valuable endeavors have followed the One Health-based dog rabies control successes of the developed world and more recently of Latin America.
Quite a few of these have been focused on parts of Asia, one of which, in Bohol, was mentioned previously as an early initiative after the formation of GARC. This is a program that explicitly sought to elicit community-based advocacy, planning, and execution of rabies control actions. Since its inception, many partners—other than GARC and the provincial government—have contributed with treasure and/or talent (66). The successes within this program illustrate modern-day successes in rabies control in keeping with the One Health paradigm and should be inspirational to others concerned with the devastation of rabies in the entirety of Southeast Asia.

In Sri Lanka, the World Society for the Protection of Animals (WSPA), the Blue Paw Trust, and the Colombo Municipal Council formed a partnership to address management of the Colombo dog population, including vaccination of the entire dog population and creating rabies awareness (67). In Indonesia, rabies was recently introduced in Bali. Toward the end of 2009, a coordinated and effective rabies control program developed and supported mass vaccination projects (59, 68).

THE FUTURE
A key concept from the programs described above, and those that will follow in the aspiration for a world free of dog rabies, is a clear comprehension of the complexity of a classical zoonosis that can only be addressed with a One Health approach that embraces both human and animal public health doctrines inclusive of scientific method and research, community and governmental function, communication and education, and secured priority funding.

Many drivers contribute to the recurrent neglect of rabies in the modern world (Fig. 3). Important key words reflect classical features of neglect: (i) “a lack of” priority, supplies (vaccines or affordable biologics), capacity (local and beyond), data (to understand burden), models (to demonstrate feasibility), persistence (toward sustainability), and awareness (about the disease or options for control); and (ii) “poor or insufficient” notifiability of rabies, availability of educational materials and initiatives, communication among stakeholders, technology transfer from research to practice, and ability to interest major funding bodies.

Rabies remains endemic throughout the developing world and, for all the reasons discussed, loses visibility as it falls between authorities concerned with human health and with animal health. Poor epidemiological surveillance and inconsistent reporting—including to the responsible global authoritative bodies—have created a lack of rabies awareness and lack of appreciation of the burden that it conveys to the peoples of the world. The absence of reliable and sustained rabies data compromises the priority that the control of rabies should be given, to the extent that the ultimate objective of eradication will always be difficult to justify on national levels or to global funding agencies.

The above issues need to be effectively addressed if the cycle of neglect is to be overcome. To a large extent the new global partnerships and road maps, with resultant pilot and demonstration programs, are exactly focused on these considerations that have been identified as the major drivers of the current-day dog rabies crisis. For example, the value and importance of dog ecology and welfare, inclusive of new inventions such as effective and appropriate immune contraception and the quest for efficacious and cost-effective vaccines for oral vaccination of dogs, are key paradigms in the global rabies expert community. The demand for better surveillance is supported by the offering of new diagnostic tests that are as reliable as the classical gold standard but faster and simpler to perform (69). The value of molecular epidemiology with added possibilities to determine and predict transmission pathways is and should be promoted, as this will have a major impact on the fine-tuning of operational steps during rabies control campaigns.

It is true that recent rabies control partnerships and initiatives have been progressive, productive, and promising of true global benefits. However, as with any disease control program, big or small, collective persistence will be required to ensure consistent progress and sustainability of early successes. Herein lies a significant challenge. For stakeholders and experts concerned with rabies, it will be important to qualify and advocate the burden that this disease inflicts on humanity. As an opportunistic virus, rabies continues to spread into an expanding global dog reservoir, and the dynamics of the impacts of the disease need to be reassessed in line with its past and continued neglect. Such assessment is the cornerstone of responsible global advocacy toward achieving and maintaining appropriate priority on the national and international agendas for meaningful disease control. Although an earlier estimate of the burden of rabies was a useful exercise (54), it was primarily based on evidence from fragmented areas/countries in Africa and Asia and is in danger of becoming outdated as rabies rapidly progresses in the modern era. Therefore, a priority of the PRP and GARC had been to re-evaluate the universal burden of rabies, inclusive of prophylaxis costs, disability-adjusted life year (DALY)
scores, and economic burden models that would allow for meaningful evaluation within the entire spectrum of public health interests and priorities. But while rabies is a serious public health issue, it remains, in the developing world, primarily a disease of dogs. Its agricultural impact is fairly minimal—so the economic burden, while not zero, is perhaps easily dismissed when compared with those presented by a plethora of livestock diseases. Thus the necessity for the veterinary sector to buy into the One Health paradigm remains a primary mission. It is in this regard that international, national, and/or local organizations promoting animal welfare (WSPA, Humane Society International, International Fund for Animal Welfare, etc.) have become important players, by advocating and implementing appropriate practices for the care, treatment, and management of dog populations in areas where dog rabies is endemic. In addition, the OIE has recently released its Fifth Strategic Plan, which includes the One Health approach, committing to improved cooperation with human-animal-environment interfaces (70). This uniformity will require true collaboration between medical, veterinary, and wildlife sectors—the One Health approach. Because of the need for consistent and transparent data (74), appropriate actions and changes will be necessary and feasible. In addition, pathways for rabies control will have to be pan-continental and rely on promising declarations of global cooperation between the OIE, WHO, and the Food and Agricultural Organization of the United Nations (71), as they hone respective disease-fighting coordination mechanisms.

CONCLUDING REMARKS

Rabies control is a long-term goal that cannot be driven by economics alone. Those countries and regions willing to attempt elimination of rabies will have to realize that the substantial investment required will yield slow, albeit inevitable returns. The One Health model perfectly applies to rabies and reminds us that, even in the modern world, collective thinking is capable of producing simple but novel concepts that will allow for the solving of age-old and new public health problems, given appropriate and sustained institutional and sociopolitical support.

REFERENCES

Factors Impacting the Control of Rabies


