Rabid about rabies: why, how, and when

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Whilst COVID-19 swept the globe in 2020, the rabies virus continued its steady march through communities across Africa and Asia. This ancient disease, which has been possible to eliminate for a century, still wreaks devastation on those living at the margins of society. The development of an effective human vaccine in 1885 made it possible for those bitten by rabid dogs to avoid rabies infection, but it did nothing to abate propagation of the virus through dog populations which serve as the reservoir species. The ultimate solution to this intractable issue lies with the veterinary sector to implement annual dog vaccination campaigns on a massive scale (Gibson *et al*. 2022). Recent examples of success and a coordinated global community are igniting new momentum for the global elimination of dog-transmitted rabies.

So as the world has become better at addressing public health disparities, why has rabies been left behind? The rabies virus is known for its unparalleled ability to evade detection by the host immune system; however, its deftness at avoiding the political spotlight is perhaps even more fascinating. Unlike HIV, Ebolavirus and SARS-CoV-2 which blaze through human populations like wildfire, the rabies virus burns more slowly in a companion species, dogs. This particular reservoir species, and how the virus spreads within it, enable the rabies virus to evade prioritisation by both human and animal health sectors.

Rabies has the highest case-fatality rate of any disease, approaching 100%, and kills millions of dogs each year, but these animals have no economic value to governments. By comparison, the catastrophic impact of rinderpest on agricultural economies around the world galvanised governments and veterinary departments to unite in its global eradication. Although the cost-effectiveness of dog rabies elimination has been well described (Fitzpatrick *et al*. 2016; Gibson *et al*. 2022; Shim *et al*. 2009), the economic gains fall between stools in existing political structures. Expenditure by veterinary services to control rabies in dogs, provide subsequent benefits through reduced livestock losses, diminishing human healthcare costs, and a strengthened economy through prevented human deaths, however this is a complicated sell in the world of political campaigning. When pitched against the more tangible upswing of controlling production animal diseases like foot & mouth disease, African swine fever and avian influenza, prioritisation of rabies has consistently failed to gain traction in veterinary ministries.

Paradoxically, whilst the idea of controlling rabies remains inconspicuous, the disease itself does not shy away from tabloid headlines. The uniquely violent mode of transmission, contorting the minds of once amicable dogs to seek out and bite people without provocation, is traumatising and terrifying for those involved. Children are at a disproportionate risk of rabies, due to their close contact with community dogs and poor awareness of the risks following a dog bite, and so public outrage understandably follows a spate of rabid dog encounters. But regardless of any response taken by government, the natural epidemiology of rabies results in the apparent disappearance of the virus for long stretches of time. Rabid dogs are inherently peppered through time by the protracted incubation period of weeks or months following the infected bite of a rabid animal (Mancy *et al*. 2022). During this time the virus is undetectable, being slowly shuttled within neurones from the bite location to the brain. Once in the brain, rabies only reveals itself for the short infectious period prior to death and many of these animals go unnoticed due to nondescript signs such as lethargy and paralysis. Months or years may therefore pass between dogs identified as rabid in any one community, meaning that the virus continues to circulate unseen in dogs living alongside people in the community. This sporadic epidemic picture fails to generate any sustained public or political pressure for a comprehensive control strategy. The veil is only lifted once robust surveillance systems are established revealing the pervasive nature of the rabies virus and its significant impact across communities.

There is, however, reason for optimism. The occult persona of the rabies virus exposes a chink in its strategy. The virus remains below the radar of widespread public awareness by constantly teetering on the edge of decline. It is, in fact, far less transmissible than many other diseases, as measured by the reproductive number (the number of animals an infectious individual will typically infect in a susceptible population). This, in turn, determines how easy it is to eliminate the disease through mass vaccination. The reproductive number of rabies is consistently reported between 1.2 and 2, requiring only around 40% of dogs to be vaccinated to push the virus into a downward spiral toward elimination (Hampson *et al*. 2009). This low threshold makes rabies elimination low-hanging fruit, even at the recommended annual vaccination coverage of 70% to account for the death of vaccinated individuals between campaigns. The first reports of successful rabies elimination through mass dog vaccination date back over one hundred years (Umeno and Doi 1921) and have since been replicated at varying scales across the rabies endemic world. The greatest example of this was the continental rabies control programme in Latin America launched in the 1980s and vaccinating more than 50 million dogs annually at its peak (Freire de Carvalho *et al*. 2018). The challenge is now to replicate this success in countries of Africa and Asia, where most human rabies deaths continue to occur (Hampson *et al*. 2015).

For the past decade, Mission Rabies has been working to develop effective strategies and tools to achieve dog rabies elimination at scale. Innovation in smartphone technology has enhanced the spatial management of dog vaccination teams, ensuring that pockets of population are not left unvaccinated and maximising the chances of elimination (Monroe *et al*. 2021). Exploration of existing and novel vaccination methods across diverse settings provide governments with data upon which to develop effective district and national strategies (Evans *et al*. 2019; Gibson *et al*., 2015, 2019; Mazeri *et al*. 2021; Sánchez-Soriano *et al*. 2019, 2020). Development of education programmes have been shown to improve knowledge of rabies prevention in school children (Burdon Bailey *et al*. 2018) and have reached millions of children in India and Malawi (Gibson *et al*., 2018); and intensification of rabies surveillance systems through central public reporting, active response and improved laboratory diagnostics have supported governments to generate the political will needed to mount a sustained offensive against the disease (Gibson *et al*. 2022; Yale *et al*. 2019).

Goa recently documented a tour de force in rabies control at the Indian state level through a seven-year campaign instigated by the Government of Goa in partnership with Mission Rabies. In 2021 the state became the first in India to be declared a Rabies Controlled Area under Indian legislation and the programme was found to be highly cost-effective in the prevention of 121 deaths over a 10-year period (Gibson *et al*. 2022). Whilst the Goa example is a fraction of what will ultimately be required, it provides a template from which to support other governments of South Asia to achieve their own success in rabies control.

Today rabies is a disease of inequality, inflicting an abhorrent toll on those with least opportunity, agency, and political influence to address the issue themselves. A person's chances of survival following the bite of a rabid dog depends entirely on their financial and logistical ability to access post-exposure prophylactic rabies vaccine. This disparity is further compounded by higher densities of unvaccinated roaming dogs in underprivileged communities (Mazeri *et al*. 2019) and inequities in access to health education. Our generation of veterinarians has an opportunity to redress this imbalance through a One Health perspective. The medical sector, experiencing the human cost of rabies, must support veterinary solutions until the last victim of a rabid dog bite leaves their clinic, and veterinarians need to unite to realise the biggest dog vaccination campaigns the world has ever seen. As smallpox eradication represented success for global human health, and rinderpest eradication was a victory for animal health, global dog rabies elimination can be an historic triumph for One Health.

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