Challenges and opportunities for the next miles in global rabies control

R.M. Wallace* [(1)] & T. Müller [(2)]

(1) Poxvirus and Rabies Branch, Division of High Consequence Pathogens and Pathology, National Center for Emerging and Zoonotic Infectious Diseases, Centers for Disease Control and Prevention, World Organisation for Animal Health (WOAH) Reference Laboratory for Rabies, 1600 Clifton Road, Atlanta, GA 30329-4027, United States of America

(2) Institute for Molecular Virology and Cell Biology, Friedrich-Loeffler-Institut, Federal Research Institute for Animal Health, WOAH Reference Laboratory for Rabies, Südufer 10, Greifswald-Insel Riems 17493, Germany

*Corresponding author: euk5@cdc.gov

Summary

The World Organisation for Animal Health (WOAH) has led animal rabies control efforts since 1924 and is responsible for several of the most impactful advances in rabies diagnostics, surveillance and animal vaccination of the 20th and 21st centuries. Primarily advancing rabies control through its formalised country partnerships, WOAH is responsible for the validation and recognition of official rabies tests and has developed the largest rabies vaccine bank in use in Africa and Asia. WOAH has also fostered technical collaborations and modern-day guidance through the formation of the Rabies Laboratory Network. While rabies is among the deadliest of all zoonotic pathogens, future efforts to control and eliminate the virus hinge on improvements in coordination among partners, financial commitments from international organisations and governments, and advances in diagnostic and vaccination methods. WOAH has a long-standing history of driving these changes and is positioned to lead many new advances in the coming years.

Keywords

Control – Dogs – Rabies – Rabies Laboratory Network – RABLAB – Surveillance – Vaccines – Wildlife.

Introduction

The World Organisation for Animal Health (WOAH) is an international organisation that was established in 1924 to collect, analyse and disseminate scientific information and encourage international alignment and coordination to control animal diseases. Rabies is one of many animal diseases for which WOAH has developed guidance for international control and coordination. This includes guidance on the surveillance and control of rabies in the *Terrestrial Animal Health Code* (*Terrestrial Code*), as well as on laboratory testing and vaccine development in the *Manual of Diagnostic Tests and Vaccines for Terrestrial Animals* (*Terrestrial Manual*) [1,2]. As rabies is a prime target for a One Health approach, in 2011 the Tripartite formed by the Food and Agriculture Organisation of the United Nations, WOAH and the World Health Organisation identified rabies as one of three technical topics to advance this concept and highlight the importance of cross-sectoral collaboration for effective risk management [3,4]. In this respect, WOAH, supported by *ad hoc* expert groups, has been a leader in scientific advances in rabies control, primarily through its support for the WOAH Rabies Reference Laboratory programme, but more recently through the development of the WOAH Rabies Laboratory Network (RABLAB), through the WOAH-endorsed rabies control programme initiative, and as technical lead for the United Against Rabies (UAR) Forum and the WOAH Rabies Vaccine Bank [5]. The article discusses the recent initiatives and impact of WOAH's global rabies programmes as well as the challenges ahead and actions required in the coming years for significant progress in rabies control.

Elimination of dog-mediated rabies

With a lethality of almost 100% in humans and animals alike, rabies is a global threat that kills tens of thousands of people every year. Dogs are the source of more than 99% of human rabies cases, particularly in low- and middle-income countries (LMICs) in Africa and Asia [6]. To be controlled and eliminated, this deadly zoonosis must be combated at its animal source. WOAH has long been committed to fighting the disease and supporting its Members on the road to a canine rabies-free future. In 2018, the Tripartite and partners developed Zero by 30, a global strategic plan to end human deaths from dog-mediated rabies by 2030 [7-9]. At the heart of this comprehensive strategy is a One Health approach that recognises the close links between human, animal and environmental health and promotes cross-sector collaboration to tackle public health challenges [7].

Developing and implementing effective dog rabies control programmes is critical to reducing the health and economic burden of the disease but is still a major challenge for many countries [10]. Adequate funding for disease elimination, both internationally and domestically, and prioritising the issue on governments' agendas are key to helping these countries make progress towards the elimination of dog-mediated human rabies deaths. WOAH has continuously encouraged governments and international donors to invest in rabies control programmes, particularly the vaccination of dogs. The development of national strategic plans is of particular importance, as strategic plans not only align multi-sector partners but also provide international partners with insight necessary to allocate resources adequately. Based on a template developed by WOAH, technical support and advice to countries in this regard must be strengthened in the coming years [11].

Despite an increase in international interest in the elimination of dog-mediated human rabies deaths, formalised as a Tripartite goal in 2015 [7], numerous intrinsic and extrinsic barriers have limited large-scale progress [10]. While many of these challenges are addressed through global initiatives, WOAH has several key leadership roles around aspects of dog vaccination programmes, animal disease surveillance and government-led rabies programme development. WOAH's Members agreed to foundational rabies control programme standards, reflected in the *Terrestrial Code* and *Terrestrial Manual* [1,2]. WOAH has played a critical role in improving alignment among partners from the field, governments and international agencies to ensure that these foundational components of rabies control are at the forefront of all new initiatives.

Animal vaccines

Most critical to reducing the burden of rabies is vaccination of dogs. For decades, WOAH has offered guidance on the development of animal rabies vaccines and the implementation of dog vaccination programmes. A recent study estimates that more than 130 million dogs are vaccinated against rabies each year in dog-mediated rabies endemic countries, an impressive number that contributes to the prevention of thousands of animal and human rabies deaths annually [12]. However, despite this tremendous display of veterinary capacity, vaccination coverage is three times lower than required to eliminate dog-mediated rabies globally, and recent evidence suggests challenges to scaling up vaccination to meet necessary levels without increased support for critical veterinary infrastructure [13]. Currently, parenteral vaccination is used for dogs, yet this method is ineffective at reaching herd immunity in communities with meaningful populations of dogs that cannot easily be brought to vaccination points (e.g. community

dogs, dogs unaccustomed to walking by leash, and dogs unaccustomed to receiving veterinary care) [14].

WOAH recognises that parenteral vaccines are the cornerstone of rabies elimination efforts, but in 2020 the WOAH RABLAB highlighted the need for immediate inclusion of oral rabies vaccination (ORV) as a well-studied and undervalued tool for vaccinating dog populations not easily reached through traditional parenteral campaigns [14]. In fact, despite the relatively high cost of oral rabies vaccine baits, integration of ORV into existing vaccination programmes can be a very cost-effective and efficacious strategy while overcoming logistical barriers that are currently stifling parenteral vaccination programmes [15-17]. RABLAB members detailed a strong case for the use of safe and effective oral rabies vaccines but cautioned that any live vaccines must comply with *Terrestrial Manual* requirements [2]. RABLAB recommended two routes for advancing ORV as part of dog vaccination programmes, including encouraging governments and industry partners to seek formal licensure of oral rabies vaccines for dogs and encouraging governments to recognise existing licensure through the WOAH Veterinary Convergence programme. In September 2023, Indonesia became the first country to license an oral rabies vaccine for use in dogs [18,19]. Together with the release of updated Tripartite guidance on how to implement ORV in a dog vaccination campaign [20], this is a signal that WOAH's efforts to advance the role of ORV in rabies vaccination programmes are taking effect.

Another threat to dog rabies vaccination programmes is the manufacturing and distribution of low-quality vaccines. Several countries have utilised low-quality vaccines as part of large-scale dog vaccination programmes, resulting in rabies outbreaks, loss of human and animal lives [21,22] and significant setbacks in dog-mediated rabies elimination. Studies have demonstrated that routinely available vaccine products have variable quality, with some antigenic contents too low to offer protection [22,23]. Dog vaccination programmes are critical to preventing human deaths, and while they are cost effective, they are more expensive to implement at an estimated US$2 per dog, with over 75% of this cost due to non-vaccine activities such as personnel and logistics. The use of low-quality vaccines not only jeopardises community health but also wastes resources. To counter the use of poor-quality vaccines, WOAH has long-standing recommendations in the *Terrestrial Manual* for the production and evaluation of vaccines. To promote the use of high-quality vaccines while also increasing access in LMICs, WOAH developed a Rabies Vaccine Bank that utilises a tender process and thorough product evaluation to negotiate favourable purchasing options for governments and donors. Since inception,

the vaccine bank has provided more than 26 million animal rabies vaccines to LMICs. Looking to the future of rabies vaccines, mechanisms like the WOAH vaccine bank should consider including qualified oral rabies vaccines, serve as a mechanism for pre-qualification and expand access to more LMICs so that dog vaccination programmes can ensure they are utilising effective products.

Surveillance, diagnostics and control

While there is general agreement that herd immunity of 70% in free-roaming dogs can halt rabies transmission [24,25], evaluating dog vaccination coverage has proven difficult, inaccurate and expensive. WOAH recommends post-vaccination evaluation, but the gold standard of dog vaccination is a documented reduction in rabies cases through robust surveillance [26]. Unfortunately, very few rabies-endemic countries have the infrastructural capacity to rely on their surveillance systems to inform rabies management actions. A scoping review of rabies surveillance systems found that from 2010 to 2019, 169 WOAH Members, the majority from Africa and Asia, did not report any rabies surveillance activities. Further emphasising the dearth of surveillance capacity in endemic countries, the review found that countries at the greatest risk for dog-mediated rabies outbreaks had a 16-fold lower rate of rabies testing [27]. This lack of surveillance has led to questioning of the actual burden of rabies, threatening to diminish the importance of the 2030 goal [28]. Unfortunately, even when surveillance data is available, many WOAH Members in which canine rabies is enzootic do not faithfully fulfil their reporting obligations to WOAH via the World Animal Health Information System.

WOAH has long been the leading agency for developing guidance on the establishment of animal disease surveillance systems. The *Terrestrial Code* and *Manual* and other pivotal documents have established standards such as case definitions, diagnostic methods and veterinary systems requirements for effective rabies surveillance [1,2,29]. To further encourage countries to adopt these standards, in 2019 WOAH announced a new initiative to recognise Members that have established strong rabies control programmes. Such government-led official control programmes for dog-mediated rabies must have proven effective surveillance, vaccination, dog management and public awareness programmes that are also aligned with WOAH standards [30]. In the first four years of this programme, numerous countries applied for endorsement and three were recognised: Namibia, the Philippines and Zambia.

WOAH initiatives such as its recognition of official control programmes are excellent for promoting standards and recognising programmes that have invested in rabies control

infrastructure, but even these recognised programmes face numerous logistical and financial barriers to dog-mediated rabies elimination. Notably, rabies diagnostic capacity is frequently lacking, with many countries relying on centralised national laboratories or external agencies as their only diagnostic services [31]. One of the root causes of a lack of decentralised rabies laboratories is the high cost and antiquated methods necessary to ensure accurate rabies virus detection, in addition to the need for highly trained diagnostic staff and expensive laboratory infrastructure. The most commonly utilised diagnostic method, the direct fluorescent antibody test (DFA), was developed in the 1970s [32]. While this has been the gold standard for over 40 years, it requires expensive fluorescent microscopes and relies on commercial diagnostic reagents that can be difficult to procure. In the 2010s, WOAH approved a new method, the direct rapid immunohistochemical test (DRIT) [33], which requires lower laboratory investment. While the DRIT offers a lower-cost alternative to DFA, no commercial entity has shown interest in producing the required reagents, which has blunted the impact. The most recent test WOAH recognised, in 2017, is pan-lyssavirus real-time reverse transcriptase polymerase chain reaction. Despite numerous advances in rabies diagnostic technology and WOAH's efforts to validate and promote these methods, rabies testing remains inadequate in many countries and inaccessible for many communities.

One of WOAH's mandates is to ensure that only accurate and formally validated test methods are used for official disease programmes. A potentially promising development for easier and low-cost rabies diagnosis has been the commercial release of numerous lateral flow devices (LFDs) for field diagnosis of suspected rabid animals. As of December 2023, at least 14 different LFDs were available for purchase, yet none were recognised by WOAH as adequate for use. Despite the lack of WOAH recognition, many organisations have begun to implement and recommend the use of these tests. In response, the WOAH RABLAB undertook two formal evaluations of these products, finding significant limitations in sensitivity and specificity [34,35]. To ensure that inaccurate diagnostics are not used for official rabies programmes, RABLAB released a statement in 2023 cautioning against the routine use of these tests until they are approved through a formal WOAH validation process, just as for all other official diagnostic tests [2]. Low-cost, field-based tests could improve the woeful state of rabies surveillance; however, widespread use of inappropriate tests jeopardises the health and safety of people and animals. The WOAH processes for validating diagnostic methods should not be circumvented, and until an LFD manufacturer successfully completes this validation process, LFDs should be used with caution.

Wildlife rabies management and control

It is well accepted that rabies virus is maintained independently in numerous reservoir species of the orders Carnivora and Chiroptera [36]. In many parts of the world, foxes, raccoon dogs, skunks, raccoons, coyotes, mongooses, ferret badgers and bats have replaced domestic dogs as the main rabies reservoir, with partially overlapping distribution areas in which species-adapted rabies virus lineages have co-evolved [37]. WOAH recognises that, as a result, rabies control has become more complex over the last 50 years. WOAH supports regional initiatives, but given the large number of wildlife reservoirs, it is difficult to develop a universal blueprint or guidance for controlling wildlife rabies as opposed to dog-mediated rabies. For wildlife, the outcome of rabies intervention measures depends on many factors, including the variant of rabies virus, the reservoir species that is being targeted, its behavioural ecology and biology, the species-specific efficacy of the oral rabies vaccine being used and the landscape features of the rabies-infected area [38]. Today, rabies control in terrestrial wildlife has evolved from a largely ineffective, ethically and environmentally questionable strict culling operation to a more comprehensive approach centred on vaccination involving the use of several tools such as point infection control (PIC), trap–vaccinate–release (TVR) and ORV [39].

Although PIC – which includes population reduction, TVR and ORV – and modified PIC (without population reduction) have been used successfully at the local level to eliminate raccoon-variant rabies in Canada [40], this tactic is not suitable for large-scale use and is very expensive [41]. Meanwhile, ORV of wildlife based on strategic, large-scale distribution of vaccine baits into the environment is considered highly effective for rabies control in some wildlife. The elimination of i) fox rabies in Canada [42,43], Western Europe [44-46], Israel [47] and Türkiye [48], ii) grey fox and coyote rabies in the United States [49,50] and iii) raccoon dog rabies in South Korea [51] demonstrates the potential of this concept and raises (often overly optimistic) expectations for wildlife rabies control. However, this impressive list of successes should not obscure the fact that ORV still faces significant challenges for basic and applied research as well as for regular implementations and continuation of existing ORV programmes, particularly in resource-limited settings. Türkiye has been an example of how slackened efforts to eliminate dog-mediated rabies and resulting spillovers can create a sustained rabies problem in wildlife [52].

Oral rabies vaccines

Red and grey foxes, raccoon dogs and raccoons are among the reservoir species for which short-term success in rabies elimination at the regional level seems possible. However, there are challenges to the future commercial availability of oral rabies vaccines for wildlife. For example, today's ORV wildlife programmes often rely on oral rabies vaccines, both attenuated and recombinant, that were developed more than 30 years ago [53]. One cause for concern is that the original variety of these vaccines is no longer available, resulting in little competition in the market. In fact, in recent years, ORV campaigns in Western Europe and North America have been based on only two commercially available vaccines that meet the WOAH minimum standards for safety and efficacy [2], while production of most of the original 15 oral rabies vaccines [53,54] was discontinued. In Eastern Europe, some oral rabies vaccines for wildlife are licensed primarily for the domestic market, but it is unclear whether these meet WOAH minimum requirements [2]. In addition, recombinant oral rabies vaccines are favoured over highly attenuated vaccines in North America, and *vice versa* in Europe [53,54], due to ongoing reservations about the nature of these vaccines (genetically modified organisms), resulting in even less flexibility in the choice of appropriate vaccines.

Fox rabies control

The control of fox-mediated rabies in Canada and Europe is still the flagship for ORV in wildlife [42-46]. In Europe in particular, it will be important in the coming years to secure the successes achieved [55]. Unfortunately, re-introductions of rabies as a result of high infection pressure from neighbouring countries to the east, i.e. Russia, Belarus, Ukraine and Moldova, where wildlife rabies is largely uncontrolled, prevented the European Union (EU) from achieving its goal of becoming rabies-free by 2020 [46]. With the implementation of the new Animal Health Law (Regulation [EU] 2016/429), rabies control has become mandatory for EU member states. This results in a particular responsibility for EU member states bordering rabies endemic non-EU countries, as they must maintain a sufficiently large vaccination belt along common borders. However, the re-emergence and subsequent spread of fox rabies in Poland in 2021 as a result of an undetected infiltration of the vaccination belt [56] and in border areas of Romania, Hungary and Slovakia in 2022 [57] highlight the need for constant diligence, accuracy and vigilance in the implementation of these vaccination belts, as well as for contingency plans to protect free areas in other parts of Europe. Unfortunately, current political tensions may make cross-regional cooperation on ORV in these border areas impossible in the coming years. Thanks to technical and financial support from the EU, rabies case

numbers decreased dramatically in Western Balkan countries to almost zero [46]. Since the last mile is always the most difficult, as it is disproportionately the costliest, and increasing ORV effort leads to an ever-smaller decrease in rabies cases [44], efforts must not be slackened if a rabies-free status in the Western Balkans is to be achieved. Sufficient and secure long-term funding is crucial. In view of the vast wildlife rabies-affected areas in Russia, Ukraine, Belarus and Kazakhstan, large-scale ORV programmes are not expected to be implemented or to yield major successes in the foreseeable future [45,55].

Rabies control in other wildlife reservoirs

Another frequently overlooked fact is that ORV cannot be easily applied to different wildlife reservoir species using a single vaccine and protocol. While ORV is highly effective in foxes and raccoon dogs, its effectiveness in other reservoir hosts is lower for a multitude of reasons. In particular, raccoons and skunks appear to be quite refractory to ORV, even when high virus titres are administered [58-61]. Evidently, the responsiveness of various reservoir species to ORV correlates with differences in vaccine uptake of mucosa-associated lymphoid tissues, suggesting host-specific limitations to ORV [62]. These findings call for research to improve vaccine uptake and efficacy under field conditions, yet there have been few recent advances in vaccine development. Although numerous new oral rabies vaccine constructs have been developed, they have rarely reached market maturity [53]. Furthermore, the focus of research has been on increasing safety rather than efficacy of vaccines, while the development of new species-specific baits has been largely neglected. This could be one of the reasons why, despite local successes, implemented large-scale ORV programmes targeting raccoons in the United States and Canada are aimed at containing rather than eliminating rabies [41,63,64]. Only measurable successes in the next few years that go beyond containment are likely to improve the sustainability of the ORV programme with regard to the goal of broader elimination of raccoon rabies [64].

From today's perspective and experience, it seems important that countries try to carefully consider whether the implementation of a wildlife rabies control programme is necessary from a public health perspective and feasible according to the current state of science. Realistically, skunks, Arctic foxes, mongooses and ferret badgers are not target species for rabies control programmes in the next few years, as there is a need for research – e.g. concerning effective oral rabies vaccines, attractive baits and cost-effective bait distribution strategies – to arrive at workable and economically viable ORV

concepts for these species that would enable large-scale implementation of control programmes.

Rabies control in bats

Given the more than 1,400 species of bats [65], their role as lyssavirus reservoirs and the antigenic complexity of known (and still unknown) bat-associated lyssaviruses against which cross-protection with commercial rabies vaccines is limited or non-existent [66], it remains rather speculative whether vaccine-based strategies can be used to combat bat-associated lyssaviruses, and implementing such strategies would be scientifically challenging [67,68]. Traditional vaccination methods such as parenteral injections are operationally impossible to implement for bat populations. Transferrable vaccines may be a path forward for reducing rabies infections in bats. Transferrable vaccination of bats often involves a paste containing a modified live rabies vaccine capable of limited bat-to-bat transmission and leveraging bat colony grooming and social behaviours. However, this approach would still require extensive workforce for vaccine delivery and remains a theoretical control measure at this time. From a practical point of view, this seems a utopian undertaking in view of the increasing protection of bats and their widespread inaccessibility [69]. Recent interest in live-replicating vaccines for bats has shown promise in a controlled laboratory setting, but it is unclear whether this approach can comply with WOAH's vaccine safety requirements. In addition, the international community has raised concerns about the ecological and human health impacts of unintended mutations from a product that is released with the intention of uncontrolled replication and spread [70-72].

Conclusions

For continuing success, clear priorities in the global fight against rabies have to be set. As terrestrial wildlife rabies realistically is not a candidate for eradication [73], from a global public health perspective priority must be given to the global elimination of dog-mediated rabies. At the 2023 UAR Forum Meeting, the Tripartite renewed its commitment to fight dog-mediated rabies worldwide. Combined efforts from the global community are required to meet the global goal to end human dog-mediated rabies cases by 2030. Strengthening capacity building and providing technical assistance in rabies surveillance and control through the WOAH Laboratory Partnership Programme or Tripartite-supported country partnerships, as well as cooperation at all levels, including a broad range of stakeholders, are essential prerequisites on the road to success. A critical component will be ensuring that canine rabies-endemic countries are willing to take

action. Latin America shows how this can be achieved at national and regional level. A wealth of guidance and tools have been developed or made available by the UAR Forum and other organisations [74]. Thus, the stage is set for their implementation in all regions of the world.

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