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Review

Rationale and support for a One Health program for canine vaccination as the most cost-effective means of controlling zoonotic rabies in endemic settings

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ABSTRACT

Although dog vaccination has been demonstrated to reduce and eliminate rabies in humans, during meetings there are often calls for further pilot studies. The assembled data proves that a widespread approach is now required. While zoonotic rabies has a minimal presence in developed nations, it is endemic throughout most of Asia and Africa, where it is considered to be a neglected tropical disease. In these areas, rabies causes an estimated annual mortality of at least 55,000 human deaths. Worldwide rabid dogs are the source of the vast majority of human rabies exposures. The World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations and the World Organization for Animal Health (OIE) advocate a collaborative One Health approach involving human public health and veterinary agencies, with mass canine vaccination programs in endemic areas being the mainstay of strategies to eliminate dog-mediated human rabies. While post-exposure prophylaxis (PEP) is effective in preventing deaths in people exposed to rabies, it is comparatively expensive and has little impact on the canine reservoir that is the primary source of zoonotic rabies. Indiscriminate culling of the dog population is expensive and there is little evidence that it is effective in controlling rabies in non-island locations. Mass canine vaccination programs using a One Health framework that achieves a minimum 70% vaccination coverage during annual campaigns have proven to be cost-effective in controlling zoonotic rabies in endemic, resource-poor regions. Case studies, such as in Tanzania and Bhutan, illustrate how an approach based on mass canine rabies vaccination has effectively reduced both canine and human rabies to minimal levels. The multiple benefits of mass canine rabies vaccination in these cases included eliminating rabies in the domestic dog reservoirs, eliminating human rabies cases, and decreasing the rabies economic burden by reducing expenditures on PEP.

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1. Introduction

In the bid to control rabies in humans many approaches have been tried. Of these, wide-scale vaccination of dogs has proven the most effective and impactful. However, during meetings on rabies eradication during 2015 and 2016 it is often been heard by the authors that some stakeholders consider further pilot studies are required before dog vaccination can be adopted as the primary method to improve human health. Here we gather current information to demonstrate that this approach, and the benefit, is now sufficiently understood to justify taking the next step on a larger scale, especially when combined with a One Health approach integrating efforts by both the human and veterinary health sectors.

Rabies is an incurable disease and has the highest case fatality rate of any zoonotic disease [1,2]. An understanding of the epidemiology of this disease is essential in the planning and implementation of the most cost-effective control measures, however the epidemiology of zoonotic rabies is distinctly different depending on the geopolitical locale where it exists. In the industrialized nations of North America, Europe, Japan, Australia, New Zealand, Malaysia, and the Arabian peninsula, human rabies cases are rare. In contrast, in developing regions of Asia and Africa, and to a limited extent in Latin America (i.e., Haiti, Honduras, Paraguay), human rabies cases occur widely, particularly in poor, rural communities, where rabies is considered a neglected tropical disease by the WHO [3]. It is in these resource-poor regions, representing more than 80% of the world's population, where canine rabies is endemic and human rabies imposes an economic burden which these countries can ill afford [4].

An effective public health policy for eliminating human rabies exposure is based on universal canine vaccination. This approach has been well established since the mid-20th century and has been successfully implemented in locations where a low risk of human exposure now prevails [5,6]. More recently, various examples exist of a successful "One Health" collaborative strategy that focuses on elimination of canine rabies as the most expedient and cost effective way of preventing human exposure and infection [1]. One Health initiatives recognize that the health of people is connected to the health of animals and the environment and forge partnerships between physicians, veterinarians and other health-related scientists. This framework, strongly advocated by the World Health Organization (WHO), the Food and Agriculture Organization (FAO) of the United Nations, the World Organization for Animal Health (OIE) and other non-government organizations including the American Veterinary Medical Association, has several essential components supporting a canine vaccination program as its central feature, as described in the 2015 WHO review [3]. The pivotal role of vaccination is based on the fact that canine and human rabies are 100% vaccine-preventable diseases [3]. This report also describes how mass canine vaccination programs played a central role in reducing canine and human rabies to negligible levels in two endemic regions of Africa and Asia. A Tanzania case study describes how canine rabies declined by 70% and 97%, respectively, after two successive vaccination campaigns, resulting in significant reductions in the demand for post-exposure prophylaxis (PEP) as the primary means of disease prevention in cases of human exposure [7,8] . A Bhutan case study describes how mass dog vaccination can eliminate canine rabies and be cost-effective even in a resource-poor country [9]. Statistical models showed that a mass vaccination program in that country from 2001 to 08 was estimated to eliminate canine rabies foci within 2–3 years and lower the combined cost of PEP plus canine vaccination to less than the cost of PEP alone within 3 years.

2. Epidemiology of human rabies exposure

Rabies mortality exceeds that of any other zoonotic disease [4,10]. The latest estimates of human rabies mortality range from 55,000 to 59,000 deaths per year worldwide, 99% of them in Africa and Asia where rabies is endemic [1,3,4,11,12]. Due to the lack of laboratory confirmation, sporadic epidemiologic surveillance, and unreported clinical cases in developing countries, current mortality estimates are considered to be the best estimates that we have but almost certainly under-represent the true incidence of human rabies deaths [4,11,12].

More than 99% of all human cases worldwide result from the bite of a domestic dog [13]. Although the regional incidence of dog bites is difficult to determine with certainty, WHO estimates based on survey data indicate that animal bites in Asia totaled 3,529,000 per year and were associated with 31,539 human rabies deaths, 85% of them in India. In Africa, estimated animal bites totaled 802,100 per year, resulting in 23,823 human rabies deaths [12,14]. Without PEP, WHO investigators predicted that worldwide human rabies deaths would exceed 327,160 annually. Using less conservative statistical models, other investigators estimated bite incidence in Africa ($n = 847{,}326$) to be somewhat greater than the WHO estimates, and exposures in Asia to be considerably higher (>14,000,000) [11]. The Centers for Disease Control (CDC) reported 33 cases of human rabies cases in the US in the decade from 2003 to 13, ten of which originated in other countries and one from Puerto Rico, providing a stark contrast with the far greater incidence in Asia and Africa [15]. Similarly, human autochthanous rabies cases in Europe average <9 per year and most European countries have been designated rabies-free [16]. During 2010–12, 111 human rabies cases transmitted by dogs were reported in ten Latin American countries [17]. In contrast, no countries on the Asian mainland have been declared rabies-free by the WHO and there is evidence that canine rabies has spread to new regions of Asia in the past decade [18]. Statements from the OIE and CDC indicate that they expect that rabies will never be entirely eradicated due to its wildlife reservoir, particularly its global presence in bats [4,19,20].

3. Canine vaccination as an immunologic barrier against human exposure

The WHO has accepted that generalized canine rabies vaccination is the only feasible method of limiting human rabies exposure and is also the most cost effective means of doing so [3]. Sole reliance on costly PEP, consisting of multiple vaccine and rabies immunoglobulin doses, and pre-exposure prophylaxis (PreP) in rabies-endemic areas is not effective in eliminating zoonotic rabies due to limited access to these interventions in developing countries, treatment expense, and lack of diagnostic services on which treatment is based. When laboratory diagnosis is lacking, it has the effect of sharply increasing demand and costs for precautionary PEP in cases where individuals are potentially exposed when bitten by an animal of unknown rabies status [1]. In such cases, increasing the demand for PEP is self-defeating because it leaves the source of endemic rabies intact while increasing rabies associated costs. Although rabies is a 100% preventable disease, human PreP and PEP are inefficient approaches to prevention when compared to canine vaccination programs, which neutralize the maintenance host that is the principal source of human exposure [21].

Widespread vaccination of dogs has been shown to virtually eliminate human rabies exposure. Statistical modeling studies indicate that vaccinating 70% of the canine population annually will induce sufficient herd immunity to successfully eliminate canine rabies and subsequent human exposure [21]. Because many campaigns fail to reach a 70% vaccination rate [22], authors have suggested that fertility control through immunocontraception may make a vaccination campaign more successful [23]. An assessment of a canine vaccination campaign in endemic districts in Tanzania found that vaccination of 64% of owned dogs resulted in virtual elimination of canine rabies in the vaccination zone [7]. Even in Africa and Asia with their large populations of wildlife and free-roaming dogs, a 70% canine vaccination coverage rate has been shown to be sufficient to successfully eliminate canine rabies [1,21]. Because rabies has a relatively low basic reproduction number (R_0) of 1.05–1.72, referring to the number of secondary cases arising from a primary case in a susceptible population, even relatively low rates of vaccination coverage can potentially eliminate rabies in the canine population [21].

4. Cost effectiveness of canine rabies vaccination

Because >95% of all human rabies cases are due to contact with rabid dogs, canine vaccination is considered to be the most cost-effective approach to eliminating human rabies exposure [3,24]. In contrast, expanding PreP and PEP or relying predominantly on human rabies prophylaxis is not only prohibitively expensive but has a long history of failing to reduce the prevalence and economic burden of rabies, particularly in developing countries [11]. To illustrate, recent estimates indicate that India has both the world's highest human rabies mortality rate (>20,000 deaths per year) as well as the second highest PEP utilization (>8.2 million cases per year, exceeded only by China). India has an estimated canine rabies vaccination rate of only 15%. These data indicate that over-reliance on human PEP without adequate canine vaccination coverage may prevent some human rabies cases while still allowing deaths to occur, particularly in poor, disadvantaged communities [11,25,26]. This is further reinforced by the fact that *per capita* spending on PEP is considerably higher in Asia than in Latin America, yet the incidence of dog-mediated human rabies is almost 30 times higher in Asia (9.3 cases/million) than in Latin America (0.34 cases/million). This difference is attributed to the higher investments in canine vaccination in Latin America ($0.11 per capita spend) in comparison with Asia ($0.01 per capita) [11]. Conversely, various public health initiatives have demonstrated that mass vaccination of dogs, usually involving central-point vaccination strategies, can successfully prevent human rabies exposure by controlling canine-mediated disease as the source of its transmission.

4.1. Cost of human rabies prophylaxis

Human rabies prophylaxis in the form of PreP vaccination and PEP consisting of vaccination in combination with rabies immune globulin (RIG) is highly effective in preventing disease, and in locations where it is administered a substantial number of deaths have been prevented. The number of people who receive PEP is conservatively estimated at 15–20 million per year, the great majority following dog bites [4,27]. A recent global epidemiologic study estimated a much higher number of individuals receive PEP annually, >29 million in rabies endemic regions, preventing an estimated 2.9 million deaths [11]. The roughly 1:10 ratio of preventable deaths to individuals receiving PEP treatment indicates that in the great majority of cases PEP is administered on a precautionary basis rather than in cases where a biting animal is genuinely suspected as having rabies or was diagnosed with rabies. In other words, most PEP treatments are given without clinical benefit, in effect representing cost without value. Investigators calculated the global cost of PEP to be $3.01 billion, including $1.7 billion for direct costs of treatment and $1.31 billion due to travel and lost income associated with receiving a multi-dose PEP regimen [11]. If the 1:10 ratio of preventable deaths to PEP treatments is applied, approximately $2.7 billion spent on PEP each year is wasted, representing 31% of the estimated $8.6 billion economic cost of canine rabies. Pre-exposure prophylaxis, consisting of vaccination of individuals at high risk of exposure, generally represents a small percentage of the economic burden of rabies control. For example, the cost of PreP in an Indonesian rabies control campaign amounted to 1.4% of total rabies control expenses including culling, PEP, pre-exposure treatment, and canine vaccination [28].

4.2. Other economic costs of rabies

Estimates of the economic cost of human rabies vary due to the same reporting deficiencies affecting rabies incidence reporting. However, by all accounts the direct and indirect costs of rabies are very high. A recent publication by Hampson et al., involving a multi-national group of epidemiologists and public health experts, conducted a careful analysis of the global economic burden of canine-mediated rabies. The authors determined that the cost of an estimated 59,000 annual human rabies cases in endemic regions was $8.6 billion (US dollars) per year [11]. The components of the economic burden were premature death (55%), cost of PEP (20%), lost income during PEP (15.5%), canine vaccination (1.5%), and livestock losses (6%). The cost of canine rabies vaccination was estimated to be $130 million in the endemic countries of Africa and Asia [11]. The authors concluded that the relatively low cost of additional investment in canine rabies vaccination is the single most effective way of reducing the rabies burden.

Using an annual human rabies mortality figure of 59,000, a recent, statistically validated study estimated that 3.7 million disability-adjusted life years (DALYs) are lost each year due to rabies deaths (DALY is a composite of years of life lost plus years of life lived with a disability) and that the cost of PEP totals $1.7 billion globally each year [11]. Other statistical models calculate that, when the large number of children among rabies deaths is considered, >2 million DALYs are lost per year with an annual global economic cost of $4 billion [4]. Other epidemiologists have proposed a per capita value of $1.8–2.2 million per human rabies death, excluding PEP costs [4].

When the cost of human, canine, and livestock rabies are combined, the global burden of canine-mediated rabies increases exponentially. A recent USDA study calculated the economic impact of canine rabies in Latin America, Africa, and Asia. Including the cost of human mortality, PEP, canine vaccination and control, rabies diagnostic testing, and cattle mortality due to canine-mediated rabies, the authors estimated the global burden of canine rabies to be approximately $124 billion per year [29], a figure in broad agreement with estimates by other experts [4,30]. The relevance of an overall global economic burden estimate is that it provides a benchmark against which the cost effectiveness of a rabies elimination program can be determined.

4.3. Culling of stray dogs as a rabies control strategy

Although it is not supported by data, culling of roaming dogs is often mistakenly viewed as essential to reducing canine population density and the prevalence of canine rabies [1,31]. Canine euthanasia programs involving the widespread killing of dogs regardless of infection status are considered to be ineffective and often counterproductive because they lead to increased inter-dog aggression and may increase the spread of rabies [13]. The euthanasia-only method of animal control assumes that transmission is density-dependant [32] and is not endorsed by any animal organization or public health entity, does not control stray animal populations, and promotes instability within the population [33,34]. Euthanasia programs often drive the wrong behaviours for healthy human-dog interactions. Not only do they send a message to the public that stray dogs must be feared and therefore put down, but it also leads to dog owners hiding their dogs thus limiting access for vaccination and reducing herd immunity [1]. Because rabies has a consistently low basic reproduction number across all demographic settings, transmission tends to be independent of population density [1,21]. The exact relevance of canine population density is unclear but the evidence indicates that culling is ineffective [32].

While stray dog control should not be ignored in any setting, herd immunity based on vaccination coverage is considered far more important than culling in bringing the R_0 value to <1 and therefore having a significant effect on rabies transmission. Culling is also expensive and much less cost-effective than canine vaccination. For example, in response to a 2008 outbreak in Bhutan, the direct outbreak cost was estimated to be 2.75 million Bhutanese ngultrum ($59,923). Of that total, 55% was spent on human PEP, 18% for culling and impounding stray dogs, and 2% on canine vaccination [31]. Culling represented the second most expensive component of the outbreak costs in this case, but had little apparent effect on rabies transmission. In a study that calculated the costs of rabies control measures in an eastern Indonesian island of 1.8 million inhabitants from 2000 to 11, annual costs of the program averaged $1.12 million [28]. The cost of culling roaming dogs represented the highest portion, about 39% of the total costs, followed by PEP (35%), mass canine vaccination (24%), pre-exposure treatment (1.4%), and all other costs (1.3%). Not only was culling dogs in this setting was >60% more costly than mass canine vaccination, but the authors noted that culling failed to prevent the spread of rabies. Others have noted that ownerless dogs are responsible for only a small percentage of dog bites, and as long as the proportion of ownerless dogs of unknown vaccination status is <20%, mass vaccination of dogs can still achieve sufficient herd immunity to eliminate human rabies exposure [35]. In view of the lack of a demonstrated benefit from culling, the WHO does not recommend culling or impounding roaming dogs as a priority in rabies control programs [2,28,36].

4.4. Cost effectiveness of local canine rabies vaccination initiatives

Various local canine rabies vaccination programs in endemic regions of Africa and Asia have demonstrated that this approach can significantly reduce the incidence of human rabies exposure, cases of canine rabies, demand for PEP, and the overall economic burden of rabies. The following case examples in Africa and Asia illustrate how controlling canine rabies has a positive effect on resource utilization and cost effectiveness of human rabies control programs, in effect providing a proof of concept that controlling canine rabies reduces the incidence of human rabies exposure and treatment.

4.4.1. Tanzania case study

A government sponsored mass vaccination program in Tanzania was carried out at four yearly intervals from 1996 to 2001 at central vaccination sites in 72 villages [1,8]. Based on post-vaccination questionnaires, annual vaccination coverage ranged from 64% to 76% following each respective annual campaign, and at 66.3% overall for the four campaigns (Table 1). Rabies cases were confirmed by laboratory diagnosis, and incidence data were collected from vaccination zones and an adjacent control zone. The incidence of canine rabies declined significantly by 70% ($P < 0.001$) in the vaccination zone by the start of the second campaign and by 97% after the second campaign, but was not significantly different from year to year in the control zone ($P > 0.05$). No cases of canine rabies were reported in the vaccination zone after the second campaign, two cases were reported after the third campaign, and one case after the fourth campaign. The incidence of dog-bite injuries was significantly ($P < 0.001$) lower in the vaccination zone beginning after the first campaign but was not significantly different in the control zone ($P > 0.05$). Demand for human PEP declined significantly within 18 months after the first campaign was initiated,

Table 1
Effect of canine vaccination programs on incidence of human rabies cases in Tanzania and control strategy costs in Bhutan.

Parameter	Tanzania	Bhutan
Owned dogs vaccinated (total owned dogs)	2274 (3352)	42,716 (77,314)
Total dog vaccinations	>21,399 (campaigns 1–3)	106,790 (est. 2001–08)
Length of canine vaccination program (years)	4 (1996–2001)	6 (2001–2008)
Key results	(1) Vaccination coverage by campaign: Campaign 1: 64.5% Campaign 2: 61.3% Campaign 3: 64.3% Campaign 4: 76.1% (2) Reduction in new canine rabies cases: 69.5% after 1st campaign 97.4% after 2nd campaign (3) Annual reduction in human rabies bite injuries from suspected rabid dogs vs. pre-vaccination period: 51% post-1st campaign 90% post-2nd campaign 92% post-3rd campaign	(1) Vaccination coverage by year: Year 1: 70% Years 2–4: 60% Years 5–6: 50% (2) Cumulative 6-year program costs: PET + dog vaccination: $0.61 million PET alone: $0.70 million (3) Cost-effectiveness estimate: Program becomes cost-effective after year 5
Reference	Cleaveland 2003 [8]	Tenzin 2012 [9]

PET = post-exposure treatment.

which program administrators attributed not only to fewer dog-bite injuries but also to public awareness programs explaining the benefits of canine vaccination. The program results indicated that vaccination of 66% of owned dogs resulted in a significant reduction in canine rabies, human dog-bite exposure, and demand for PEP, and also reduced the number of positive rabies wildlife diagnoses.

A subsequent study of the Tanzania rabies reservoir concluded that domestic dogs are the only population necessary for rabies maintenance and that mass vaccination of domestic dogs reduces or eliminates rabies in wildlife [37]. Interestingly, the reduction in wildlife rabies in this study occurred despite a recent increase in the African wild dog population, which has shown signs of recovering after a long period of decline.

This case example evaluated rabies and bite-exposure incidence and service utilization, but did not evaluate cost effectiveness. However, in a later study conducted by the same research group in two adjacent, rural districts of Tanzania, the cost effectiveness of canine rabies vaccination in reducing human rabies mortality was compared with the *status quo* of no canine vaccination [24]. Although canine density was nearly seven times greater in one district compared to the other, rabies was endemic or epidemic in either district. An annual canine rabies vaccination campaign in both districts proved to be cost effective in preventing human rabies mortality compared to the economic cost of no canine vaccination. Even relatively low rates of canine vaccination coverage of 20–30% proved to be "very cost effective" using an incremental cost-effectiveness ratio <$1430 for a life-year saved.

4.4.2. Bhutan case study

Rabies is endemic in the south Bhutan region bordering India. A cost-benefit analysis was conducted to compare the cost of mass canine vaccination versus total direct and indirect cost of human rabies interventions, including PEP [9]. The analysis was based on local demographic, public health, and economic data available from 2001 through 2008. A total of 106,790 dogs were estimated to have been vaccinated during the first 6 years of the campaign, with vaccination administered at biannual intervals (Table 1). Vaccination coverage was estimated to be 70% in year 1 of the program, 60% in years, 2–4, and 50% in years 5 and 6. The number of PEP cases per year was estimated to be 3440.

The combined cost of mass canine vaccination and human PEP was estimated to exceed the cost of human PEP alone during the first 2 years of the campaign. However, during the third year, the total estimated combined cost (canine vaccination plus human PEP) was less than the total cost of PEP, with a further annual reduction in combined costs occurring from years 4 through 6. At the end of 6 years, the total cumulative cost of the combined strategy was estimated to be lower than the cost of PEP alone, $730,000 versus $770,000, thus representing a cost-saving as well as cost-effective intervention. The average cost per dog vaccination or sterilization was much lower compared to the individual cost of human PEP. It is noteworthy that the case example included the cost of canine sterilization, an additional cost not considered essential for rabies control. If the cost of canine sterilization were not included, the cost-effectiveness calculation and break-even point of the program would have been even more favorable. The average direct and indirect cost of PEP using a 5-dose Essen vaccination regimen alone or vaccination plus human RIG was estimated to be $45 and $442 per person, respectively. Per dog vaccination cost was estimated to be $1.20 and the average cost of dog sterilization was estimated to be $6.36. The cumulative cost of mass canine vaccination and sterilization was estimated to total $280,000 after 6 years. Mass canine vaccination was expected to dramatically reduce dog rabies incidence and eliminate canine rabies infection foci within 2–3 years after program implementation.

The study indicated that even in a resource-limited country with endemic rabies, mass canine rabies vaccination and sterilization would be cost effective within 3 years compared to a public health policy of haphazard dog vaccination and reliance on human PEP in cases of animal-bite exposure. The multiple benefits of mass canine rabies vaccination in this case included elimination of rabies reservoirs in the domestic dog population, prevention of canine-mediated livestock rabies deaths, elimination of human rabies cases, and reduction in the rabies economic burden by reducing expenditures on PEP, the intervention that represents the bulk of rabies control expenditures in endemic countries.

5. Rabies vaccines for developing countries

Although canine rabies vaccines are available from various sources worldwide, inactivated vaccines of cell culture origin have become the *de facto* global standard [38]. Studies have not demonstrated superiority of any licensed canine rabies vaccine versus another. Vaccine efficacy in field settings is most likely the result of the health status of the host animal, proven duration of immunity of the vaccine used, successful administration, and how the vaccine is transported and conserved [35].

The price per dose of rabies vaccines used in government or NGO-led vaccination campaigns are not readily available but are certainly cheaper than vaccine used in the normal commercial setting. Estimates of rabies vaccine prices used in vaccination campaigns in the developing world have been ranged from $0.20-$1.00 per dose [11]. The lower cost is driven by the large volumes required and the recognition of major vaccine companies that there is a corporate social responsibility with many of these campaigns, so vaccines are often provided free of charge or paid through donor organizations. In addition, vaccine banks maintained by organizations such as the OIE allow the large-scale management and deployment of needed vaccine.

The major cost of vaccination campaigns is not considered to be the vaccine itself but the associated logistics and required personnel resources. Rabies has been estimated to lead to $8.6 billion economic losses per year, of which only 15% comes from the veterinary sector and dog vaccination [11].

5.1. Vaccine thermostability

Effectiveness of rabies vaccination in tropical or subtropical settings will be enhanced by using vaccines with proven thermostability and by monitoring vaccine storage and transportation temperatures. To avoid loss of potency from prolonged exposure to high temperatures, label instructions specify that commercial inactivated, MLV and recombinant rabies vaccines should be stored at 2–7 °C (35–45°F.). In tropical regions where rabies is endemic, equipment and facilities needed for cold-chain storage are vulnerable to service interruption with the potential for loss of vaccine efficacy, and are a major source of costs [39]. Rabies vaccines that are thermostable for a defined period of time at ambient temperatures would offer a significant advantage in cost, would reduce dependence on cold-chain storage, avoid potential vaccine damage and loss of efficacy, and enable vaccine usage outside the cold chain.

New approaches to developing thermostable liquid vaccine formulations have the potential to ensure minimal loss of vaccine potency during excursions outside the cold chain. Examples include use of novel stabilizers, adjuvants, or excipients; high-throughput screening to monitor the effect of excipients on destabilizing changes from unwanted reactions such as heat-induced oxidation, hydrolysis, and alteration of chemical bonds; and use of buffering systems to enhance antigen stability [40].

In reality, because post-development clinical testing and regulatory approval of changes to licensed vaccines are expensive and time consuming, manufacturers resist reformulation or changes in manufacturing procedures, particularly for low-margin products such as rabies vaccines [40]. The preferred alternative is to make thermostability a priority early in the vaccine development process so that product reformulation is unnecessary. This is particularly true in the case of vaccines being developed against high morbidity/high mortality diseases such as rabies. In these settings, vaccines with a high degree of thermostability will have maximum value. Although thermostable vaccines can be more costly to develop and manufacture than conventional vaccines, they can be cost-effective if thermostability increases their efficacy and utilization. For example, single-dose, thermostable vaccines against measles, yellow fever, BCG, and DTP-hepatitis B were more costly than their conventional counterparts but were all found to be cost-effective when used in the tropical, low-resource countries of Cambodia, Ghana, and Bangladesh [41,42].

6. An integrated rabies control strategy for animals and humans

The WHO, OIE, Food and Agriculture Organization of the United Nations, and the Global Alliance for Rabies Control jointly advocate a global One Health framework with the achievable goal of eliminating canine-mediated human rabies in participating countries by 2030 [42]. The essence of the One Health approach is a collaboration of multiple disciplines, including human public and animal health agencies, to achieve its objectives, including a canine rabies vaccination coverage rate of 70%. This is a departure from the frequent practice in rabies-endemic countries, where public health or human medical agencies play either a dominant or independent role in implementing human rabies control programs, with comparatively little attention given to canine rabies, the principal source of the disease [1,43]. Experience has shown that intersectional coordination and sharing of resources between human medical and veterinary services, where public health officials respond to human rabies exposure, and mass canine vaccination programs are administered and monitored by veterinary personnel, result in lower incidence of disease and reduced societal costs associated with human rabies [1,9,11].

The One Health approach for elimination of canine-mediated rabies is outlined in detail in the 2015 Report of the Rabies Global Conference in Geneva, Switzerland [42]. The Conference proposed a comprehensive framework of five "pillars" for rabies elimination in participating countries.

7. Conclusions

Expert opinion, including that of OIE and CDC officials, is that rabies will never be entirely eradicated due to its wildlife reservoir, notably its worldwide presence in bats [4,19,20]. Bats are the source of a tiny minority of rabies cases and would be difficult to vaccinate with bait as is done with terrestrial wildlife reservoirs. However, a realistic goal is the elimination of canine-mediated human rabies, underpinned by strategies that achieve a sustainable 70% vaccination coverage rate in dogs, the host animal responsible for the almost all human rabies exposure. Canine vaccination campaigns have demonstrated that elimination of rabies is both feasible and cost-effective, and in some instances cost-saving (i.e., representing a greater economic benefit versus cost reduction compared to another option), in endemic locations in Asia and Africa, the regions where almost all human rabies deaths occur. This achievement is enabled by a One Health approach involving a collaborative effort by human public health and veterinary agencies with the support of political, educational, social, and non-government stakeholders.

The success of the One Health approach has been demonstrated in Latin America and Asia. The Pan American Health Organization initiated a program for rabies control in the 1980s which included mass dog vaccination as well as surveillance on the human sector [44]. In Asia, similar programs involving local government alongside the veterinary services have also been successful in countries such as Bali [45] and the Philippines [46].

This report collates the necessary available information to support the arguments for the adoption of widespread vaccination of dogs and to move the discussion away from proposals for further pilot studies. Other approaches, such as culling, do little to improve the long term situation and may increase costs and worsen the overall spread of disease. The referenced success stories, when taken alongside other experiences with rabies control, conclusively demonstrate that a One Health approach is key to the elimination of dog bite transmitted rabies in humans.

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