Feature

Veterinary Record Towards One Health

ONE HEALTH

Rabies control and elimination: a test case for One Health

One Health approaches have already been shown to be successful in controlling rabies in different parts of the world. In this article, the latest in *Veterinary Record's* series promoting One Health, Sarah Cleaveland and her colleagues at the University of Glasgow discuss why integrated strategies are needed to enhance the cost effectiveness of measures to control and eliminate rabies, particularly in low-income countries

AS One Health becomes more widely advocated, particularly within the veterinary profession, practitioners are coming under increasing scrutiny to demonstrate the added value of these approaches. Despite an intuitive appreciation that complex health problems need to be tackled through an integration of the interdisciplinary and transdisciplinary approaches that define One Health, there still remains a need to generate quantitative and qualitative evidence to clearly demonstrate these benefits (Okello and others 2011, Zinsstag and others 2011, Häsler and others 2012, Gibbs 2014).

Mass dog vaccination underpins the success of canine rabies control and has been shown to be feasible in most settings in Africa and Asia. Here, owners wait in line to get their dogs vaccinated by an NGO-funded programme in Matongo village, close to the Serengeti National Park in Tanzania

One Health encompasses a wide variety of disease and health problems; however, zoonoses have always been an area of interest and, of these, rabies provides an exemplar of the benefits of a One Health approach. In this paper, we outline how One Health has underpinned successful rabies control programmes, and why integrated approaches are likely to be essential to enhance the cost-effectiveness of control and elimination measures, particularly in low-income countries.

The global rabies problem

Rabies is a devastating and often fatal disease caused by neurotropic RNA viruses of the Lyssavirus genus. It is a globally distributed zoonosis that can infect and be transmitted by all mammal species, but the vast majority of human deaths worldwide are the result of bites from rabid dogs. Although rabies has been successfully controlled in many parts of the world, it is estimated that every year more than 50,000 people die from rabies – mostly children in Asia and Africa, where canine rabies remains endemic (Knobel and others 2005, Hampson and others 2008, Shwiff and others 2013). While rabies evokes less fear and concern than zoonoses that can spread by human-to-human transmission, such as SARS and Ebola, the death toll is substantial; equivalent to over 100 people dying every day. The disease also has the highest case-fatality rate of any zoonosis, with the onset of clinical signs almost invariably resulting in death.

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As with many neglected tropical diseases, rabies is essentially a disease of poverty. The disease attracts little attention from national policymakers because of an ongoing cycle of neglect. Few human or animal cases are officially reported and, because the communities most affected are marginalised and poor, the disease remains relatively invisible. Although rabies can be prevented in people bitten by rabid animals by postexposure prophylaxis (PEP), which involves the administration of immunoglobulin and a multidose course of vaccination, PEP is costly, needs to be administered very promptly (within 24 hours of a bite), and is often not available in poor or remote communities. As a result, it is almost only ever the poor, who have little access to health services and struggle to raise funds to reach health facilities quickly, who die from rabies.

Inequalities in healthcare access are clearly not unique to rabies, but the consequences of rabies exposure are particularly feared, the uncertainties in outcome are often harrowing and the psychological trauma experienced by those witnessing a case is profound (Cleaveland and others 2007, Hampson and others 2008). The reality of healthcare provision across much of Africa means that victims of rabies receive little palliative care and often die in profoundly distressing circumstances. Given that rabies is a disease that is 100 per cent preventable, this level of suffering should not be tolerated.

From the perspective of veterinary services, rabies also remains neglected in Africa and Asia because it is not considered to be an important disease of economically

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valuable livestock species, which are the priority for government veterinary services in these regions. As with the human health sector, a lack of data exacerbates the problem, with few livestock keepers reporting rabies cases to the authorities. However, it is clear that the consequences of a rabies incident can be serious for farmers, as a single rabid animal may attack many individuals within a herd or flock. Preliminary data from contact tracing studies in a pastoral district in northern Tanzania indicate an average annual incidence of 25 cattle deaths per 100,000 cattle per year, with a peak incidence of 100 cattle deaths per 100,000 cattle per year.

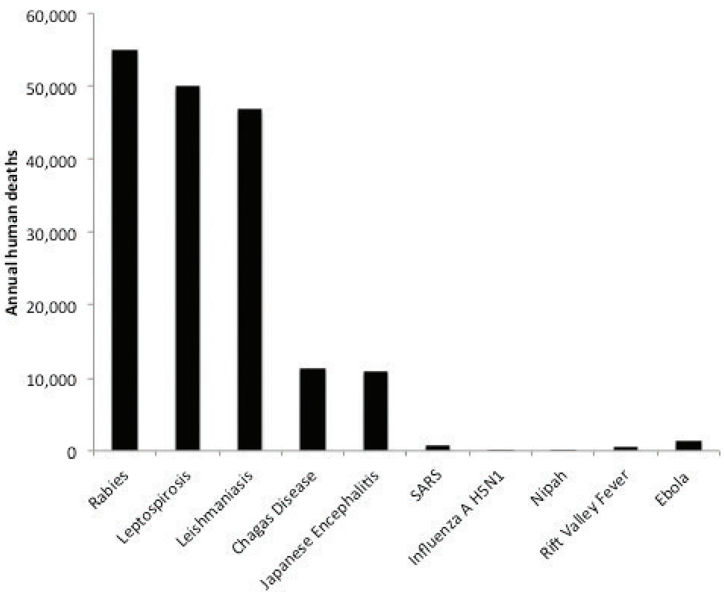

Chart showing the estimated annual number of human deaths from major zoonotic diseases, adapted from Lembo and others (2010). Additional data on leptospirosis were obtained from WHO (1999), based on a 10 per cent case fatality rate for an estimated 500,000 cases worldwide. Revised figures for Ebola deaths (1427 deaths in 2014) were also obtained from the WHO (2014)

An important constraint affecting the control of rabies is that many veterinarians in Africa and Asia have little experience or confidence in handling dogs or implementing veterinary interventions involving domestic dogs. This gives rise to a widespread misperception that free-roaming dogs are difficult or impossible to handle and vaccinate. A generally poor

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understanding of dog population biology, which has often resulted in inappropriate and ineffective approaches to rabies control, further exacerbates the situation (Lembo and others 2010). New initiatives, such as the African Small Companion Animal Network (AFSCAN) project, led by the World Small Animal Veterinary Association Foundation, have great potential to facilitate the growth of companion animal veterinary networks that can support canine rabies control efforts where they are most needed.

Although multiple factors contribute to the lack of effective canine rabies control across Africa and Asia, there is substantial evidence that the disease can be controlled and eliminated through approaches that are centred on the mass vaccination of dogs. Even in wildlife-rich areas in Africa, dogs act as maintenance hosts and reservoirs for canine rabies (Lembo and others 2008), and vaccination of 70 per cent of the dog population is sufficient to disrupt transmission cycles and eliminate the disease, not only in domestic dogs, but in all other mammalian hosts (Hampson and others 2009), with corresponding declines in rabies exposures in people (Cleaveland and others 2003). Operational research has demonstrated that, even where most dogs are free-roaming, as is the case in most communities in Africa and Asia, it is feasible to implement campaigns that achieve 70 per cent vaccination coverage (Kayali and others 2003, Kaare and others 2009, Davlin and Vonville 2012, Putra and others 2013). Dog vaccination campaigns are also likely to be more cost-effective for preventing human rabies deaths than relying on human PEP alone, and over five- to 10-year horizons have the potential to result in net economic benefits (Bögel and Meslin 1990, Zinsstag and others 2009, Tenzin and others 2012, Fitzpatrick and others 2014).

Why the need for a One Health approach?

Rabies demonstrates one of the enduring dilemmas that hampers the control of zoonotic diseases, in that the costs and benefits of control measures are often not distributed equitably across sectors. It is the human health sector that derives the public health and economic benefits from canine rabies control – the reduction or elimination of human rabies deaths, and reduced need for costly PEP for people bitten by suspected rabid animals. However, it is the veterinary services that generally incur the costs for canine rabies control, but derive few economic benefits, as domestic dogs are not an economically valuable species. Without a sharing of costs and benefits across sectors, there may be little incentive for veterinary services in low-income countries to prioritise investments for rabies control, rather than for economically important diseases of livestock, such as peste des petits ruminants, foot-and-mouth disease, or contagious bovine pleuropneumonia.

Cost-effectiveness analyses using detailed data derived from epidemiological contact tracing and vaccination campaigns in rural Tanzania indicate that a 70 per cent dog vaccination coverage is likely to provide the optimal scenario for cost-effective prevention of human rabies (Fitzpatrick and others 2014). This threshold is not only sufficient to disrupt rabies transmission, but is also a level of vaccination coverage that can be achieved at relatively low incremental cost through central-point vaccination strategies, where owners bring dogs for vaccination.

However, in all scenarios that demonstrate the cost-effectiveness of dog vaccination to prevent human rabies deaths, initial investments are needed to implement dog vaccination and achieve the 70 per cent coverage that will bring canine rabies under control and reduce human rabies exposures. At the outset of rabies control programmes, these investments are likely to exceed operational budgets available to veterinary services alone. In the discourse surrounding One Health, there has been much discussion about the need for joint programmes involving ministries of health and ministries of livestock. However, sharing of budgets across ministries is invariably complex. While progress has been made in several countries by creating interministerial 'One Health' platforms for joint planning, implementation and budgeting of

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interventions for zoonotic disease control, considerable practical and political challenges remain. Issues of ownership and trust remain critically important, which requires effective communication among all stakeholders, and adequate and equitably distributed resources (WHO 2013).

Catalytic funding from external donors provides a potential solution, but these investments need to be made within sustainable funding strategies that involve long-term government support and commitment. Interest is growing in the potential use of novel funding mechanisms and partnerships, including development impact bonds (a form of social impact bond [a payment-by-results agreement]) for low-income countries, whereby initial costs of disease control are supported by private investors and repaid by donors and governments once agreed outcomes are achieved. These schemes are currently being piloted by the UK Department for International Development (DfID) for the control of sleeping sickness in Uganda (http://devtracker.dfid.gov.uk/projects/GB-1-203604/), and have considerable potential for rabies control, given the relatively high initial investments needed for the implementation of dog vaccination campaigns to generate human health and economic benefits.

Although it is recommended that rabies control should be considered a public good (OIE 2011), government veterinary services often remain committed to a sustainability model that involves cost recovery, including charging dog owners for vaccination. However, in low-income settings, where rabies control is urgently needed, it is unlikely that any fees recoverable during a mass dog vaccination campaign would offset the additional costs involved (for example, an extra person handling cash during vaccination campaigns). Moreover, there are many reasons why charging a fee at the point of vaccine delivery is likely to be counterproductive. Owners will be discouraged from bringing their dogs, and it is hard to envisage a scenario where vaccinators would refuse to administer vaccine to dogs brought by children who have no means of payment. Indeed, in low-income communities where fees have been charged during campaigns, vaccination coverage has been far below the 70 per cent threshold required (Dürr and others 2008a). Nonetheless, other mechanisms may exist for supporting dog vaccination campaigns through owner payments, particularly in middle- and higher-income countries, for example through charging dog registration fees, as has been introduced successfully in the Philippines (Lapiz and others 2012), or through establishing community insurance schemes. While some consider that owner fees are needed to encourage commitment from dog owners, the time and effort required to bring dogs to central vaccination stations demonstrates that owner participation is often already high in many low-income settings.

For all financing scenarios, a key assumption underpinning the cost-effectiveness of dog rabies vaccination is that the demand for and use of PEP will decline as dog rabies is brought under control. However, in reality, this is likely to vary considerably across different socioeconomic settings. In Tanzania, for example, the incidence of bite injuries reported at health clinics declined rapidly as the incidence of rabies fell (Cleaveland and others 2003), and can decline to zero where canine rabies has been eliminated (Lembo and others 2010). This suggests that people in these communities mostly seek PEP only when they recognise the risk of rabies, and not for bite injuries from animals that are not suspected to be rabid. This is a situation which reflects both a high level of rabies recognition, and the high private costs associated with seeking PEP in comparison with household incomes in Africa (Sambo and others 2013) – poor people will not allocate time and money to travel to clinics for PEP if they are not convinced of the risk. However, in more affluent communities, where people can more easily travel to clinics and PEP is more widely available and more affordable, PEP is likely to be administered even when the incidence of animal rabies cases and risk of exposure to rabies is extremely low (Lardon and others 2010). This has important implications for the cost-effectiveness of animal interventions for human rabies prevention.

'The lack of laboratory capacity for rabies diagnosis and poor exchange of information across veterinary and medical sectors is exacerbated by a perceived need for the separation of human and animal diagnostic facilities'

Kost Bezginsky/Demotix/Press Association

While rabies vaccines are widely available and rabies control should be considered a public good, many government veterinary services charge dog owners for vaccination. In low-income areas, this can discourage owners from vaccinating their animals, thereby detracting from control efforts

In order to reduce the high costs associated with human PEP and to realise the potential savings that can arise from mass dog vaccination, good communication between human and animal health services will be essential. Medical clinicians will only have confidence in withholding PEP if they are reassured that biting animals are rabies-negative, either through postmortem sampling and laboratory diagnosis, by the animal surviving a 10-day observation period, or by reliable reporting of the circumstances of the bite incident (including vaccination status of the animal). One Health approaches that promote integrated rabies surveillance and effective communication between veterinary and human health sectors have the potential to optimise the use of costly PEP for administration to those at genuine risk of rabies exposure, thereby saving money.

Integrated rabies surveillance

In Africa, there are currently few effective rabies surveillance systems for either human or animal rabies (Nel 2013), and although rabies is a notifiable disease in most countries, official reports are often deficient or misrepresentative. It has long been recognised that annual statistics reported to the World Health Organization (WHO) provide a highly misleading impression of the true human rabies situation, leading to the closure of the Rabnet website in 2011 (Nel 2013). For animal rabies, reporting in Africa and Asia is also fragmentary and is often not provided in a timely fashion. For example, from July to December 2013, the WAHID online database of the World Organisation for Animal Health (OIE), recorded no information on rabies for 13 canine rabies-endemic countries of Africa and current disease events for only a single African country (OIE 2014).

Many difficulties contribute to poor levels of rabies surveillance in Africa and Asia. To date, most attention has been given to lack of laboratory capacity for rabies diagnosis. For example, while Bhutan reported more than 10,000 PEP administrations between 2001 and 2008, only around 200 animals were tested during the same period (Tenzin and others 2012). This contrasts starkly with the USA, where approximately 120,000 animals are tested each year for rabies in more than 120 laboratories (CDC 2014). This lack of diagnostic capacity contributes to the very high demand and costs of PEP in Asia (currently approximately US $1.5 billion annually), as the infectious status of a biting animal is known for only a small fraction of suspected exposures and a full course of PEP is therefore recommended for most animal bites.

The lack of laboratory capacity for rabies diagnosis and poor exchange of information across veterinary and medical sectors is exacerbated by a perceived need for the separation of human and animal diagnostic facilities. This is a problem that bedevils the effective diagnosis and integrated surveillance of many zoonotic diseases, not only rabies. While the risk of transmission of zoonotic pathogens to laboratory personnel is often cited as a potential hazard, these risks do not logically translate into a recommendation to separate human and animal diagnostic testing. Laboratories in which humans routinely handle and diagnose human pathogens should have sufficient biosecurity and safety precautions in place to minimise the risk of zoonotic transmission within laboratories. Risk assessments should be made on a pathogen-by-pathogen basis to ensure that adequate biosecurity and safety measures are in place to allow for the safe handling of any diagnostic sample, irrespective of the host species of origin.

A lack of integration at the level of laboratory diagnosis is reflected at all levels of rabies surveillance. Thus, at the community level, when people report to health facilities following being bitten by a suspected rabid animal, medical personnel often do not communicate with livestock or veterinary field officers to instigate a follow-up investigation. Similarly, timely reporting of animal cases by veterinary staff to medical officers could encourage the appropriate distribution of human PEP to the areas where it is most needed. The widespread use of mobile phones has enormous potential in this respect, allowing for rapid communication between human and animal health sectors to ensure follow-up of animal cases and improve distribution of vaccine stocks to avoid the vaccine shortages that occur frequently in many of the more remote parts of Africa (Mtema 2013).

Although much emphasis has been placed on deficiencies in laboratory capacity, many additional constraints need to be considered in the context of developing integrated rabies surveillance systems. For example, submitting animal samples can be costly, unpleasant and hazardous; families rarely give consent for postmortem sampling of human cases; and efforts to submit diagnostic samples or disease reports often do not result in rapid feedback or beneficial responses for those affected (Halliday and others 2012). New approaches are now available to address some of these challenges. For example, less invasive sampling techniques, such as supraorbital needle biopsy of brain tissue or skin biopsies can provide valuable material for postmortem confirmation of human rabies (Mallewa and others 2007, Dacheux and others 2008). New diagnostic tests have also now been developed that provide simple and effective tools for diagnosis in the field (for example, lateral flow assays; Markotter and others 2009) or within local, non-specialised laboratories (for example; immunohistochemical assays, Lembo and others 2006, Dürr and others 2008b). These techniques

Laboratory personnel in Tanzania performing rabies diagnostic testing on animal samples. Separation of laboratory facilities for diagnostic testing of human and animal samples is costly and hampers the exchange of information and expertise needed for integrated surveillance and control of zoonoses

should empower frontline workers to rapidly communicate information about rabies cases and to instigate appropriate local response measures. However, the support of central authorities is critical to

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respond to surveillance information with appropriate control measures, such as mass dog vaccination campaigns and provision of adequate human PEP. Not only is this essential for mitigating the rabies burden, but without a response, healthcare and veterinary workers in the field will rapidly become demotivated to report cases, further perpetuating the cycle of neglect.

Effective One Health approaches

The most notable successes in rabies control in recent decades have come from Latin America, where the strong political and technical commitment of countries to rabies control and elimination in the 1980s started with a regional programme coordinated by the Pan American Health Organization (PAHO), including the implementation of mass dog vaccination campaigns and more integrated surveillance across human health and veterinary sectors (Vigilato and others 2013a). In these regions, the ministries of health recognise that mass canine vaccination campaigns are one of the most important actions for rabies control, and in the majority of Latin America countries, mass vaccination campaigns are coordinated annually or biannually by the health authorities, but include wide intersectoral involvement from veterinary services, communities and education sectors in the planning, promotion, implementation and evaluation of the campaigns (Vigilato and others 2013a). As a result there has been a marked decline in the prevalence of canine rabies in Latin America (Belotto and others 2005, Vigilato and others 2013b), while human deaths from the disease are now vanishingly rare. A target for the elimination of canine-mediated human rabies has been set for 2015 (WHO 2012).

While a key lesson from Latin America has been the importance of commitment and engagement from the health sector, a further lesson has been the integration of rabies control within broader public health programmes, with the PAHO including rabies within the group of 12 neglected and poverty-related diseases that were targeted for elimination (Vigilato and others 2013a). The rabies elimination programme has also received support from non-governmental organisations (NGOs), animal welfare organisations and public-private partnerships. These organisations support and significantly contribute to other entities, such as local health networks, local agencies connected to the ministry of agriculture, and communitarian and international organisations.

Similar partnerships have been established to support rabies control measures in Asia, with programmes involving NGOs, such as the Global Alliance for Rabies Control, animal welfare organisations, local governments and veterinary services implementing mass dog vaccination campaigns in Bohol, Philippines (Lapiz and others 2012), Bali, Indonesia (Putra and others 2013) and India (*VR*, September 28, 2013, vol 173, p 281). A key element of success of these campaigns has been the effective engagement and communication with communities, as well as broad cross-sectoral involvement, for example, including the department of education in the Bohol rabies elimination programme (Lapiz and others 2012).

In Africa, although the feasibility of reaching a 70 per cent dog vaccination coverage has been shown through pilot projects in a wide range of settings (Cleaveland and others 2003, Kayali and others 2003, Kaare and others 2009, Davlin and Vonville 2012), the reality is that, with the exception of recent rabies elimination demonstration projects funded through the Bill and Melinda Gates Foundation with the WHO, few large-scale rabies control programmes have been implemented over the past three decades. Dog vaccination campaigns implemented through government veterinary teams are often only carried out on a local scale, can be costly, and are rarely sustained, with resources frequently diverted to other veterinary priorities. It is becoming increasingly clear that sustained, contiguous and large-scale programmes are needed for effective control, as even small pockets of low vaccination coverage (for example, involving less than 0.5 per cent of the dog population) can significantly hamper progress (Townsend and others 2013). Sporadic campaigns that achieve patchy coverage are likely to be both ineffective and costly, and new approaches need to be considered to ensure more complete and sustained coverage.

Greater integration with public health platforms provides some potential opportunities. As with PAHO neglected diseases in Latin America, rabies is listed within the group of 17 diseases identified in the WHO programme for neglected tropical diseases (NTDs), and is included in several national NTD programmes in Africa that are managed by ministries of health. Control measures for many of parasitic NTDs involve mass administration of anthelmintic drugs (MDA) delivered by a network of community-based healthworkers, and there is growing interest in the potential for operational integration of rabies control measures within these programmes. Using the same cadre of healthworkers together with animal healthworkers and other community members (such as teachers), community-directed interventions within the NTD programme could be expanded to include mass dog vaccination campaigns, integrated rabies surveillance measures, and public health education programmes, with regulatory oversight and supervision provided by health and veterinary authorities. The advent of field diagnostic tests, the enormous potential for mobile phone communication and coordination, and the likely high thermostability of animal rabies vaccines, all suggest that community-directed interventions may be feasible, and deliver more cost-effective and sustainable approaches to rabies control in Africa than centrally coordinated strategies implemented by the veterinary services alone. The development of integrated 'control packages' that address several zoonotic disease problems has often been advocated (WHO 2009, Del Rio Vilas and others 2014), but rarely implemented, partly because of different operational requirements and intervention schedules. However, the greater flexibility offered by community-directed interventions may provide opportunities for combining rabies control measures with control of other canid-associated zoonoses, such as hydatidosis and leishmaniasis.

Dog population management

An enduring question is the potential contribution of dog population management interventions to the successful control and elimination of canine rabies. The discussion is complicated by the fact that the objective of canine rabies control and elimination has often been subsumed within a distinct objective – that of managing free-roaming dog populations. Yet neither the problems nor the solutions are the same, and while some approaches may be complementary, others will be counterproductive.

Critically, the basic reproductive rate of rabies (R_0), a measure of the transmissibility of a pathogen, is consistently low across all demographic settings (R_0 is less than two) and is independent of dog population density (Hampson and others 2009, Morters and others 2013, Townsend and others 2013). This indicates that reducing population density through dog population control will have very little effect on rabies transmission, whereas dog vaccination measures that bring R_0 to less than one will be highly effective in all settings. Despite this, and the empirical evidence that canine rabies can be eliminated through mass dog vaccination, there remains a perception that rabies cannot be controlled without reducing dog population densities, and indiscriminate culling of free-roaming dogs is still carried out by government authorities in response to rabies outbreaks in many parts of the world. But, not only is indiscriminate culling ineffective, it can often be counterproductive and has major welfare implications. Culling campaigns often result in owners hiding and moving dogs to other areas, and new dogs are acquired to replace those that have been killed, with human-mediated movement of dogs contributing to the spread of rabies, as was documented in Bali, Indonesia (Townsend and others 2013). Furthermore, dogs that are easiest to vaccinate are often those that are easiest to cull, and without clear identification of vaccinated dogs, culling of free-roaming dogs can often lead to culling of vaccinated dogs, reducing population immunity and increasing rabies risk.

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As rabies transmission does not depend on dog population density, sterilisation campaigns that aim to reduce dog populations are also not likely to be effective for rabies control. Sterilisation programmes can provide an important contribution to other dog management objectives, such as reducing nuisance and aggressive dog behaviours, improving people's acceptance of roaming dogs (Hiby and others 2012), and may improve the health and survival of free-roaming dogs. In some areas, addressing community concerns about these issues can also provide a valuable entry point for community engagement and generate community support for dog vaccination campaigns. Although empirical evidence is lacking, sterilisation may also have the potential to improve cost-effectiveness of rabies interventions, for example, by decreasing dog population turnover rates, or reducing dog bite injuries and hence demand for human PEP.

However, despite the potential benefits of some dog management interventions, mass dog vaccination must be considered the main priority for canine rabies control.

Conclusion

To date, only two diseases have been eradicated globally: smallpox and rinderpest – diseases that have been the exclusive provinces of human and veterinary medicine, respectively. Rabies provides a test case for the feasibility of eliminating a disease that spans these sectors. The evidence and arguments for a One Health approach to rabies control and elimination are compelling – but it remains to be seen whether we can achieve the necessary integration, coordination and collaborative partnerships to eliminate canine rabies as a global human and animal health problem.

It is clear that no single model of rabies control will be successful in all communities. Nonetheless, key One Health principles characterise all successful rabies efforts: effective intersectoral partnerships and communication; high levels of community ownership and participation; and strong political support at the local and national levels. Above all, an open-minded, pragmatic and flexible attitude is required to explore novel strategies and approaches – we owe it to the millions of people who are at daily risk from rabies to listen, to learn and to act.

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