# Human rabies: prospects for elimination

**Joel Changalucha[1,2,3]*, Katie Hampson[2], Gurdeep Jaswant[2,4,5], Felix Lankester[6,7] and Jonathan Yoder[7,8]**

**Address:** [1]Environmental Health and Ecological Science Department, Ifakara Health Institute, P.O. Box 78373, Dar es salaam, 14112, Tanzania.
[2]Boyd Orr Centre for Population and ecosystem Health, Institute of Biodiversity, Animal Health and Comparative Medicine, University of Glasgow, Glasgow, G12, 8QQ, UK.
[3]College of Veterinary Medicine and Biomedical Science, Sokoine University of Agriculture, P.O. Box 3021, Morogoro, 23, Tanzania.
[4]University of Nairobi Institute of Tropical and Infectious Diseases (UNITID), P.O. Box 30197, Nairobi, 00202, Kenya.
[5]Tanzania Industrial Research Development Organisation (TIRDO), P.O. Box 23235, Dar es salaam, Tanzania.
[6]Global Animal Health Tanzania, Ngorongoro Conservation Area Authority Building, P.O. Box 1642, Arusha, Tanzania.
[7]Paul G. Allen School for Global Animal Health, Washington state University, P.O. Box 647090, Pullman, Washington, WA 99164 United States of America.
[8]School of Economic Sciences, Washington State University, P.O. Box 646210, Pullman, Washington, WA 99164-6210, United States of America.

ORCID information: Joel Changalucha (orcid: 0000-0003-0758-2480); Katie Hampson (orcid: 0000-0001-5392-6884); Gurdeep Jaswant (orcid: 0000-0002-5027-454X); Felix Lankester (orcid: 0000-0002-0802-0693); Jonathan Yoder (orcid: 0000-0002-9049-9591)

***Correspondence:** Joel Changalucha. Email: jchangalucha@ihi.or.tz

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## Abstract

Almost half of all countries in the world are effectively free of human deaths from dog-mediated rabies. But the disease still affects people in low- and middle-income countries, especially the rural poor, and children. Successful regional elimination of human rabies is attributable to advances in significant and sustained investment in dog vaccination, post-exposure vaccination and surveillance, illustrated by productive efforts to reduce human rabies in Latin America over the last 35 years. Nonetheless, countries still facing endemic rabies face significant barriers to elimination. Using the 2017 Global Strategic Plan to end human rabies deaths from dog-mediated rabies by 2030 as a reference point and an organizing framework, we assess progress toward global rabies elimination by examining the characteristics of successful regional control efforts and barriers to elimination. Although substantive barriers exist for countries where rabies remains endemic, advances in knowledge, technology, institutions, and economics provide a basis for optimism.

**Keywords:** vaccination, dogs, intervention, global health, Zero by 30, One Health

**Review Methodology:** JC searched the articles and removed duplicates while KH, JY, and FL gave recommendation of the additional relevant articles. Two authors (JC and GJ) independently assessed the titles, abstracts, and full texts to extract data from the articles while guided by the Zero by 30 logical framework. A manually designed spreadsheet-based tool was used to extract data that align with activities and outcomes of the logical framework. JC and GJ harmonized the differences observed in the extracted data by jointly reviewing the respective article. For each article, we extracted the overall message of the study, the activity/intervention employed in each study and its respective results. Specifically, in each study, we extracted data on the year of publication, the country where the study was conducted, and where the overall message of the study fits within the three Zero by 30 strategic objectives. In fitting within the strategic objectives, we extracted information related to rabies awareness and improved education; dog vaccination; human PEP; policies, guidelines, and governance to prevent human rabies; availability of appropriate technology and information; monitoring and reporting of progress towards goal; engagement of key stakeholders consistently; the efficient use of finances and other resources; and lastly, the mechanism of reporting the results and impact of UAR collaboration to stakeholders.

## Introduction

Rabies, one of the oldest known zoonotic diseases, is caused by a negative-stranded RNA virus from the *Lyssavirus* genus [1]. The disease is a considerable public health problem, every year killing an estimated 59,000 people worldwide, and causing over 3.7 million disability-adjusted life years and 8.6 billion USD economic losses [2, 3]. While inevitably fatal following onset of symptoms [4], human rabies is preventable through prompt administration of post-exposure prophylaxis (PEP) following a bite [2]. Moreover, the virus can be eliminated from source populations through mass dog vaccination (MDV) [5]. Although rabies has been eliminated in high-income countries and has been controlled in many middle-income countries, dog-mediated rabies remains endemic in much of Africa and Asia, with people in poor, rural communities and children most likely to die of the disease [3]. Consequently, human rabies can be described as a disease of poverty.

A variety of strategies have been used to reduce human rabies incidence. Post-exposure vaccination was successfully trialed by Louis Pasteur 135 years ago [6], and since then vaccination has been used extensively as the mainstay of PEP. Application of PEP alone, however, does not tackle the primary animal source of human rabies: the domestic dog. Several approaches have been used to control rabies in dogs, with varying success. For example, culling is often undertaken in response to outbreaks but has generally been counterproductive [7]. Surgical sterilization has been conducted, but is expensive and evidence is lacking on the benefits for rabies control [8]. By contrast, MDV has been shown to be a practical and effective method for control that has been used successfully to eliminate canine rabies from Japan [9], North America [10], and Europe [11]. Consequently, the combination of PEP provisioning and MDV are now considered the key pillars for eliminating human deaths from dog-mediated rabies [2].

Countries with histories of sustained investment in both PEP and MDV have mostly eliminated dog-mediated human rabies. There is typically a transitional phase of rabies control, when cases of canine and human rabies cases decline prior to elimination, as exemplified by the trajectories of many Latin American countries [12, 13]. In 1983, the Pan American Health Organization (PAHO) initiated an ambitious plan to eliminate rabies in the Americas [13, 14]. The regional plan promoted accountability, monitoring, and, crucially, coordination of efforts across the region, including increased diagnostic laboratories for surveillance, provisioning of PEP and free-of-charge MDV, funded from national budgets and the PAHO revolving fund [13].

However, rabies control in low- and middle-income countries (LMICs) lags behind in comparison to other regions of the world. In these countries, MDV has not been implemented at the scale required and for the duration necessary to control rabies, and access to PEP remains limited [15, 16]. In some countries, rabies has emerged in previously unaffected areas [17, 18], while in others, rabies has reemerged despite being previously controlled [19–21]. Rabies has not generally been considered a priority on the global health agenda resulting in scant investment and action [22]. Rabies management in most LMICs is therefore in a nascent phase for rabies elimination, wherein elimination may be an aspiration, but efforts to date have not yet met the challenge.

Recognizing that rabies remains endemic in many LMICs, the United Against Rabies (UAR) coalition was formed, comprising the World Health Organization (WHO), the World Organization for Animal Health (OIE), the Food and Agriculture Organization of the United Nations (FAO), and the Global Alliance for Rabies Control (GARC). The UAR launched a global strategic plan, "Zero by 30," to support countries to eliminate human deaths from dog-mediated rabies by 2030 [23]. The start-up phase of Zero by 30 (2017–2020) focuses on engaging countries to prepare sustainable One Health national rabies elimination plans that emphasize coordinated and integrated approaches to human and animal health [23].

The purpose of this review article is to assess progress and prospects for global rabies elimination. To do so, we identify and review recent relevant scientific literature published from 2017 to date about developments toward zero human rabies deaths. We rely on the Zero by 30 Theory of Change as an organizational framework to synthesize the current science, provide a basis for describing developments, and assess prospects for success.

The Zero by 30 Theory of Change (Fig. 1) defines three objectives and associated overarching outcomes that they aim to achieve:

1. Objective 1, Outcome 1: effectively use vaccines, medicines, tools, and technologies to reduce human rabies risk.
2. Objective 2, Outcome 2: generate, innovate, and measure impact to provide guidance and data.
3. *Objective 3*, Outcome 3: sustain commitment and resources to harness multi-stakeholder engagement.

Each of these objectives and associated outcomes are organizational focal points for this analysis and are highlighted in summary in Tables 1–3, respectively.

## Methods

We followed the Preferred Reporting Items for Systematic reviews and Meta-analysis (PRISMA) statement for reporting of healthcare interventions [24]. A literature search was conducted in March 2021 using three online databases (PubMed, Web of Science and Ovid SP (MEDLINER® and Embase)), identifying articles published from 2017 to date, that is, from the launch of the Zero by 30 plan. The primary search term "rabies" OR "rabid" was combined with the following search terms "dog vaccination," "post-exposure" OR "postexposure," "surveillance" OR "epidemiolog*," "One-health" OR "One health," "Elimination" and "policy" OR "strategy" OR "plan" OR "program*" OR "region*" OR "national." Additional relevant articles were also included following manual


**Figure 1.** The theory of change from the Zero by 30 global strategic plan.

searches. Identified articles from each database were combined and duplicates removed prior to title and abstract screening. Two authors (JC and GJ) independently assessed the titles, abstract, and full texts to extract data guided by the Zero by 30 logical framework. We included only primary research studies on dog-mediated rabies in endemic countries published in English from 2017, with the data collection period from these studies including time from 2017 onward. We excluded review articles and studies that exclusively reported wildlife or bat rabies and studies in countries without endemic canine rabies. Information was extracted for each article including the year of publication, the country where the research was conducted, the study design, and the main message of the article including its fit within the three Zero by 30 strategic objectives. In line with these objectives, we extracted information related to rabies awareness/education; dog vaccination; PEP; policies, guidelines and governance; technology and tools; monitoring and reporting; stakeholders engagement; and resource use.

## Results

We identified 67 articles that fulfilled inclusion criteria, and 12 additional articles were found to be relevant (Fig. 2).

**Table 1.** Summary table showing the activities expected to lead to short- and long-term outcomes for Zero by 30 (*Objective 1* (Outcome 1): Effectively use vaccines, medicines, tools and technologies to reduce human rabies risk).

| Long-term (2030) sub-outcome | Short-term (2020) sub-outcome | Activity (2017–2020) | Performance status |
|---|---|---|---|
| 1.1 Rabies is prevented through increased awareness and improved education | Effective, locally adaptable communication and awareness tools and strategies | Coordinate communication campaigns for World Rabies Day (WRD) in priority endemic countries<br>Engage partners, communities, and media to build rabies awareness | Prominence of awareness campaign ahead of MDV [25–28]<br>Promote innovative approaches to enhance dog vaccination campaign coverage [62, 63, 65–68] |
| | Sustainable responsible dog ownership and bite prevention education programmes | Develop coherent strategies for responsible dog ownership and bite prevention education | |
| 1.2 Rabies is prevented through increased and effective dog vaccination | Coherent, standardized, evidence-based tools and strategies for effective dog vaccination | Leverage existing tools to support effective SOPs for dog vaccination at the country level | Increased access to dog vaccines through OIE vaccine banks [25, 27], and use of low tech cooling devices in remote communities [63] |
| | Strengthened, vitalized and supportive regional networks | Organize regional workshops for coordinators to train in best practices and share lessons learned | Demonstration of using surveillance data to identify regions needing to improve MDV coverage [46, 37] |
| | Improved availability and access to dog rabies vaccines | Establish a biological bank to increase access for affordable dog rabies vaccines | |
| | Local, regional and global reporting structures established to facilitate data collection and sharing | Support effective use of monitoring and surveillance data to validate vaccination coverage | |
| 1.3 Human deaths from rabies exposures are prevented by ensuring equitable, affordable and timely access to healthcare, medicines and vaccines | Increased access to basic healthcare, especially for underserved populations | Support national plans that expand access to basic healthcare for all | Expanded access to PEP in some Asian countries [15, 16, 38, 79] |
| | Coherent, standardized, evidence-based tools and strategies for use of PEP, PrEP and RIG | Leverage existing tools to support prudent use of PEP, PrEP and RIG by health services<br>Regional workshops to build capacity in best-practice rabies prevention and care | Implementation of IBCM aiming to reduce unnecessary use of PEP [60, 91] |
| | Improved availability and access to human rabies biologicals (see Annex 4–Banks) | Establish a biological bank to increase access to affordable human rabies biologicals<br>Promote the use of surveillance data for forecasting of vaccine needs | |
| | Mechanism to reduce rabies biological usage where rabies incidence is low | Investigate bite prevention education and IBCM as strategies to reduce biological usage | |

Twenty-five focused on countries in Africa, 27 on countries in Asia, 4 in Latin America, and 3 that were global in scope. These studies focused on 43 different countries, with 11 articles using data from more than one country. Sixteen studies were conducted in India, 12 in Tanzania, 8 in the Philippines, 6 in China, and 5 each in Kenya and Iran, while the remaining countries had fewer than 4 studies each (Fig. 2). While 43 countries are represented in our sample, they represent only one third of current rabies-endemic countries. The number of articles identified by the search are provided in appendix Table A1, and individual paper characteristics of interest are summarized in Table A2 (Fig. 3).

The articles were distributed across the Zero by 30 objectives as follows: (1) to effectively use vaccines, medicines, tools, and technologies (34 articles); (2) to generate, innovate, and measure impact (41 articles); and (3) to sustain commitment and resources (4 articles). Tables 1–3 summarize information relating to these objectives, respectively, and provide a focal point for the review discussion to follow.

**Table 2.** Summary table showing the activities expected to lead to short- and long-term outcomes for *Objective 2* (Outcome 2): Generate, innovate and measure impact to provide guidance and data.

| Long-term (2030) outcome | Short-term (2020) outcome | Activity (2017–2020) | Performance status |
|---|---|---|---|
| 2.1 Policies, guidelines and governance to prevent human rabies deaths are created and adopted at regional and national levels | Coherent, standardized tools and strategies to prevent human rabies deaths<br>Harmonized international recommendations for rabies prevention in humans and animals<br>Established reporting structures and cross-sec-toral working groups within countries | Review existing rabies guidelines and manuals to identify conflicts and gaps<br>Engage countries and stakeholders to adapt existing tools for rabies prevention<br>Develop and validate guidance for countries on roles, responsibilities and accountability | Policies for PEP have been updated [2, 84]<br>Gaps in systems to monitor the use of PEP have been identified [16, 75, 76] |
| 2.2 Appropriate technology and information are made available | Innovative technological solutions in vaccines, diagnostics and supply chain<br>Online tools for policy-makers, scientists, medical professionals, teachers and public<br>Coherent, standardized tools and strategies for robust rabies surveillance | Review current vaccine and diagnostic technologies to identify research gaps and needs<br>Review and update online tools for rabies education and elimination<br>Engage stakeholders to promote innovation in rabies diagnosis and vaccine delivery<br>Promote development of a reliable, safe, sensitive point-of-care diagnostic tool<br>Update existing laboratory manuals to provide harmonized, evidence-based guidance<br>Regional workshops to train technical staff in sampling, transport and laboratory diagnosis | Reliable technology is available to improve surveillance and monitoring data to inform decision making [26, 42, 48, 60, 110]<br>Web-based platforms that align with IDSR 2 exist and engage countries in reporting human and animal data [42] |
| 2.3 Progress towards the goal is constantly and consistently monitored and reported | Improved tools for rabies surveillance, data collection and analysis<br>Integrated regional and global reporting systems for human and animal rabies data<br>Established process for validation and verification of reaching zero human rabies deaths<br>Regular programmatic monitoring at national and regional levels | Design and disseminate information on surveillance and data collection tools<br>Organize regional workshops to train technical staff in best-practice rabies surveillance<br>Engage countries to highlight importance of data reporting, and support them to improve<br>Support establishment of clear reporting chains within human and veterinary health services<br>Use surveillance data to demonstrate impact of investment in rabies elimination | Evidence of using routine surveillance data across countries to monitor control progress [20, 28, 73, 78, 103, 104, 119, 125, 129] |

### *Objective 1: to effectively use vaccines, medicines, tools and technologies*

Table 1 shows how key activities support this objective and are hypothesized to lead to three long-term outcomes (1.1–1.3), and several short-term outcomes to be achieved by 2020. Brief summary of progress is reported in the table.

#### *Outcome 1.1. Rabies is prevented through increased awareness and improved education*

In nascent rabies control programs, community-based awareness campaigns are commonly held prior to implementation of MDV to improve participation [25–28]. The reported awareness campaigns involved school programs covering topics like responsible dog ownership

**Table 3.** Summary table showing the activities expected to lead to short- and long-term outcomes for *Objective 3* (Outcome 3): To sustain commitment and resources to harness multi-stakeholder engagement.

| Long-term (2030) outcome | Short-term (2020) outcome | Activity (2017–2020) | Performance status |
|---|---|---|---|
| 3.1 National rabies elimination plans integrated to strengthen health systems | Investment in rabies elimination by countries, and regional and international partners<br>Regional advocacy strategies, including for Africa and Asia<br>National rabies elimination plans integrated to strengthen health systems | Design and implement partnership strategies with the public and sectors<br>Roll out communication campaigns to endemic countries<br>Support development of robust, integrated national rabies elimination plans | National plan established in Namibia, Philippines, Brazil, Peru and a few other countries in Asia and Africa [16, 25, 28, 50, 125] |
| 3.2 Finances and other resources are effectively and efficiently used | Detailed budget formulated including established models, supply landscapes and resource projections<br>Sustainable resource mobilization strategies available for countries to finance national plans | Review mechanisms for resource allocation, cost-sharing mechanisms and fundraising<br>Organize regional workshops to engage countries in developing resource mobilization strategies<br>Map existing and innovative funding mechanisms<br>Synergize rabies elimination with other programmes, and engage new partners | Model exist for policy makers in countries to project resources required for elimination [48, 110]<br>Although at limited scale, local governments in many countries are responsible for PEP procurement [15, 16, 75, 76] |
| 3.3 Results and impact of the United Against Rabies collaboration are regularly monitored and reported to key stakeholders | Regular reporting of the activities and impact of the United Against Rabies collaboration<br>Sustained financing of rabies elimination efforts to achieve Zero by 30 | Advocate globally, regionally and at the country level for investment in elimination<br>Deliver a resource mobilization campaign<br>Review implementation and lessons learned in Phase 1 to inform and refine Phases 2 and 3 | |

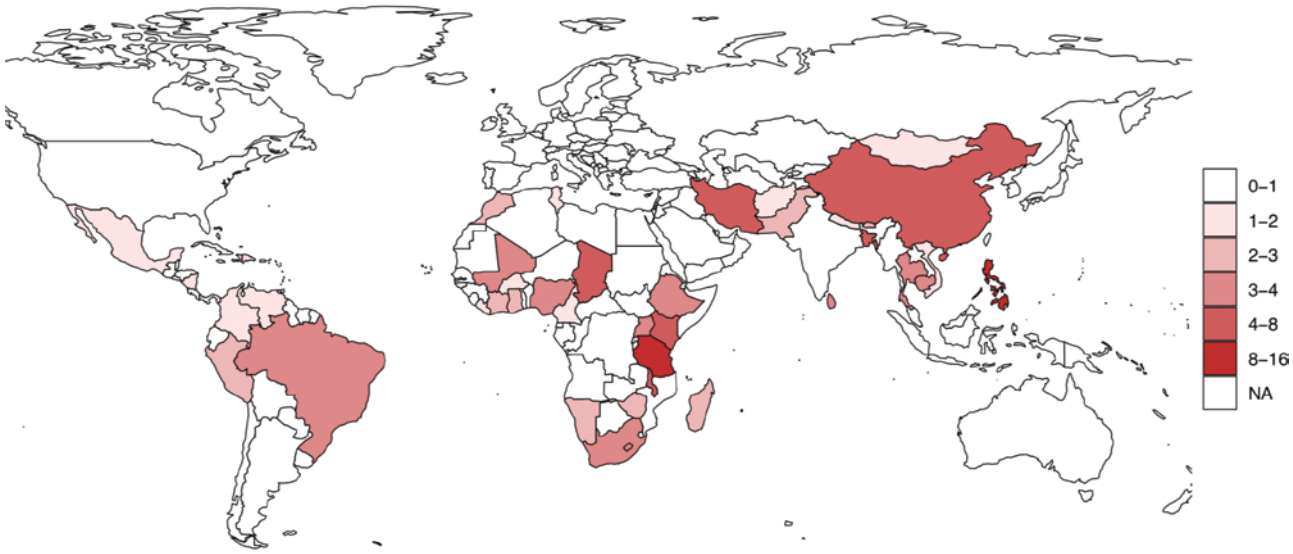


**Figure 2.** Geographical distribution of articles identified for this review.

and PEP [29]. Further efforts include meetings and symposia with community stakeholders organized to enhance participation of dog owners during vaccination campaigns [25, 26]. Two studies reported an increase in MDV coverage following these activities [25, 26], even though poor MDV coverage was also reported with the two other studies [27, 28]. Mixed outcomes of awareness campaigns can be explained from Knowledge, Attitudes

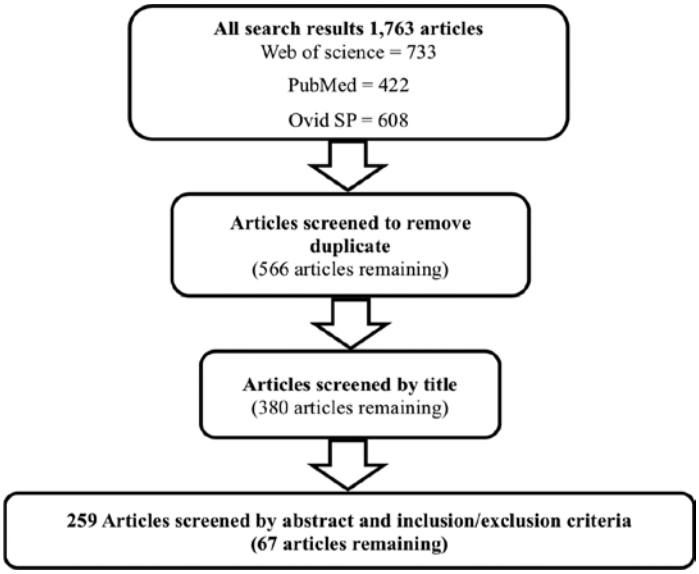


**Figure 3.** PRISMA flow diagram detailing the search and screening stages.

and Practices (KAP) studies showing that higher knowledge does not always translate into adoption of preventive measures [30–33]. Several studies reported misconceptions about appropriate preventive measures following a rabies exposure like a bite [30, 34–36]. Nonetheless, information programs associated with MDV campaigns appear to have provided measurable contributions to the effectiveness of control programs in Latin America [30, 37].

Various sources of rabies information are available, including online platforms such as those of GARC, World Animal Protection (WAP), and OIE that provide Information, Education and Communication (IEC) materials [25], and some countries mandate that ministries provide IEC materials [38]. World Rabies Day (WRD) was initiated in 2007 and an increasing number of WRD events have been registered annually [39], although the impact of WRD is unknown.

*Outcome 1.2. Rabies is prevented through increased and effective dog vaccination*

Experience from countries that have eliminated rabies shows that success depends on extensive and sustained investment in and use of MDV. However in most LMICs where rabies elimination programs are in the nascent phase, MDV efforts have been limited. Rather than being routine and large scale with the goal of elimination [25, 40], reported MDV campaigns have been mostly confined to just part of a country [27, 41], in response to outbreaks or implemented as a proof of concept [26, 42–45]. Sustained and comprehensive vaccination campaigns are required for progress toward elimination [46], and gaps in coverage can support persistence of the virus [47]. Likewise, inadequate cross border control efforts pose significant challenges in securing health gains, especially when neighboring countries have weak control programs [48–50].

Availability of dog vaccines varies across countries [51, 52]. Evidence from two studies show countries in the nascent phase of rabies elimination typically depend on external partners to supply dog vaccines [26, 41]. In response to the UAR recommendation for affordable and high-quality vaccines, three active OIE vaccine banks have been established for Africa and Asia, and records show that over 25 million doses of dog vaccine have been distributed by 2020 [53]. However, just two studies in our search, conducted in Namibia and Kenya, respectively, reported the use of vaccines from OIE banks [25, 27]. The use of high-quality vaccines, such as those offered through the OIE vaccine bank, is critical to maintaining herd immunity [54], with poor quality vaccines having shown to result in major resurgences of infection [54]. Given the evidence of inadequate funding for larger scale MDV in many rabies endemic countries, one study reported a reduction in cases of dog rabies through a vaccination strategy that targets transmission hotspots [42]. This example highlights the conundrum of countries in the nascent phase of elimination programs prior to funding being secured for sustained MDV programs. In Latin America, regional coordination and vaccine donations from neighboring countries aimed to prevent shortages [13]. Recent studies from Vietnam, South Korea, South Africa, and Tanzania not only demonstrate the feasibility of elimination when high-coverage MDV campaigns are carried out but also highlight challenges in sustaining their implementation [55–58].

Adequate veterinary infrastructure is also needed to deliver MDV. A needs assessment identified a shortage of dog vaccinators in LMICs with nascent rabies elimination programs [59] and limited capacity has been reported within the veterinary system more generally, including for collection of diagnostic samples [60]. One study demonstrated the feasibility of using community volunteers to bolster

vaccination efforts [27]. Vaccinator training materials and free digital data collection tools available online from the UAR attempts to address this challenge [26].

The literature describes a few strategies aiming to increase vaccination coverage and/or reduce costs. From 12 articles that report MDV activities, five report the use of standard delivery approaches involving a combination of central point strategies and door-to-door vaccination [25–27, 41, 50, 61]. These approaches tend to be carried out annually (pulsed) and are usually implemented by teams of vaccinators using centrally-stored vaccines (e.g., in refrigeration units in towns where electricity is available). Novel approaches have also been investigated. For example, a study in Tanzania demonstrated that a commonly used canine rabies vaccine (Nobivac Rabies) retained potency equivalent to cold chain-stored vaccine following storage at elevated temperatures (up to 25°C for 6 months and 30°C for 3 months) [62]. A subsequent study demonstrated the value and effectiveness of locally made and relatively cheap passive cooling devices for keeping canine rabies vaccines cool outside of the cold chain [63]. These studies demonstrate that canine rabies vaccines can be effectively stored in remote rural areas where power resources are limited. Decentralized storage may enable the vaccines to be managed by the communities themselves and allow continuous vaccination effort (throughout the year) and increased numbers of dogs being vaccinated at reduced cost.

Five studies assessed the use of Oral Rabies Vaccination (ORV) in India, Thailand, and Bangladesh to reach free-roaming dogs that are not captured by routine parenteral vaccination [64–68]. These studies were focused on the establishment of preferred baits [64, 68], and their potency following consumption [65–67]. ORV also fared well compared to Capture,Vaccinate and Release (CVR) strategies for reaching free-ranging dogs in terms of the percentage of dogs reached and implementation logistics [65].

Estimating vaccination coverage is still a challenge as countries struggle to establish whether they are achieving the 70% required for elimination. Problems reported on coverage estimation included initial dog population estimates being lower than total dogs subsequently vaccinated [25] and counting only owned dogs without including free-roaming animals that are more likely to transmit rabies [50, 69]. Likewise, difficulties were reported in how to mark dogs for estimating coverage when conducting ORV [64, 65]. Studies of parenteral vaccination in Kenya [27] and Tanzania [70] also reported that different techniques of estimating dog populations resulted in different levels of estimated coverage. One study illustrates how post-vaccination transects are a quick and low-cost means of monitoring vaccination coverage at scale [40]. In conjunction with MDV campaign data, transects can be used to guide rapid remedial vaccination of areas with low coverage, and to improve procurement and planning for future campaigns, with various apps available to support this process [71]. Post-Vaccination Surveys informed the effective placement of central points in Blantyre, Malawi, such that expensive supplementary door-to-door vaccinations were no longer necessary, greatly increasing cost-effectiveness while maintaining coverage [61].

*Outcome 1.3. Human rabies is preventable by timely access to PEP*

Human deaths following exposure by a rabid animal is preventable by timely and complete use of PEP. The WHO-recommended protocol for PEP includes immediate wound washing, administration of a course of vaccinations and, if indicated, infiltration of purified rabies immunoglobulin (RIG) into the wound. And while WHO recommends the use of cell-culture vaccine, one study in Ethiopia reports a predominant use of nerve-tissue vaccine [72].

PEP availability is a key factor for any country hoping to achieve zero human deaths from rabies. The Zero by 30 plan outlines requirements for expanding access to PEP. Despite having eliminated endemic circulation of rabies, some high-income countries continue to experience high precautionary demand for PEP [73]. Across much of Latin America, PEP is widely available, in some cases subsidized for recipients [13]; whereas across many African countries, access to PEP is often only available in a limited number of facilities, causing patients to travel long distances to find PEP. If located it often is sold at full price, which can be very expensive relative to local real incomes [30, 34, 74–77]. The literature suggests that only a limited number of LMICs currently report free or subsidized PEP at subnational level/primary care facilities [15, 16, 78, 79]. There are currently no vaccine banks for PEP in Africa and Asia, but Gavi, the Vaccine Alliance recently announced that human rabies vaccines would be supported in their vaccine investment strategy from 2021 [80], which could improve PEP access [22, 81].

A further critical aspect of human rabies prevention is ensuring that the PEP supply is conserved. Judicious use of PEP through the adoption of dose-sparing intradermal (ID) regimens helps to achieve this. ID administration can reduce the quantity of vaccine administered compared to intramuscular (IM) administration by 60%–80% [81] and enables vaccine vials to be shared by more than one patient [2]. An abridged 1-week ID regimen was recently demonstrated to be safe and effective [82, 83], informing the latest WHO position paper [84]. Subsequent modeling work demonstrated the potential high impact of adopting this regimen over current practice [22, 81]. In Madagascar where ID vaccination is already practiced, adoption of this regimen could reduce PEP use by 50% [79].

Despite over 30 years of evidence indicating the safety, efficacy, and cost savings, ID administration has not been widely embraced [2], and most countries continue to use IM administration [16, 30, 74–76, 78, 85]. Infrastructure needed for improved PEP management appears to exist in many rabies endemic countries as a result of support under the Expanded Program on Immunization [86]. However, these services apparently are often not used for rabies PEP [16, 75, 76].

Another component of PEP is the administration of RIG although recent evidence shows that timely and complete post-exposure vaccination is sufficient to prevent rabies even in the absence of RIG [76, 87]. This finding is encouraging, as RIG is in short supply in many LMICs [16, 75, 76, 81, 84, 88]. A study in India established that rabies monoclonal antibodies are equally as safe and effective [89] and the WHO changed its position to recommend only infiltration of RIG at the wound site without further intramuscular injection of the remainder [84, 90].

Integrated Bite Case Management (IBCM) is a recent approach in rabies control for reducing human deaths through enhancing prudent use of PEP. IBCM is a "One Health" approach that aims to establish the health status of the biting animal to inform PEP use [60, 91] and reduce human deaths while minimizing unwarranted PEP use [92–94]. IBCM has potential to reduce overuse of PEP in low-risk settings [78], and improve access to PEP in high-risk settings [34]. Three studies that involved training of health workers report a general improvement in risk assessments and delivery of PEP [60, 91, 95]. However there are context-specific challenges to its effective implementation. A lack of funding for animal health workers and the overall rigidity of human health and veterinary systems that limit intersectoral coordination are barriers to effective implementation [60, 91].

### *Objective 2: to generate, innovate, and measure impact*

Zero by 30 Theory of Change (Fig. 1) Objective 2 promotes effective policies, guidance, governance, and reliable data to enable effective decision making. Table 2 summarizes this objective, sub-objectives, and related outcomes.

#### *Outcome 2.1. Policies, guidelines, and governance to prevent human rabies deaths are created and adopted at regional and national levels*

The Zero by 30 plan advises that international standards and guidance for rabies control be tailored to local settings. So far, formulation of legal frameworks at local and regional scales to guide control efforts is limited [74]. For example, although evidence shows that it is safe to vaccinate puppies less than 8 weeks of age [96, 97], many countries do not include vaccination of puppies in their vaccination guidelines [98–100]. Similarly, several studies have recommended standardization of PEP protocols, as some countries facilities concurrently use different regimens, including both IM and ID routes [16, 30, 76, 85, 101, 102]. Studies have highlighted the importance of monitoring PEP use [103], the absence of which makes accurate demand forecasting impossible and contributes to inadequate supply [15, 16, 75, 76]. Improvements in strategic placement of diagnostic laboratories [74, 104, 105] and rabies treatment centers [34, 38, 75, 76, 106, 107] can improve access [13, 108]. Moreover, enforcement of proposed legislation on responsible dog ownership, intersectoral collaboration, and dog population management are lacking [109].

#### *Outcome 2.2. Appropriate technology and information are available*

Technological innovations continue to advance opportunities for MDV and related rabies management activities [48, 110]. Rabies intervention efforts have traditionally relied on general public information campaigns for raising awareness and knowledge, mostly disseminated via control interventions. Recent increases in the use of low-cost information technologies such as mobile phones and social media are now commonplace, allowing for broader and potentially more effective rabies-related information dissemination. Increasing experience in using these technologies in a wide variety of health information campaigns is transferable to rabies. In particular, information campaigns could better target defined audiences, focusing on behavioral change, and using stronger research designs to assess and learn from awareness campaigns [111].

Based on modern information technologies, targeted platforms are being developed, including software for data collection and analysis [42], laboratory diagnostics [42], and risk assessment technologies [60]. Two Web-based tools, RabiesEcon and Global Dog Rabies Elimination Pathway (GDREP) are used to estimate resources required for implementing MDV and their potential impacts [48, 110]. Likewise, the Web-based integrated surveillance system Rabies Epidemiological Bulletin (REB) facilitates interactive geo-spatial maps of reported suspect cases and positive laboratory diagnoses [42]. The GARC Data Logger (GDL), which supports REB, facilitates the rapid collection and storage of dog vaccination data [42]. While GDL can be used by end users in the field to collect dog vaccination data, REB offers additional analytical information for decision-making. In particular, the REB platform is aligned with the widely used District Health Information System 2 platform for reporting, analysis, and dissemination of health program data. Likewise, various geo-spatial tools are being used to characterize information on phylogenetics, dog ecology, and demography [112, 116]. Smartphone applications (apps), including the Mission rabies app and the Rabies SES app, are available for free to download on android and iOS platforms. The Mission Rabies app can collect information on MDV [26], while the Rabies SES is adapted as an IBCM application and includes linked forms for risk assessments [60].

A major challenge for rabies surveillance is diagnostic capacity, but several new technologies can enhance surveillance in resource-limited settings. The gold standard laboratory method for rabies diagnosis, the Direct Fluorescent Antibody test, requires expertise in fluorescent microscopy techniques and an expensive and difficult to maintain microscope [117]. By contrast, the Direct Rapid

Immunohistochemistry Test (DRIT) is an effective alternative requiring fewer resources [105]. The lateral flow immunochromatographic assay (LFA) offers a practical tool for surveillance in the field that does not require specialized or expensive equipment or laboratory training [118]. However, the LFA has limited sensitivity, precluding its use to rule out a suspected case, and would benefit from investment to improve and standardize quality across manufacturers. Nanopore technology can cost-effectively increase the capacity of laboratories to generate genomic data for surveillance [20], as countries are increasingly using sequencing to inform their control programs [113, 117, 119, 120]. Laboratory diagnosis of human rabies remains inadequate in most LMICs, but examples from China and India are reported to demonstrate improvements [121, 123].

*Outcome 2.3. Progress toward the goal is constantly and consistently monitored and reported*

The surveillance database for Latin America, SIRVERA, provides a repository of standardized data to monitor the epidemiological situation across the region. Some individual countries in the region have other national systems working alongside SIRVERA for laboratory or health data. Reports from Brazil highlight differences in the national system used for reporting bites and PEP use and the laboratory confirmed case data in SIRVERA, indicating a need for improvements in risk assessments, PEP administration, and data reporting [124, 125]. In comparison to Latin America however, evidence from Africa and Asia is limited. Although some countries have well-developed national health information systems, the available regional databases are often not used, which is likely a consequence of limited capacity dedicated to rabies surveillance [42].

To improve data quality and management, adoption of the WHO standard case definition for rabies clinical diagnosis and laboratory investigations is recommended [74, 104]. Efforts to build capacity and improve collection and reporting of surveillance data include regional and national level training on reliable laboratory methods [42] and the use of electronic surveillance platforms [48]. A few articles report countries' self-assessments using the Stepwise Approach towards Rabies Elimination (SARE) tool [126], for example, Haiti, Kenya, and Liberia have used their SARE score for effective advocacy [117, 127]. Despite data limitations, results from these assessments indicate most countries in Africa are in early stages of SARE, whereas some countries in Asia are further progressed [49, 126, 128]. Two studies demonstrated the feasibility of engaging multiple countries using electronic data collection tools and showed that their use increased case reporting rates [26, 129]. Evidence from IBCM pilot studies in Tanzania and the Philippines demonstrate the possibility of having verifiable reporting chains spanning the human and veterinary sectors that can improve accountability and data quality [60, 91]. These studies also highlight major differences in health-seeking behavior and PEP provision between the two countries [60, 130], with very high incidence of bite patients presenting in the Philippines despite a relatively low risk of rabies, compared to much fewer patients presenting in Tanzania but with the majority presenting due to actual rabies exposures. These differences underscore the importance of utilizing accurate IBCM risk assessments, rather than the number of bite patients or the level of PEP demand, to quantify exposures and evaluate rabies control program impacts.

### *Objective 3: to sustain commitment and resources*

This third objective aims to harness multi-stakeholder engagement by demonstrating the impact of activities completed under the UAR collaboration (Table 3).

*Outcome 3.1. National rabies elimination plans integrated to strengthen health systems*

Available evidence suggests many rabies endemic countries lack a national plan for rabies control, and rabies has not been prioritized relative to other public health needs. For instance, PEP supplies to public facilities are financed by local or national governments in many countries, but actual availability is often limited [15, 16, 75, 76, 101].

Research has shown potential benefits of integrating rabies control interventions with other health programs. A study in Namibia demonstrated the effectiveness of implementing dog vaccination alongside regular cattle vaccination for other livestock diseases [25]. A study in Tanzania demonstrated that time and cost savings could be achieved without impacting coverage through the integration of MDV with mass deworming of children against another neglected tropical disease, soil-transmitted helminths [43]. These studies indicate the utility of integrated One-Health delivery platforms and suggest an important role for novel delivery methods to control rabies in hard-to-reach communities where delivery is challenging and expensive.

*Outcome 3.2. Finances and other resources are effectively and efficiently used*

Even though there are efforts to develop national rabies control strategies, inadequate funding limits success. Several multicountry studies reveal a lack of investment by individual countries on their own behalf, with MDV and supply of PEP relying on external partners to lead control efforts [41, 79]. Further, the closure of donor-funded programs has been reported due to inadequate funding from local governments. The extent to which national governments do not contribute financial support to rabies control programs for their own countries represents a challenge for the Zero by 30 strategy, which puts countries at the heart of control initiatives.

In light of weak national funding, external funding by partners can induce stronger national commitment. Rabies control partners including OIE, WHO, Stop Transboundary Animal Diseases and Zoonoses [91], Institut Pasteur [79, 82], Gavi [74], the German Ministry of Food and Agriculture and World Animal Protection [25], GARC, the US Centers for Disease Control, Mission Rabies, Rabies Free Africa, and various pharmaceuticals [42] have been reported to lead or contribute to control efforts in a few countries in collaboration with leading ministries and local governments. One study in Kenya demonstrated how dog vaccination grew from a small crowdfunded project to a larger multiorganizational vaccination program, where the number of vaccinated dogs grew each year from 1,040 in 2015 to over 13,000 in 2017 [27]. Despite support from external partners and innovative fundraising methods to implement dog vaccination, these approaches are still far from reaching the required level of dog vaccination sufficient for eliminating rabies at national and regional levels.

*Outcome 3.3. Results and impact of the UAR collaboration are regularly monitored and reported to key stakeholders*

Multinational cooperation and international support can help develop, sustain, monitor, and report rabies mitigation and elimination. Latin America offers a recent example of international cooperation playing a central role in a long-term regional elimination effort. Many other cross-national coordination networks, such as Pan Africa Rabies Network (PARACON), the Asian Rabies Control Network (ARACON), and Rabies in Asia Foundation (RIA), are other important examples of networks that work to coordinate, monitor, and report outcomes of rabies control efforts to support and promote national level efforts [26]. Other networks with broader scope of influence such as the Association of Southeast Asian Nations (ASEAN), South Asian Association for Regional Cooperation (SAARC) may play important roles in facilitating cross-national cooperation over rabies elimination as well.

## Conclusions

The literature provides a rich foundation for understanding the history of regional rabies elimination successes, the barriers faced by those regions and countries where dog-mediated rabies is still endemic, and developments that affect the landscape for global rabies elimination. Our search criteria focused on articles discussing rabies in endemic countries with emphasis on primary research, augmented by selected papers that provide important additional context, to provide a basis for drawing conclusions about the prospects for rabies elimination. However, these criteria exclude reviews and perspectives and represent only a small proportion of rabies endemic countries, covering just 43 of 120 countries.

Many high- and middle-income countries have eliminated dog-mediated human rabies through decades of investment and consistent, institutionalized management. Although recent successes in transitioning toward elimination in LMICs highlight the positive prospects for a future where dog-mediated rabies is all but eliminated, elimination efforts in many LMICs are sporadic, reactive, and limited in scale. MDV programs are usually reactive to outbreaks, rather than, proactively preventive. PEP access is often limited geographically and is economically burdensome for the families of suspect dog bites. The tragic irony of Covid-19 is that, despite the pandemic having brought the importance of taking a One Health approach to zoonotic disease control into sharp focus, a significant proportion of national health budgets will be diverted to ensuring the availability of Covid-19 vaccines [131]. As a result, the control of other diseases such as rabies may suffer.

The literature identifies several structural, political, economic, and organizational barriers to the effective implementation of these proven control measures in many rabies endemic countries [22, 109]. These barriers include lack of sustained funding, inadequate availability and use of high quality and affordable vaccines, and inadequate surveillance to project PEP and MDV demand. A critical challenge for many rabies endemic countries appears to be the ability to provide sufficient sustained financial commitment to propel the implementation of rabies control programs toward elimination. Control efforts in these settings have been subject to fiscal and administrative interruptions, discontinuance, and insufficiency, resulting in lost momentum and subsequent rabies resurgence [17-19, 21].

The Zero by 30 plan provides a roadmap for action guiding endemic countries, with international support, to reach the goal of global rabies elimination. Implementation of this plan requires investment in necessary healthcare infrastructure and delivery of strategic interventions and information, which in turn requires effective governance at national and international levels. Encouragingly, despite the barriers that have blocked transition toward elimination in rabies endemic countries, new science, recent institutional and technological innovations, and broadening international cooperation provide a basis for optimism for countries and communities still at risk.

Recent research to identify cost-effective and dose-sparing strategies for PEP delivery have been incorporated into global guidelines [84]. The near universal adoption of low-cost information technologies such as mobile phones and social media allow for broader and potentially more effective dissemination of rabies-related information. Other new technologies allow for improved monitoring and surveillance at low cost. Research showing that dog vaccines have higher thermotolerance than previously thought may allow for alternative, lower cost delivery approaches than previously possible [62, 63].

The large number of global and regional organizations coordinating or providing financial and institutional support and coordinating transnational interventions reflects an understanding of the importance of international

cooperation and support of the remaining rabies-endemic countries. The organizing concept for this review is the global Zero by 30 plan, which was developed by a consortium of international organizations and calls for their direct involvement to coordinate national efforts and support the goal of global elimination of dog-mediated human rabies. The involvement of these organizations will be critical to the goal of elimination to the extent that they become increasingly effective at supporting sustained national efforts and help coordinate cross-border collaborations.

Successful global elimination of dog-mediated human rabies will require substantive and sustained investment in and imaginative use of new science and technologies, deployed with strategies effective in the low- and middle-income countries that are still at an early stage in their rabies control efforts. The Zero by 30 timeline is ambitious and the goal may not be met by 2030, but the continued scientific, technological, and institutional innovation illustrated in this review provides a basis for optimism that global rabies elimination may be feasible in the foreseeable future.

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## A. Appendix

**Table A1.** Details of search results arranged by category and respective database.

| Search category: "rabies" OR "rabid" AND | Web of Science | PubMed | Ovid SP |
|---|---|---|---|
| "dog vaccination" | 95 | 8 | 14 |
| "post-exposure" OR "postexposure" | 154 | 165 | 177 |
| "surveillance" OR "epidemiolog*" | 175 | 88 | 150 |
| "policy" OR "strategy" OR "plan" OR "program*" OR "region*" OR "national" | 189 | 76 | 129 |
| "One health" OR "One-Health" | 55 | 34 | 62 |
| "Elimination" . | 65 | 51 | 76 |
| TOTAL | 733 | 422 | 608 |

**Table A2.** Summary of final articles included for review based on study type, strategic plan outcome (I-Reducing human risk, II-Guidance and data, III-Multi-stakeholders engagement) main message and source country.

| Title | Pub. year | Country | Strategic outcome | Main message | Study type |
|---|---|---|---|---|---|
| A 1-week intradermal dose-sparing regimen for rabies post-exposure prophylaxis (RESIST-2): anobservational cohort study [82] | 2019 | Cambodia | I | Comparing RVNA before and after the fourth dose of updated TRC dose | Observational cohort study |
| A Novel Integrated and Labile eHealth System for Monitoring Dog Rabies Vaccination Campaigns [42] | 2019 | Zanzibar (Tanzania), Zimbabwe | II | Assessing tools for targeted implementation of MDV | |
| A phylogenetic study of new rabies virus strains in different regions of Iran [116] | 2020 | Iran | II | Characterizing the molecular distribution of strains of rabies virus | |
| A retrospective descriptive analysis of rabies post-exposure prophylaxis cases in Dalian from 2016 to 2017 [78] | 2019 | China | II | Risk assessment of bite cases for efficient PEP use | Descriptive study |
| Analysis on the risks of severe adverse events in rabies post-exposure prophylaxis and appropriate decision-making procedure [103] | 2019 | China | II | Management of adverse effects following PEP administration | Clinical study |
| Assessment of Procurement, Distribution, Availability, and Utilization of Rabies Biologicals for Postexposure Prophylaxis in Seven States of India [101] | 2019 | India | I | Characterizing the supply chain of PEP | Cross sectional study |
| Assessment of serological response to the anti-rabies vaccination in pet dogs: a hospital based study [97] | 2018 | India | II | Examining the prevalence of antirabies antibodies in dogs of various age groups with varying vaccination history | Observation survey |
| Causes of delay in offering rabies post-exposure prophylaxis services in Abadeh district of Iran [77] | 2020 | Iran | II | Characterizing the reasons for delay in obtaining PEP | Retrospective patient record study |
| Concept mapping as a tool to improve medical student's learning about rabies surveillance [95] | 2019 | Iran | I | Assessing the impact of training tools on increasing awareness of rabies among medical practitioner | Cross sectional study |

*Continued*

**Table A2.** Continued.

| Title | Pub. year | Country | Strategic outcome | Main message | Study type |
|---|---|---|---|---|---|
| Cost of Rabies Post Exposure Prophylaxis in Different Healthcare Settings in Six States of India [85] | 2019 | India | I | Assessment of cost of PEP in varying healthcare settings | Cross section survey |
| Cost-effectiveness of dog rabies vaccination programs in East Africa [110] | 2018 | Tanzania, Malawi, and Chad | II | Assessing the cost-effectiveness of MDV using a spreadsheet based tools that incorporate mathematical model | Modeling study |
| Descriptive assessment of rabies post-exposure prophylaxis procurement, distribution, monitoring, and reporting in four Asian countries: Bangladesh, Bhutan, Cambodia, and Sri Lanka, 2017–2018 [15] | 2019 | Bangladesh, Bhutan, Cambodia, and Sri Lanka | I | Characterizing supply chain of PEP | Cross section survey |
| Development of a Non-Meat-Based, Mass Producible and Effective Bait for Oral Vaccination of Dogs against Rabies in Goa State, India [66] | 2019 | India | I | Comparing the uptake of egg based and gravy-bait prototype bait for ORV | Observation survey |
| Dog Owners' Knowledge about Rabies and Other Factors That Influence Canine Anti-Rabies Vaccination in the Upper East Region of Ghana [32] | 2019 | Ghana | I | Assessment of dog owners knowledge on rabies and dog vaccination | Cross section survey |
| Ecology and epidemiology of rabies in humans, domestic animals and wildlife in Namibia, 2011–2017 [104] | 2019 | Namibia | II | Using retrospective human and animal data to establish the ecology and epidemiology of rabies | Retrospective patient and animal record study |
| Epidemiology and preclinical management of dog bites among humans in Wakiso and Kampala districts, Uganda: Implications for prevention of dog bites and rabies [35] | 2020 | Uganda | II | Determining the epidemiology of dog bites and characterize the pre-clinical actions | Cross sectional study |
| Epidemiology of human rabies in South Africa, 2008–2018 [123] | 2020 | South Africa | II | Characterizing the epidemiology of laboratory confirmed human rabies | Retrospective patient record study |
| Epidemiology of Rabies in Lesotho: The Importance of Routine Surveillance and Virus Characterization [105] | 2017 | Lesotho | II | Assessing the capabilities of DRIT as alternative method to DFA in rabies diagnosis in an effort to enhance laboratory diagnostics | Observational study |
| Evaluation of an immunochromatographic assay as a canine rabies surveillance tool in goa, India [118] | 2019 | India | II | Comparing the capabilities of the rapid antigen rabies test as alternative method to DFA in rabies diagnosis in an effort to enhance laboratory diagnostics | Observational study |
| Facilities and Services of Postexposure Prophylaxis in Anti-rabies Clinics: A National Assessment in India [102] | 2019 | India | I | Assessing the capacity of PEP provision clinics for effective treatment outcome | Cross sectional study |
| Failure of postexposure prophylaxis in a girl child attacked by rabid dog severing her facial nerve causing possible direct entry of rabies virus into the facial nerve [93] | 2019 | India | II | Investigation of PEP failure in bite victim | Case report |
| Failure of postexposure prophylaxis in a patient given rabies vaccine intramuscularly in the gluteus muscle, Himachal Pradesh, India [92] | 2018 | India | II | Investigation of PEP failure in bite victim | Case report |
| Fighting dog-mediated rabies in Namibia-implementation of a rabies elimination program in the northern communal areas [25] | 2020 | Namibia | I | Describing success and challenges experienced during larger scale MDV | Descriptive study |

*Continued*

**Table A2.** Continued.

| Title | Pub. year | Country | Strategic outcome | Main message | Study type |
|---|---|---|---|---|---|
| Healthcare utilization, provisioning of post-exposure prophylaxis, and estimation of human rabies burden in Madagascar [79] | 2019 | Madagascar | I | Investigation of the burden of rabies and PEP provision | Descriptive study |
| Identification of risk factors for rabies exposure and access to post-exposure prophylaxis in Chad [30] | 2020 | Chad | II | Assessment of factors of exposure to rabid dogs and response to treatment | Cross sectional study |
| Implementation of a mass canine rabies vaccination campaign in both rural and urban regions in southern Malawi [41] | 2020 | Malawi | I | Demonstrating the feasibility of high vaccination coverage through different strategies of MDV | |
| Knowledge, Attitudes, and Practices Regarding Rabies in El Jadida Region, Morocco [31] | 2020 | Morocco | I | Assessment of knowledge attitudes and practices towards rabies | Cross sectional study |
| One Health in Practice: Using Integrated Bite Case Management to Increase Detection of Rabid Animals in Tanzania [60] | 2020 | Tanzania | I | Assessing the performance of IBCM in managing bite cases | Observational study |
| One million dog vaccinations recorded on mHealth innovation used to direct teams in numerous rabies control campaigns [26] | 2018 | 16 Countries (10 from Asia and Africa) | II | Assessment of the novel smartphone App to guide the implementation of MDV | |
| Oral bait handout as a method to access roaming dogs for rabies vaccination in Goa, India: A proof of principle study [65] | 2019 | India | I | Comparing ORV and CVR as methods of reaching dogs that are hardly reached for parental vaccination | Observational study |
| Oral bait preferences and feasibility of oral rabies vaccination in Bangladeshi dogs [64] | 2020 | Bangladesh | II | Assessment of baits uptake and dogs characteristics | Observational study |
| Overview of rabies post-exposure prophylaxis access, procurement and distribution in selected countries in Asia and Africa, 2017–2018 [16] | 2019 | 21 countries | I | Characterizing supply chain of PEP | Cross sectional study |
| Practical inter-sectoral linking: Tool to rabies One Health coordination to the grass-roots level [91] | 2018 | The Philippines | I | Development of One-Health framework that involve multiple sectors within the country | Observational study |
| Rabies surveillance-response in Mali in the past 18 years and requirements for the future [74] | 2020 | Mali | II | Characterizing the epidemiology of rabies in Mali | Retrospective patient and animal record study |
| Rabies Vaccination of 6-Week-Old Puppies Born to Immunized Mothers: A Randomized Controlled Trial in a High-Mortality Population of Owned, Free-Roaming Dogs [96] | 2020 | South Africa | II | Assessing the immunogenicity and survival rates of puppies receiving rabies vaccine at 6 weeks of age | Randomized controlled trial |
| Rabies vaccine and immunoglobulin supply and logistics: Challenges and opportunities for rabies elimination in Kenya [75] | 2019 | Kenya | I | Characterizing supply chain of PEP | Cross section survey |
| Rapid in-country sequencing of whole virus genomes to inform rabies elimination programmes [20] | 2020 | Kenya, Tanzania, and the Philippines | II | Demonstrating the feasibility of real-time sequencing to inform policy decision and rabies management | Observational study |
| Safety of new indigenous human Rabies Monoclonal Antibody (RMAb) for Post Exposure Prophylaxis [89] | 2018 | India | II | Demonstrating the safety of monoclonal antibody as alternative to equine and human immunoglobulin | Observational study |
| The Formation of the Eastern Africa Rabies Network: A Sub-Regional Approach to Rabies Elimination [48] | 2017 | Kenya, Tanzania, Rwanda, Uganda, Ethiopia | II & III | Assessing how individual country strategies can be coordinate to address regional control efforts | conference proceedings |

*Continued*

**Table A2.** Continued.

| Title | Pub. year | Country | Strategic outcome | Main message | Study type |
|---|---|---|---|---|---|
| The need to improve access to rabies post-exposure vaccines: Lessons from Tanzania [76] | 2019 | Tanzania | I | Characterizing supply chain of PEP | Cross sectional study |
| Towards rabies elimination in the Asia-Pacific region: From theory to practice [51] | 2020 | Multiple countries | II & III | Discussing efforts towards rabies elimination by 2030 | Conference proceedings |
| Trends of canine rabies *Lyssavirus* and impact of the Intensified Rabies Control Program in Davao City, Philippines: 2006–2017 [28] | 2019 | The Philippines | II | Characterizing the trends of reported rabies cases in dog population | Retrospective record of canine rabies |
| Two fatal cases of rabies in humans who did not receive rabies postexposure prophylaxis in Nigeria [34] | 2019 | Nigeria | II | Descriptive analysis of human rabies | Case report |
| Volunteer based approach to dog vaccination campaigns to eliminate human rabies: Lessons from Laikipia County, Kenya [27] | 2020 | Kenya | I | Describing the implementation of grass-root MDV | Descriptive study |
| Impact of community-delivered SMS alerts on dog-owner participation during a mass rabies vaccination campaign, Haiti 2017 [44] | 2018 | Haiti | II | Assessing the impact of SMS advertising in participation during MDV | Observation survey |
| An evaluation of Brazil's surveillance and prophylaxis of canine rabies between 2008 and 2017 [124] | 2019 | Brazil | II | Comparing the reliability of rabies surveillance system | Retrospective patient and animal record study |
| Wound-only injection of rabies immunoglobulin (RIG) saves lives and costs less than a dollar per patient by "pooling strategy" [90] | 2019 | India | I | Assessing the safety and cost of equine RIG among bite victims | Observation survey |
| Socio-spatial heterogeneity in participation in mass dog rabies vaccination campaigns, Arequipa, Peru [50] | 2019 | Peru | II | Assessing geo-spatial characteristics associated with MDV | |
| Protecting children from rabies with education and pre-exposure prophylaxis: A school-based campaign in El Nido, Palawan, Philippines [29] | 2017 | The Philippines | II | Comparing the burden of rabies in school children by active and passive surveillance | Prospective observational study |
| The evaluation of Animal Bite Treatment Centers in the Philippines from a patient perspective [130] | 2018 | The Philippines | I | Assessing awareness towards rabies treatment centres | |
| The evaluation of operating Animal Bite Treatment Centers in the Philippines from a health provider perspective [38] | 2018 | The Philippines | I | Describing rabies treatment centres | |
| Healthcare demand in response to rabies elimination campaigns in Latin America [37] | 2019 | Multiple countries | II | Quantifying the relationship between dog vaccination and human rabies | |
| An integrated health delivery platform, targeting soil-transmitted helminths (STH) and canine mediated human rabies, results in cost savings and increased breadth of treatment for STH in remote communities in Tanzania [43] | 2019 | Tanzania | III | Assessing the feasibility of integrating rabies intervention with other public health needs | Observational cohort study |
| Controlling Human Rabies: The Development of an Effective, Inexpensive and Locally Made Passive Cooling Device for Storing Thermotolerant Animal Rabies Vaccines [63] | 2020 | Tanzania | I | Assessing the capacity of low cost cooling devices for storing thermotolerant vaccine | Observational field testing study |
| Estimating the Size of Dog Populations in Tanzania to Inform Rabies Control [40] | 2018 | Tanzania | I | Comparing different strategies for estimating dog vaccination coverage | Cross sectional study |

*Continued*

**Table A2.** Continued.

| Title | Pub. year | Country | Strategic outcome | Main message | Study type |
|---|---|---|---|---|---|
| Animal Rabies Surveillance, China, 2004–2018 [120] | 2020 | China | II | Characterizing the phylogeographic distribution of rabies virus in china and neighboring countries | Retrospective study |
| Baseline epidemiology and associated dog ecology study towards stepwise elimination of rabies in Kwara state, Nigeria [69] | 2021 | Nigeria | I | Epidemiological assessment of dogs distribution and vaccination | Cross section survey |
| Investigating Possible Etiologies of Post-Exposure Prophylaxis Failure and Deaths From Rabies Infection: Case Reports [94] | 2020 | Iran | I | PEP failure is due to inadequate PEP use | Case study |
| Ecological and epidemiological findings associated with zoonotic rabies outbreaks and control in Moshi, Tanzania, 2017–2018 [45] | 2019 | Tanzania | I | Perception towards rabies control efforts | Cross section survey |
| Epidemiological and phylogenetic analysis of rabies virus isolated from humans in Henan province, China [113] | 2019 | China | II | Phylogenetic analysis of human rabies cases | |
| Epidemiological aspects of the persistent transmission of rabies during an outbreak (2010–2017) in Harare, Zimbabwe [119] | 2019 | Zimbabwe | II | Epidemiology of rabies in urban areas | |
| Epidemiological pattern of dog bites and the occurrence of rabies in humans within Srinagar district of Kashmir Valley, India [114] | 2020 | India | II | Epidemiology of human bites in india | Cross section survey |
| Epidemiology of human rabies in the state of Ceara, Brazil, 1970 to 2019 [124] | 2021 | Brazil | II | Description of human rabies in brazil | Retrospective study |
| Factors associated with owned-dogs' vaccination against rabies: A household survey in Bobo Dioulasso, Burkina Faso [33] | 2021 | Burkina Faso | I | Assessing drivers for vaccination | Cross section survey |
| Factors influencing delay in initiating post-exposure prophylaxis for rabies prevention among animal bite victims: A cross sectional study [106] | 2020 | Pakistan | II | Description of factors for delays in PEP initiation | Cross section survey |
| Factors related to delay in initiating post-exposure prophylaxis for rabies prevention among animal bite victims: a cross-sectional study in Northwest of Iran [107] | 2020 | Iran | II | Describing causes of delay in initiating PEP | Cross section survey |
| Humoral Immune Response of Thai Dogs after Oral Vaccination against Rabies with the SPBN GASGAS Vaccine Strain [67] | 2020 | Thailand | I | Comparison of immunogenicity of ORV and parenteral in dogs | Longitudinal study |
| Increasing rabies data availability: The example of a One Health research project in Chad, Cote d'Ivoire and Mali [129] | 2021 | Multiple countries (Chad, Mali, Ivory coast) | III | Demonstrating the impact of collective data collection and sharing in three countries in informing rabies epidemiology in the region | Longitudinal study |
| Paralytic rabies: An acute flaccid myelitis after inadequate post exposure prophylaxis [121] | 2019 | India | II | Paralytic form of human rabies | Case study |
| Rabies encephalitis in a preschool child following postexposure prophylaxis [122] | 2021 | India | II | Failure of PEP | Case study |
| Rabies in Tunisia: A spatio-temporal analysis in the region of CapBon-Nabeul [112] | 2021 | Tunisia | II | Geographical distribution of dog rabies | Prospective study |

*Continued*

**Table A2.** Continued.

| Title | Pub. year | Country | Strategic outcome | Main message | Study type |
|---|---|---|---|---|---|
| Single-visit, 4-site intradermal (ID) rabies vaccination induces robust immune responses 5 years after 1-week, 4-site ID primary post-exposure prophylaxis in the Philippines [83] | 2020 | The Philippines | I | 4 site ID 1 week regimen showed higher titer at one year as compared to Updated TRC | Longitudinal study |
| Situation of Rabies in Ethiopia: A Five-Year Retrospective Study of Human Rabies in Addis Ababa and the Surrounding Regions [72] | 2021 | Ethiopia | I | Description of human rabies in Ethiopia | Retrospective study |
| Trends and Clinico-Epidemiological Features of Human Rabies Cases in Bangladesh, 2006–2018 [36] | 2020 | Bangladesh | I | Impact of MDV and epidemiological characteristics of Human rabies | Retrospective study |
| Using geostatistics to better understand the epidemiology of animal rabies in Morocco: what is the contribution of the predictive value? [115] | 2021 | Morocco | II | Geographical distribution of dog rabies | Retrospective study |
| Findings from the initial Stepwise Approach to Rabies Elimination (SARE) Assessment in China, 2019 [126] | 2021 | China | II | Assessment of Stepwise Approach towards Rabies elimination (SARE) | Retrospective study |
| Rabies control in Liberia: Joint efforts towards zero by 30 [117] | 2020 | Liberia | II | Strengthening diagnostic capacity for animal rabies | |
| Using data-driven approaches to improve delivery of animal health care interventions for public health [61] | 2021 | Malawi | I | Use of data driven approach to design effective MDV campaign | |
| Feasibility and Effectiveness Studies with Oral Vaccination of Free-Roaming Dogs against Rabies in Thailand [68] | 2021 | Thailand | I | The use of ORV for dogs that are inaccessible for parenteral vaccination increases mass dog vaccination coverage | Observational study |