Development and evaluation of methods to control rabies in Goa State, India

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Declaration

I declare that the work presented is the work of the author, except where stated otherwise by reference and/or acknowledgement. Much of the material included in this thesis has been produced in co-authorship with others and some has been presented for publication. No part of this work has been submitted for award or degree at any other university. My personal contribution to each chapter is stated below.

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Abstract

Rabies represents a tragic modern-day paradox; effective methods for its elimination have been available for a century, and yet thousands of children living in low resource settings die of the disease in abject suffering every year. Countries across Latin America eliminated the dog rabies virus through coordinated mass vaccination campaigns targeting the reservoir dog population, but large-scale control efforts have failed to progress in much of Africa and Asia. An estimated 20,000 people die of rabies each year in India, representing one third of the global total. Recent innovations in human medicine have improved access to life-saving post-exposure prophylaxis, however the close relationship between people and an ever-increasing dog population make a One Health approach axiomatic to rabies elimination. Without effective strategies to monitor and control the disease in dogs, the issue of dog transmitted rabies will continue ad infinitum.

The work presented in this thesis explores operational approaches to rabies control in Goa State, India from 2013 to 2022 through a collaboration between Mission Rabies and the Government of Goa. A novel smartphone app developed during nascent campaigns formed the foundation of programme management and evaluation. The technology leveraged the enhanced data-capture and transmission capabilities of smartphones to improve the efficiency, efficacy, and political potency of mass dog vaccination campaigns in Goa and at project sites globally. Two-way data transfer between programme managers and the remote vaccination workforce within the platform revolutionised efficient spatial deployment of resource and aggregated the details of over 600,000 individual dog vaccination events in near-real time. Analysis of this high-resolution programmatic data garnered new insights into dog distribution, population composition, and parenteral vaccination accessibility across the urban-rural continuum that informed data-driven optimisation of the vaccination strategy.

Concurrent advancement of state-level rabies surveillance systems enabled monitoring of the impact of vaccination and education activities. Human rabies deaths declined to zero and the dog rabies virus was eliminated from large areas of the state, with persistence in regions bordering endemic populations. Goa became the first state in India to become a ‘Rabies Controlled Area’ in 2021 and the programme was found to be ‘very cost-effective’ by WHO criteria for public health interventions.

In recognising the operational and logistical constraints of existing mass dog vaccination methods, the potential incorporation of oral rabies vaccination of dogs was explored. A pilot study identified methods that could cost-effectively increase vaccination coverage in difficult to access dog populations, whilst also reducing human resource requirements. The results of a second study supported the use of baits made of an egg-based construct which met requirements of being widely palatable to dogs, culturally acceptable, and potentially mass producible.

The findings of this thesis provide insights for advancing feasible and politically attractive solutions for the elimination of rabies at scale through the lens of One Health. Mobile technology, developed through field experience, drove a step-change in the spatial coordination of remote vaccination resource and data quality. Detailed understanding of reservoir population dynamics offers new opportunities for resource prioritisation and efficiency-savings through modelling of rabies transmission and intervention design. The iterative process of operational learning and refinement will need to continue as campaigns progress to new geographies and scales, however the work in Goa demonstrates that dog rabies control in many parts of India is within reach. By advancing approaches to mass dog vaccination, our generation has an opportunity to change the trajectory of a disease which inflicts profound suffering on people and animals already disadvantaged by circumstance.

Lay Summary

Effective methods for dog rabies elimination have been known for a century, and yet it kills tens of thousands of people every year and has greatest impact on those at the socioeconomic margins of society. Coordinated mass dog vaccination campaigns in Latin America were successful in controlling the disease at a continental scale, however it continues to spread throughout Africa and Asia where the virus circulates in free-roaming dog populations. An estimated 20,000 people die of rabies each year in India, more than any other country. Recent efforts have improved access to life-saving post-exposure treatment, however the close relationship between dogs and people make an integrated approach, engaging both human and animal health sectors, essential to a long-term solution. Without effective strategies to tackle the disease in dogs, the issue of human rabies transmitted by dogs will remain indefinitely.

The work presented in this thesis explores operational approaches to rabies control in Goa State, India from 2013 to 2022 through a collaboration between Mission Rabies and the Government of Goa. A smartphone app developed to address field challenges formed the basis of programme management and evaluation. The app improved the ability to rapidly transmit information between field workers and project managers, which enhanced campaign efficiency, efficacy, and political impact in Goa and at project sites around the world. The system enabled project managers to share digital maps with vaccination teams of where they should focus their efforts, who then recorded and uploaded details of every dog vaccinated to be reviewed in near real-time. Analysis of over 600,000 vaccination events provided detailed insights into dog population distribution across the State to support optimisation of the vaccination strategy.

Development of state-level rabies surveillance systems enabled monitoring of the impact of vaccination and education activities. Human rabies deaths declined to zero and the dog rabies virus was eliminated from large areas of the state, with continued circulation identified at the state border where dogs mix with unvaccinated neighbouring populations. Goa became the first state in India to become a ‘Rabies Controlled Area’ in 2021 and the programme was found to be ‘very cost-effective’ by WHO criteria for public health interventions.

In recognising the operational and logistical constraints of existing mass dog vaccination methods, the potential incorporation of oral rabies vaccination of dogs was explored. One study identified methods that could increase vaccination coverage whilst reducing cost and staff requirements. The results of a second study supported the use of baits made of an egg-based material which were widely palatable to dogs, culturally acceptable, and potentially mass producible.

The findings of this thesis provide insights for advancing feasible and politically attractive solutions for the elimination of rabies at scale through approaches that address both human and animal health priorities. Mobile technology made it possible to target the work of vaccination teams in a coordinated way whilst gathering data that benefitted campaign development and visibility. The detailed understanding of dog population gained offers new opportunities to improve rabies control strategies at scale. The cyclical process of campaign implementation and refinement must continue as dog vaccination efforts grow, however the work in Goa demonstrates that dog rabies control in many parts of India is within reach. By advancing approaches to mass dog vaccination, our generation has an opportunity to change the trajectory of a disease which inflicts profound suffering on people and animals already disadvantaged by circumstance.

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A phrase that my late grandfather was fond of has resonated in the writing of this thesis, and perhaps echo the wider societal opportunity to advance rabies control:

"Go as far as you can see, and then, see how far you can go."

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Chapter 1 Background

1.1 Introduction

On the surface, dog-transmitted rabies is as simple a problem to solve as one could find in the world of public health; a disease that devastates the lives of thousands can be eliminated through mass dog vaccination. However, the subject is beset with paradoxes that have sustained my curiosity, intrigue, and bewildering frustration throughout the years of work that culminate in this thesis; rabies teeters on the edge of natural decline --- and yet is pervasive across the world; there is a growing global urge to eliminate --- in the face of widespread political malaise; the simple practicality of mass dog vaccination --- offset by the complexity of coordinating a large remote workforce. This thesis, focused on Goa State, India, endeavours to understand these conflicting realities that run throughout so many aspects of the global odyssey towards dog rabies elimination.

1.2 Rabies in the contemporary world

The rabies virus is unique in its evasion of the host immune system, but it has been equally deft at avoiding political prioritisation across the world for over a century. Its circulation in a species with limited economic value, dogs, and predominant impact on the lives of socioeconomically marginalised people, have enabled it to propagate under the radar of political and public conscience. Dog mediated rabies is a driver of inequality and poverty in developing countries globally, posing a threat to over 6.2 billion people in 122 countries (Figure 1.1) (Hampson et al., 2015; Wallace et al., 2017). The close, interwoven ecology of domestic dogs and humans allows frequent opportunity for zoonotic transmission of the virus, accounting for 99% of human rabies deaths (D. L. Knobel et al., 2005). The risk of death from canine-transmitted rabies is drastically skewed by factors of geographic isolation and economic hardship due to the need for prompt post-exposure prophylaxis following a bite from a rabid animal, making canine rabies elimination a complex socio-political issue to solve (S. Shwiff et al., 2013). A century of scientific toil is yet to translate into widespread political momentum for national and multi-national control interventions, however renewed international focus on rabies in the early twenty-first century offers an opportunity for countries to attract recognition through initiative and early success (Cleaveland et al., 2017; Rohde & Rupprecht, 2020; Umeno & Doi, 1921). Intensification of research efforts into the practicalities of rabies virus elimination are urgently needed to resolve this impasse; adapting operational mechanisms, methods and strategies that have been effective elsewhere and developing them through iterative implementation, evaluation, and expansion in rabies endemic contexts (Cleaveland et al., 2017; Kakkar et al., 2012; Shahid & Kakkar, 2015; Zinsstag, 2013).

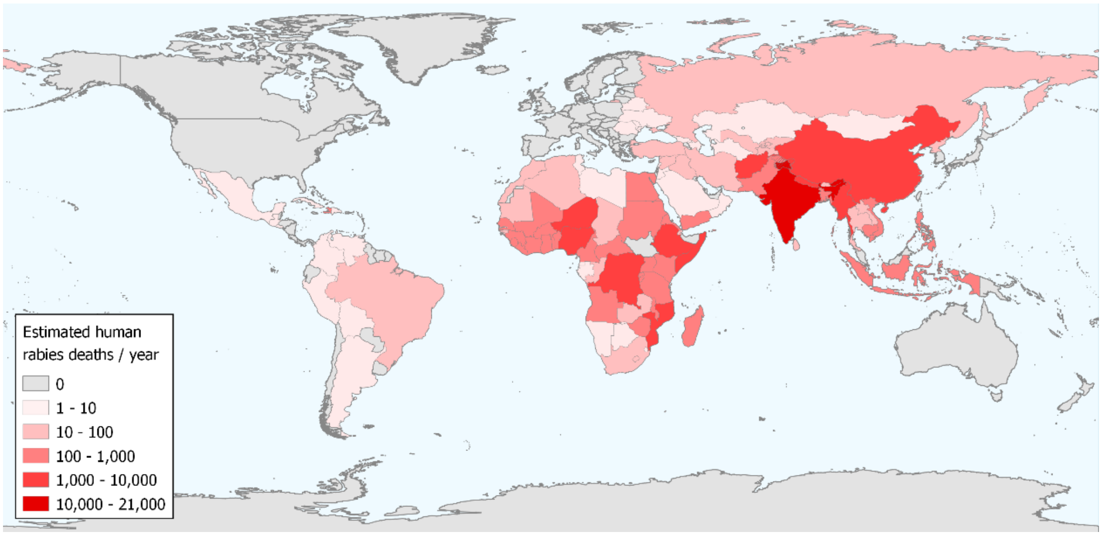


Figure 1.1 - Map of estimated annual human rabies deaths by country (Hampson et al., 2015). National boundaries are retrieved from gadm.org (version 41) and do not imply the expression of any opinion of the author whatsoever concerning the legal status or authorities of any territory or concerning the delimitation of its frontiers or boundaries.

The protracted incubation period (median 20 days, 95% range 1 – 96 days) and relatively low transmissibility of the rabies virus result in a chronic, slow-moving endemic picture (Mancy et al., 2022). Long-range human-mediated transport of asymptomatic dogs incubating rabies virus further contributes to the sporadic occurrence of canine rabies cases in any one community or region over months or years (Hampson et al., 2007). For example, in the rabies endemic Central African Republic capital city of Bangui, long periods of canine rabies virus absence were observed even though the region had never experienced mass dog vaccination (Bourhy et al., 2016). This natural fluctuation in disease incidence and heterogenous epidemiological picture makes the disease inconspicuous to individuals and communities at large, as if it is rarely present. It is only when enhanced surveillance sheds light on rabies incidence throughout a region that the widespread impact of the disease on a district, state, and nation becomes apparent (Colombi et al., 2020; Hampson et al., 2007; S. A. Shwiff et al., 2018). Without robust data on dog rabies incidence, it is impossible to communicate a clear narrative of the true impact and extent of the disease to politicians, decision makers, funders, and the public alike. News headlines appear in sporadic bursts of activity covering events of individual rabies cases which soon abate to the characteristic chronic periodic endemic pattern even in the absence of control intervention. This fleeting attention on canine-transmitted rabies in the media and public-at-large only propagates political torpor for its control.

Political inaction is exacerbated by the weighted impact of the virus falling on marginalised communities lacking visibility and societal influence to lobby for change. The suffering, death, and economic consequences of rabies for people with little socio-economic opportunity go undocumented and unreported to health authorities and therefore remain invisible to high-level policy makers (Hampson et al., 2008). Unlike diseases of production animals, rabies affects a species of no direct economic value, however many studies have revealed the substantial economic cost of rabies resulting from loss of workforce, impact on livestock, and provision of post-exposure treatment (Anderson & Shwiff, 2015; Hampson et al., 2015; S. Shwiff et al., 2013). Whilst pilot initiatives exploring mass dog vaccination implementation must forge ahead without delay, surveillance systems to effectively monitor rabies incidence will be critical in presenting the true burden of disease to stimulate and sustain political support for widespread control.

The global efforts to eliminate smallpox, polio and rinderpest, and the more recent action to control COVID-19, have shown that sustained political commitment stimulates and enables scientific advancement to meet priorities. The scientific community continues to gain a deeper theoretical understanding of rabies transmission and control, however until large-scale government-led initiatives are actioned, the most relevant and critical gaps in knowledge needed to eliminate the disease will remain opaque (Bardosh et al., 2014; Filla et al., 2021; Mpolya et al., 2017; Zinsstag, 2013).

Despite these constraints, progress has been made towards greater prioritisation of rabies in international agendas through high-level consensus amongst the scientific community, political advocacy, and core partnerships. New global momentum was injected in 2018 when the World Health Organisation (WHO), World Organisation for Animal Health (WOAH), and Food and Agriculture Organisation of the United Nations (FAO) came together in the formation of the Zero by 30 Global Strategic Plan (World Health Organization (WHO) et al., 2018). This unified international strategy serves as a single point of reference and guidance as countries consider rabies control as a viable national undertaking.

1.2.1 The rabies virus

Rabies virus is one viral species within the genus Lyssavirus and the family Rhavdoviridae (Figure 1.2). Rabies virus is the only species of lyssavirus which commonly circulates in non-bat carnivorous mammalian reservoirs; however it also circulates in bats in the Americas. Other species of lyssavirus circulate in bats in Africa, Europe, Asia, and Australasia (Fooks et al. 2014) and have been reported to cause rare human deaths with signs clinically not distinguishable from rabies infection (Banyard & Fooks, 2021; Johnson, Vos, et al., 2010). These may become a greater threat in the future, particularly as the existing rabies virus vaccines may not cross-protect against other lyssavirus species in different phylogroups (Figure 1.2) (Evans et al. 2012).

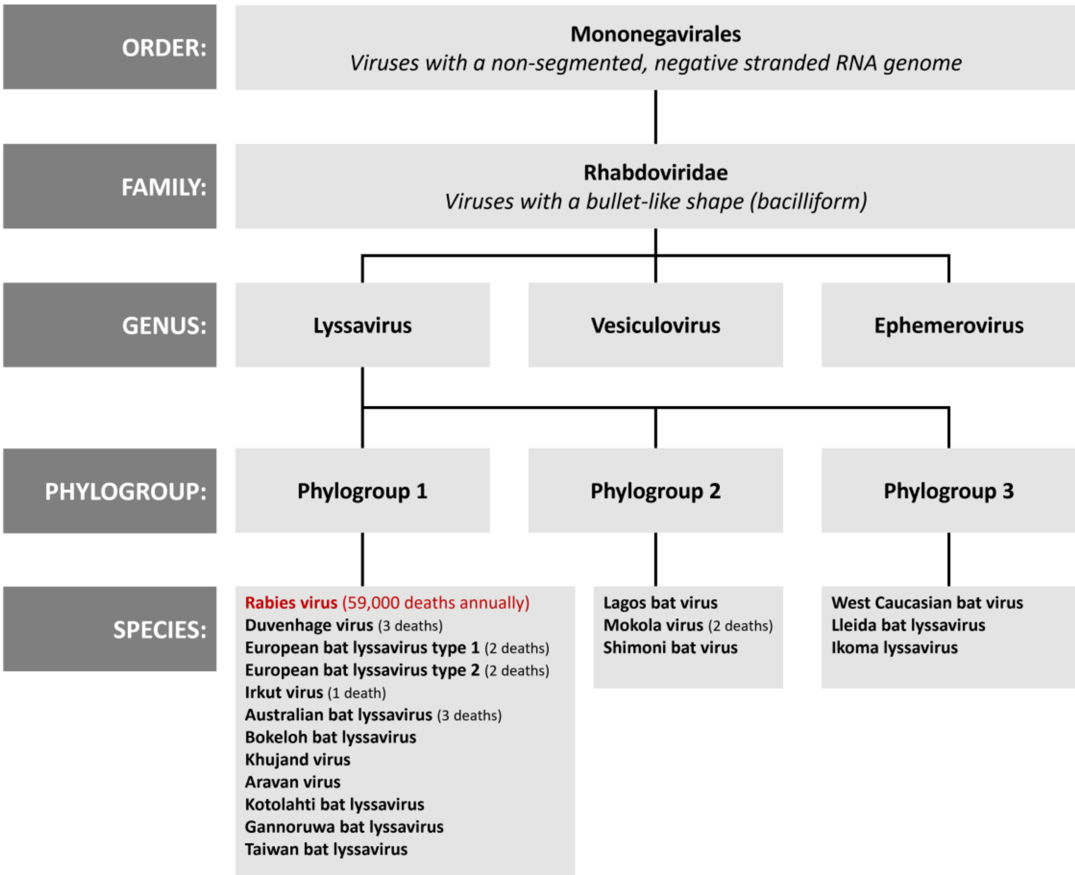


Figure 1.2 – Illustration of the order, family, genera, and phylogroup of the rabies virus and other species within the Lyssavirus genus. Created from summarised information from Evans et al. 2012, Fooks et al. 2014 and WHO 2018).

Rabies virus concentrates in the saliva during the infectious stage of the disease and can be transmitted through bite wounds, contamination of broken skin, or the mucous membranes. The rabies virus then enters the peripheral nervous system through the motor end plates of motor axons and travels within the axon to the dorsal root ganglion within the spinal cord (Hemachudha et al., 2013). From here it infects other ipsilateral dorsal root ganglia via interneurons in which it is transported to the brainstem and brain (Hemachudha et al., 2013; A. C. Jackson, 2020). After replication in the central nervous system the virus spreads centrifugally via ventral and dorsal roots by slow anterograde transport through sensory nerves to organs such as the salivary glands, heart, visceral organs, and skin (Fooks et al., 2014; A. C. Jackson, 2020). The incubation period from the time of exposure to clinical signs in humans is highly variable from days to years, however is typically 1-2 months (A. C. Jackson, 2020).

Clinical presentations include paralytic and furious forms of the disease, however many atypical presentations of the virus have also been described. Higher viral loads with a wider distribution within the brain have been reported in people with furious rabies compared with paralytic, however rabies virus is present within the brainstem in all cases (Laothamatas et al., 2008; Mitrabhakdi et al., 2005). Fatality is almost 100% in clinical rabies cases. There are rare reports of survival, however duration of survival and recovery of neurological function has been limited in all cases (De Souza & Madhusudana, 2014; Subramaniam (Mani), 2016). Treatment with rabies immunoglobulin and post-exposure vaccination has not been shown to be of benefit once clinical signs begin and may accelerate the progression of disease in some cases (Willoughby, 2009).

1.2.2 A One Health example

The close connection between dogs, their owners, and the communities in which they live make canine-transmitted rabies control exemplary of the One Health concept. Effective control of the rabies virus both requires and benefits human health, animal health and environmental management sectors, however this multidisciplinary approach presents administrative and managerial challenges at the point of implementation (Coetzer et al., 2016; Lechenne et al., 2017). Funding, operational and reporting systems are most often structured vertically within government departments, making truly joint-departmental initiatives complex to realise. Efforts to create a single focal point of coordination across departments on aspects of One Health, including rabies control, have been reported from Latin America, Uganda, and Kenya (A. Belotto et al., 2005; Buregyeya et al., 2020; Mbabu et al., 2014).These inter-sectoral taskforces, or One Health offices, can be an important driving force on issues such as rabies, as was demonstrated in Latin America, however challenges remain in a lack of resources, operationalising beyond meetings, and insufficient political prioritisation, even where such initiatives have been embraced (Buregyeya et al., 2020; Munyua et al., 2019).

Domestic dog populations have remained dependent on human habitation; surviving and reproducing due to the resources provided either intentionally or unintentionally by people (Butler & Bingham, 2000; Perry, 1993). As a result, there is a predictable association between human and dog populations, with expansion in the former providing opportunity for growth in the latter. The size of dog populations is therefore expected to rise over the coming decades and unless measures are taken to control rabies, the disease will pose an increasing threat to people. This growing disease burden will also have the potential to drive emergence and re-emergence in wildlife species, as has been seen in mongoose populations in the Caribbean and foxes in Turkey respectively (Nadin-Davis et al., 2006; Vos et al., 2009).

The importance of the sustained collective contribution and support from a broad majority of society must not be underestimated in the success of mass immunisation programmes. Top-down, government-led initiatives can carry the risk of misalignment with the health and social priorities of people most needed to contribute. National dog vaccination campaigns require the mobilisation of a huge workforce who must be united in their understanding of the purpose and benefit of the initiative to be able to deliver sustained success. Furthermore, the perceived importance and benefit of such a visibly enormous undertaking to address the singular issue of rabies must be perceived as worthwhile by the general population, whose contribution in facilitating dog vaccination is critical to achieving high vaccination coverage (Bardosh et al., 2014). Grounding the planning and implementation of rabies control efforts within the wider social and cultural context of the local area is imperative. Building relationships and trust with leaders and gatekeepers at the community level provides the opportunity for two-way information exchange, not only helping to improve contribution from important groups of society, but in garnering grassroots feedback to iteratively adjust the campaign strategy in response to concerns and issues.

1.3 An integrated approach to dog bite management and rabies surveillance

1.3.1 Dog bite management

In most instances the moment of rabies transmission to people is conspicuous; it involves the violent event of a bite from an infected animal. The requirement for immediate prophylactic intervention at the time of the exposure creates a scenario in which the One Health concept has a direct tangible impact at this interface between animal and human disease.

Bites inflicted by rabid dogs may not constitute a high proportion of bite presentations at medical clinics, making up just 3% of bites in a study in Haiti (Medley et al., 2017). Therefore, health systems indiscriminately administering PEP to all dog bite presentations result in dispensation of vaccine to individuals at no risk of rabies, whilst people with high-risk exposures may go without treatment due to stock shortages (Lushasi et al., 2020). A study from Bangladesh showed that 31% of bite victims surveyed posed no risk of rabies transmission (Ross et al., 2022). Methods of integrated bite case management (IBCM) combine veterinary assessment of the biting animal with the human PEP decision-making to improve the prioritisation of vaccine to those at risk of rabies infection. This approach has not only been shown to be cost-effective, but also improved compliance in individuals with high-risk exposures to complete the full course of treatment (Etheart et al., 2017; Lushasi et al., 2020; Undurraga et al., 2017).

In addition to the benefits to human health outcomes and economics, the veterinary components of IBCM contribute to the objectives of canine rabies control. In the first instance, active removal of rabid dogs from the population during the animal investigation prevents continued viral transmission and supports the hastened control of the disease in dogs (Laager et al., 2019; T. N. Leung & Davis, 2014; Wallace et al., 2015). Additionally, the data generated on canine rabies incidence and distribution provides insight into the burden of disease and forms a basis on which to plan and adapt mass dog vaccination and community engagement strategies. Finally, the increased submission of field samples from suspect rabies cases provides demand and incentive for sufficient laboratory capacity to be developed for timely rabies diagnosis (Lushasi et al., 2020).

Progress has been made to increase access to pure, safe, and efficacious post-exposure treatment, thereby reducing human deaths from rabies, however challenges remain in reaching many at-risk individuals (Madjadinan et al., 2020; Sudarshan & Ashwath Narayana, 2019). Dose-sparing intra-dermal regimens requiring fewer clinic visits not only reduce the cost to the individual seeking treatment, but also enable existing stocks of vaccine to treat more people (Hampson, Abela-Ridder, et al., 2019; Hampson, Ventura, et al., 2019; World Health Organization, 2018). These advances in PEP usage, along with improved mechanisms of IBCM will amplify the potential impact of the inclusion of rabies vaccination in the 2021-2025 strategy of the Gavi (Gavi—The Vaccine Alliance, 2021).

Rabies surveillance is a core tenet to rabies control with significance to understanding disease burden, monitoring the efficacy of vaccination activities, and in validating rabies freedom status (OIE, 2018; World Health Organization, 2018b). Establishing functional processes for reporting, investigation and diagnosis of suspect cases are central to the success of rabies surveillance.

1.3.2 Rabies surveillance

Establishing and sustaining the laboratory infrastructure needed for rabies diagnostic tests has been a major barrier to effective surveillance across much of the rabies endemic world (Banyard et al., 2013). The need for experienced laboratory personnel, specialised equipment and costly reagents are barriers to building sub-national laboratory capacity (Yang et al., 2018). Innovations in tests such as direct rapid immunohistochemical test (dRIT) and real-time PCR overcome the need for rabies-specific equipment or expertise respectively (Madhusudana et al., 2012; World Organization for Animal Health (OIE), 2021), however developing regional laboratory testing capacity remains an expensive and resource intensive undertaking (Banyard et al., 2013).

In addition to laboratory constraints, ensuring the logistical feasibility of sample collection and safe transport to the laboratory is fraught with challenges (Mpolya et al., 2017). From maintaining a secure cold chain during the journey to timely transport links from remote areas, the chances of samples being of diagnostic quality on arrival at the laboratory is minimal in many settings. The considerable effort needed to safely take brainstem samples is only worth undertaking if there is a high confidence that a rabies diagnosis will result. And so, when many submitted samples fail to provide timely diagnosis, the rate of submission will invariably be low, which in-turn reduces the justification for maintaining laboratory capacity for rabies diagnostic testing. The recent development of cadaver-side lateral-flow diagnostic tests present the possibility of increasing confirmation of the presence of rabies virus in resource limited settings and in-turn may increase the chances of sample submission to laboratories (Yale et al., 2019).

Lateral flow assays (LFAs), also known as rapid immunochromatographic diagnostic tests, are inexpensive, are easy to perform and do not require expensive equipment (Mauti et al., 2020). Viral RNA is inactivated by the LFA buffer solution and fixed in the test strip during the test and can therefore be shipped to laboratories at ambient temperature for molecular confirmation and genotyping where available. Several recent evaluations of these tests have, however, highlighted concerns over unsatisfactory sensitivity of all devices tested, with wide variation between manufacturers and batches (Eggerbauer et al., 2016; Klein et al., 2020). Two field evaluations of the Anigen, Rapid Rabies Ag Test Kit manufactured by Bionote Inc, Republic of Korea, reported sensitivities of 95.3% and 96% (Léchenne, Naïssengar, et al., 2016; Yale et al., 2019). If consistent performance can be demonstrated, LFAs are likely to increase sampling and submission of suspect rabid animals due to the opportunity to gain immediate information and improving the ease of shipping (Léchenne, Naïssengar, et al., 2016; Yale et al., 2019).

1.4 Rabies control at source

1.4.1 Dog population reservoir

The frequent, unrestricted interaction between free-roaming dogs provides sufficient opportunity for the rabies virus to transmit through contact during the infectious period and to propagate within the dog population. The elimination of canine rabies from the UK by 1902 exploited this epidemiological feature through enforcement of strict dog confinement laws (Carter, 1997). However, such measures are not possible to implement to the degree required to eliminate the virus in modern-day endemic settings (Srinivasan et al., 2019).

Rabies virus transmission dynamics are influenced by myriad factors of dog demography, ecology, and human behaviour, however the basic reproduction number (R_0) for canine rabies, that is the average number of secondary cases from an infectious individual in a naïve population, is consistently low across numerous settings (Bourhy et al., 2016; Coleman & Dye, 1996; Hampson et al., 2009; Hou et al., 2012; P. Kitala et al., 2001; Mancy et al., 2022; Masud et al., 2020; Townsend, Sumantra, et al., 2013; Zinsstag et al., 2009). Estimated values for R_0 varying between 1.2 – 2.4, as compared to R_0 estimates of 6.9 for smallpox, 15.7 for measles, and 2.87 for SARS-CoV-2 (however these vary considerably by location) (Billah et al., 2020; Eichner & Dietz, 2003; Guerra et al., 2017). Crudely, without considering the complexity of population compartments, the proportion of immune individuals in a population required to reduce R_0 below 1, and therefore progressively reduce disease prevalence, can be calculated as $1 - 1/R_0$ (Fine, 1993). The estimated vaccination coverage required to eliminate rabies has been repeatedly estimated to be 20 – 40% (Figure 1.3) (Conan, Akerele, et al., 2015;

Hampson et al., 2009). Nevertheless, high rates of population turnover rapidly diminish vaccination coverage achieved during a single pulse vaccination effort and human-mediated transport of dogs poses high risk of viral reintroduction from endemic regions, adding complexity to the potential for canine rabies elimination (Hampson et al., 2007; Laager et al., 2019; Layan et al., 2021). Some studies report a seasonal element to rabies incidence, such as in Tunisia (Hassine et al., 2021), whilst others show no seasonal trend as in Mali (Traoré et al., 2020).

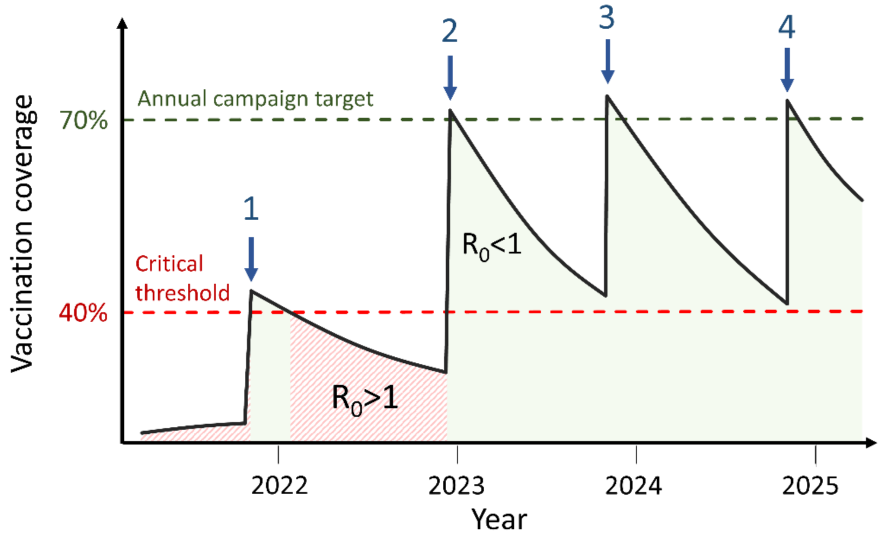


Figure 1.3 – Illustration of hypothetical vaccination coverage following annual vaccination campaigns (blue numbered arrows), campaign coverage target (dotted line at 70%) and critical vaccination threshold (dotted line at 40%). Where annual campaign target coverage is not met (Campaign 1), population turnover results in coverage declining below the critical threshold enabling sustained rabies virus transmission between campaigns. The reproductive number (R_0) is above 1 below the critical vaccination coverage threshold. Adapted from Figure 2 in Cleaveland et al. (2018).

Contact rates between dogs vary within dog populations at the community level, with some dogs posing a greater potential for rabies virus spread through their increased connectivity within the population (Castillo-Neyra, Zegarra, et al., 2017; Hassine et al., 2021; Hudson et al., 2019; Laager et al., 2018; T. Leung & Davis, 2017). Dog ownership and confinement practices have been shown to influence dog contact networks and therefore may be of significance to both rabies virus transmission and dog vaccination campaign strategy (Warembourg et al., 2021). It is yet to be determined whether targeting vaccination efforts at sub-populations of dogs estimated to be more connected has a positive impact on rabies virus elimination or even whether such a campaign would be feasible to implement at scale (Hou et al., 2012; Laager et al., 2019; T. Leung & Davis, 2017). Involving the dog owning public is crucial to the success and sustainability of any rabies control programme. However, promoting responsible dog ownership, wherein guardians take responsibility for the vaccination, reproductive management, confinement, and social impact of the dogs in their care, may yield additional benefits for rabies control by reducing contacts between susceptible dogs (Mustiana et al., 2015; Warembourg et al., 2021).

The role of dog density in sustaining and driving rabies virus transmission is still unclear (Morters et al., 2013). Two studies in the Serengeti region of Tanzania reported a low prevalence of rabies below dog population densities of 4.5 – 5 dogs/km^2 (P. M. Kitala et al., 2002; Lembo et al., 2008). Typically, areas of high dog density also have the highest canine rabies incidence (Laager et al., 2019; Lembo et al., 2008), however peri-urban and rural areas have also shown to be of significance in maintaining endemicity (Bourhy et al., 2016; Zinsstag et al., 2017). Efforts to eliminate the virus through population reduction by culling have invariably failed to control rabies and may worsen the situation through removal of vaccinated dogs and destabilising the population (Beran, 1982; Hossain et al., 2011; Putra et al., 2013; Tenzin et al., 2015; Townsend, Sumantra, et al., 2013; Windiyaningsih et al., 2004).

Naturally acquired immunity to rabies following non-lethal exposure in the absence of vaccination has been demonstrated at several project sites in Africa (Alexander et al., 1994; Cleaveland et al., 1999; Lankester et al., 2016). This may contribute to the sustained low incidence of rabies in endemic settings (Gold et al., 2021).

1.4.2 Rabies vaccines in animals

The first effective vaccine against rabies virus was demonstrated by Louis Pasteur in 1885 using a crudely attenuated (weakened) rabies virus. The safety of such nerve tissue vaccines, for administration by intramuscular or subcutaneous injection, was improved over several decades by increasing attenuation and eventually total inactivation of the rabies virus (Dreesen et al., 2007). Further advancement of vaccine safety and potency continued through vaccine production methods using passage through embryonated eggs in the mid-20th century and later the introduction of inactivated cell culture vaccines in the 1970s and 80s (Dreesen et al., 2007; C. E. Rupprecht et al., 2002). Consequently, the production of vaccines of nerve tissue origin has been phased out in all but a few countries (World Health Organization, 2018).

Most vaccines used in domestic animals today are inactivated (killed) parenteral vaccines. Adapted virus strains are propagated in cell cultures or embryonated eggs and then inactivated and combined with an adjuvant (World Organisation for Animal Health, 2018). Whilst both cell-mediated and humoral immune responses are stimulated, assessment is typically conducted using serological assays for detection of virus neutralising antibodies in animals travelling internationally (Johnson, Cunningham, et al., 2010). Assays include rapid fluorescent focus inhibition test (RFFIT) and fluorescent antibody virus neutralising (FAVN) test.

The vaccine used across Mission Rabies projects, including the work reported in this thesis, was Nobivac® Rabies (MSD Animal Health) which contains inactivated Pasteur RIV rabies virus with an aluminium phosphate adjuvant (MSD Animal Health, 2016). The vaccine is licenced for subcutaneous or intramuscular administration and produces an adequate serological response within 2-3 weeks. The licence reports a three-year duration of immunity following a single administration, however the manufacturer recommends that animals vaccinated at less than three months old should be given a repeat dose at three months. International guidance for mass dog vaccination programmes recognises the limitations of repeat vaccination and so recommends vaccination of dogs of all ages during vaccination campaigns (World Health Organization, 2018). Recent assessment of thermotolerance showed that dogs vaccinated with Nobivac® Rabies vaccine stored at 30°C for 3 months, or 25°C for 6 months, produced a comparable immune response to that of dogs receiving cold chain stored vaccine (Lankester et al., 2016).

Oral rabies vaccines (ORVs) have been used extensively in the control of wildlife rabies in Europe, and Northern America for over 40 years. The first oral rabies vaccine was developed in the 1960s using attenuated rabies virus with the Street Alabama Dufferin (SAD) rabies virus strain, which continues to be the origin of almost all modified-live oral rabies vaccines used today (T. Müller & Freuling, 2020). This strain underwent extensive passaging and thermal stabilisation to create the first-generation modified-live ORVs, including SAD-Bern, ERA and SAD-B19. These vaccines formed the basis for the successful control of rabies in red foxes (*Vulpes vulpes*) in Europe and over 500 million doses have been distributed since 1978 (T. F. Müller et al., 2015; T. Müller & Freuling, 2020).

Concerns existed about the risk of reversion to virulence in vaccinated individuals, and sporadic vaccine-associated rabies cases were reported from the field, representing 1 in 48 million doses distributed (T. F. Müller et al., 2015). The stability and safety of modified-live vaccines was improved by inducing selection mutations using monoclonal antibodies to create the second-generation modified-live vaccines (SAG-1, SAG-2, SAD-VA1). In recent years, targeted site-specific mutations using reverse genetics has produced a third generation of modified-live ORVs (SPBN GASGAS and ERA G333), with improved safety and immunogenicity for use in canids (Kamp et al., 2021; Wallace et al., 2020).

The number of field assessments of the use of SPBN GASGAS has increased in recent years, with pilot programmes delivering the vaccine to dogs in communities in Haiti, Namibia, and Thailand (Chanachai et al., 2021; Freuling et al., 2022; Molini et al., 2021; T. G. Smith et al., 2017). A study of kennelled dogs in Thailand reported that the immune response following oral vaccination using SPGN GASGAS via a boiled pig intestine bait was non-inferior to dogs vaccinated with inactivated parenteral vaccine (Leelahapongsathon et al., 2020). I co-authored and supervised a review article on the potential use of ORVs in India, in which we populated a model developed by others to estimate the public health risk of using modified-live ORVs in mass dog vaccination campaigns (Yale et al., 2022). It was estimated that distribution of 40,000 SPBN GASGAS baits by the handout method in Goa would result in 5 human exposures to vaccine (95% CI: 0-14), but that no deaths would occur (95% CI: 0-0), nor were any deaths predicted following a campaign distributing 10 million doses. Modified-live virus vaccines induce both humoral and cellular immune responses following uptake and limited replication in the palatine tonsil (Kamp et al., 2020; Vos et al., 2017). A recent study, extending over 30 months, demonstrated long-term immunity conveyed following a single administration of SPBN GASGAS (Vos et al., 2023).

Recombinant vector-based rabies virus vaccines mitigate the risk of reversion to pathogenicity that exists with modifies-live replication competent rabies virus vaccines. This class of ORVs has been used extensively in the control of grey fox, racoon, and skunk rabies in North America through the distribution of over 200 million doses (T. Müller & Freuling, 2020). They were developed by inserting a segment of rabies virus cDNA, encoding the rabies virus glycoprotein, into the genome of a vector virus. The rabies glycoprotein antigen is subsequently expressed within the cells of vaccinated individuals to incite an immune response. Two vector-based vaccines are currently in use: RABORAL V-RG, which uses a recombinant vaccinia vector virus (Orthopoxvirus genus), and ONRAB, consisting of a recombinant human adenovirus-5 vector (Brown et al., 2014; Maki et al., 2017; R. C. Rosatte et al., 2009; C. E. Rupprecht et al., 2005). A concern with the distribution of vector-based vaccines near human population is the risk of adverse effects of infection with the vector virus. Reports of severe skin disease in people exposed to V-RG and complications in pregnant women are barriers to its widespread use in the control of dog rabies (Roess et al., 2012; C. Rupprecht et al., 2001). Use of V-RG has also declined in recent decades in the control of skunk and racoon rabies due to concerns about variable antibody response (Fehlner-Gardiner, 2018; Fehlner-Gardiner et al., 2012; Mainguy et al., 2013). Similar concerns exist around the risk of human exposure to recombinant human-adenovirus vector vaccines, which can cause conjunctivitis and respiratory disease, particularly in children (Ghebremedhin, 2014). Reports of variable rates of immune response in dogs vaccinated with ONRAB also throw doubt on its potential application in mass dog vaccination programmes (Aubert, 1992; Berentsen et al., 2016; Cliquet et al., 2008).

There is increasing advocacy from international health agencies, including WOAH, WHO, FAO, and the US CDC, for the active exploration of ORVs as a component of mass dog vaccination programmes where dog accessibility is a barrier to accessing high vaccination coverages via parenteral vaccination methods (Wallace et al., 2020). Whilst hesitancy remains over the theoretical risk of modified-live rabies virus vaccines, third-generation vaccines provide the most robust safety profile of any ORV to date, whilst retaining potency (Bobe et al., 2023). Further work is needed to understand the financial, operational, and epidemiological impact of incorporating ORVs in dog rabies control programmes and many hurdles remain in reaching widespread availability. In the meantime, effective, low-cost parenteral vaccines are broadly accessible for use in dogs at scale and progress can be made to benefit human and animal health through investigation of existing approaches rooted in parenteral vaccination methods.

1.4.3 Rabies control interventions

Rabies control programmes can be divided into four broad stages to aid operational strategy; 1) endemic, 2) control, 3) elimination, 4) freedom (Brunker et al., 2020) (Figure 1.4).

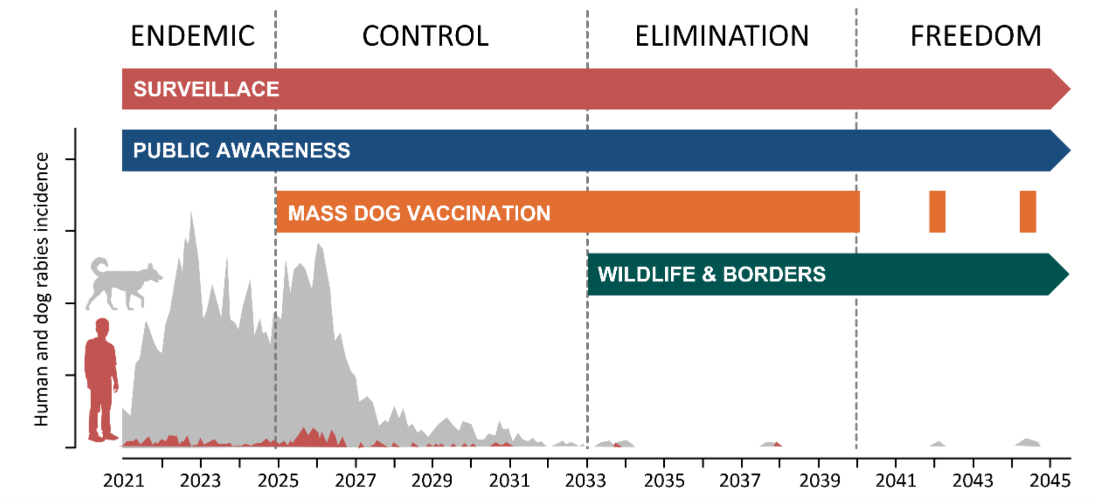


Figure 1.4 – Illustration depicting the stages of rabies elimination and the timing of activities focused on surveillance, awareness, vaccination, and reintroduction risk. Adapted from Brunker et al., 2020. Data are not from a real-world location and illustrative only.

1) *Endemic*. During the endemic phase priorities focus on establishing surveillance processes to reveal the incidence and distribution of human and dog rabies and consequently solicit public and political support. Dog vaccination activities are likely to be uncoordinated resulting in endemic rabies virus circulation with frequent human exposure through rabid dog bites. Building public awareness about the risk of rabies aims to increase engagement and support for subsequent dog vaccination activities and reduce human rabies deaths through an increase in access to PEP.

2) *Control*. Dog vaccination activities are piloted, refined, and expanded through the control phase, with a resulting decline in dog rabies incidence. Surveillance and awareness activities must be sustained to monitor the impact of vaccination activities and maintain public support for the programme. Rabies virus circulation persists in problem regions with low vaccination penetration, or high rates of rabies transmission or dog population turnover.

3) *Elimination*. As vaccination efforts intensify the programme enters the endgame or elimination phase. Surveillance must detect remaining pockets of rabies virus persistence and vaccination activities must adapt to establish and maintain herd immunity in these areas. Investigation of potential sources of rabies virus

reintroduction from wildlife reservoirs and dog populations in bordering regions will guide the strategy for achieving elimination and maintaining freedom.

4) *Freedom*. Once rabies freedom has been achieved, surveillance, awareness and reintroduction risk management must continue so that reintroduction of rabies virus is swiftly detected, and vaccination activities can recommence until elimination can be demonstrated. A comprehensive analysis of rabies elimination from Bali, Indonesia determined that vaccination must continue for at least two years after a period of six consecutive months with no detected cases (Townsend, Sumantra, et al., 2013). Viral sequencing can support effective campaign planning throughout this process (Brunker et al., 2020).

1.4.4 Vaccination campaign structures

High-income countries benefit from established, widely distributed human and veterinary healthcare systems, which serve to immunize susceptible individuals as they enter the population and thereby establishing herd immunity against many diseases (D. L. Knobel et al., 2020; Wallace et al., 2017). The lack of such healthcare services in many low- and middle-income countries (LMICs) precluded this approach in the short-to-medium term, resulting in differing perspectives on the optimal strategy to communicable disease control in such settings. Some believe that sustainable progress is best achieved from investing in the broad development of health services, providing a foundation upon which to deliver treatments and immunization for a range of health priorities (Abraham, 2018). The growth of health services, however, is expensive and complex to realise at scale and direct impacts can be difficult to quantify, inherently spanning multiple areas of health over several decades.

Many health interventions emerge from action-groups, funders, and policymakers looking to address a specific issue, delivering measurable results over a period of years rather than decades. This has driven programmes targeting vaccine-preventable diseases to ground their method in supplementary immunization activities in the form of vaccination campaigns; periodic mass delivery of certain vaccines to target populations, irrespective of previous vaccination status to rapidly increasing population immunity against a specific disease (Hayman, 2019; Helleringer et al., 2014; Khetsuriani et al., 2011; D. J. Nokes & Swinton, 1995; Utazi et al., 2019). Whilst global successes of this approach include the eradication of smallpox and rinderpest, the Global Polio Eradication Initiative has highlighted the risk of misalignment with domestic priorities, particularly in areas facing unforeseen challenges (Abraham, 2018). Pulse vaccination programmes must often intensify vaccination efforts until disease elimination is achieved, despite low prevalence and therefore perceived importance to communities fatigued from years of campaigns and who inevitably have far more tangible public health concerns. The low reproductive number of dog rabies and low-cost low-risk of existing effective rabies vaccines, make rabies an ideal candidate for elimination through pulse vaccination programmes (Cleaveland et al., 2014).

1.4.5 Mass dog vaccination

All examples of successful rabies elimination have used pulse campaigns as the basis for mass dog vaccination (Cleaveland et al., 2003; Cleaveland & Dye, 1995; Conan, Akerele, et al., 2015; P. M. Kitala et al., 2002; Zinsstag et al., 2017). The critical vaccination threshold for sustained rabies transmission is estimated to be 20 – 40% of the population, however vaccination coverage will decline following a pulse vaccination campaign through the death of vaccinated dogs and birth of unvaccinated puppies (Cleaveland et al., 2018). Therefore, a sufficiently high proportion of the population must be vaccinated during each pulse campaign to maintain herd immunity above the critical threshold until the next campaign (Hampson et al., 2009; Morters, Mckinley, et al., 2014). Many examples have reported substantial reductions in dog rabies incidence following annual campaigns achieving 60 – 70% vaccination coverage, resulting in the longstanding recommended from WHO for the annual vaccination of 70% of the dog population

(Cleaveland et al., 2003; Cleaveland & Dye, 1995; Conan, Akerele, et al., 2015; P. M. Kitala et al., 2002; World Health Organization, 2018; Zinsstag et al., 2017).

The current ubiquitous 70% vaccination target is being increasingly questioned and will likely be possible to adjust as greater understanding is gained about dog ecology, population heterogeneity, and its implications for rabies transmission and herd immunity (T. Leung & Davis, 2017). Robust data on dog population turnover in diverse settings is lacking, however several studies indicate that mean dog lifespan in areas of high dog density is less than three years, and therefore population turnover is high, resulting in more rapid decline of vaccination coverage than in areas with a comparably stable dog population (Acosta-Jamett et al., 2010; Butler & Bingham, 2000; Czupryna et al., 2016; P. Kitala et al., 2001; Kumarapeli & Awerbuch-Friedlander, 2009). Furthermore, the population composition of dog ownership and confinement is likely to impact on both population turnover and rabies transmission dynamics within the population (Kumarapeli & Awerbuch-Friedlander, 2009; Sparkes et al., 2016; Warembourg et al., 2021). It is therefore inevitable that the campaign vaccination coverage required to interrupt rabies transmission would differ based on dog ecology (Kotzé et al., 2021). The time taken to ultimately achieve elimination will be further impacted by the dog population size, distribution, connectivity, demography, campaign interval and vaccination coverage (Brunker et al., 2020; Cleaveland et al., 2003; E. A. Ferguson et al., 2015; Kotzé et al., 2021; Zinsstag et al., 2017).

The detriment of patchy vaccination coverage to the goal of disease elimination is well known in the field of epidemiology and was documented during early dog vaccination programmes (Belcher et al., 1976). Variation in vaccination intensity across the dog population of a region (heterogenous coverage) allows for sustained rabies virus transmission within unvaccinated patches, providing a source of rapid reintroduction into vaccinated areas as coverage wanes (E. A. Ferguson et al., 2015; P. M. Kitala et al., 2002; Suseno et al., 2019; Townsend, Sumantra, et al., 2013).

Modelling of a campaign in the Philippines concluded that targeting areas of low coverage, even at the expense of reduced coverage in previously high coverage area, would significantly enhance prospects for elimination (E. A. Ferguson et al., 2015). Achieving lower peak vaccination coverages may also represent a cost saving because as the proportion of vaccinated dogs in the population increases, vaccinating the remaining dogs becomes more expensive (Anderson et al., 2019).

The massive logistical undertaking of delivering vaccine to dogs throughout the population is wasted if the vaccine administered does not incite immunity against rabies. Ensuring that the vaccine is managed in such a way that it is effective at the point of delivery is of central importance to the success of any rabies elimination programme. Most of the expense associated with mass dog vaccination campaigns lies in human resource and logistical components, with the cost of the vaccine itself comprising a small proportion of the cost per dog vaccinated (Undurraga et al., 2020). Cutting costs in this area by using inferior quality vaccines that may confer low rates of immunity is counter sensical to rabies control (Clifton, 2010; Hu et al., 2008). The procurement of inferior vaccines for the 2014 vaccination campaign contributed to resurgence of rabies in Bali during 2015 (Suseno et al., 2019). The identification of high-quality thermostable vaccines offers an opportunity to improve cost-efficiency of operations and explore vaccination methods using low-cost cold-chain systems (Lugelo et al., 2021). Modern parenteral vaccines have been demonstrated to remain effective after several months of storage at 30°C (Lankester et al., 2016). A recent study in Tanzania explored continuous vaccination methods using community workers, which may offer improved feasibility of scaling, higher vaccination coverage and greater community engagement in some settings (Lugelo et al., 2022).

Large-scale, effective campaigns require sustained support over many years to develop from concept through to enduring high-coverage vaccination programmes across large expanses of a country (Mpolya et al., 2017; Vigilato et al., 2013;

Wallace et al., 2017). The early stages of development involve field studies to generate understanding about the dog population, evaluate vaccination methods, develop methods for effective community engagement, build operational experience, and create training processes. This is followed by a period of continuous refinement and progressive scale-up of methods in which logistical, administrative, and operational challenges must be overcome. Finally, these activities are sustained with ongoing evaluation of impact on rabies incidence over large geographic areas (LeRoux et al., 2018; Wallace et al., 2017).

Global guidance recommends the inclusion of puppies under the age of 3 months in dog vaccination campaigns (World Health Organization, 2018; World Organization for Animal Health (OIE), 2021). Juveniles under 12 months of age are more likely to present with rabies and may be a higher risk group for rabies transmission both to other dogs and to people (Beran, 1982; Kayali, Mindekem, Yémadji, Oussiguéré, et al., 2003; Malaga et al., 1979). Population turnover in puppies is invariably greater than the general population and so vaccination coverage in puppies rapidly declines following a vaccination campaign (Beran, 1982; Czupryna et al., 2016; Hampson et al., 2009; Reece et al., 2008). Reece et al. reported survival to one year of just 25% of puppies born in Jaipur, India, whilst several studies reported death of 50% of puppies within the first month of life in Zimbabwe (Brooks, 1990; Butler & Bingham, 2000; Reece et al., 2008). Nevertheless, mathematical models have highlighted the importance of including this population in mass dog vaccination campaigns (Anderson et al., 2019) and vaccination of puppies against rabies is effective at preventing infection (Morters et al., 2015). Accessing this population for vaccination may be more difficult as people are less likely to present puppies for vaccination, assuming they are too young (Arief et al., 2017; Davlin & VonVille, 2012; Flores-Ibarra & Estrella-Valenzuela, 2004; A. D. Gibson et al., 2016; Kaare et al., 2009; Lugelo et al., 2022; Suzuki et al., 2008). Studies have reported seasonal dog breeding patterns in many settings (Fielding et al., 2021; Morters, Mckinley, et al., 2014; Ortega-Pacheco et al., 2007; Pal, 2003; Totton et al., 2010), which may support planning of population interventions during months likely to achieve greatest impact (Fielding et al., 2021).

The role of dog sterilization in rabies control remains a contested subject among politicians and policy makers, however guidance from the WHO and scientific community is clear; sterilization activities should only be considered to support rabies control where high vaccination coverage has been achieved and surplus funds are available, or the source of funds for sterilization are separate from that for vaccination (World Health Organization, 2018). Some rabies control programmes describe sterilization as being implemented alongside mass vaccination, including Latin America, South Africa, the Philippines and cities in India (Kumarapeli & Awerbuch-Friedlander, 2009; Lapiz et al., 2012; LeRoux et al., 2018; Reece & Chawla, 2006). However only Latin America, and South Africa ultimately demonstrated rabies elimination at greater than district-scale and both abandoned mass sterilization from their strategy during scale-up due to its operational complexity, cost, lack of scalability and inapparent impact (del Rio Vilas et al., 2017; LeRoux et al., 2018). The primary objectives of mass dog sterilization are generally to reduce dog population density and slow population turnover by reducing birth rates (ICAM Coalition, 2008). There is little evidence that sustained population reduction is achievable from sterilization alone and even if a moderate reduction in dog density were to be achieved, its impact on rabies virus transmission is believed to be minimal (Morters et al., 2013). The impact of reducing population turnover through reduced birth rates and increased mean lifespan would theoretically contribute to sustaining herd immunity and therefore enable rabies elimination at lower campaign vaccination coverages or extended campaign intervals (Laager et al., 2019), however there are currently no robust studies demonstrating that this is achieved through mass sterilization (Anderson et al., 2019; Collinson et al., 2020).

1.4.6 Methods of dog vaccination

At present, there are three methods upon which to base parenteral mass dog vaccination campaigns; central point (CP); door-to-door vaccination (DD); and capture-vaccinate-release (CVR). The methodological intensity increases from CP, to DD, to CVR, in terms of cost per vaccination team, logistical complexity, and human resource requirement. Each vaccination method has a weighted likelihood of accessing dogs from specific demographics within the population (Wallace et al., 2019). Therefore, the selected approach, or combination of approaches, must be matched to the composition of the local dog population to achieve the desired overall population coverage at the lowest possible cost and effort (Undurraga et al., 2020). More recently tools have been developed to aid campaign planners in the exercise of programmatic alchemy required to design the optimal campaign strategy (Mazeri et al., 2021; Wallace et al., 2019).

Dog ownership offers an opportunity to confine dogs at periods, both to limit the risk of rabies virus transmission, but also to avail of opportunities for vaccinations. In such settings communities can be engaged to bring dogs to temporary central vaccination points for inoculation. Mobilising the general populous as a workforce for dog transportation in this way has huge efficiency savings at the campaign level and was the basis for the vaccination of over 15 million dogs in Mexico during one week every year in the early 2000's (Velasco-Villa et al., 2017). Similar CP approaches have been used to achieve high vaccination coverages in urban settings of Chad and Malawi, however these are yet to be expanded to the national level (A. D. Gibson et al., 2016; Léchenne, Oussiguere, et al., 2016; Mazeri et al., 2021; Mpolya et al., 2017; Zinsstag et al., 2017). Typically, a CP clinic will constitute two to three people; a vaccinator and an assistant. Together they vaccinate dogs presented to them and issues certificates of vaccination.

Community engagement strategies to improve dog owners' ability to handle their dogs and education on the importance of vaccination are a priority to increase vaccination output from CP vaccination approaches. A lack of awareness of the vaccination campaign is often cited by dog owners as a reason for non-presentation at CP clinics and so effective methods for information exchange are essential (Barbosa Costa et al., 2020; Castillo-Neyra, Brown, et al., 2017; Mazeri et al., 2018; Mulipukwa et al., 2017; Yoak et al., 2021). The potential for mass SMS messages as a method of broadcasting campaign dates and locations was recently reported in a study in Haiti (Cleaton et al., 2018). In another recent study, the strategic adjustment of the distribution of CP clinics enabled vaccination coverage to be increased in an urban setting of Malawi, dramatically increasing campaign efficiency (Mazeri et al., 2021).

CP strategies fail to achieve sufficient vaccination coverage in areas where a high proportion of dogs are unowned or where dog owners are unable or unwilling to bring them to CP vaccination clinics during the campaign (A. W. Ferguson et al., 2020; Muthiani et al., 2015; Tohma et al., 2016). Where the coverage of CP vaccination cannot be increased to the required level, more resource intensive methods of DD vaccination either in combination with CP or alone may be required. The DD approach involves teams typically consisting of two people; a vaccinator and an assistant, who travel through communities, house-to-house requesting dog owners to present dogs for vaccination. This method has been demonstrated to be effective in numerous African settings, particularly in areas where most dogs are owned and can be manually restrained for parenteral vaccination (Jibat et al., 2015; Morters, McKinley, et al., 2014).

In contrast to many areas of Africa, dog populations of Asia often comprise a higher proportion of unowned dogs that are not readily amenable to handling for parenteral vaccination (A. D. Gibson et al., 2015; Sánchez-Soriano et al., 2019; Sudarshan et al., 2001; Totton et al., 2010). As a result, CP, and DD methods, that rely on the manual restraint of dogs by their owner/guardian, fail to reach high coverages in the free-roaming dog population (Belsare & Gompper, 2013). The CVR method typically involves vaccination teams comprising six to eight people, including three or more dog handlers working as a team, using nets to catch free-roaming dogs for parenteral vaccination. The programme developed in Bali, Indonesia between 2009 to 2011 demonstrated how these methods could be scaled to a campaign vaccinating 250,000 dogs per 6-month campaign (Putra et al., 2013).

1.4.7 Dog vaccination campaign evaluation

The vaccination coverage achieved by a particular vaccination method, or combination of methods, will be affected by the composition of the local dog population, community engagement and sociocultural factors. During the initial phases of campaign development, it is beneficial to evaluate vaccination coverage to assess the efficacy of a particular vaccination approach in a specific locality (LeRoux et al., 2018; Sambo et al., 2017). This enables the strategy to be refined in the short-term to reach a target vaccination coverage across much of the population and thus increase the chances of achieving the objective of rabies control. Ultimately the vaccination requirement to successfully control rabies at the community level will vary depending on local epidemiological factors, with viral elimination occurring at lower coverages in some areas than others (Coleman & Dye, 1996; T. Leung & Davis, 2017; Reece & Chawla, 2006). Therefore, monitoring canine rabies incidence with robust surveillance is essential to guiding vaccination strategy through course of a control effort, determining regions where vaccination must persist or intensify and areas that have achieved elimination.

1.4.8 A review of mass dog vaccination

A search of the peer-reviewed literature was performed to identify the current distribution, methods, and scale of mass dog vaccination experience (Appendix A). Most articles reported studies in Africa (27), followed by 22 from Asia and seven from Latin America (Figure 1.5, Figure 1.6). The largest reported programme was that of the rabies elimination campaign in Latin America coordinated by the Pan American Health Organisation (PAHO) involving the annual vaccination of 51 million dogs (Vigilato et al., 2013). Campaigns exceeding annual 500,000 doses were rare outside of Latin America and included reports from South Africa, South Korea, Vietnam and Sri Lanka (Harischandra et al., 2016; Lee et al., 2001; S. a Shwiff et al., 2014; S. A. Shwiff et al., 2018; Yang et al., 2018). The Sri Lanka campaign was the largest in South Asia, reporting that “about 1.5 million dogs” were vaccinated in 2015, however details of the sub-national distribution of this effort, dog vaccination methodology, or regional vaccination coverage are not provided (Harischandra et al., 2016).

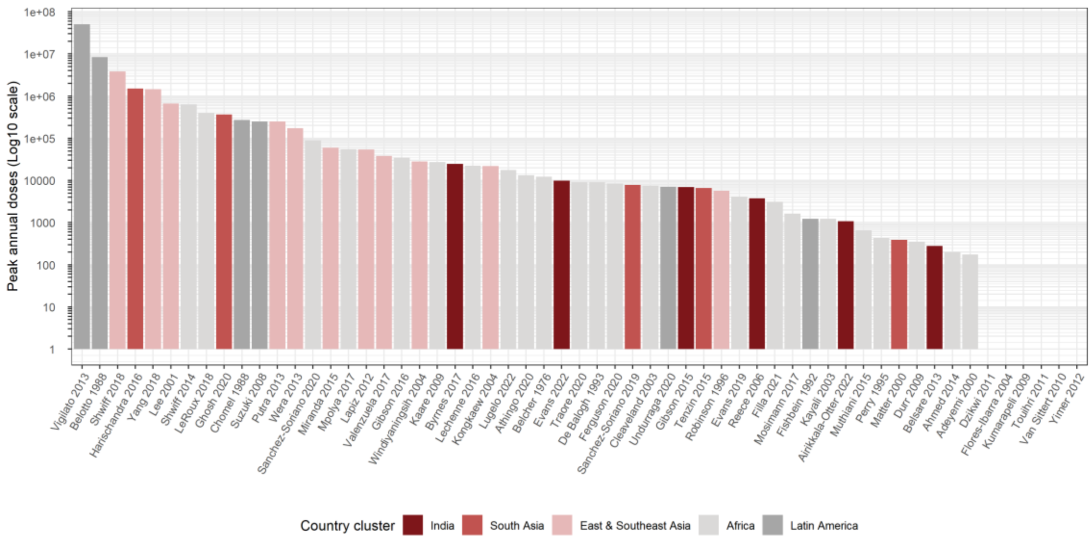


Figure 1.5 - Chart of peak annual vaccination doses in articles reporting the implementation of mass dog vaccination programmes, coloured by geographic region. Scale is Log10.

There is a dearth of published research studying the approach to mass dog vaccination in India. Only five peer-review reports of dog vaccination programmes were identified in this review, two of which also involved sterilization of dogs, and one was a small programme vaccinating 277 dogs in rural Maharashtra (Airikkala-Otter et al., 2022; Belsare & Gompper, 2013; Byrnes et al., 2017; A. D. Gibson et al., 2015; Reece & Chawla, 2006). The largest vaccination programme reported was a campaign in Sikkim which vaccinated 24,500 dogs in its peak cycle (Byrnes et al., 2017) (Figure 1.6). An additional 16 studies from India reported studies of dog demography and mathematical models predicting the impact of population interventions (Abbas et al., 2014; Brookes et al., 2019; Gill et al., 2019, 2022; Larkins et al., 2020; Nadal et al., 2022; Radhakrishnan et al., 2020; Srinivasan et al., 2019; Tamim Vanak et al., 2022; Tiwari et al., 2018; Tiwari, Robertson, O'Dea, & Vanak, 2019a, 2019b; Tiwari, Robertson, O'Dea, Gogoi-Tiwari, et al., 2019; Totton et al., 2010; Yoak et al., 2014, 2016).

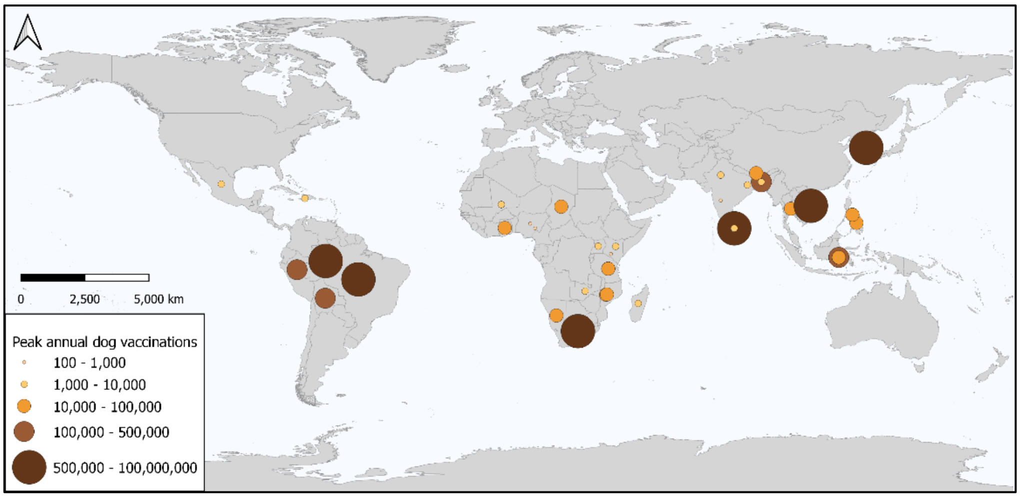


Figure 1.6 - World map of the location and peak annual dog vaccinations published in articles reporting mass dog vaccination programmes.

Methods reported by study were summarised, with each study potentially using multiple methods (Figure 1.7). The CP method of dog vaccination was most frequently reported (53%), followed by DD (31%), CVR (10%) and finally three studies reporting decentralised approaches (two from Tanzania and one from Madagascar). In this context, decentralised referred to approaches which deferred the planning and implementation of the campaign to community animal health workers, or were delivered through continuous vaccination by routine veterinary services. There was considerable variation in the frequency of methods described by region, with CVR methods being more commonly reported in Asian countries and the most frequently integrated method in studies from India. This may reflect the importance of CVR to access sufficient dogs in India, or the need for further assessment of CP as a component of dog vaccination programmes in the region. Subsequent analysis of the literature could collate total vaccinations delivered via each method to give a greater insight into the scale of deployment.

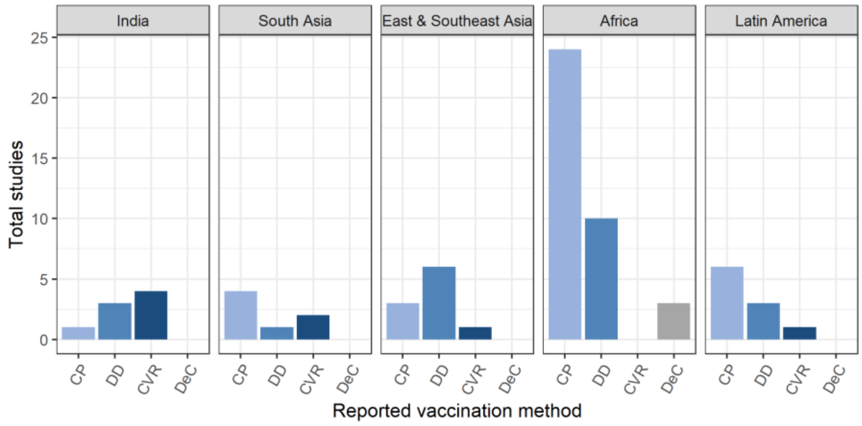


Figure 1.7 - Chart of studies reporting use of each vaccination method by region. CP = Central Point, DD = Door-to-Door, CVR = Capture-Vaccinate-Release, DeC = Decentralised.

Cost per dog vaccinated was reported in 11 articles, with a median cost per dog vaccinated of 3.44 USD (range 1.28 – 19.4) (Byrnes et al., 2017; A. W. Ferguson et al., 2020; Filla et al., 2021; Kaare et al., 2009; Kayali, Mindekem, Yémadji, Vounatsou, et al., 2003; Miranda et al., 2015; Mpolya et al., 2017; S. a Shwiff et al., 2014; Valenzuela et al., 2017; Wera et al., 2013; Zinsstag et al., 2009).

Peak vaccination coverage was reviewed in each study to assess whether adequate methods for dog access had been identified. Mean peak coverage across all studies was 61% (range 17 – 89%). Methods to achieve approaching 70% vaccination coverage were reported across regions (Figure 1.8).

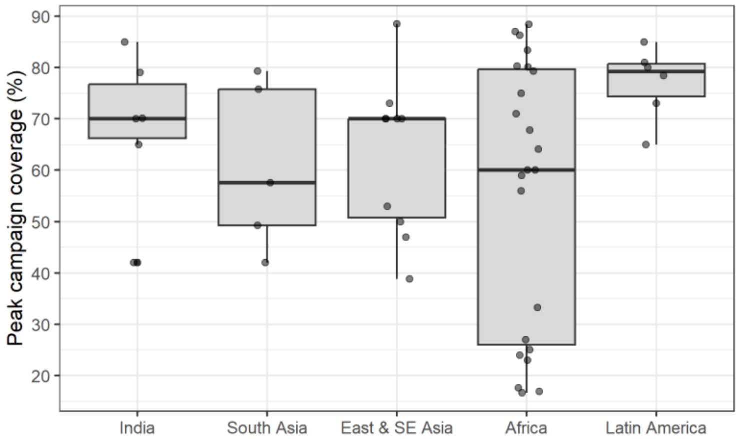


Figure 1.8 - Box plot of peak vaccination coverages reported in each study by region. The reported peak coverage of each study is shown as a point.

1.5 Rabies control in India

1.5.1 Historic context

In 2022 India was the world's second most populous country and the fifth largest economy by GDP (International Monetary Fund, 2022), however there is considerable cultural, political, and economic variation across its 28 States and eight Union Territories (Smits & Permanyer, 2019) (Figure 1.9). Numerous global burden studies have estimated that one third of global human rabies deaths occur in India, more than any other country (Gan et al., 2022; Hampson et al., 2015; D. L. Knobel et al., 2005). The lack of widespread robust human rabies surveillance systems precludes the reliable monitoring of current human rabies burden (Sudarshan & Ashwath Narayana, 2019), however the figure of approximately 20,000 annual human rabies deaths in India has been repeatedly estimated (Hampson et al., 2015; D. L. Knobel et al., 2005; Sudarshan et al., 2007).

Zoonotic disease prioritisation exercises aim to generate a broad consensus on which diseases should be a priority for control efforts through the systematic evaluation of criteria pertaining to human and animal health, outbreak potential, socioeconomic impact, and availability of interventions amongst others (Rist et al., 2014). Rabies has consistently scored as the most important zoonotic disease in such exercises from locations around India at national, state and city scales (Kurian, 2014; Sekar et al., 2011; Thukral et al., 2023; Yasobant et al., 2019). Thus, it is clear that in relation to other zoonotic risks in India, including leptospirosis, brucellosis, anthrax, Japanese encephalitis, influenza A (H1N1), glanders and avian influenza, rabies should be considered a public health priority.

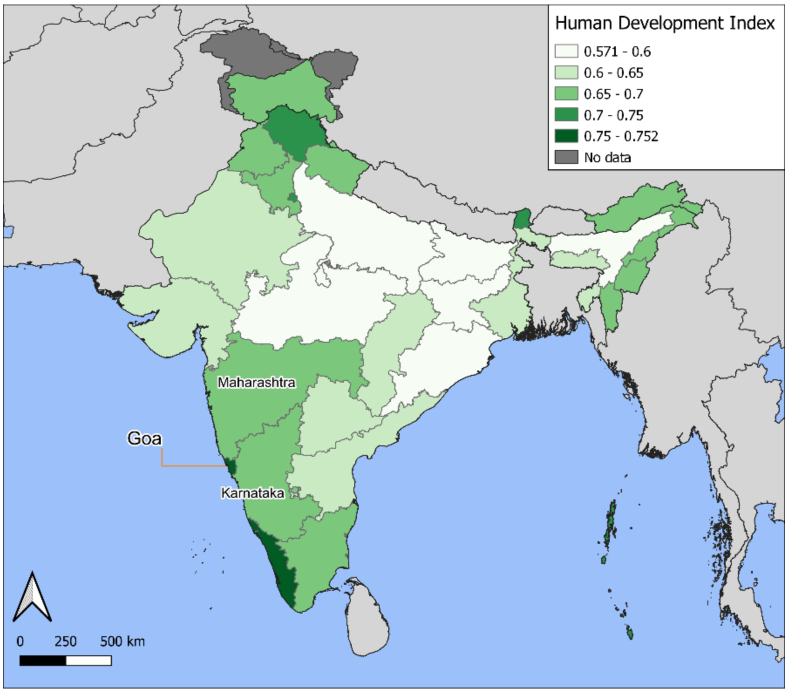


Figure 1.9 - Map of India showing Human Development Index (2022) by state as calculated by Smits et al. (2019). State and national boundaries are retrieved from gadm.org (version 41) and do not imply the expression of any opinion of the author whatsoever concerning the legal status or authorities of any territory or concerning the delimitation of its frontiers or boundaries.

Reflecting on the historic context of rabies in India provides insights into the prospects for national control. Rabies has been present in India since time immemorial, with accounts featuring in texts dating back between 2,000 to 3,000 years and more recently in records from the time of the Mughal emperor Jahangir (1569 – 1627) and throughout the British colonial period (Radhakrishnan et al., 2020). The discovery of rabies vaccine by Louis Pasteur in 1885 marked a global turning point in humanity's ability to prevent rabies and opened the floodgates of scientific interest to improve access to life-saving post-exposure treatment. Institutes producing and distributing rabies vaccine were established across India by the 1920s, preventing death from rabies in 99.5% of those receiving treatment (Radhakrishnan et al., 2020).

The scientific focus on improving access to effective PEP sustained through the 20th and 21st centuries with the adoption of safer cell culture vaccines in the 1970s, and cessation of production of nerve tissue vaccines in 2004 (Acharya et al., 2012;

Lahariya, 2014). India is a world leading producer of rabies biologicals and has contributed research to the development of monoclonal antibodies and intradermal methods of vaccination, both of which increase the availability of PEP (Gogtay et al., 2018; Gongal & Sampath, 2019; John et al., 2021; Kansagra et al., 2021; Madhusudana et al., 2001; Sudarshan et al., 2010). Hampson et al. (2015) estimated 8.2 million doses of PEP were delivered in India annually, preventing the death of 849,658 people at a direct cost of $491 million USD. This investment in human health, however, has done nothing to prevent continued transmission of the rabies virus in the dog reservoir or abate ongoing human exposure. Whilst the virus remains pervasive in the dog population, disadvantaged individuals, underserved by health and education services, remain at risk of death from rabies. A 2007 study found that most human rabies deaths in India were of low socioeconomic status (88%) and from rural areas (76%) (Sudarshan et al., 2007). It is therefore widely accepted that approaches focused solely on human PEP only broaden the gulf in public health disparity and are neither sustainable nor cost-effective (Cleaveland et al., 2017).

1.5.2 Split priorities of dog population management

The issue of rabies is often enveloped by the wider discussion of dog overpopulation which dominates the political and public debate relating to dogs in India. In a survey of public attitudes towards roaming dogs in the city of Chennai, India, 70.6% of respondents felt that dogs were a ‘nuisance’, whilst only 15% reported rabies as a problem (Srinivasan et al., 2019). Similarly in a survey from Goa, 58% of respondents reported dogs to be a ‘nuisance’ as compared to 17% citing rabies as a concern (Corfmat et al., 2022). In this study rabies was preceded by barking, chasing, bites, fouling, and traffic accidents in frequency of reported problems caused by dogs. The overwhelming public, and therefore political, concern is for the frequent nuisance caused by overpopulation of roaming dogs, whilst rabies features less frequently in the mainstream public conscience. Between 0.26% - 2.5% of the population are reported to suffer dog bites in India annually, with unowned (stray) dogs responsible for most bites (John et al., 2021). Just 3% of dog bites were caused by rabid dogs in a study in Haiti (Medley et al., 2017), and even where exposure to rabies virus does occur, widespread access to PEP prevents many human rabies deaths that might otherwise incite greater political commitment on the issue. The highly variable clinical presentation of rabies in dogs and lack of routine diagnostic testing further contribute to the general ignorance of the true rabies burden and the risk it poses to the public. Rabies may be seen as a problem within the problem of dog overpopulation, however a proven solution to the former is available, whilst effective strategies to address the later are yet to be demonstrated (Collinson et al., 2020).

In the absence of clear a scientific evidence-base for effective methods of dog population management, public and political perspectives have become polarised between extremes of peaceful co-habitation with roaming dogs and zero-tolerance for their existence (Radhakrishnan et al., 2020; Srinivasan et al., 2019). In the centre ground many people can hold paradoxical views that dogs are a nuisance, whilst also having a right to live on the streets (Corfmat et al., 2022; Srinivasan et al., 2019). It is feared that as dog population density increases, the rate of life-altering and fatal non-rabies related dog attacks will rise (Belsare, 2022). Data on dog population size, composition, and incidents of human-dog conflict are urgently needed to monitor changes over time and the impact of population management interventions (Belsare & Vanak, 2020; Fielding et al., 2021).

The historic tendency to conflate rabies elimination efforts with activities targeting dog population management has the potential to undermine the advancement of both objectives (Radhakrishnan et al., 2020). Dog vaccination and surgical sterilization have often been combined in an effort to curb the dog population reproductive capacity; however, the cost, resource requirement, and operational complexity of this approach is orders of magnitude greater than dog vaccination alone (Belsare & Vanak, 2020). To achieve herd immunity against rabies, annual vaccination must penetrate every pocket of the population annually, which is neither feasible nor economically viable when every dog is transported for surgery. Conversely, dog vaccination alone does nothing to impact on the reproductive capacity of dogs, however it does create a broad platform from which to promote responsible dog ownership. Mass dog vaccination campaigns provide an opportunity for the government veterinary workforce to rapidly engage with all dog owners through the provision of free rabies vaccine. At the same time, data captured during mass vaccination programmes serves to benefit both the planning and monitoring of dog population management interventions.

A combined approach achieving rabies elimination through widespread, efficient mass dog vaccination, whilst developing effective targeted interventions to address dog overpopulation in priority regions is therefore necessary. This thesis focuses on exploration of the former but contributes findings to support the planning of dog population management programmes and recognises the urgent need for additional research in this area.

1.5.3 Prospects for rabies control in India

Dog rabies elimination from the Indian subcontinent will require dog vaccination campaigns of a scale and complexity the world has never seen and will only be possible through the might of the Government of India. Not only would this achievement catalyse progress throughout South Asia, but would also be a flagship for advancing dog rabies elimination globally. The government has repeatedly demonstrated its capacity to successfully deliver disease elimination programmes at the national scale, first through the human health sector in the elimination of smallpox in 1979 and later through the elimination of rinderpest by animal health services in 1995 and 2003 (Basu et al., 1979; Gangadharan, 2010).

Since India's independence in 1947, development of the nation has been strategized through Five-Year Plans (FYP) created, implemented, and monitored by the Government of India. Rabies control first features in the 11th FYP (2007 – 2012) in the proposal of pilot programmes for the control of human and animal rabies (Radhakrishnan et al., 2020). The National Rabies Control Programme was later launched by Ministry of Health and Family Welfare, Government of India, in 2014 during the 12th FYP (2012 – 2017) under the umbrella of the National Health Mission. The programme was coordinated by the National Centre for Disease Control (NCDC) and Animal Welfare Board of India (AWBI) and comprised funding for both human and animal components. The human component was implemented in 26 states and Union Territories, whilst the animal component, consisting of both dog vaccination and sterilization, started as pilot programmes in Haryana and Chennai (Bagcchi, 2015).

Despite these advances in policy and clear need for prioritisation, reports of learnings from large scale dog vaccination programmes remain lacking (Section 1.4.8). Several commentators in India have emphasised the urgent need for greater emphasis on operational research in mass dog vaccination to support the development of effective strategies at scale (Bagcchi, 2015; Kakkar et al., 2012; Radhakrishnan et al., 2020; Shahid & Kakkar, 2015).

The NCDC recently injected new momentum into the National Rabies Control Programme through the publication of roadmap for the national rabies strategy in 2021, named the National Action Plan for Dog Mediated Rabies Elimination from India by 2030 (NAPRE) (National Centre for Disease Control et al., 2021). As part of this announcement, human rabies was also declared a nationally notifiable disease for the first time. The NAPRE strategy applies a One Health approach "to progressively reduce and ultimately eliminate human rabies in India through sustained, mass dog vaccination and appropriate post-exposure treatment". Activities remain organised under human and animal health components, with strategies under the animal health component consisting of the following priorities:

- Estimation of canine population
- Identification of rabies risk zones

- Planning & implementing strategic mass dog vaccination programmes
- Assessment of post-vaccination coverage
- Dog population management (DPM)
- Promote responsible dog ownership
- Solid waste management (SWM)
- Community involvement
- Confinement and containment
- Operational research

1.5.4 Goa state

Excluding Union Territories, Goa is the smallest of India's 28 States in terms of land mass (3,702 km^2) and fourth least populous with 1.459 million residents in 2011 (Government of India et al., 2011). The state is divided administratively into two Districts; North Goa and South Goa, which are further divided into a total of 12 talukas. These talukas are made up of local administrative units of village panchayats (villages) and municipalities (towns and cities), of which there are a total of 412 (Figure 1.10). The state literacy rate of 88% in the 2011 census was higher than the national average of 74% and it can be considered a more developed region of India, with an estimated HDI of 0.75 in comparison to the national HDI of 0.63 in 2022 (Smits & Permanyer, 2019). Goa's natural beauty and culture has made it an attractive destination for both domestic and international tourists which supported the economic growth of the state through the 1980s and 1990s. The zoonotic risk of rabies has periodically threatened to tarnish the state's reputation as a safe holiday destination, giving an added incentive for the government to prioritise control measures (Mudur, 2005; Solomon et al., 2005).

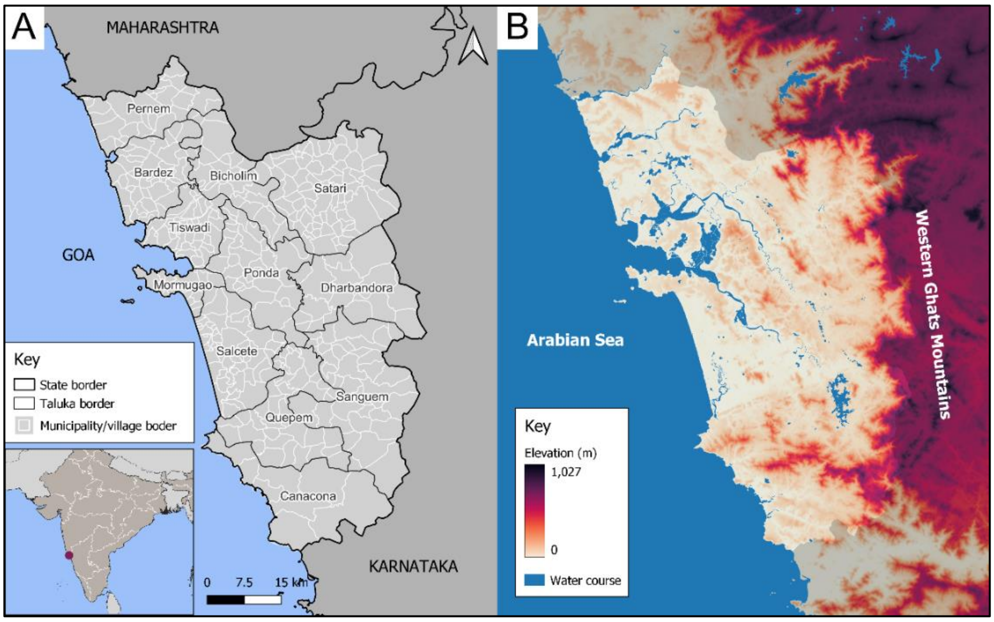


Figure 1.10 - Maps of Goa state. A) Map of administrative boundaries in Goa (State/taluka/village), inset map shows map of India with Goa's location (red dot). B) Map of elevation and water courses in Goa. States outside of Goa are shaded darker to depict boundaries. Elevation from NASA Shuttle Radar Topography Mission (global 3 arc V0003). Water bodies from Open Street Map (2022-12-05).

Goa possesses several advantages that improved prospects for dog rabies elimination. Its comparatively small size in relation to other states makes implementing state-wide initiatives both financially and logistically more feasible. Natural barriers to dog movements in the form of the Arabian Sea to the west and the Western Ghats Mountain range to the east limit reintroduction of the rabies virus from bordering rabies endemic regions and water bodies within the state further compartmentalise the population.

Human health services are well-developed in Goa under the authority of the Directorate of Health Services, Government of Goa, as reflected in its high HDI in comparison to other States of India (Figure 1.9). Whilst shortages of rabies biologicals were occasionally reported, rabies PEP was provided free of cost to the public at government hospitals and primary health centres distributed across the state prior to the onset of this project. Human rabies cases were managed at Goa Medical College and diagnostic testing was provided by the National Institute of Mental Health and Neurosciences (NIMHANS).

Veterinary services and the production animal industry in Goa are overseen by the Department of Animal Husbandry & Veterinary Services, Government of Goa. Animal rabies was notifiable as a listed disease under the control of scheduled disease in 2010 (Government of Goa, 2010), however this was neither enforced, nor made aware to most veterinarians. No formal rabies surveillance system was in place prior to the onset of this project; however rabies diagnostic testing was performed at the government veterinary Disease Investigation Unit (DIU) in Panjim by identification of Negri bodies in Sellers-stained brain tissue.

Goa State had a dynamic animal welfare community in the decades preceding this project, with many non-governmental organisations (NGOs) providing owned and unowned animal populations with varying degrees of veterinary services. These included the treatment of sick and injured animals, sterilization of dogs and cats, and routine vaccination. In some cases, funding and facilities were provided to these organisations by the government, however they relied heavily on private donations and/or charging fees to sustain their services. Vaccination and sterilization activities were not implemented on a large scale or strategized to impact at the population level.

1.5.5 Mission Rabies

Mission Rabies is an international NGO headquartered in the UK and supporting rabies control programmes throughout the rabies endemic world (www.missionrabies.com). It began as a project of the international veterinary charity, Worldwide Veterinary Service, which works to benefit societies through improved veterinary services. The encounters with rabid dogs, the devastating impact that they have on families, and the central role of veterinarians in preventing rabies through control in the dog population spurred the founder, Luke Gamble, to launch an initiative showing the world that dog rabies could be eliminated within our lifetime if enough people cared to make it happen. Activities were focused on field implementation, learning through doing, and enabling stakeholders to engage and participate in the process of mass dog vaccination and community education. To date the charity has delivered over 2 million doses of rabies vaccine and now focuses on supporting governments to develop their own successes.

1.6 Conclusion

This literature review has identified the need for greater research into the operational aspects of dog vaccination and its impact in many rabies endemic settings, including India. It highlighted the need for research that supports the development of rabies control interventions in India and South Asia. My research objective was to implement mass dog vaccination in Goa, India and evaluate the impact on rabies incidence in humans and dogs. My initial priority was to develop technology that improved the quality and availability of programmatic data from which to explore aspects of operational efficiency and the spatial deployment of vaccination resources (**Chapter 2**). Innovation in this space evolved into designing technology-aided methods using a smartphone app to guide the geographic movements of vaccination teams. Chapter 2 is therefore a methods chapter which describes the methodologies that underpin vaccination campaign implementation and data collection used in subsequent results chapters. In **Chapter 3** I questioned 'What are the optimal campaign structures and vaccination methods to achieve annual high vaccination coverage across Goa state?'. During the process of expanding dog vaccination, a wellspring of data was amassed, representing a high-resolution cross-sectional sample of the dog population in Goa. From this I asked, 'How does dog population composition and vaccination methodology differ across the urban-rural gradient?'. Systems to enhance rabies surveillance were developed, in addition to mass community awareness activities, which are described in **Chapter 4**. The resulting data enabled the evaluation of the impact of dog vaccination on dog rabies incidence across the state. I was also interested to explore the cost-effectiveness of the programme using analysis of project expenditure. Finally, through identifying limitations of scaling current dog vaccination methodologies, I broadened my research focus to explore the potential role that oral rabies vaccines could play in improving the efficiency of immunising dogs that are not readily amenable to handling (**Chapter 5**). The lack of a mass-producible, culturally appropriate oral bait constructs prompted my evaluation of two potential bait constructs in Goa (**Chapter 6**). Finally, I reflect on the implications of this research for rabies control in Goa and more broadly in the region in **Chapter 7**.

Chapter 2 Technology-aided vaccination methods

2.1 Abstract

Rabies suffers a chronic under prioritisation by governments, as reflected in its categorisation within the 20 neglected tropical diseases (NTDs) defined by WHO. The uncomplicated epidemiology of rabies, availability of effective vaccines, and widely documented health and economic benefits following successful large-scale elimination programmes have failed to translate into action in most endemic countries of Africa and Asia. This impasse is rooted in a lack of data conveying the true burden of rabies to policy makers and the public at large, in addition to a dearth of scientifically robust vaccination interventions that demonstrate the feasibility of control. Smartphone technology offers the potential for a step-change in the rapid collection and transmission of programmatic data at the point-of-service delivery, with transformational implications for immunisation campaign development, spatial management of a remote vaccination workforce, and stakeholder engagement.

Early Mission Rabies field experience of mass dog vaccination campaign implementation across diverse settings identified priorities for a novel smartphone app-website interface to aid mass dog vaccination campaign implementation, monitoring, and evaluation. The system supported efficient two-way communication of operational data between vaccination teams and project managers to implement a microplanning approach that improved vaccination coverage and homogeneity to hasten elimination. Offline dog-side digital recording of each vaccination event, including GPS (Global Positioning System) location and demographic data for each animal, generated a wellspring of data from which to interrogate dog distribution, population composition, and campaign efficiency. The near real-time availability of data from the field enabled programme managers to adjust their geographic strategy during the campaign, responding to the ever-evolving understanding of the field implementation on-the-fly. Finally, the robustness of campaign data fostered unprecedented political engagement on the issue of rabies in key project sites using technology-aided methods. The auditability

of field activities through the data diminished political risk of investing public funds in the immunization initiative and clear reports communicated that rabies control was achievable. A second app facilitating the investigation of suspect rabies dogs was released in 2018 and bolstered surveillance activities.

This methods chapter describes the WVS App technology, and the rabies control methods that it supported. These components underpinned the gathering of data used in subsequent results chapters. To date the platform has been used to record the details of approaching 3 million dog vaccination events in 29 countries and has been implemented through government at the national scale. This tool was used for data collection of dog vaccination, community rabies education, and surveillance activities in Goa, forming the foundation of the research conducted in this thesis.

2.2 Introduction

Coordinated mass immunization campaigns have become central to the control and elimination of vaccine-preventable diseases in both human and animal health over the past century (WHO, 2020). The eradication of smallpox in 1979 and rinderpest in 2011 marked global triumphs for human and animal health respectively and highlighted the transformative benefit that mass immunization can have for humankind (Henderson, 2011; Roeder et al., 2013). The impact of mass vaccination programmes on disease transmission and prevalence is influenced by factors relating to the pathogen, host, vaccine, and the environment. Diseases with high rates of transmission or mutation are typically difficult to control by vaccination, as in influenza, those with intermediary vectors can require additional control measures, as in the case of malaria, and those for which there is not an optimal vaccine, as in polio, all impact on prospects for control and elimination (Abraham, 2018; D. J. Nokes & Anderson, 1988). However, in the pantheon of diseases that might be considered for elimination, dog rabies can be considered low-hanging-fruit (Cleaveland et al., 2018). Dog rabies endemicity is maintained through an uncomplicated transmission cycle involving direct dog-to-dog transmission, low transmission rates necessitate only a small proportion of the population to be immunised to drive stochastic viral extinction, and the availability of effective, low-cost vaccines leave only political, economic, and operational questions unanswered (D. Knobel et al., 2007).

The continental success of dog rabies elimination from much of Latin America is yet to be replicated in more resource limited settings, where a lack of data underpins the political, ecological, and operational challenges that have held back progress. The absence of robust surveillance data on burden of rabies diffuses any meaningful political interest in its control and a paucity of accurate information about the size, distribution, and ease of accessing the target dog population make it impossible to accurately determine the requirement or feasibility of any proposed vaccination initiative. Finally, the practical process of efficiently coordinating large numbers of remote vaccination teams to systematically deliver vaccine throughout an unconfined dog population presents a considerable logistical and managerial barrier to the implementation of vaccination campaigns of a scale to eliminate rabies. Strategies grounded in a data-driven approach are needed to rapidly develop mass dog vaccination campaigns that efficiently deliver vaccine to geographies and populations identified as at risk.

Traditional paper-based approaches to data capture are inimical to dynamic, data-driven methods of intervention development. Reliance on paper records at the time of capture limits opportunity to record detailed information, such as GPS location, and time and resources are lost in subsequent digitisation. Not only does this open the possibility of human error during transcription, but often necessitating the further loss of detail through data aggregation by geography (e.g., vaccinations per district) or time-period (e.g., vaccinations per week). At the district, or national level, the aggregated campaign data will often offer limited opportunity to explore campaign processes, and leaves room for diminished public and political confidence in the validity of reports due to a lack of auditability. Finally, the lag in centralised collation of data affects the speed of reporting, engagement with stakeholders and the ability to rapidly adjust strategy in response to the field situation. The importance of technology in improving the ease and quality of programme implementation has been recognised by the United Against Rabies forum (supported by WHO, FAO and WOAH), who have established a working group under the topic of “Effective use of vaccines, medicines, tools and technologies” to evaluate and disseminate clear information on tools that are available (Tidman et al., 2022).

Novel digital technologies offer an opportunity to dramatically improve the quality and availability of data from public health initiatives, through the ability to digitally record and transmit data at the point of service delivery. Such technologies are often referred to under the banner of ‘eHealth’, with those incorporating mobile handheld devices, such as smartphones, representing the subset of ‘mHealth’ (Cameron et al., 2017). Immunisation programmes have benefitted from digital tools supporting several areas of campaign implementation including immunization registries, dose tracking and decision support systems, as well as disease surveillance, vaccine confidence monitoring and tracking of adverse events following immunization (Tozzi et al., 2016). The adoption of technology to support rabies control programmes, however, had been limited at the outset of this project. Field experience during the initial 2013 launch of Mission Rabies across 10 locations in India identified several potential opportunities to leverage the enhanced data capture and transmission capabilities of mHealth to drive three areas of programme enhancement: improve the quality of data to accelerate iterative campaign development; enhance the remote spatial management of vaccination teams to maximise epidemiological impact; and increase political engagement through auditability of campaign outputs and clear reporting.

Pockets of unvaccinated population undermine the elimination objective by enabling sustained viral transmission and so coordinating the vaccination workforce to cover all areas, whilst avoiding lost efficiency through overlap, is of central importance to immunization initiatives (E. A. Ferguson et al., 2015; Moran et al., 2022). Several large-scale immunization programmes, including those combatting polio, cholera, and measles-rubella campaigns, have reported the importance of programme implementation through microplans to limit the chances of missing areas or groups within the population (Kar et al., 2014; Ministry of Public Health, 2016; Sarma et al., 2019). Microplans are developed from campaign data at the village or sub-village scale to consider the specific requirements of vaccine delivery at the community level (Ministry of Public Health, 2016). The early field experiences of Mission Rabies identified the practical challenge of directing large numbers of remote vaccination teams at this geographic scale when working across densely populated cities and expansive rural geographies alike. City ward delimitations and village boundaries and are often poorly defined and can change with administrative restructuring. As a result, many vaccination teams in the field struggled to identify the precise extent of their assigned region of work or where other teams had already covered, even with the help of printed maps. Design of a smartphone app to improve the two-way communication of programmatic data between programme managers and remote vaccination teams began through Mission Rabies and Worldwide Veterinary Service (WVS) at the end of 2013.

Active development of the platform, initially called ‘Mission Rabies App’ began in April 2014, with the initial focus on functionality that allowed vaccination teams to record details of vaccination events and project managers to direct teams through polygons displayed on Google maps (A. D. Gibson et al., 2015). The platform launched in September 2014 and development of additional functionality to support programme implementation continued through direct field experience and close consultation with programme managers and the vaccination workforce. The backend architecture of the system expanded in 2017 to enable independent organisations and institutions to securely use the platform, as well as functionalities to aid research activities and multi-species interventions. At this time the system was renamed the WVS App. Development of simplified vaccination entry formats (‘1-click’ vaccination tracking) were developed in collaboration with the US Centres for Disease Control (CDC) in 2017. This collaboration drove the development of a second app called Rabies Exposure Assessment and Contact Tracing (REACT) App in 2018 to digitise the process of Integrated Bite Case Management (IBCM). The REACT App integrated with the WVS App platform to support the investigation of suspected rabies cases.

This chapter outlines the methods enabled through the WVS App system, which came to underpin the rabies control programme in Goa and at several other project sites around the world. My role was in conceptualising the system in 2013, followed by designing the user interface and workflow and subsequently project managing development and maintenance. The technology supported the collection of high-resolution data about campaign outputs including dog vaccinations, community education activities, rabies surveillance events, that form the foundation of the research presented in this thesis.

2.3 Materials and methods

2.3.1 System structure

The WVS App system consisted of 'frontend' apps, used on smartphones by field personnel implementing programme activities ('frontend users'), and a 'backend' web interface used by project managers to administrate their programme and access their data ('backend users') (Figure 2.1A). Independent organisations conducting rabies control programmes were provided with a ringfenced account within the system, ensuring data ownership, security, and privacy to that organisation. Each organisation account was administrated by an Organisation Administrator who accessed the system through a secure login to the WVS App website where they were able to access their full organisation database, create new users, manage data entry forms, and direct field activities. Within each organisation, regions of work could be divided through the creation of 'Projects' within the app for the purpose of sub-administration of data and users (Figure 2.1B). This provided an opportunity for project administrators to provide additional backend user access, for example to allow regional project managers to view vaccination data and direct teams, whilst restricting access only to their catchment area. Division into Projects also restricted frontend users with access to upload data to a specific Project. Figure 2.1 shows an illustration of the structure of data access within existing projects in India, however the same model was applied in other countries with flow of data and restriction of access at the user, district, region, and country levels.

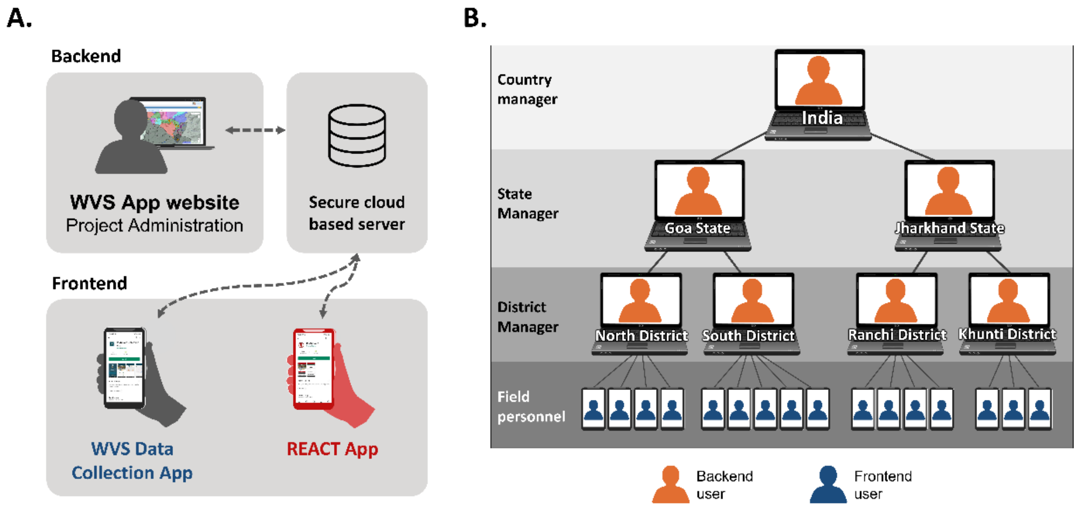


Figure 2.1 - Illustration of WVS App system (A) and user access structure (B).

There were two smartphone apps that both connected to the WVS App backend. The 'WVS Data Collection App' was used for project implementation, monitoring and evaluation, whilst the 'REACT App' supported longitudinal event tracking for suspect rabid animal investigations. Both apps could be downloaded to smartphones via the Play and App stores for Android and iPhones respectively (Figure 2.1A). The apps required a password login which was provided by the project administrator enabling frontend users access to specific projects within an organisation. The user interface (UI) of both apps was designed to be intuitive for those with little experience using smartphone devices or for whom English was not a first language. Core functionalities in the app were to be able to view maps displaying polygons assigned by project managers, to enter details of events relevant to the programme, and to synchronise information with the server once internet connection was available.

Since launch, data were collected using a variety of smartphone devices, however most commonly these were smartphones costing in the region of 60 – 100 USD, with 4.3-inch screen displays and running on an Android operating system. Updates were made available for download through the Play and App stores and ensured that the app remained functional on both the latest and historic versions of Android and Apple operating systems. Portable power banks were provided to vaccination teams to enable charging in the field where reliable power was not available during the lunch break.

The backend database was initially managed using a Microsoft SQL Server and was migrated to Azure in 2019. The interface was written in C# and hosted on asp.net webform. The Android application was written in JAVA and the iOS application was written in Objective C. Data entered on secure smartphones were stored offline locally to the handset before being uploaded through SSL certificate secured connections to a cloud-based server, which were accessed through a password protected website.

2.3.2 Activities and training

The WVS App was used by project managers and field personnel as a project management and data collection tool in three main areas of activity for rabies control: 1) mass dog vaccination, including population surveys; 2) school and community rabies education; and 3) rabies surveillance. Each project site had one or more project managers who were responsible for implementing the programme and reporting its outcomes. These individuals all had at least basic computer skills and an ability to use Microsoft Office tools and online systems. They received approximately one hour of remote training on use of the web platform, followed by additional remote training through streamed online videos about updates to the system.

The phone app was typically used by trained programme staff in every project site, with varied levels of formal education and previous experience using smartphones, however most users were educated to high-school level or higher. Training varied by project location and role, however training in data entry using the app generally took place over half a day, including interactive assessment and data review. Refresher training was conducted annually and when new staff were recruited, with debrief feedback sessions at the end of mass campaigns. Periodic checks through co-supervision by management staff in the field during mass vaccination campaigns were used to correct any variation from standard operating procedures.

2.3.3 Data collection

The initial purpose of the app system was to gather data from the field for central collation and review by project management staff in near real-time.

Data were entered on customised forms, which were created on the web-interface and assigned to individual projects. Dynamic question logic enabled the creator to set question dependencies on responses so that the form expanded as the user completed the form, displaying only relevant questions (Figure 2.2A). This made it possible to keep forms concise for common events, such as routine vaccinations, but to capture more extensive details where required, for example if the dog exhibited health issues. Compulsory fields ensured completeness of data. Questions were displayed in groups on scrolling screens to facilitate rapid data entry and, where necessary, division of long surveys into several pages of questions. Forms could be translated into any language script format.

During initial pilot campaigns, more comprehensive data about each dog were collected to generate an understanding of population size, structure, and ownership for the benefit of planning future work. In most cases an additional staff member was employed in each vaccination team to record data about the dogs being vaccinated. During implementation on a large scale, once methods had been refined, data entry requirements were minimised to core parameters of interest, such as ownership status, negating the need for additional staff dedicated to data entry. For implementation in optimised projects, where minimal data were required, a format was created to enable each vaccination to be recorded with a single click (‘1-click’), capturing the GPS location, date, time, and vaccination team details for each event (Figure 2.2B).

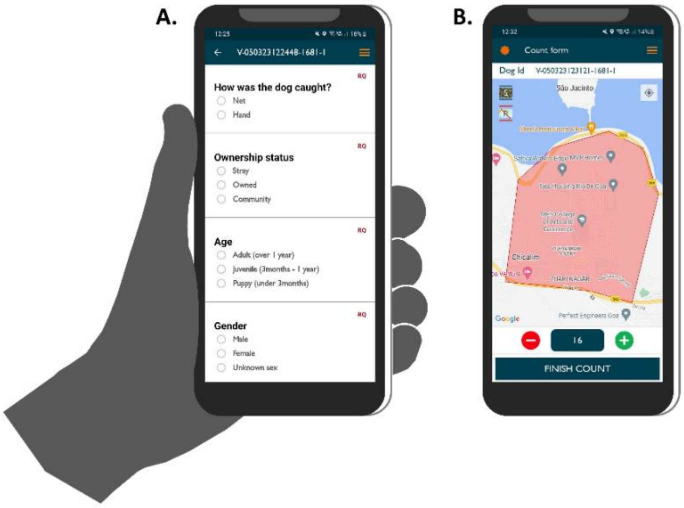


Figure 2.2 - Example of data entry form in the WVS App (A) and the ‘1-click’ form (B). ‘RQ’ indicates a required field making entry of data compulsory before form completion. Both forms automatically captured vaccination team details, time, date, and GPS location of each dog vaccinated.

Whenever internet connection was available, users could synchronise data from the smartphone app to the server with the click of a button. This included the upload of data entered by the user in forms and download of maps assigned by the project manager and any edits made to form question formats. Internet connection was generally poor in rural areas, however vaccine distribution points were often located in urban centres where connection was available, allowing for data upload at least once a day. The data were automatically compiled into a web-based database for access by the project manager.

2.3.4 Team direction

In addition to transfer of data from the field to the project manager, the system also enabled the team manager to effectively communicate the geographical boundaries (Working Zones) within which the team was required to operate.

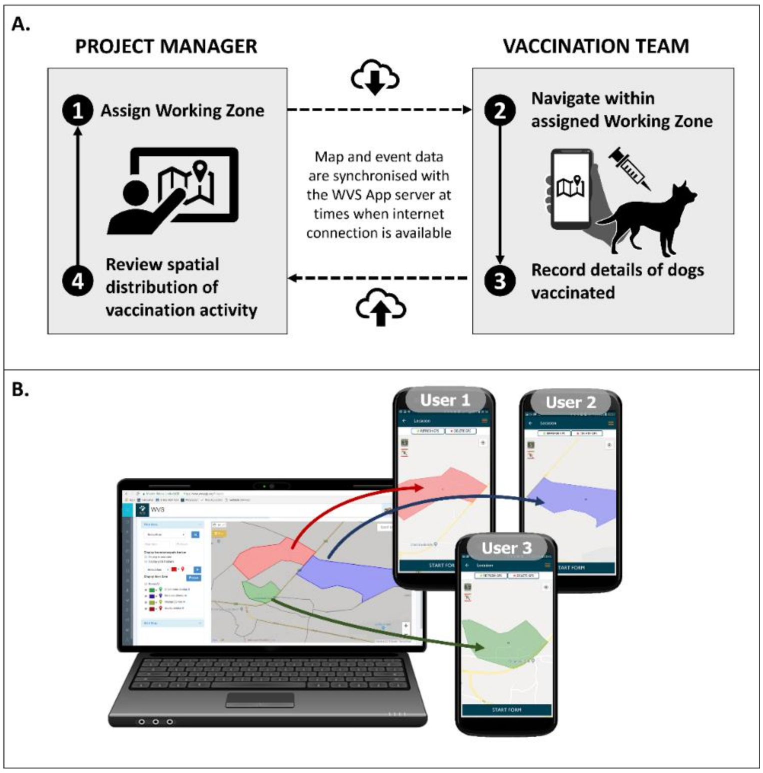


Figure 2.3 - Illustration of workflow within the WVS App (A) and an example of user interface for region assignment (B).

Working Zones were created in GIS software using existing administrative boundaries, land type, and dog population data to divide a region of work into contiguous zones of an appropriate size for a team to work in for approximately one day. The size of regions depended on the amount of data available for each project site; for example, in Goa, regions containing approximately 100 dogs or of a size of 1km^2 was applied. These contiguous zones were converted into KML format for uploading into the WVS App web platform where the project manager assigned each team regions, which appeared as boundaries on Google Maps within the smartphone forms (Figure 2.3). Teams then navigated with the help of their current location and a line showing the path of where they walked during that vaccination session (Path Tracker), with the aim of visiting all populated parts of the region and avoiding repeating areas that have already been completed. Toggling between Google Satellite and Google Road maps is of particular use in rural areas, enabling the user to visit all households during door-to-door work, even where defined roads do not exist.

A set of regions were generally allocated to each team for them to work through over several days. Each vaccination team synchronised their data when internet connection was available, enabling the project manager to assess the work completed through the backend web interface. Simple mapping functionality allowed the project managers to review plotted data in the web interface and assess whether the assigned Working Zones had been completed based on vaccination point distribution and feedback of completeness from the team reported through the app (Figure 2.3). The number of regions and frequency of redirection varied by location, with the system having the flexibility for project managers to use an approach that suited their local project structure. Summaries of form data could be reviewed in the backend system or downloaded in CSV format for more comprehensive analysis in external software. This two-way transfer of information between project managers and the field workforce enabled systematic movement of vaccination effort across the landscape (Figure 2.4). The system was also used to coordinate dog population surveys, education activities, and rabies surveillance efforts.

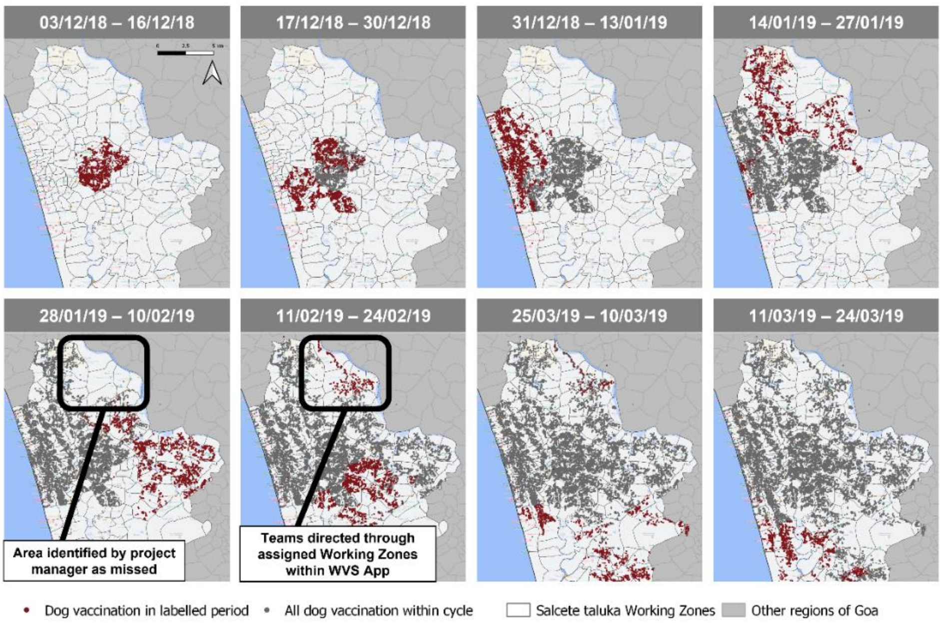


Figure 2.4 - Maps demonstrating systematic vaccination team movements in South Goa from 3rd December 2018 to 24th March 2019, achieved through navigation within assigned Working Zone polygons within the WVS App.

2.3.5 REACT App

The REACT App was designed based on the Integrated Bite Case Management workflow developed by the US CDC in Haiti and other project sites (Etheart et al., 2017; Medley et al., 2017; Undurraga et al., 2017). There are five stages to the investigation structure; Event Notification; Rabies Assessment; Quarantine; Laboratory Results; and Reporting (Figure 2.5A). As the user enters the details of a case, the workflow branches depending on their entry. For example, during the rabies assessment, if they report that the dog is being placed under quarantine, they will be prompted to enter the schedule for quarantine checks. However, if they report that the dog has died and they have submitted samples to the lab, the next section to appear will be to record the results reported from the lab. The user can review clear lists of ongoing cases and the next action required, with reminders of when tasks are due. The current status of the dog, according to WHO case definitions of 'Non-case', 'Suspect', 'Probable', and 'Confirmed', is updated as the user enters details of the case (Figure 2.5B). As for other data in the WVS App, the project manager can review surveillance data in the backend interface, such as number, distribution, and outcome of investigations, as well as maps of confirmed cases (Figure 2.5C).

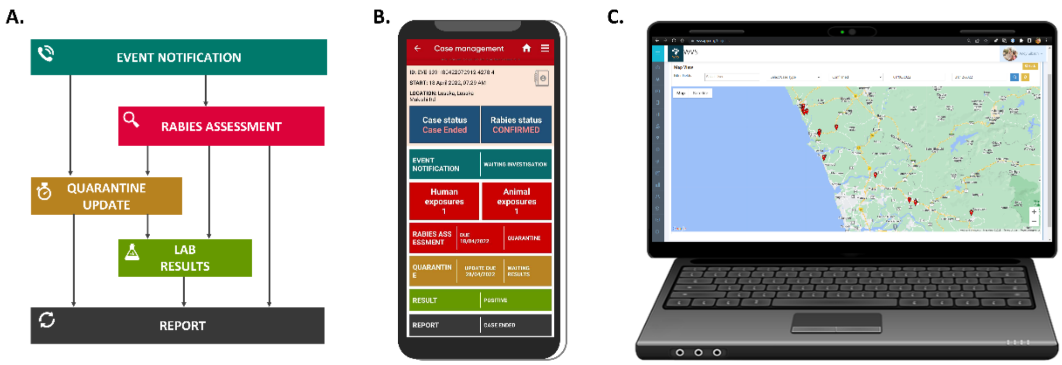


Figure 2.5 - REACT App case flow (A), case management screen (B), and backend project manager view of confirmed cases (C).

2.4 Results

2.4.1 Data entry

A total of 3,020,134 animal rabies vaccination events were recorded by technology-aided methods between September 2013 to December 2022 in 29 countries (Figure 2.6). The WVS App technology launched in November 2014 and has recorded 3,020,134 vaccination events, of which 2,856,776 were dog vaccinations (Figure 2.7, Table 2.1). Vaccinations in Goa constituted 640,667 records during the study period.

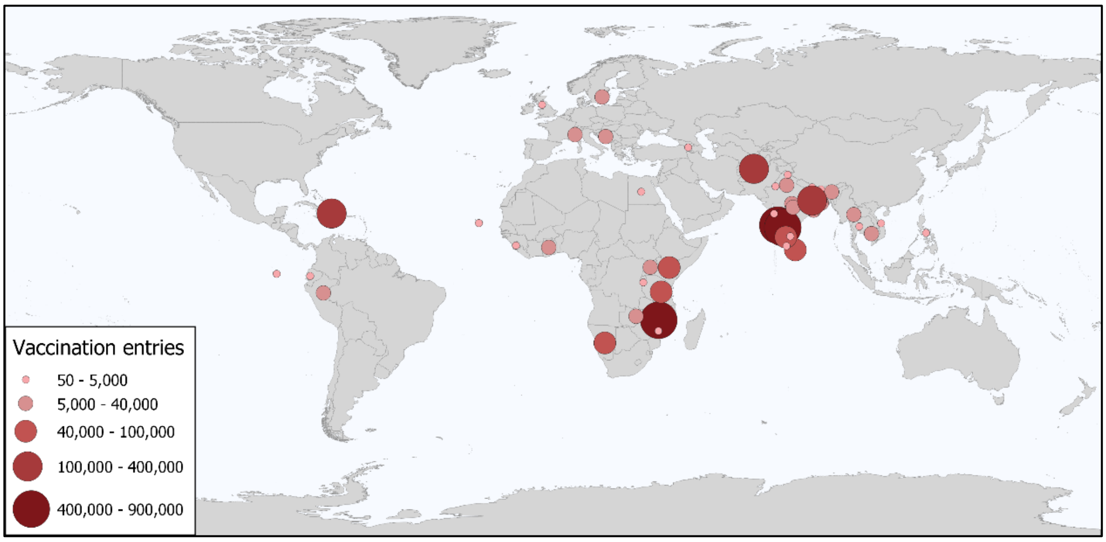


Figure 2.6 - Global distribution of dog vaccination entries in the WVS App by country and Indian State.

Table 2.1 - Total vaccination records in the WVS App system by project and year.

Year	Goa rabies campaign	Other MR-WVS projects	Partners	Total vaccination records
2013	5,092	51,006	0	**56,098**
2014	22,059	7,430	0	**29,489**
2015	56,954	116,699	434	**174,087**
2016	51,302	174,924	15,235	**241,461**
2017	97,376	181,754	174,256	**453,386**
2018	97,290	166,374	97,418	**361,082**
2019	96,189	212,643	73,889	**382,721**
2020	82,181	164,679	61,006	**307,866**
2021	75,887	170,134	154,503	**400,524**
2022	56,337	186,885	370,198	**613,420**
Total	**640,667**	**1,432,528**	**946,938**	**3,020,134**

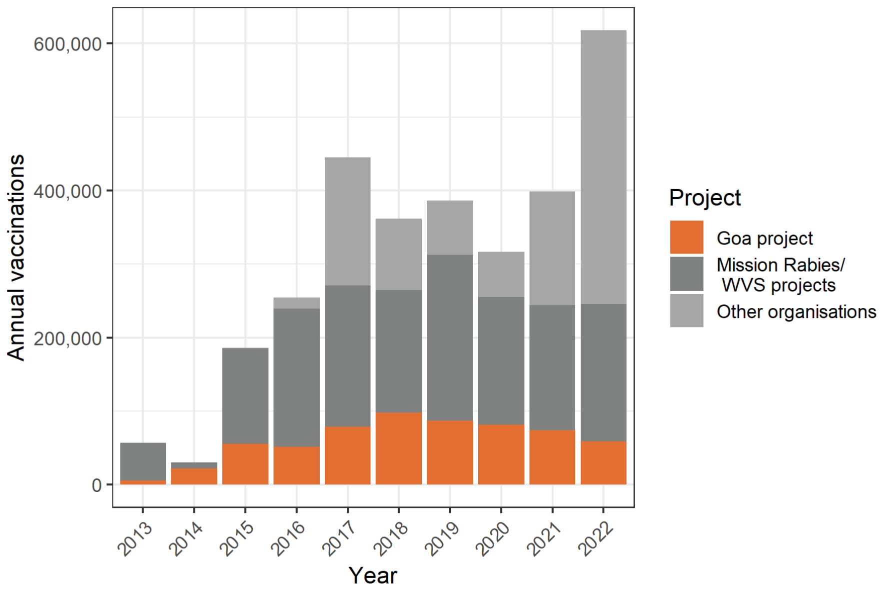


Figure 2.7 - Total vaccination records in the WVS App system by project and year

In addition to vaccination records reported above, a further 1.2 million records were made in the WVS App for the implementation of other research and dog population management activities. These forms were under categories of dog population surveys and community questionnaires (666,726), research activities (358,497), dog captures for sterilization (212,587), and rabies education events (40,115).

The REACT App is currently being used in eight countries and is available in English, Creole, French and Vietnamese. There have been over 50,000 case investigations recorded in the system to date.

2.4.2 Reporting & research

The progressive increase in usage of the system has coincided with expansion of the Goa campaign from a focal pilot project in 2013 to a systematic campaign covering the entire State of Goa. In 2017 the Centres for Disease Control and Prevention used the app to support the national mass dog vaccination campaign in Haiti, implemented by the Ministry of Agriculture (MARNDR). Feedback on the app from the Chief Veterinary Officer of Haiti included “The Mission Rabies [App] maps that show the day’s vaccination record are very helpful to me as the CVO when I want to update[…] the Minister of Agriculture of Haiti on the progress of our rabies vaccination campaign." (M Millien, written communication March 2018). The system has supported data collection in at least 30 peer review publications (Adrien et al., 2019; Barbosa Costa et al., 2020; Bonwitt et al., 2020; Burdon Bailey et al., 2018; Cleaton et al., 2018; Corfmat et al., 2022; Evans et al., 2019, 2022; Fielding et al., 2021, 2021; Freuling et al., 2022; A. D. Gibson et al., 2015, 2016, 2022; A. D. Gibson, Mazeri, et al., 2019; A. D. Gibson, Yale, et al., 2019; D. G. Gibson et al., 2017; Kirkhope et al., 2021; Lugelo et al., 2022; Mandra et al., 2019; Marron et al., 2020; Mazeri et al., 2018, 2019, 2021; Meunier et al., 2019; Monroe et al., 2021; Puente- Arévalo et al., 2022; E. Rayner et al., 2019; E. L. Rayner et al., 2018; Sánchez-Soriano et al., 2019, 2020; Sargison et al., 2021; Wallace et al., 2019).

2.5 Discussion

The global quest to eliminate dog-mediated human rabies by 2030 has gained momentum in recent decades through advocacy by WHO, WOAH, and FAO, however challenges remain in coordinating large scale, effective mass dog vaccination campaigns in many endemic regions. I, with colleagues and collaborators, developed a unique fit-for-purpose mHealth innovation which was successfully used at scale across project sites in numerous countries, recording the details of almost three million dog vaccination events. The platform enhanced the remote oversight and direction of dog vaccination teams, providing clear, engaging reports to motivate stakeholders from campaign implementers to policymakers, and generated high-quality data driving research in dog population distribution, composition, and rabies transmission to support the development of more effective control measures. This is a rare example of an mHealth system which has been successfully scaled to national and India state level implementation and demonstrates the potential for transfer of functionalities across several rabies endemic settings to support the accelerated development of government-led rabies control programmes.

The WVS App has been a powerful aid to research activities leading data-driven approaches in dog vaccination campaign development. The efficient digital capture and aggregation of dog-specific data from individual vaccination events transforms pilot activities into rich opportunities for operational research into dog ecology and accessibility. In addition to the profound benefits gained through boots-on-the-ground experience during pilot activities, tracking vaccination activities through the WVS App enabled demographic data from a high proportion of the population to be captured, supporting refinement of the campaign approach for operational efficiency. Use of the WVS App in a rabies control programme in southern Malawi has supported research enquiry into aspects of dog demography, public awareness, school education, and dog vaccination strategy (Burdon Bailey et al., 2018; Marron et al., 2020; Mazeri et al., 2019; Sánchez-Soriano et al., 2020). I led an initial study in 2015 reporting the outcomes of a 35,000 dog vaccination campaign in which the WVS App was used for data capture and vaccination team coordination (A. D. Gibson et al., 2016). I then designed and implemented the field component of a study using the GPS location capabilities and customisable forms in the WVS app to identify the precise location of 22,000 dogs in the community and which central point clinic they had attended. Analysis conducted by others to calculate the distances travelled and barriers to attendance enabled the strategic restructuring of the campaign in 2018 to ensure that most of the dog population was within catchment of a central point clinic (Mazeri et al., 2018). This resulted in an almost doubling in campaign-efficiency and provides a model for efficient urban dog vaccination campaign strategies in comparable LMIC settings (Mazeri et al., 2021). The typical distance communities are willing to transport their dogs for vaccination has been reported from other LMICs, revealing that optimal Central Point vaccination clinic catchment areas are likely to vary by location (Barbosa Costa et al., 2020; Kaare et al., 2009).

The system was, however, customisable enough to meet the evolving data needs of a project. From more comprehensive forms during early campaign development, to streamlined data entry for efficient programme monitoring of large-scale programmes. In the vaccination form optimised for scale, the need for additional personnel dedicated to data entry was eliminated, however the benefits of spatial direction of vaccination teams were still possible. With the click of a button, the time, date, GPS location, and team name were captured, whilst a single form at the start and end of each day captured details about team size, completeness of the Zone, and the occurrence of any dog bites (Kirkhope et al., 2021).

The spatial management of large numbers of vaccination teams working throughout expansive urban, peri-urban, and rural environments has presented a major operational challenge for the implementers of large-scale campaigns. Patches of low coverage undermine the success of rabies elimination efforts by enabling sustained viral transmission in pockets of susceptible populations. Evenly distributed vaccination effort throughout a population is likely to achieve a greater impact on rabies transmission than the 'Swiss-cheese' appearance to the coverage of high-intensity campaigns in which vaccination teams miss areas of dog population (E. A. Ferguson et al., 2015; Putra et al., 2013). Functionalities within the WVS App have addressed the challenge of real-time vaccination team co-ordination, through the spatial direction of vaccination teams using assigned boundaries displayed on maps with the WVS App. An evaluation led by the US CDC in partnership with the Haitian Government and the author, on behalf of Mission Rabies, demonstrated that this technology-aided approach not only increased overall mean vaccination coverage to 80% as compared to 44% by traditional methods, but also reduced the heterogeneity of vaccination effort across campaign areas (Monroe et al., 2021). The technology was subsequently implemented at a national scale in Haiti in 2017, recording over 300,000 dog vaccination events through the simultaneous management of over 100 vaccination teams. In 2022 the platform was adopted by the state government of Karnataka, India, where over 200,000 dog vaccination events were recorded by more than 2,000 app users in the space of a month.

Technology makes it possible to automate many activities for which capacity is lacking. In this example, many campaigns would not have the time to collate and report on hundreds of paper reports from vaccination teams, whilst the WVS App system automatically gathered and presented these data in near real-time. Similarly, it is not feasible to train all project coordinators in the use of mapping (GIS) software to support campaign planning and reporting, however technologies can increase access to such functionalities through simple interfaces that support mapping of campaign data and developing a geographic strategy. This level of monitoring and review would simply not be possible through paper-based data records (Mwabukusi et al., 2014; Sherin et al., 2018).

Field-level, functional rabies surveillance systems are not only critical to exposing the true burden of disease, but also in assessing the impact of control programs on disease transmission (Velasco-Villa et al., 2017). Integrated bite case management (IBCM) describes a cost-effective approach to rabies surveillance and dog-bite victim management, co-ordinating human, and animal health sectors (Etheart et al., 2017; Undurraga et al., 2017). The REACT App serves to digitise the field implementation of IBCM, providing in-hand guidance to rabies officers on best practice approaches to rabies investigations. As for in other areas of work, technology makes it possible to simplify complex processes. The REACT App provides structure to rabies case investigations which may unfold over several days, involving dog owners, bite victims, veterinarians, laboratories, and health clinics. Management of these details through the REACT App enables the capture and central aggregation of valuable surveillance data whilst clearly presenting the key information that rabies officers need to stay on top of their work. At the conclusion of a case, the REACT App prompts the user to report the outcome to all persons involved in the case, including people bitten by the dog and health services. This guidance within the system helps to improve intersectoral communication between human and animal health services.

A recent study performed by CDC evaluated outcomes of national usage of the REACT App in Haiti as compared to paper based IBCM methods. The cost per death averted using paper based IBCM was $2,629 USD, with data taking 26 days to reach national staff and 180 days before analysis, whilst through use of the REACT App the cost per death averted was $1,247, data transmission took 3 days to reach national staff and 30 days until analysis (Schrodt et al. under review). The App was reported by government field staff to be “easy to use, facilitated investigations, and hastened data reporting” (Schrodt et al. under review).

The improved data generated using field-side smartphone apps for rabies surveillance reveals new horizons for understanding the disparities in access to both human and animal health services. In the Haiti evaluation comparing paper and the REACT App based IBCM, not only was the transmission of investigation data more than eight times faster in cases logged in REACT, but there were almost six times as many data parameters (174 in the REACT App compared to 30 on paper). During the field investigation, the IBCM approach increases the chances of identifying people with high-risk bites for rabies, but who did not seek treatment. Part of the life-saving impact of IBCM is through the intensive counselling of these people to access PEP. The enhanced detail of data capture, including GPS information, makes it possible to research demographic, socio-economic and geographic predictors of rabies exposure and non-presentation for PEP and therefore develop ways to prioritise resources to these high-risk groups.

Functionality to capture and store data offline negated the need for network coverage in the region of work, however an internet connection was required to synchronise data to the server and therefore share information with the supervision team and to refresh regions for team direction. There was usually an opportunity to connect once a day or every few days for this purpose and it is expected that this will continue to improve as local network infrastructures expand (International Telecommunication Union (ITU), 2017). In areas where regular connection is not available for extended periods of the campaign, all Working Zones could be assigned at the start of the campaign for teams to work through sequentially offline and uploading all data at the end of the campaign. In this case adjustment to the approach would need to be done, either through local review of vaccination activity on the phones or at the end of the campaign. Limitations of battery life and the need for charging points were overcome using power banks for use in the field.

2.6 Conclusions

Mobile technologies create an opportunity to innovate new approaches to the delivery and evaluation of mass immunisation initiatives. The enhanced ability to digitally record information at the point of service delivery and transmit these data from remote locations provided greater clarity of field operations in near-real-time. Analysis of this high-resolution data in Malawi and elsewhere generated new insights into the relationships between dog population structure and vaccination methodologies that drove iterative refinement of programmes for maximum efficiency and impact. Use of geolocation and sharing of mapped polygons gave campaign managers new capabilities to spatially direct vaccination team movements, enabling a more epidemiologically informed approach to vaccination. This functionality could leverage future research into the drivers of rabies transmission by allowing campaign planners to be spatially prescriptive about the populations targeted for vaccination. Finally, the increased transparency afforded using technology-aided approaches fostered political confidence in several campaigns, providing the momentum required to sustain and grow government-led interventions to combat rabies. A successful government-led programme in an Indian State could act as a catalyst, sparking momentum for rabies control in other parts of India and the South Asia region. Given the absence of a proven approach to mass dog vaccination, the initial focus was on comprehending existing methods of rabies control. Positive engagement with the Government of Goa created an opportunity for partnership with Mission Rabies to develop a state-wide programme for mass dog vaccination, which is the focus of the next chapter.

Chapter 3 Goa rabies vaccination campaign development

3.1 Abstract

Dog vaccination programmes conducted during early campaign development present an opportunity to build field capacity and experience, whilst at the same time testing the efficiency of methods and gathering data about dog population composition. The collaboration between stakeholders in Goa enabled the progressive development of dog vaccination activities from a small programme vaccinating 5,000 dogs over two weeks in 2013, to one vaccinating over 97,000 dogs in 2017.

This chapter describes the evolution of dog vaccination methods in Goa state, India, in terms of geographic extent, vaccination output, and population coverage. Pilot activities identified that resource-intensive approach of Capture-Vaccinate-Release (CVR) was required to access a high proportion of roaming dogs that were not readily amenable to handling. An effort to condense the campaign to a 1-month 'pulse' was found to be infeasible due to the complexity and human resource requirement of CVR methods. A rotating cyclical approach enabled a permanent, highly trained workforce to reach high vaccination coverages throughout the state by 2017. The vaccination method was refined through the introduction of smaller Door-to-Door (DD) teams focusing on dogs that could be held for vaccination without special equipment. The combined DD-CVR method made it possible to restructure the workforce of approximately 55 staff, increasing the number of vaccination teams from 7 to 9 and increasing the number of days spent vaccinating in each Working Zone from a median of 2.34 days to 3.72. Overall, this resulted in a significant increase in the mean village-wise vaccination output in comparison to all other methods, from 71% to 84% (village-wise vaccinations as a proportion of all-time maximum).

A subset of vaccination data, representing vaccination throughout Goa using consistent methodology, was used to assess population structure across the urban-rural continuum and exploration of how this impacted on the performance of

vaccination methodologies. A significantly higher proportion of dogs were owned in low density hamlets (60%) as compared to high density cities (30%). This had a considerable impact on how the population was accessed for vaccination, with 62% of vaccinated dogs being restrained by hand in hamlets as compared to 49% in cities. It also affected the productivity of vaccination methods with DD teams accounting for 41% of all vaccinations in hamlets, compared to 30% in cities, however overall efficiency in terms of cost per dog vaccinated was lowest in hamlets at 240 INR as compared to 166 INR in cities.

The findings of this study demonstrate the importance of understanding dog population structure to enable the vaccination strategy to be adapted for maximum coverage and efficiency. The use of smartphone technology as a programme implementation proved to be an invaluable tool in supporting a data-driven approach.

3.2 Introduction

Over a century of scientific endeavour has provided a compelling case for the public health and economic benefits of rabies elimination, however, with only a few examples of implemented success in the south Asia region, the journey appears too uncertain for most health authorities to embark on. Despite increasing international and national cajoling through global goals and national action plans, translation into boots-on-the-ground progress remains stagnant (C. E. Rupprecht, 2021).

Numerous prioritisation tools have been developed to provide governments with an actionable roadmap progressing from endemic to eliminated, including the One Health Zoonotic Disease Prioritization (OHZDP), Stepwise Approach to Rabies Elimination (SARE) and the Global Dog Rabies Elimination Pathway (GDREP) tools (Q. Chen et al., 2021; Coetzer et al., 2016; Rist et al., 2014; Wallace et al., 2017). These tools are typically completed through multiday roundtable workshops in which stakeholders from across government and other relevant groups review current rabies-related activities. Zoonotic prioritisation exercises across India have repeatedly identified rabies as the highest scoring disease (Kurian, 2014; Sekar et al., 2011; Thukral et al., 2023; Yasobant et al., 2019). Whilst these trans-disciplinary gatherings serve to foster engagement on rabies management and clarify the need for action, the anticipated snowballing of activities in their aftermath often fails to materialise, indicating that more is needed to breakover the threshold towards meaningful progress (Thumbi et al., 2022).

Ultimately dog rabies elimination hinges on the practical process of administering vaccine to a high proportion of the dog population. Operational practicalities of programme delivery become increasingly important in resource-constrained environments. The ease with which programmes can be implemented, in terms of cost, operational efficiency, and time, therefore define the political and financial bar that must be reached to progress towards rabies control (Undurraga et al., 2020; Wallace et al., 2017). This threshold will be far lower in regions where dogs can be easily accessed for vaccination as compared to places where the vaccination approach is complex and expensive. All successful programmes are underpinned by a comprehensive understanding of the target population and the availability of a workforce with the skills and resources to reliably deliver the required method across the population, however these foundations of success take time to develop.

Dog ecology in Africa and Latin America offers a distinct advantage for rabies control as compared to many parts of South and Southeast Asia, in that most dogs in these settings have an owner or guardian that can hold the dog for parenteral vaccination when the opportunity presents (Jibat et al., 2015; Lembo et al., 2010). As a result, a high proportion of the dog population can be accessed through vaccination campaigns using central point (CP) and/or door-to-door (DD) approaches (Borse et al., 2018; Castillo-Neyra, Brown, et al., 2017; Cleaveland et al., 2003; Zinsstag et al., 2009). Mobilisation of the dog-owning community serves to extend the vaccination workforce, increasing the efficiency of accessing dogs for vaccination. The campaign in Latin America demonstrated how it was possible to scale these approaches through government workforces and sustainably deliver millions of vaccine doses for decades (Velasco-Villa et al., 2017). However, these methods fail to reach a sufficient proportion of dogs in many Asian settings where a large proportion are unowned, or where dog owners are not able to readily restrain their dogs (Belsare & Gompper, 2013; Kumarapeli & Awerbuch-Friedlander, 2009; Valenzuela et al., 2017; Wera et al., 2015). Here it is necessary to develop and demonstrate alternative vaccination campaign structures that can be grown to a similar scale whilst retaining cost-effectiveness.

As reviewed in Chapter 1, the overlapping priorities of rabies control and dog population management (DPM) have the potential to create political confusion in how best to prioritise the allocation of finite resources in India (Belsare & Gompper, 2015; Radhakrishnan et al., 2020). Whilst the cost-effective benefits of a long-term intensive sterilization programme have been demonstrated in Jaipur, Rajasthan (Larkins et al., 2020; Reece & Chawla, 2006), it is unlikely that these methods could be scaled to sustain herd immunity against rabies throughout the population at the district, let alone the Indian state, scale (Collinson et al., 2020). DPM programmes do, however, document the need for more resource intensive methods to access a high proportion of dogs. The capture-vaccinate-release (CVR) approach relies on larger teams of dog handlers working together to catch dogs for vaccination using butterfly nets (MacFarlane & Gibson, 2018). This method requires the workforce to have a knowledge of dog behaviour, athletic agility, and additional equipment as compared to other vaccination methods. The mass dog vaccination programmes of Bali, Indonesia from 2008 to 2011, demonstrated that combined DD and CVR methods could be scaled to vaccinate over 250,000 dogs per year (Putra et al., 2013).

The largest annual output of a dog vaccination programme reported in India to date was that conducted in the state of Sikkim from 2005 to 2016, scaling to a programme vaccinating 24,000 dogs per year, of which 5,000 were also sterilized (Byrnes et al., 2017). In this population only 18% of dogs vaccinated required restraint using a net and that CP vaccination alone was considered effective in 'most villages', although details of vaccination coverage and rate are not given. Tiwari et al. report lower prevalence of unowned roaming dogs in rural settings (Tiwari, Robertson, O'Dea, & Vanak, 2019a), indicating that manual restraint of dogs by hand may garner high coverages, and Airikkala-Otter et al. reported vaccination coverages of 79% through DD methods in rural Tamil Nadu (Airikkala-Otter et al., 2022). The large-scale programmes of Sri Lanka and Bangladesh, reporting the annual vaccination of 1.5 million and 365,000 dogs respectively do not describe the specific methods, rate, or coverage of vaccination efforts (Ghosh et al., 2020; Harischandra et al., 2016).

Operational research and development are essential to growing innovative population health projects that succeed in uncertain environments, however it can be unlikely for government to lead such efforts, given that the benefits are seen through the implementation of successful programmes in years to come, potentially beyond their term in office. It is often the case, therefore, that early programmes are driven through multi-institution collaborations between government, non-governmental and academic partners, where the financial, administrative, and logistical burden is shared, thus sufficiently reducing the political risk in green lighting such activities (Gamble et al., 2019; Léchenne et al., 2021). Studies of dog population ecology often form the starting point of investigation in areas lacking existing experience or data relating to mass dog vaccination methods (Gill et al., 2022; Tiwari et al., 2018; Tiwari, Robertson, O'Dea, Gogoi-Tiwari, et al., 2019), however pilot vaccination activities themselves can serve as valuable opportunities to build operational expertise, develop training resources, gather data about the dog population, and assess the suitability of the deployed vaccination approach (Evans et al., 2019; A. D. Gibson et al., 2016; Sánchez-Soriano et al., 2019). It was from this standpoint that the international charity, Mission Rabies, launched in 2013 with an audacious initiative to deliver vaccination programmes across 10 locations, vaccinating over 50,000 dogs in one month (Gamble, 2014).

Goa state was one of the project locations during that initial Mission Rabies programme and engagement with the Government of Goa enabled continued exploration of rabies control in the state. The creation of a sustained, high-output dog vaccination campaign at the state level in India offered the potential to serve as both a testbed for the evaluation and refinement of vaccination methods, but also as an example from which other governments and institutions could derive confidence to advance their own programmes. Goa was a favourable location for such a grassroots initiative in India due to its progressive government, the added political priority of growing the economy through tourism, its size, and its relative geographic isolation as discussed in Chapter 1. Implementation of technology aided methods discussed in Chapter 2 generated a large spatio-temporal dataset of individual vaccination events and dog population survey sightings from which to evaluate campaign efficiency and dog population composition.

The iterative process of programmatic implementation, evaluation, refinement, and reimplementation was repeated many times during the project period, whilst at the same time generating evidence to demonstrate value to stakeholders. Like a flywheel gaining momentum with every turn, the project grew from a 2-week pilot vaccinating 5,000 dogs to one reaching 97,000 per year (Collins, 2019). This study describes the development and evolution of dog vaccination methods in Goa state, India, from 2013 to 2022. A subset of a state-wide vaccination cycle using constant methods enabled assessment of population structure across the urban-rural gradient and how this impacts on the performance of vaccination methodologies. Through my role in Mission Rabies, I was responsible for the strategic direction of surveillance and vaccination activities on the Goa project throughout the project period, providing line management to the project managers, data analysis, and project reporting. In this role I led the development of smartphone technology to support implementation of field activities and directed the exploration of new vaccination methodologies based on insights gained from the data. Vaccination activities were implemented by a workforce in Goa under the management of the

Goa Project Manager, Julie Corfmat, and under the direction of our nodal officer within the Department for Veterinary Services and Animal Husbandry in the Government of Goa.

3.3 Materials and methods

3.3.1 Campaign structure

For analysis, the project period can be divided according to three components: calender year; geographic cycle (campaigns); and periods of consistent methodology. The initial intent was to conduct vaccination by annual campaigns of vaccination, with each campaign representing a single round of vaccination in every region. This aligned with the current recommendations for annual revaccination to control rabies (Chapter 1), but was also convenient for project planning, budgeting, and reporting. Ideally the vaccination campaigns would align with the calender year, however operational factors often resulted in variation to when each campaign cycle started and finished, with some periods when a campaign cycle was as short as a month and others when it would extend beyond 12 months depending on vaccination methodology. An important consideration in analysis of the vaccination data was the vaccination method being employed during each period. Again, the intention was to keep methodology consistent within each campaign cycle, however on several occasions significant changes in vaccination method occurred mid-campaign, either due to our own investigations, or due to environmental changes such as during the COVID-19 pandemic. Figure 3.1 shows the annual geographic extent of vaccination in Goa, with colour defining the division of campaign cycle, and finally periods of methodological change labelled in the timeline.

Whilst there were several periods of methodological change, this study explores two important periods of consistent vaccination methodology highlighted in Figure 3.1. These periods were labelled '*CVR method*' (October 2015 – March 2018) and the '*DD-CVR method*' (October 2018 – February 2020). The DD-CVR approach was considered the optimal approach and so data from this period of fixed methodology were also used in a more in-depth analysis of the dog population structure and vaccination efficiency across the urban-rural gradient of Goa.

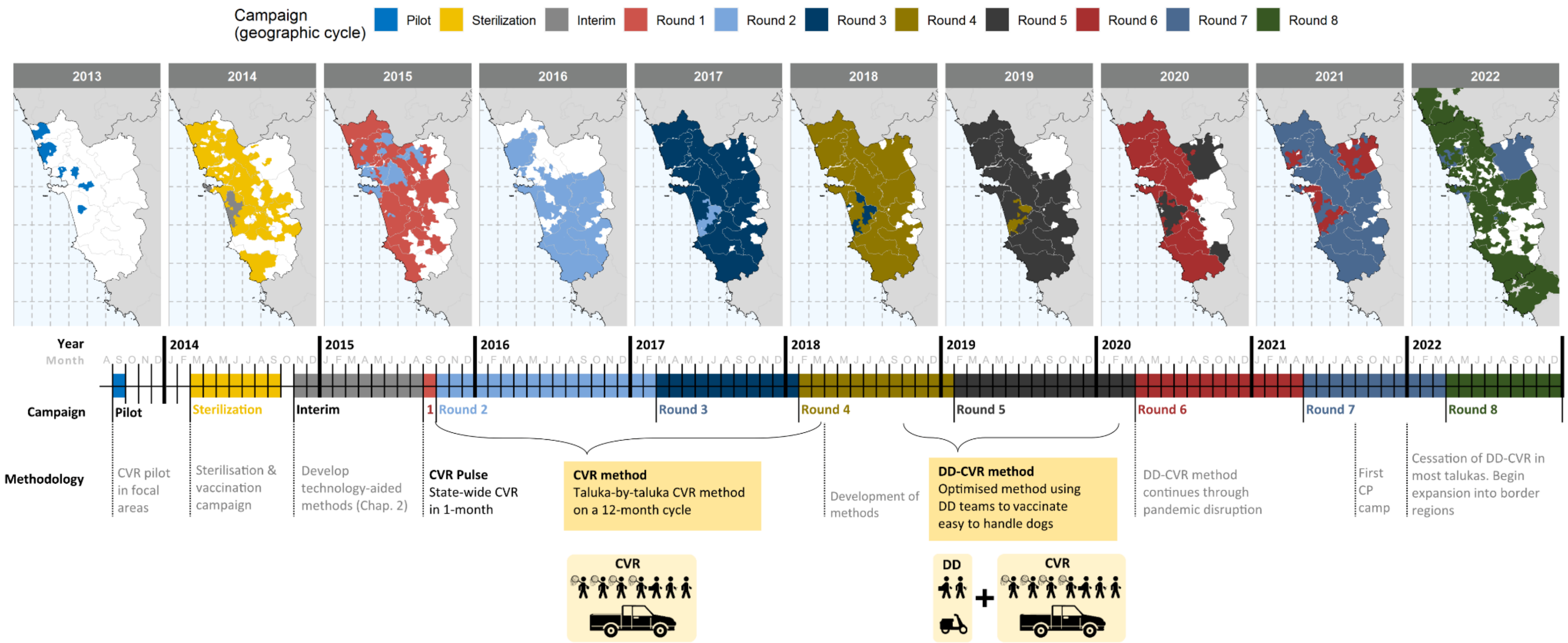


Figure 3.1 – Maps and timeline of Goa vaccination by calender year, campaign (geographic cycle), and methodology. Highlighted methodology periods of 'CVR method' and 'DD-CVR method' define periods used in sub-analyses. DD = Door-to-Door vaccination (teams of 2-people focused on dogs that can be held by hand). CVR = Capture Vaccinate-Release (teams of 7-8 people catching dogs by net that cannot otherwise be handled).

3.3.2 Vaccination protocol

Vaccinations were provided free of charge and each dog was administered with a 1ml dose of rabies vaccine (Nobivac® Rabies – MSD Animal Health) either subcutaneously or intramuscularly, depending on animal position and restraint method. A new needle was used for every dog vaccinated. Each dog was marked with a non-toxic paint spot on the top of the head, which remained visible for several days enabling identification of vaccination status on post-vaccination surveys (Figure 3.2) (Conan, Kent, et al., 2015). Consent was obtained from each owner prior to vaccination of dogs that were identifiably owned, and a vaccination certificate was provided.

Figure 3.2 – Temporary paint marks on the dogs' head identifies vaccination status for 3-5 days.

The geographic management of vaccination teams and post-vaccination surveyors was conducted through the WVS App as described in Chapter 2. The information recorded offline for each dog at the time of vaccination included: vaccination team ID, time, date, GPS, sex, age, ownership, neuter status, confinement, and health status. Dogs were defined as 'owned' if the dog had signs of ownership (wearing a collar) or someone could be identified as an owner or guardian at the time of vaccination. From 2018 onwards, the method of restraint (hand/net) was also recorded for every dog. Field teams uploaded data from the WVS App daily, enabling the project manager to review the geographic extent of vaccination work in maps on the website and assign new Working Zones to each vaccination team which then displayed on their phone handsets (Chapter 2, (A. D. Gibson et al., 2015)). Post-vaccination surveys were directed through the same approach, assigning Working Zones in which vaccination activity had just been completed.

3.3.3 Vaccination methods

3.3.3.1 CVR method

The initial method used to access dogs for vaccination until March 2018 was CVR (Figure 3.1). Each CVR vaccination team typically consisted of 7-8 people travelling by truck, including one vaccinator, one assistant, one driver and four to five dog handlers using aluminium framed butterfly nets (Figure 3.3A) (MacFarlane & Gibson, 2018). These teams were assigned Working Zones through the WVS App and systematically moved throughout each zone vaccinating both owned and unowned dogs. Dogs that could be held by hand, either by an owner or the team, were manually restrained for vaccination, whereas dogs that were not amenable to handling were caught using nets, vaccinated, and released. Vaccination continued in the Working Zone until the team reported that no more dogs could be vaccinated, prompting assignment to a new Working Zone and deployment of a surveyor to conduct a post-vaccination survey (Chapter 2).

Figure 3.3 – Dog vaccination methodology. A) Capture-vaccinate-release (CVR) teams – seven or more people travelling by truck. Dogs were caught for vaccination either by hand or using butterfly nets. B) Door-to-door (DD) vaccination teams – two people travelling by motorised scooter.

3.3.3.2 DD-CVR method

In March 2018, two-person DD vaccination teams were introduced as part of the development of a combined approach, termed here as the DD-CVR method. DD teams travelled by motorised scooter and consisted of a vaccinator and an assistant (Figure 3.3B). The DD-CVR method involved assignment of each Working Zone to vaccination teams over several days, with each vaccination team focusing their effort on vaccinating a specific type of dogs within the population. The normal sequence of vaccination was DD vaccinating easy to handle dogs, followed by CVR focusing on unowned roaming dogs, and finally CVR focused on owned dogs that could not be held. First, each Working Zone was assigned to a DD team to go door-to-door, who vaccinated and marked all dogs that could be held by hand. Once the Working Zone was deemed complete by the DD team, they were moved to a new area and the zone was assigned to a CVR team to now focus on vaccinating unowned free-roaming dogs. These teams were referred to as '*CVR-roaming-dog'*.

Finally, a second CVR team was deployed to again go house-to-house focusing on owned dogs that could not be held by the DD team (referred to as '*CVR-household*').

3.3.3.3 Post-vaccination surveys

Post-vaccination dog-sight survey methods have been described previously and enabled immediate re-deployment of vaccination teams to Working Zones with low vaccination coverage (A. D. Gibson et al., 2015). Surveys were conducted by one or two people travelling throughout a Working Zone by motorised scooter recording the details of dogs sighted in the WVS App, including age, sex, neuter status, and presence of a vaccination paint mark (Figure 3.2). In 2013 and 2014 only free-roaming dogs sighted were recorded, however from 2015, dogs confined to private property at the time of sighting were also recorded. It was often possible to sight dogs confined on private property from the road through gated areas. These surveys were performed following completion of dog vaccination in each Working Zone to evaluate vaccination methodologies until 2017. In 2018 and 2019, post-vaccination surveys were used to spot-check coverage, and whilst vaccination teams were re-deployed to boost areas of low coverage, repeat surveys were not conducted in all areas as had been done in previous years.

3.3.4 Data analysis

Anonymised vaccination data were exported from the WVS App in CSV format for analysis. All analysis was performed in R Studio (R version 3.6.2) and QGIS (version 3.20.3). Final figure compilation and annotation was performed in Affinity Designer. Spatial scales of analysis included a 0.5km^2 hexagonal grid (n = 7,530), sub-village Working Zones (n = 1,035), villages/municipalities (n = 412) and talukas (n = 12).

Two broad analyses were conducted. The first analysis included the full programme dataset to explore evolution of the campaign strategy and comparison of vaccination methodology. The second analysis used a subset of the data representing a single geographic cycle of vaccination across Goa with consistent vaccination methodology to explore differences in vaccination output and dog population structure across the urban-rural gradient. Confidence intervals throughout this analysis were computed at the 95% level through use of t-tests.

3.3.5 Analysis 1 – Comparison across vaccination campaigns

3.3.5.1 Vaccination teams and rate

The rate of vaccination (vaccinations/team/day) and the number of active vaccination teams per day was calculated using vaccination records per unique user identity (i.e., vaccination team) per day. Team outputs of less than 3 vaccinations on a given day were not included in the calculation of number of 'active' teams as these were likely to be entries on off-days or opportunistic vaccination, instead of true working vaccination days. Mean number of staff per team per day were calculated from daily records of team size entered in the WVS App.

3.3.5.2 Vaccination coverage

Vaccination coverage was estimated from post-vaccination dog sight surveys conducted after vaccination in each Working Zone. Where multiple surveys were conducted of the same Working Zone during the same campaign cycle, the last survey was used for estimation of final vaccination coverage of the Zone. Estimated vaccination coverage was the number of dogs sighted with marks as a proportion of all dogs sighted. Mean campaign coverage and 95% confidence intervals were calculated using the *survey* package (Lumley, 2004, 2021). In several campaigns, post-vaccination surveys were not routinely conducted in all Working Zones. Survey outcomes were therefore weighted by the proportion of surveys completed in each human density bandings to reflect the distribution of Working Zones vaccinated across human density bandings.

3.3.5.3 Village-wise campaign output

Completion of post-vaccination surveys varied between talukas within campaigns based on evolution of the project methods and the COVID-19 pandemic, meaning that data from post-vaccination surveys was not comprehensive across the project period. A second metric of using village-wise vaccination output per campaign was therefore also used for comparison between campaigns. The total number of vaccines delivered per village per campaign as a proportion of the maximum doses delivered in the zone in any single campaign across the project period (V_{pmax}) as outlined in the following formula:

$$V_{pmax} = \frac{V_x}{\max(V_{x1}, V_{x2}, \dots V_{xn})}$$

Where V_x is the total vaccinations in a particular village for a specific campaign (n). A paired t-test was used to assess the village-wise difference in V_{pmax} between CVR methods (campaign Round 3) and DD-CVR methods (campaign Round 5).

3.3.6 Analysis 2 – Comparison across the urban-rural gradient

Efficiency of the DD-CVR vaccination method and dog demography across the urban-rural landscape were analysed using data from a single geographic cycle with consistent methodology across Goa, from 01/10/2018 to 29/02/2020 (Figure 3.1).

3.3.6.1 Definition of urban-rural gradient

High-resolution (approx. 30m) raster map files of human population distribution in the Goa region were downloaded from DigitalGlobe for the year 2021 (Facebook Connectivity Lab and Center for International Earth Science Information Network – CIESIN – Columbia University, 2016). These raster data were used to calculate total human population and subsequently human density (people per km^2) within vector map layers of Working Zones, villages, talukas and a 0.5km^2 hexagonal grid. Stratification of human density was standardised across analysis to provide greater insight into the urban-rural gradient as opposed to the use of arbitrary 'urban /rural' definitions. Human density strata were defined using natural breaks (Jenks) method applied to human densities of the 0.5km^2 hexagonal grid using the *BAMMtools* package in R (J. Chen et al., 2013; Rabosky et al., 2022). The following human population density bands, in people per square kilometre, were used across analyses: city (3156.3 - 7676.7); town (1424.1 - 3156.3); village (450.9 - 1424.1); hamlet (1 - 450.9); and uninhabited (0 / no data). A crude approximation of dog population by density groups was made by dividing the number of dogs vaccinated in each group by the mean estimated proportion of the population vaccinated. Robust estimates of vaccination coverage by human density strata were not available, therefore a campaign-wide mean estimated vaccination coverage from post-vaccination surveys during this campaign (0.714) was applied across human density groups (Table 3.1). Estimates of dog density (dogs/km^2) and human:dog ratio (HDR) were estimated for each density grouping.

3.3.6.2 Population demography

The proportion of dogs vaccinated by ownership, confinement, type of vaccination team delivering the vaccine, and handling method were calculated for each population density banding. Parallel set plots were created using the *ggplot2* and *ggforce* packages (Thomas Lin Pedersen, 2022; Wickham, 2016). A chi-squared test for trend in proportions was used to assess the statistical significance of differences in the proportion of owned and unowned dogs by human density strata and the proportion of dogs vaccinated by DD teams by density using the *prop.trend.test* function in R.

3.3.6.3 Cost per dog vaccinated

The estimated cost of each vaccine delivered was calculated using the following calculation:

$$Cost\ per\ dog\ vaccinated = \frac{C_f}{N} + C_v$$

Where C_f is the fixed daily cost associated with vaccination teams delivering the vaccine based on the method used (CVR/DD) (staff salaries, equipment, vehicle, and fuel), N is the total number of dogs vaccinated by the team that day and C_v is the cost associated with each vaccine administered (vaccine, syringe, needle, vaccination certificate).

Each vaccination event was also ascribed a human density banding according to the GPS location at which the vaccination was administered, paired against the 0.5km^2 hexagonal grid described in Section 3.3.6.1. A multivariable linear regression model was used to examine the influence of human density grouping (as a measure of urban-rural gradient), season, and team type on the cost per dog vaccinated. Human population density bands (in people/km^2) were: city (3156.3 - 7676.7), town (1424.1 - 3156.3), village (450.9 - 1424.1, hamlet (1 - 450.9), and uninhabited (0 / no data). Team types were DD, CVR-roaming-dogs, and CVR-household. Season was defined as winter (Dec – Feb), summer (Mar – May), monsoon (Jun – Aug), and rainy (Sep – Nov) (Fielding et al., 2021). The log transformed cost per dog vaccinated was used due to non-normal distribution of the residuals when using cost-per-dog vaccinated in the model. Estimated coefficients were exponentiated for interpretation. The Variance Inflation Factor (VIF) for each variable included in the regression model was calculated to evaluate potential multicollinearity among predictor variables. The *emmeans* package (Lenth, 2018) was used to calculate the estimated marginal means (also known as least-squares means) (Searl et al., 1980) of the predicted cost per dog vaccinated by season and for each human density banding. Results were plotted using the *ggplot2* package (Wickham, 2016).

Importantly, the estimated cost per dog vaccinated calculated here only includes the expenditure pertaining to the vaccination teams. This differs from the cost per dog vaccinated estimated in Chapter 4, which is derived from annual project expenditure and so includes other cost of project implementation not included here.

3.4 Results

3.4.1 Overview

A total of 640,667 doses of rabies vaccine were delivered to dogs at a median rate of 5,355 doses per month (IQR 3,507 - 7,527) (Figure 3.4). There were 11 geographically distinct campaign cycles over the 10 years from 2013 to 2022 (Figure 3.1, Figure 3.4). The median inter-campaign interval by taluka was 12 months (interquartile range (IQR) 9 - 15) (Figure 3.5).

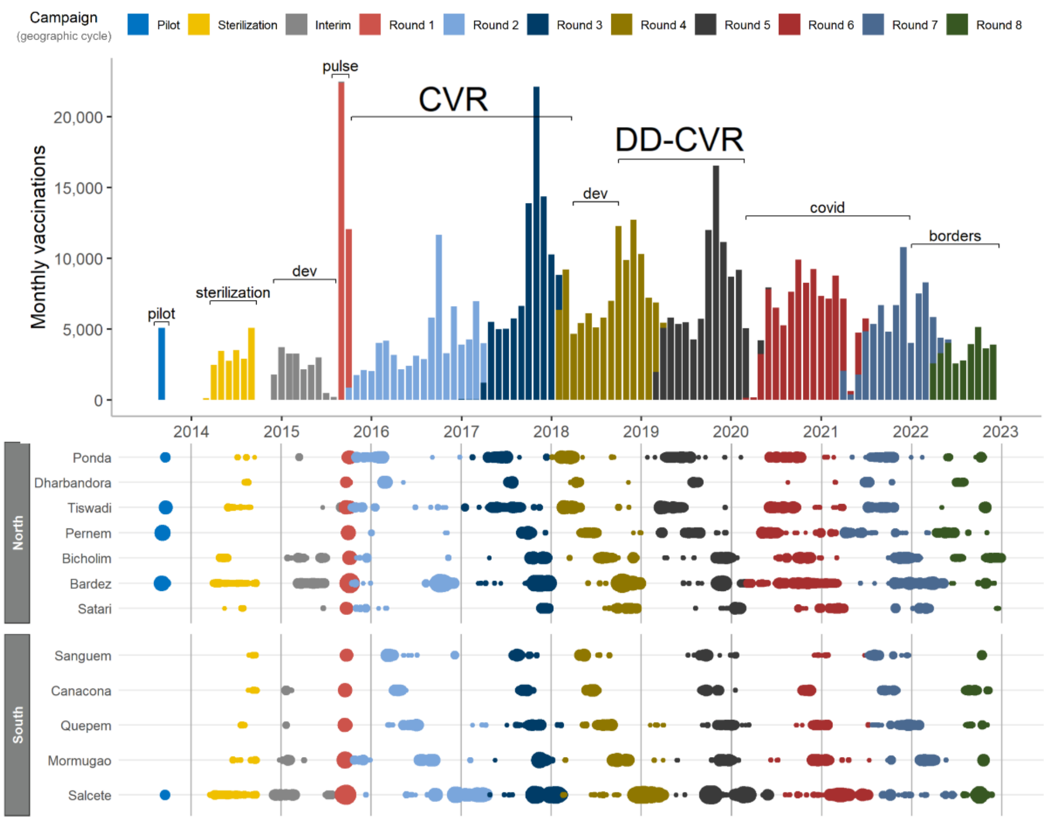


Figure 3.4 - Goa vaccination output by campaign, year, and taluka. Top – Bar plot of monthly vaccinations, coloured by campaign cycle. Bracketed labels show periods of consistent methodology (Figure 3.1), CVR = Capture-Vaccinate-Release method, DD-CVR = combined Door-to-Door and CVR method, dev = periods of methodology development. Bottom – Timeline point plot of monthly vaccinations by taluka.

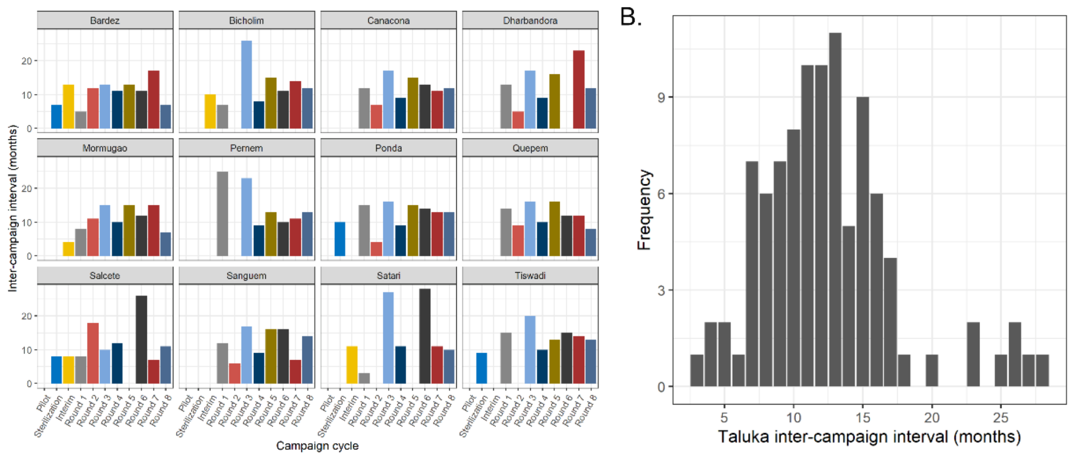


Figure 3.5 – Inter-campaign intervals by taluka (A) and frequency distribution of inter-campaign intervals by taluka (B).

3.4.2 Analysis 1 – Comparison across vaccination campaigns

Vaccination began in 2013 with a 2-week vaccination pilot using CVR methods vaccinating 5,029 dogs, followed by a campaign from March to September 2014 in which 20,283 dogs were vaccinated and sterilized in densely populated regions (Figure 3.1). During the early period of 2015, technology-aided vaccination methods of vaccination team direction were developed and a further 20,410 dogs vaccinated. From these early experiences, it was determined that the CVR approach was necessary to access a high proportion of dogs and that less intensive approaches would result in coverages below the 70% target (A. D. Gibson et al., 2015).

A Memorandum of Understanding was formed between Mission Rabies and the Government of Goa in September 2015, in which government funds would contribute to expanding the campaign to a state-wide dog vaccination, rabies surveillance and education program. It was decided to condense the vaccination campaign into a single month to leverage the advantages of a ‘pulse’ campaign approach. In September 2015 a workforce of 16 CVR teams vaccinated 33,573 dogs across all the talukas of Goa, however this was unsuccessful in terms of vaccination coverage and geographic homogeneity. As a result, the campaign structure was changed to a rotating taluka-by-taluka approach using permanently employed CVR teams from October 2015. Through this approach it was possible to vaccinate nine talukas and 73,875 dogs in Round 2 (2016), expanding to all 12 talukas and 92,263 dogs in Round 3 (2017) (Figure 3.4).

Field experience and programmatic data recorded during expansion of the CVR method revealed that a high proportion of the dogs vaccinated could be manually restrained by an owner/guardian, or a member of the vaccination team, therefore mitigating the need for the large net-catching team in such cases. This prompted a second period of methodological development, which began in March 2018, to establish the DD-CVR method. The new vaccination approach (described in the methods) was implemented from October 2018, pushing the vaccinations in Round 4 to 107,379 in Round 4 (2018) and 97,301 in Round 5 (2019). Taluka-by-taluka vaccination using DD-CVR methods continued until disruption caused by the COVID-19 pandemic in April 2020 until December 2021.

A pilot Central Point (CP) vaccination campaign was launched in collaboration with the Department of Animal Husbandry & Veterinary Services in September 2021 in preparation for cessation of DD-CVR vaccination in most parts of the state in 2022. In 2022 intensive vaccination stopped in 8 of the 12 talukas and vaccination resources were redirected beyond Goa’s borders to develop a cordon sanitaire in neighbouring populations (Figure 3.1). Intensive DD-CVR vaccination continued in talukas adjacent to neighbouring rabies endemic dog populations (Pernem, Bicholim, Satari, and Canacona). Data and experience from the 2021 CP campaign identified awareness and accessibility of central point vaccination locations as barriers to presentation of dogs for vaccination by owners/guardians. The CP campaign structure was adjusted in September 2022 to increase the number of vaccination points and improve the media coverage of the programme, resulting in the vaccination of 5,021 dogs as compared to 1,899 the previous year.

3.4.2.1 Vaccination teams and rate

The median number of active vaccination teams per working day over the whole project period was 6 (IQR 3 - 8). The number of vaccination teams progressively increased campaign-on-campaign during the CVR period (Oct 2015 - Mar 2018) from a median of 2 CVR teams in Round 2, to 7 in Round 4 (Figure 3.6). Restructuring of the workforce created a median of 3 DD teams (IQR 2 - 4), 3 CVR-roaming-dogs (IQR 2 - 4), and 3 CVR-household teams (IQR 3 - 4) (Figure 3.6). This configuration of 9 DD-CVR vaccination teams would represent a workforce of 54 staff, as compared to 7 CVR teams consisting of at least 56 staff (7 people per team).

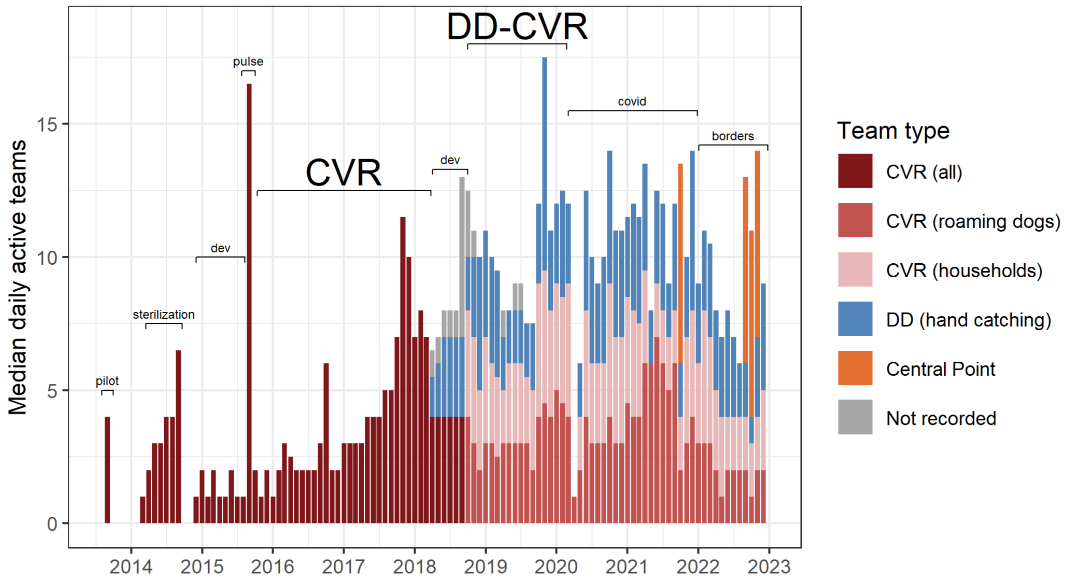


Figure 3.6 – Bar plot of the mean number of active daily teams each month, coloured by team type. CVR = Capture-Vaccinate-Release method, DD-CVR = combined Door-to-Door and CVR method, dev = periods of methodology development.

As the number of teams increased, so did the number of days spent vaccinating in each Working Zone. The mean number of days spent vaccinating in each Working Zone per campaign increased, from 1.73 days in Round 2 (95% CI: 1.67 - 1.8) to 2.32 days in Round 4 (CI: 2.13 - 2.51) through the CVR method (Figure 3.7A). Following the further increase in vaccination teams with introduction of DD-CVR, the mean number of days spent vaccinating each Working Zone increased to 3.72 days (CI: 3.57 - 3.87), despite an overall reduction in staff requirement.

Conversely, the rate of vaccination per team per day progressively decreased over the project period both in consecutive rounds of CVR and after the shift to DD-CVR

(Figure 3.7B). During Round 1, teams vaccinated a mean of 71.6 dogs/team/day (CI: 68.3 - 74.8), dropping to 48.7 dogs/team/day (CI: 45.7 - 51.6) in Round 4 (Appendix B). Following the transition to DD-CVR, the rate remained stable at a mean of 47.3 dogs/team/day (CI: 45.9 - 48.7) for the remainder of Round 4, but then fell to 34.5 dogs/team/day (CI: 33.0 - 36.0) by Round 7 (Figure 3.7). The catching rate varied between team types in the DD-CVR method, with DD teams averaging 48.0 dogs/team/day (CI: 46.1 - 49.8), CVR-roaming-dogs at 35.9 (CI: 33.1 - 38.8), and CVR-households at 32.9 (CI: 31.1 - 34.7) after the implementation of DD-CVR in Round 4 (Appendix B).

3.4.2.2 Vaccination coverage

A total of 4,372 post-vaccination surveys were conducted during the study period, recording 371,932 dog sightings. 22.2% of surveys were repeat surveys of the same region during the same campaign cycle, typically re-checking coverage following additional vaccination activity. Post-vaccination surveys only recorded the vaccination status of free-roaming dogs prior to Round 2, with weighted mean coverage of 35.7% (CI: 32.5 - 39.0) in Round 1 (Figure 3.8A). From Round 2 onwards, the mean vaccination coverage in all dogs sighted was 71.4% (CI: 70.9 - 72) and 53.8% (CI: 53 - 54.5) in free roaming dogs (Figure 3.8A).

3.4.2.3 Village-wise campaign output

Median V_{pmax}, the village-wise vaccination output per campaign as a proportion of the maximum campaign output for each village, was 27.7% (IQR 16.0 - 39.7) during the 2015 pulse campaign (Round 1), increasing to 70.5% (IQR 49.2 - 85.7) during the period of CVR methods. Following the initiation of the DD-CVR approach, median V_{pmax} was 83.9% (IQR 63.2 - 100) (Figure 3.8C). This increase in V_{pmax} from CVR methods to DD-CVR was statistically significant (p <0.001). Vaccination in rabies-free talukas ceased in 2022, replaced by the annual CP campaign which correlates to a drop in median V_{pmax} to 19.2% (IQR 5.9 - 66.5) (Figure 3.8D).

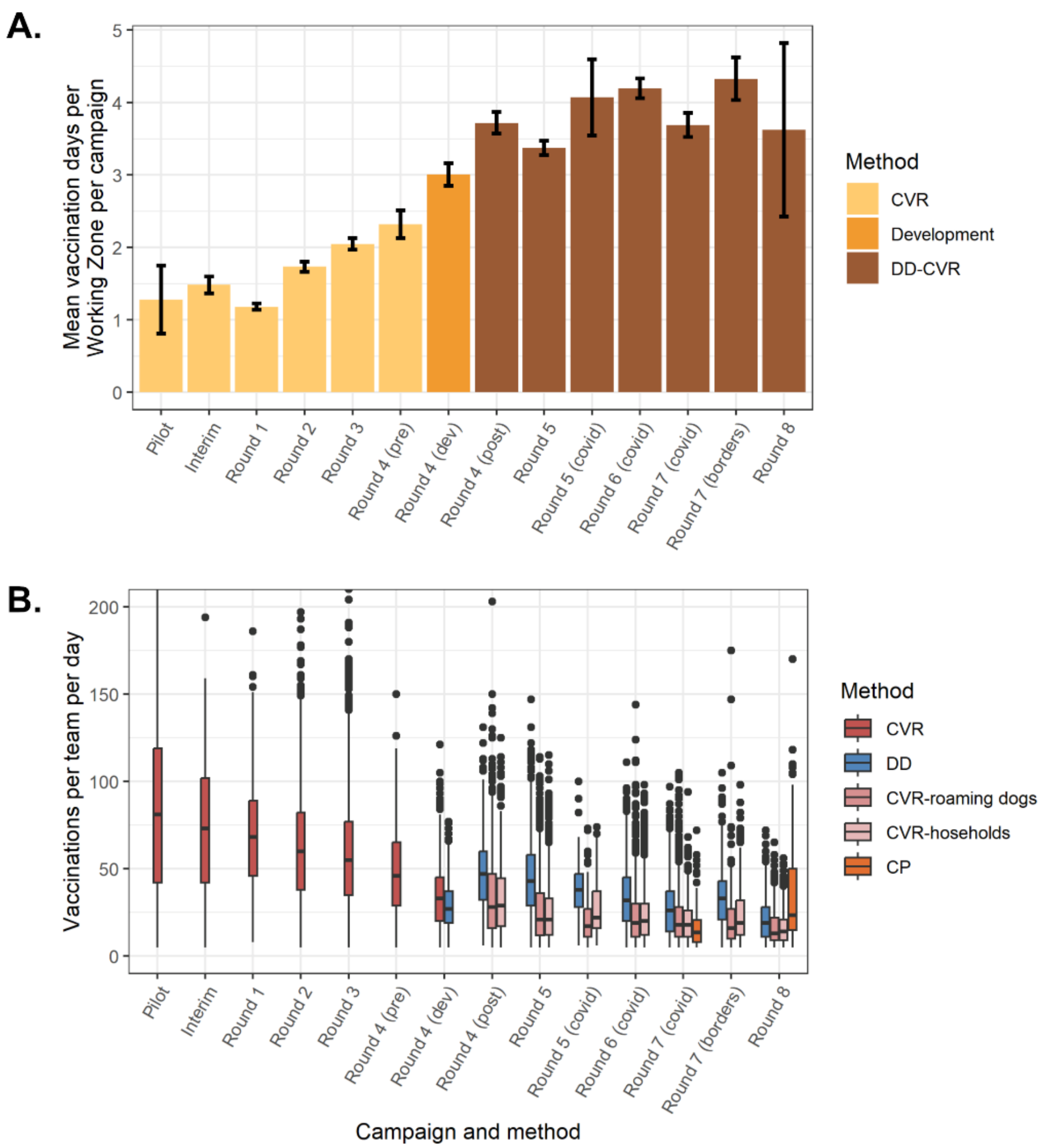


Figure 3.7 – Measures of vaccination intensity. A) Bar chart of mean number of days spent vaccinating in each working zone by campaign. B) Box plot of team daily vaccination rate (vaccinations / team / day) by campaign and method. Boxes indicate the median, first, and third quartiles. Bracket labels in the x-axis labels indicate periods of distinct methodology within campaigns. Dev = period of methods development.

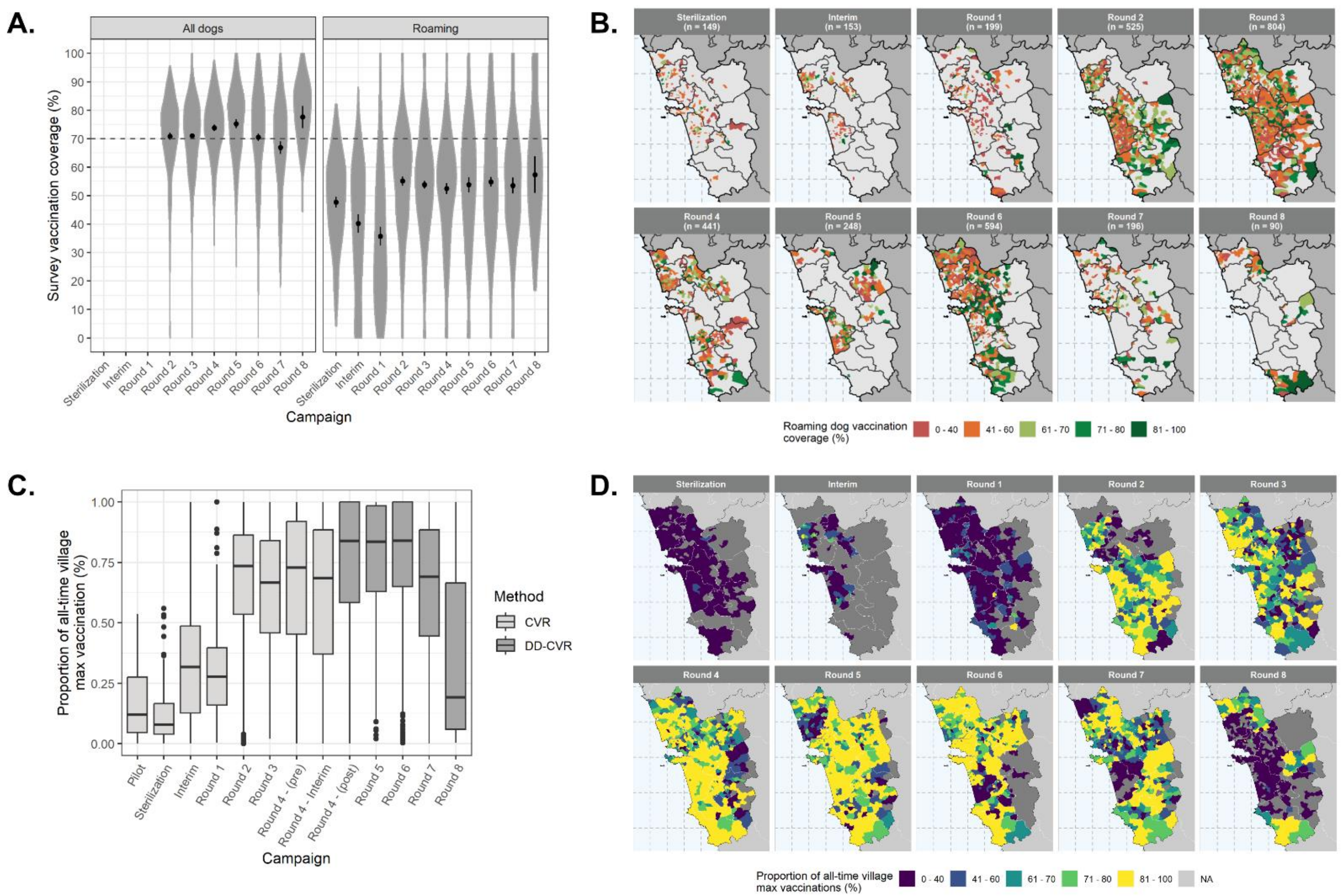


Figure 3.8 – Evaluation of vaccination output by campaign period. A) Post-vaccination survey vaccination coverage distribution, survey weighted mean coverage (point), and 95% confidence intervals (line) from final Working Zone post-vaccination surveys. B) Maps of post-vaccination surveys by campaign, coloured by vaccination coverage in free-roaming dogs. Total number of surveys in each campaign is shown in the map facet strips. C) Boxplot of V_{pmax} (village-wise vaccination output as a proportion of maximum vaccinations from any single campaign), Colour shows distinction following establishment of optimal vaccination method. D) Maps of V_{pmax} by campaign.

3.4.3 Analysis 2 – Comparison across the urban-rural gradient

The analyses presented in the remainder of the results were conducted on data from a single geographic cycle of vaccination in all talukas using consistent DD-CVR methods (Figure 3.1). All data were from Round 5, except for Bardez and Salcete talukas, which were from Round 4 due to the Covid-19 pandemic disruption in these areas in Round 5.

3.4.3.1 Definition of the urban-rural gradient

Goa represents a diverse urban-rural landscape in terms of human population density. Human population was estimated at a resolution of 0.5km2 hexagons and allocated according to human density. Table 3.1 shows the land area, human population, and dog vaccinations. Half of the human population lived in areas categorised as 'city' and 'town' however these constituted just 9% of Goa's land area (Figure 3.9A). The total dogs vaccinated by campaign across human density groups can be found in Appendix B. From the DD-CVR campaign data, crude dog estimates follow the pattern reported elsewhere of higher dog densities in urban settings, but few dogs per person as compared to rural areas Table 3.1.

Table 3.1- Tables of area, human population, dog vaccinations (in demography analysis sub-dataset), and approximation of dogs based on mean vaccination coverage for human density bandings of a 0.5km² hexagonal grid across Goa (a map of these data is shown in Figure 3.4).

Density group (people/km²)	**Area** (km²)	**Human populat-ion**	**Dog vaccinat-ions**	**Human: vacc ratio**	**Mean coverage** (%)	**Dog estimate***	**Dog density** (dogs/km²)	**Human: dog ratio**
City (>3157)	76 (2%)	325,967 (21%)	16,724 (15%)	19.5	0.714	23,423	310	13.9
Town (1425-3156)	251 (7%)	508,309 (33%)	35,509 (32%)	14.3	0.714	49,732	198	10.2
Village (451-1424)	603 (16%)	497,768 (32%)	38,538 (35%)	12.9	0.714	53,975	89	9.2
Hamlet (1-450)	1,403 (38%)	214,613 (14%)	18,586 (17%)	11.5	0.714	26,031	19	8.2
Uninhabited (0)	1,354 (37%)	0 (0%)	324 (0%)	0.0	0.714	454	0	0.0

Mapping human density shows the population heterogeneity within Goa, as well as the contiguity of population at the north Goa border and a high-density centre close to the south border, both of which present risk of re-introduction of rabies virus from unvaccinated dog populations (Figure 3.9A). Review of the method of vaccination across the urban-rural continuum shows the increasing proportion of dogs vaccinated by DD vaccination teams moving from urban-to-rural environments (reported in the next section) (Figure 3.9B).

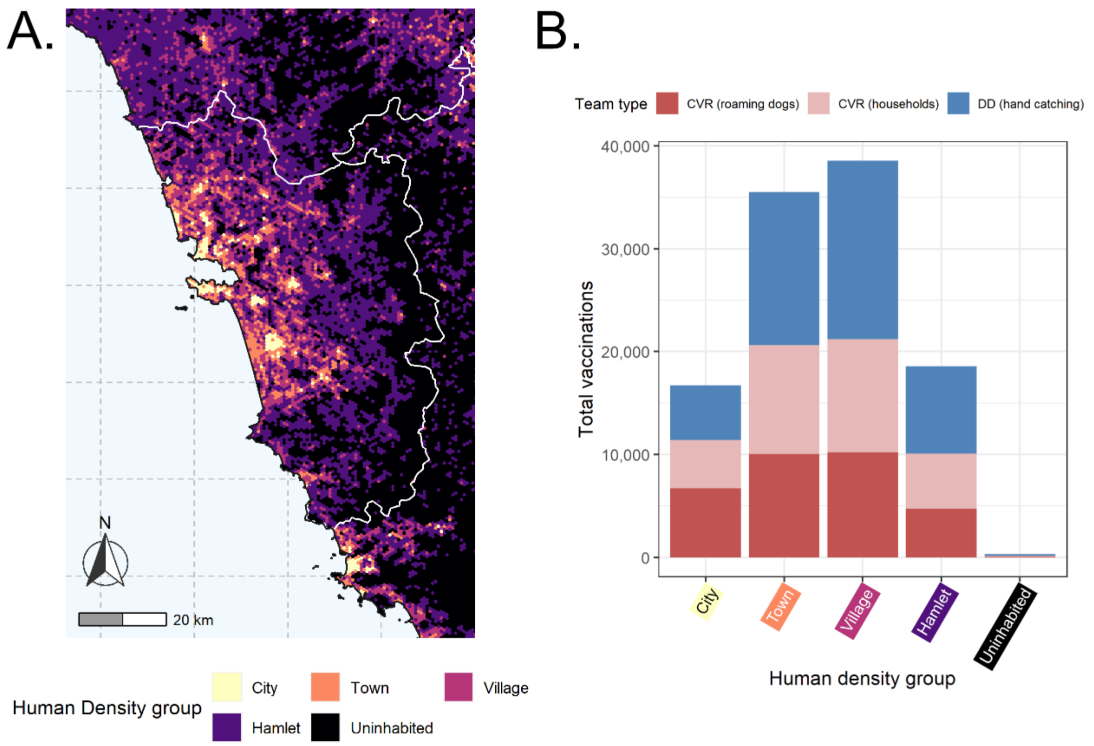


Figure 3.9 – Definition of Goa's urban-rural gradient. A) Map of Goa and bordering region by human density grouping (0.5km^2 hexagons). B) Bar plot of total vaccinations by human density grouping and team type from data used in demographics analysis. Density groups (in people/km^2): City >3157, Town 1425-3156, Village 451-1424, Hamlet 1-450, Uninhabited 0.

3.4.3.2 Population demography

Of all dogs vaccinated in the cycle (n = 130,522), 49% were owned (n = 64,455). Of owned dogs, 24% were always confined (n = 15,414), 70% were allowed to roam unsupervised for some of the time (n = 44,950) and 6% were always free to roam (n = 4,091) (Figure 3.10). There was a statistically significant trend in increasing ownership as population density reduced ($Chi^2 = 3966$, df = 1, $p < 0.001$) (Figure 3.11). Most dogs were vaccinated by CVR teams (62.6%, n = 81,644), however 34.4% of these were still restrained by hand without the use of nets.

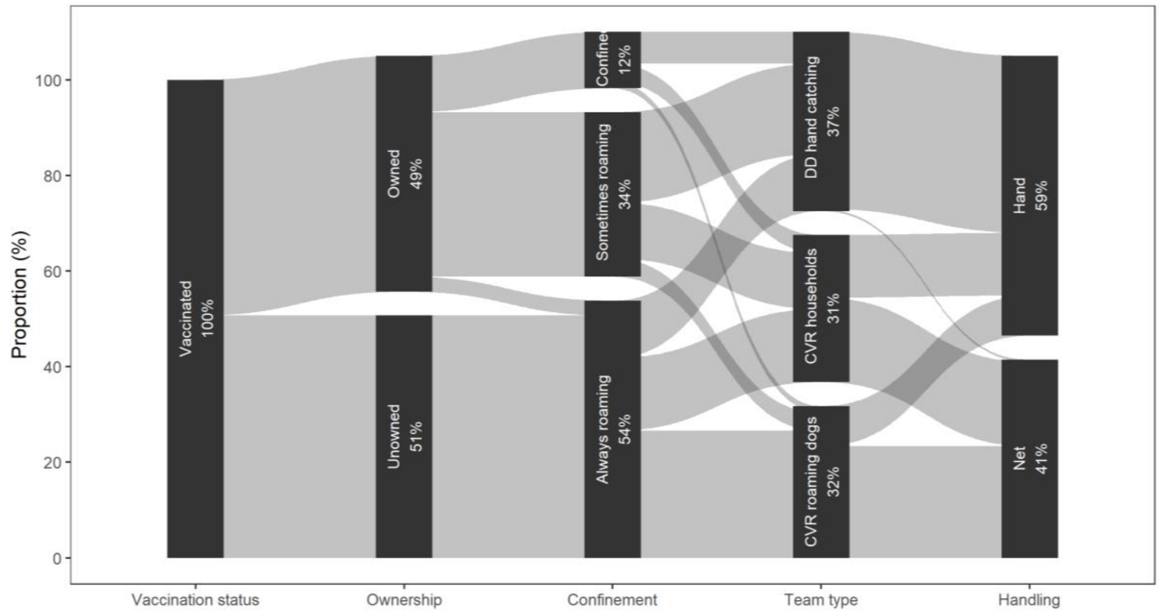


Figure 3.10 – Parallel set showing proportions for dogs vaccinated by ownership, confinement, vaccination method, and handling.

DD teams, using hand-catching, predominantly vaccinated owned dogs, however they were also able to vaccinate a significant number of unowned dogs by hand, representing 34.4% of all dogs they vaccinated (n = 13,845). The variation in dog ownership and dog access across the urban-rural gradient is reflected in vaccination team output across these settings, with DD team output constituting an increasing proportion of dogs vaccinated moving from urban (30% in cities) to rural (41% in hamlets), a trend which was also statistically significant (Chi^2 = 660, df = 1, p = <0.001).

A considerable proportion of dogs could be held by hand; however, DD teams alone were unlikely to be sufficient. Overall, 58.5% of dogs could be held by hand, but most of these were owned, with 62.3% of unowned dogs requiring net-capture for vaccination and indicating that hand-catching alone would not achieve adequate coverage in the roaming dog population to control rabies. Given that the DD-CVR method was estimated to access 52.5% of roaming dogs during this period (Figure 3.8A), it was estimated that the DD teams alone were able to access 18.3% (17.7 - 19.0) of the roaming dog population.

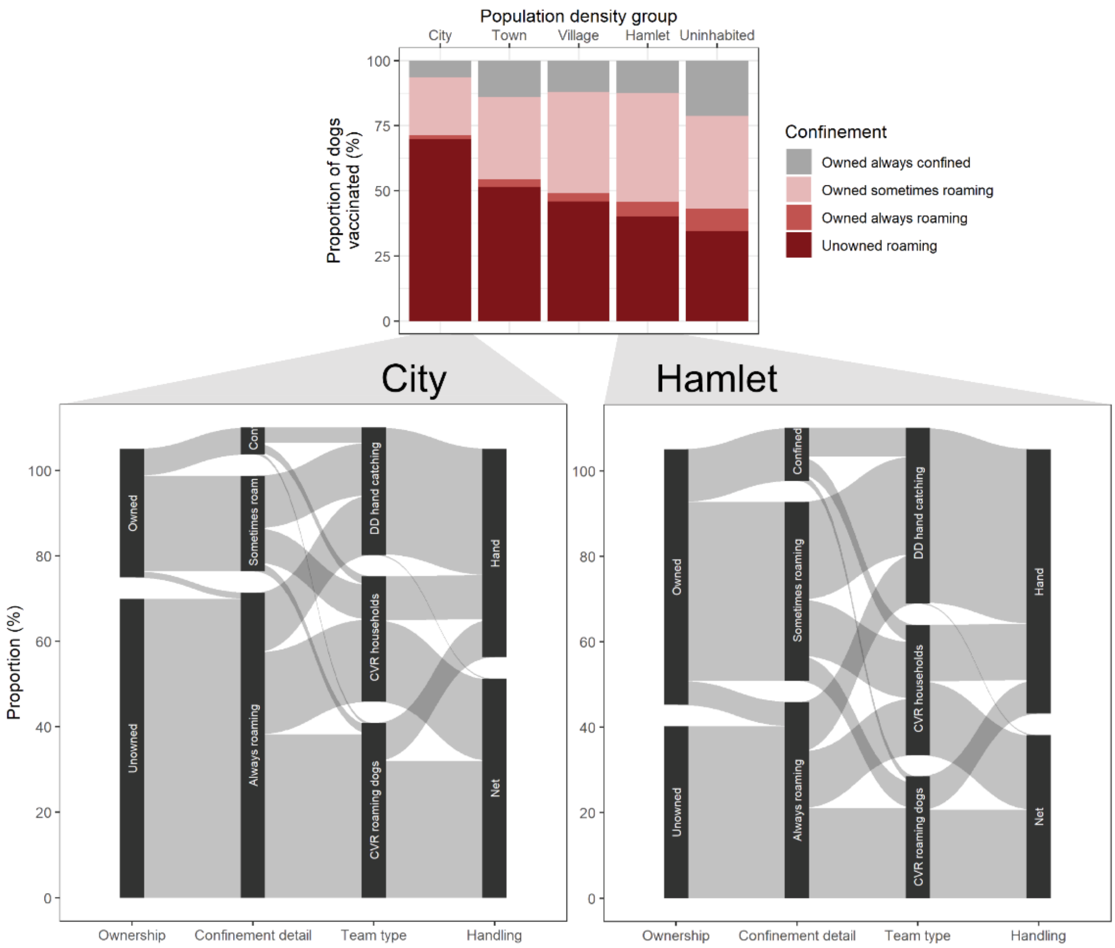


Figure 3.11 – Dog demography and vaccination method by population human density. Top – bar plot of ownership and confinement by density strata. Bottom - Parallel set of the proportions of ownership, confinement, team type and handling method for city and hamlet density groups. Density bands (in people/km²): City >3157, Town 1425-3156, Village 451-1424, Hamlet 1-450, Uninhabited 0. NB: the number of dogs in 'uninhabited' regions was very small (n = 324) (Table3.1), and sporadic 'owned always confined' dogs in this group may have been the result of occasional households not identified by the reference human population data.

3.4.3.3 Cost per dog vaccinated

The multivariable linear regression model showed that the estimated cost per dog vaccinated increased moving from urban to rural settings and that this association was statistically significant when adjusting for season and team type (Table 3.2). The estimated marginal mean cost per dog vaccinated in cities was 166 INR (CI: 165– 167) compared to 239.5 INR (CI: 238 - 241) in hamlets, adjusting for team and season (Figure 3.12). Season also had a statistically significant effect on cost per dog vaccinated with the estimated a marginal mean cost per dog vaccinated being lowest in the rainy season (191 INR CI: 189 - 192) as compared to monsoon (240 INR 238 - 243) when it was highest (Table 3.2, Figure 3.12).

Table 3.2 – Table of multivariable linear regression model outputs examining the influence of human density, land type, and season on cost per dog vaccinated. Table shows estimated coefficients with 95% confidence interval, standard error and p-values.

Variable	Estimate (95% CI)	Std. Error	P-value
(Intercept)	73.841 (73.211 - 74.477)	0.0044	<0.001
Density: Town	1.171 (1.164 - 1.178)	0.0031	<0.001
Density: Village	1.267 (1.259 - 1.275)	0.0031	<0.001
Density: Hamlet	1.443 (1.432 - 1.453)	0.0038	<0.001
Density: Uninhabited	1.821 (1.745 - 1.899)	0.0216	<0.001
Team type: CVR(roaming-dogs)	3.736 (3.718 - 3.755)	0.0026	<0.001
Team type: CVR(households	4.066 (4.046 - 4.087)	0.0026	<0.001
Season: Rainy	0.794 (0.788 - 0.799)	0.0038	<0.001
Season: Summer	0.966 (0.957 - 0.974)	0.0045	<0.001
Season: Winter	0.886 (0.879 - 0.892)	0.0038	<0.001

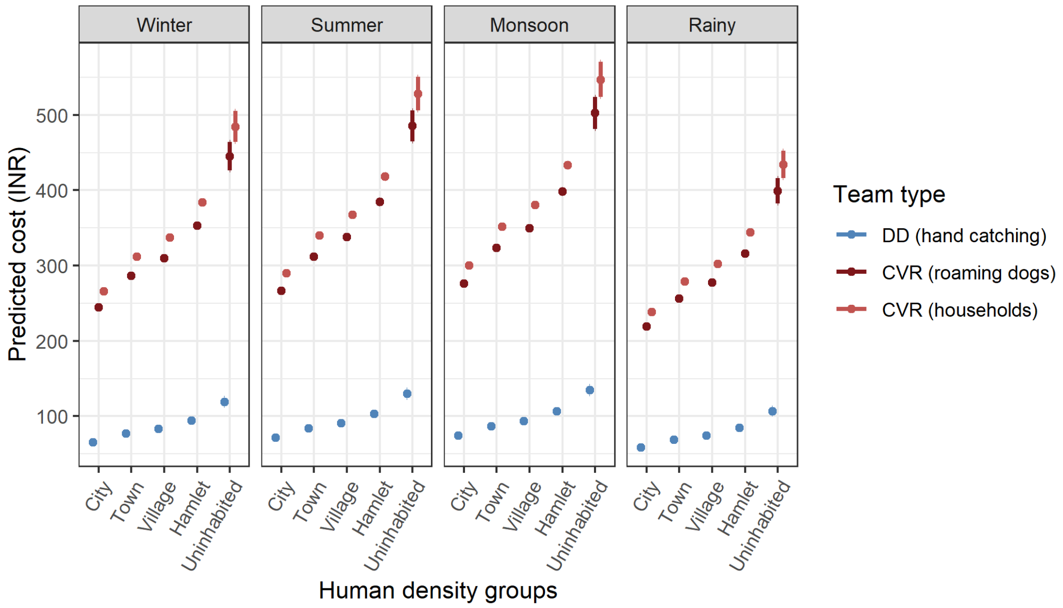


Figure 3.12 – Estimated marginal means (least-squares means) of cost per dog vaccinated using the DD-CVR vaccination method controlled for human density, team type, and season. Density bands (in people/km²): City >3157, Town 1425-3156, Village 451-1424, Hamlet 1-450, Uninhabited 0.

3.5 Discussion

This study documents the progressive development of methods for mass dog vaccination across the urban-rural continuum from a starting point of limited data and experience to a programme reaching 70% of the dog population throughout Goa state annually. Learnings can be taken from this implementation-focused data-driven approach to state-level campaign development, in addition to the application of optimised methods to other settings. Insights into the relationship between dog ownership and optimal vaccination campaign structure are of significance to planning approaches for the control of rabies across larger areas of India and to inform economic and epidemiological modelling of programme feasibility and impact at scale.

During the early stages of project development, the decision was made to replicate the approach of other large-scale pulse immunization programmes by condensing the state dog vaccination campaign into a single month. Synchronised, high-intensity, short-duration pulse vaccination campaigns have political, epidemiological, and operational advantages over more protracted programmes, however the feasibility of a 'pulse' approach to mass dog vaccination has not been reported in India. The importance of coordinating large-scale vaccination efforts at the national and multi-national level was highlighted by Hampson et al., who identified synchrony between rabies epidemics across extremely large spatial scales (Hampson et al., 2007). There have been two well documented examples of coordinated continental-scale immunisation initiatives; the elimination of dog rabies from Latin America through the annual delivery of over 50 million dog vaccinations and the elimination of polio from South Asia involving the annual vaccination of 248 million children (Andrus et al., 2001; Freire de Carvalho et al., 2018). Both titanic programmes were rooted in national immunisation days, whereby an enormous workforce was mobilised to deliver the pulse immunisation programme across whole countries in a matter of days. Condensing this rapid pan-population increase in immunity can be timed for maximum epidemiological impact based on epidemic cycles, or for maximum operation impact based on season or target population accessibility/abundance (D. Nokes & Swinton, 1997). Short-duration campaigns also benefit from maximised mass media attention, condensing all efforts to increase public and political awareness of the issue into a defined period (Murphy, 2012). Finally shortening the pulse duration enables government departments and other contributing organisations to commit their workforce for a short period, alleviating management and administrative burden through the remainder of the year. In September 2015 the programme leadership team, of which I was a contributor, planned and executed a state-wide pulse CVR campaign (Round 1), aiming to vaccinate 70% of the dog population in all regions of Goa in a single month. The workforce was expanded to 16 CVR teams, representing over 110 vaccinators and dog handlers, who vaccinated 33,573 dogs in the campaign. The population penetration of this campaign, however, was poor, as reflected on post-vaccination dog-sight surveys in which only 35.7% of roaming dogs were vaccinated. In comparison to the maximum number of doses delivered in these villages in subsequent campaigns, this drive only vaccinated a median of 27.6% of that maximum. This low coverage was attributed to the lack of experience of many of the dog catchers enlisted for the drive and the creation of teams that had not previously worked together. The exercise highlighted that attaining competency in the CVR catching method requires months of working within an experienced team and that team cohesion is crucial to catching success. It was concluded that the CVR method was not feasible for implementation as a short-duration pulse due to the lack of an existing skilled workforce of sufficient size and the complexity of training such a team.

Learnings from Round 1 informed the development of the cyclical 12-month approach to covering the state through the delivery of focal taluka-by-taluka pulse vaccination efforts under the central state direction of the Department of Animal Husbandry & Veterinary Services. The permanent workforce made it possible to develop and retain a skilled team that worked methodically through each taluka on a village-wise basis. This translated into higher vaccination coverage; however, the size of the dog population was found to be larger than initially estimated and only nine of Goa's 12 talukas were completed in the first 12-month period. Progressively increasing the number of vaccination teams enabled the systematic vaccination of all talukas and at high coverage in Round 3 (Figure 3.6). The more protracted approach brought additional administrative challenges in coordinating with local authorities (village sarpanch) to inform the community of the upcoming vaccination drive in their region. Unlike short-duration pulse campaigns, where the date of vaccination across all regions is synchronised across all regions, the village-wise movement of vaccination teams made it difficult to reliably predict when vaccination would take place in each village weeks or months in advance. This was due to aspects of human resource, weather, and field conditions impacting on how long each village would take to complete. Consequently, a system was developed where the village authorities were informed of an estimated vaccination date several weeks in advance, which was then refined and confirmed in the days before vaccination began. Without the advantages of mass media attention garnered by a state-wide pulse, community sensitization relied on information dissemination through the networks of local government, key community figures, and the rabies education initiative that was concurrently implemented in schools. Despite these compromises of year-round managerial and administrative burden, the programme was able to achieve state-wide vaccination at high coverage for the first time.

The integration of small two-person DD teams leveraged the differences in ease with which dogs could be handled within the population. A recent study that vaccinated 1,300 dogs in rural Tamil Nadu, India, reported that over 98% of dogs vaccinated could be held for vaccination without special equipment, achieving an estimated vaccination coverage of 79% (Airikkala-Otter et al., 2022). Experience from the large campaign in Sikkim also cited high rates of hand catching (Byrnes et al., 2017). The abundance of dogs that could be held by an owner or experienced handler for vaccination was a clear source of inefficiency in the initial CVR approach in Goa, as the net catching staff in each vaccination team were redundant whilst these dogs were vaccinated. Although a significant difference in post-vaccination survey vaccination coverage was not observed before and after the change from CVR to DD-CVR, the number of dogs vaccinated in each village did increase significantly, suggesting increased population penetration. DD vaccination methods have the advantage of lower fixed operating costs, human resource, and equipment requirements than CVR, in addition to prioritising the vaccination of dogs in closest contact with people, increasing the total number of dogs vaccinated, and being better for dog welfare. Therefore, is would be logical to recommend the implementation and evaluation of DD vaccination approaches as the initial implementation of mass dog vaccination programmes more broadly in India. Whilst this study demonstrates that vaccination coverages from DD alone would be insufficient to eliminate the rabies virus, its early adoption would provide an opportunity to develop methods, gather data about the dog population, and build community engagement on which to expand more intensive approaches directed towards the unowned dog population.

This campaign constitutes the longest running programme using CVR at this scale in India to date and offers insight into the long-term impact of this method on dog catchability. A concerning trend observed in the data was the declining daily team vaccinations over the project period (Figure 3.7), which has the potential to undermine efficiency-saving from the gains made by the DD-CVR method. Whilst the rate of vaccination in later campaigns was affected by the pandemic, this pattern is evident before the change to DD-CVR vaccination method in 2018. The increase in days revisiting the same Working Zone from 2.3 days in the CVR method to 3.7 days in DD-CVR may cause a reduction in catching rate as vaccination coverage in the population increases over consecutive days and unvaccinated dogs become scarcer. The declining daily catching rate in CVR teams, in addition to observations from the field, indicate that dogs in Goa are becoming more difficult to catch by net. Catching rates and changes over time have not been reported from other large-scale CVR programmes and would warrant further research to inform the development of both rabies vaccination and dog population management interventions. The potential for oral rabies vaccination to simplify the immunisation of dogs that are not amenable to handling and enable the development of more a sustainable and scalable approach was recognised, leading to the investigations reported in Chapters 5 and 6 (A. D. Gibson, Mazeri, et al., 2019; A. D. Gibson, Yale, et al., 2019; Yale et al., 2022).

Understanding of population structure and dog access in Goa contributed to the development of a tool by the US CDC to help programme planners to demystify the programmatic alchemy required to design mass dog vaccination interventions based on the population composition and predicted penetration of vaccination methods (Wallace et al., 2019). The tool, named VaxPLAN, was used to review the output and workforce requirements of hypothetical campaign structures in India and provides an accessible way to communicate the complex interdependency between dog population structure and optimal campaign methodology (A. D. Gibson et al., 2020). More work is needed to improve the usability of this tool, but broadly, the development of intuitive online technologies that make it easy for programme planners to understand the recommendations of researchers and apply them to their own setting will be key to scaling-up rabies control activities. Tools that improve access to the benefits of mathematical modelling and lower the threshold for campaign planning through simple cartographic tools will all be of benefit to programme planners at the district and city level. Increasing national engagement in dog vaccination campaign planning is also a priority and in December 2022 I led a team in Mission Rabies to co-host a workshop in Bengaluru through collaboration with the World Organisation for Animal Health and Bengaluru Veterinary College (KVAFSU), sharing the learnings of this research and other work to government representatives from 10 countries (Chapter 7).

In 2022 intensive vaccination ceased in eight of Goa’s 12 talukas due to sustained vaccination for two years beyond the last detected dog rabies cases. This aligns with recommendations from dog rabies simulation modelling by Townsend et al., as well as protocols that were successful in the elimination of fox rabies from Europe (Freuling et al., 2013; Townsend, Lembo, et al., 2013). The simulations consider elimination likely in regions where vaccination has continued for two years beyond the last detected case through surveillance systems typical of endemic regions detecting at least 5% of cases (Townsend, Lembo, et al., 2013). Surveillance activities are discussed in the next chapter and continue to ensure the investigation and testing of suspect rabid dogs throughout Goa. Should a rabid dog be identified in a previously free region, intensive vaccination efforts will need to recommence until two years following the final rabies positive case.

Intensive annual DD-CVR vaccination continued in the four talukas at Goa's north and south border where roaming dogs can mix with populations in adjacent districts (unpublished data). Expansion of DD-CVR vaccination and rabies surveillance into neighbouring endemic regions began in 2022 (Round 8) through agreements with the state governments of Maharashtra and Karnataka, to establish a cordon sanitaire beyond Goa's borders (Figure 3.1). Whilst specific research on cordon sanitaire extent and coverage is lacking, there are several examples of maintained rabies freedom through ongoing vaccination at the limits of a campaign's reach, including in the control of sylvatic rabies in Europe (G. Smith et al., 2008) and the prevention of reintroduction of rabies in Malaysia (Wells, 1954). Reintroduction through human mediated transport of infected dogs will remain an ongoing risk for the transboundary spread of rabies (Talbi et al., 2010).

In 2021 a state-wide CP campaign was planned under the leadership of the Department of Animal Husbandry & Veterinary Services to provide dog owners with ongoing access to annual rabies vaccination even beyond the end of the DD programme. Whilst these methods have been widely researched in Latin American and African contexts (Chomel et al., 1988; Evans et al., 2019; Filla et al., 2021; Fishbein et al., 1992; A. D. Gibson et al., 2016; Léchenne, Oussiguere, et al., 2016; LeRoux et al., 2018; Mazeri et al., 2018, 2021; Mosimann et al., 2017; Sánchez-

Soriano et al., 2020; Undurraga et al., 2020), exploration of their use in South Asian settings has been limited. CP campaigns took place in Goa in October of 2021 and 2022, providing free rabies vaccinations to all dogs present at temporary clinics held throughout the state. As rabies cases decline, there is invariably a risk of diminishing concern about the disease and so the CP initiative not only intends to promote a culture of dog owners presenting their dogs for vaccination, but also serves as an annual opportunity to generate ongoing public and political awareness on the issue of rabies. The first CP campaign vaccinated 1,899 in 2021, learnings from which were taken into the planning of the 2022 programme, where awareness activities were refined and CP distribution was increased, resulting in the vaccination of 5,021 dogs. The only study from India reporting coverage from a CP campaign was from the vaccination of 277 dogs in rural villages of Maharashtra where peak coverages of 42% were achieved (Belsare & Gompper, 2013). Several studies form Sri Lanka have reported vaccination coverages from CP vaccination campaigns of between 42% and 57%, however dog ownership, confinement, and handling appear more prevalent than observed in Goa (Kumarapeli & Awerbuch-Friedlander, 2009; Matter et al., 2000; Sánchez-Soriano et al., 2019). Subsequent campaigns in Goa will continue to refine the CP approach, and whilst it is unlikely that the method would ever achieve sufficient vaccination coverages in the roaming dog population to eliminate rabies, it may have a role in rabies control initiatives at scale.

As for other rabies control interventions, the COVID-19 pandemic had a profound impact on the Goa rabies programme (Nadal et al., 2021). Lockdown restrictions introduced during the COVID-19 pandemic halted vaccination on two occasions, first at the start of Round 6 in April 2020 and again at the end of Round 6 in May 2021. Social distancing restrictions impacted on the normal DD-CVR method throughout Round 6 and Round 7, with DD teams being unable to operate for certain periods, affecting vaccination in some talukas (Figure 3.8D). CVR methods for roaming dogs did not require interaction with the public and could, therefore, largely continue, however the pandemic had a broad impact on logistics, operations, and team morale. A study involving both modelled and field surveillance data predicted that a decrease in dog vaccination and rabies surveillance could lead to a sharp rise in rabies cases within months (Raynor et al., 2020). The impact of the decrease in dog vaccination on rabies incidence will be discussed in Chapter 4.

New insights into dog population structure and distribution in Goa were made possible through use of smartphone technology to record the details of every dog vaccinated. Understanding metapopulation structure is of increasing interest in advancing the discovery of opportunities to prioritise resource to regions and subpopulations that contribute most to sustaining viral transmission. This study identified variation in dog ownership and confinement across the urban-rural continuum in Goa was of significance to the ideal method of vaccination and cost. The driving forces of rabies endemicity at the district scale relate to population interactions both between sub-populations, such as villages, and within them, (Beyer et al., 2012; Conan, Akerele, et al., 2015; Hassine et al., 2021; Laager et al., 2018), however, how this translates to the design of nascent immunization programmes is currently unclear. Warembourg et al. found that dog confinement and ownership practices were strong predictors of a dog's connectedness within a population and a network analysis in Chad by Laager et al. predicted that targeted vaccination of the most connected dogs within the population would enable rabies elimination at lower vaccination coverages (Laager et al., 2018; Warembourg et al., 2021). Insights from this large programmatic dataset can support modelling of rabies transmission to better understand the implications of dog population density, composition, and connectedness to guide the further refinement of dog vaccination programmes (Townsend, Lembo, et al., 2013; Townsend, Sumantra, et al., 2013).

Further research is warranted into the spatial roll-out of vaccination activities at the district scale. In the present study, a cyclical 12-month taluka-by-taluka approach was established for reasons of operational feasibility, however this may have impacted on efficacy of the campaign due to dog movement between talukas within a particular campaign cycle. New horizons in landscape epigenetics are emerging through modern technologies enabling whole-genome viral sequencing in resource limited settings and advanced mathematical modelling of data with high geospatial and temporal resolution (Bourhy et al., 2016; Brunker et al., 2012; Gigante et al., 2020; Hanke et al., 2016; Troupin et al., 2016). Several studies have identified that roads are facilitators to rabies virus spread via human-mediated dog transport and should therefore be considered in the planning of synchronised vaccination of connected regions (Brunker et al., 2018; Hassine et al., 2021; Talbi et al., 2010). As for the spread of wildlife rabies, rivers were identified by Brunker et al. as barriers to rabies virus dispersal on larger scales, and whilst they emphasise the need for caution in how their findings are applied to other settings, the use of rivers to define the boundaries of synchronised vaccination efforts across districts in India would be appropriate and may have aided the elimination of rabies at the taluka scale in Goa (Bourhy et al., 1999; Brunker et al., 2018; Rees et al., 2008). It is necessary to consolidate these considerations of spatial area, population structure, and campaign frequency to provide meaningful guidance to the planning of dog vaccination campaigns. Selhorst et al. reported the calculation of 'Area Index' as a way of quantifying the spatial setting of vaccination campaigns with time in the control of fox rabies in Europe (Selhorst et al., 2005). Adaptation of this approach could provide actionable guidance to the rollout of dog vaccination campaigns such as the one described in this study.

It is important to recognise limitations during the interpretation of results presented in this chapter. The analysis of dog population demography relied on sampling dogs that were accessible for vaccination and will have introduced bias to aspects of ownership and confinement. Further analysis incorporating dog-sight survey data and Bayesian approaches to consider uncertainty in this group would strengthen these analysis (Gsell et al., 2012; Kanankege et al., 2022). The limitations of the reference human settlement data used in the present study must also be recognised. The DigitalGlobe data supported the evaluation of human density across Goa, estimation of human: dog ratio, and provides the potential to extrapolate dog population estimates to other regions included in the DigitalGlobe settlement dataset. However, discrepancies in the reference human data will impact on the accuracy and validity of these estimates. Visual comparison of the DigitalGlobe settlement data with satellite images for Goa appeared congruent, but a formal evaluation was not conducted, and a small number of dogs (324 of 109,681) were recorded as vaccinated in 'uninhabited' areas in the cycle analysed in this chapter (Table 3.1). This may have been the result of dogs being present in households that were not identified in the DigitalGlobe data, or in newly populated areas since its creation, and should be considered as a limitation when using such data in future analysis.

Another limitation of the current study was the lack of a control group in the comparison of vaccination methods was another limitation of the current study. Confounding factors within the dog population and environmental conditions between campaign periods may have impacted the rate and penetration of vaccination methods. Subsequent evaluation of modifications to vaccination approach may benefit from concurrent deployment of both methods to be able to identify the specific advantages of each method. Several examples of such comparisons have been undertaken, particularly in the exploration of decentralised approaches to dog vaccination in Tanzania, and in the assessment of methods using oral rabies vaccination (Bonwitt et al., 2020; A. D. Gibson, Yale, et al., 2019; Lugelo et al., 2022; Undurraga et al., 2020). Having said this, the relevance of randomised control trials in population-health interventions has been the focus of debate in the public health research community for some time, with many emphasising that such approaches may not be as effective in such settings (Craig et al., 2012; Sanson-Fisher et al., 2007). Finally, the costs per dog vaccinated reported in this chapter only consider the direct operational cost of vaccine delivery, and do not include aspect of campaign management, training, or administration. However, these are considered in the overall cost effectiveness analysis in Chapter 4.

3.6 Conclusion

This research has demonstrated the benefit of iterative refinement of vaccination methods, using campaign-derived data to identify opportunities for efficiency-savings. Priorities of vaccination coverage, spatial homogeneity, and cost-efficiency drove the development of the mixed-methods approach that achieved high coverage throughout Goa state. The data generated through the vaccination campaign offer opportunities to study dog ecology across the urban-rural gradient to accelerate the development of efficient methods in other settings of south Asia. The next chapter explores the impact of these activities on rabies incidence in humans and dogs.

Chapter 4 Assessing the impact of the Goa Rabies Control Programme

4.1 Abstract

Surveillance is essential to the evaluation of all interventions targeting infectious disease as, without robust data on disease incidence, it is impossible to know the impact of control efforts. For this reason, beyond the huge efforts to develop mass dog vaccination, the design of enhanced methods of rabies surveillance was also prioritised. This chapter describes the approach to intensifying human and animal rabies surveillance and community rabies awareness, in parallel to mass dog vaccination activities described in Chapter 3. The impacts of these activities are reviewed in terms of the incidence of human and animal rabies cases across Goa over the project period. Cost-effectiveness analysis was performed using a previously published model for the evaluation of rabies control interventions.

Human rabies deaths declined during the early stages of the project as awareness of the risk of rabies increased, reaching zero human deaths in 2018. Detection of rabid dogs increased throughout Goa following the establishment of enhanced rabies surveillance and remained in the region of six cases per month during the period of developing methods of mass dog vaccination until 2017. As dog vaccination intensified across all talukas in 2017 and 2018, the detection of rabid dogs ceased in many parts of the state. Cases persisted at the boundaries of the intervention near unvaccinated populations in which rabies was endemic.

Cost-effectiveness analysis estimated the cost per DALY averted of 567 USD, representing 0.08× gross domestic product per capita in Goa and classifying the intervention 'very cost effective' by the WHO definition of cost effectiveness. An estimated total of 3,467 DALYS and 121 deaths were averted over the 10-year project period as compared to no intervention.

In the later stages of the programme dog vaccination and rabies surveillance expanded into neighbouring states to form a cordon sanitaire and progress prospects for dog rabies elimination from Goa state. As a result of this work, Goa was declared the first state in India to become a 'Rabies Controlled Area', allowing

the application of legislation for long-term enforcement of rabies control activities and a clear path for other states to follow.

4.2 Introduction

The evaluation of population health programmes can be challenging due to their complexity and the inherent influence of the specific circumstances in which they were conceived, developed, implemented, and evaluated (Craig et al., 2018). The research process can benefit in the identification of successful methods that can be translated elsewhere and in areas lacking success it can distinguish between failure of concept or failure of implementation, both of which offer opportunities to advance understanding, protocols, and methods (Rychetnik et al., 2002). As for many whole-population interventions, the Goa Rabies Control Programme was multi-layered, involving departments of human health, animal health, education, and civic administration. It embraced a One Health framework by addressing a human health issue through interventions encompassing human and animal components. The intervention, now spanning a decade, has involved changes to government policy, legislation, school curricula and state infrastructure.

Rabies control programmes have many potential measures of success, including effects on human and animal rabies incidence, health-seeking behaviour following dog bites, public awareness of rabies, and cost-effectiveness. A comprehensive understanding of the intervention impact on these metrics and others, in addition to the wider context in which the intervention was deployed, are crucial to identifying effective approaches and facilitating transfer to other settings. A randomised control trial to evaluate the impact of dog vaccination and community education activities would have been neither ethical nor politically viable given the positive effects that have been demonstrated from such methods in other parts of the world. Natural experimental approaches are commonly used to evaluate the outcome of population health interventions, offering the opportunity to study unplanned outcomes and events that occur at low frequency within the population, as is the case with human rabies (Craig et al., 2012). I therefore took a natural experimental approach to evaluating the impact of the Goa Rabies Control Programme, with a particular focus on measurement of human and canine rabies incidence, vaccination coverage, and programme cost-effectiveness.

Beyond mass dog vaccination discussed in the previous chapter, the development of systems for improved rabies surveillance and expanding public awareness of rabies prevention were of central importance to the programme. Surveillance is an essential foundational component in the control of any infectious disease, both at the local and regional levels (Cutts et al., 1993). Surveillance systems detecting at least 5% of all rabid dogs, and ideally 10%, are estimated to be necessary to develop, monitor and guide effective rabies control interventions (Townsend, Lembo, et al., 2013). Without data on the incidence and distribution of dog rabies cases, it is impossible to understand the burden of disease, identify actions that are having a positive impact, or strategize the ongoing allocation of resources (Banyard et al., 2013; Velasco-Villa et al., 2017). Surveillance can be active, in the form of actively seeking out and testing all animals to have died of unknown causes, including roadkill and dead dogs at points of cremation or disposal, or passive through the investigation and testing of animals that have been reported with suspect signs of rabies (Gilbert & Chipman, 2020). Active surveillance, also called 'enhanced surveillance' forms a key part of wildlife rabies control, sampling target species from specific areas to programmes (Slate et al., 2017). Passive surveillance systems, on the other hand, are more commonly employed in dog rabies control programmes due to the close relationship between dogs and people resulting in a greater likelihood of reporting of suspect cases to surveillance services and limited opportunity for active surveillance approaches for dogs in most settings (Ma et al., 2021). Sensitive passive rabies surveillance requires a robust reporting network to ensure the timely notification of animals showing possible signs of rabies, adequate capacity for the immediate investigation of reported cases, facilities for the safe retrieval and transport of diagnostic samples and functional laboratory facilities for rabies diagnosis.

Awareness of the risk of rabies and appropriate post-bite preventive measures is typically low in endemic settings globally (Al-mustapha et al., 2021; Auplish et al., 2017; Dodet et al., 2008). Children are overrepresented in studies of human rabies deaths, and whilst definitive research on the reasons for this disparity in risk is not available, a greater frequency of contact with dogs and decreased chances of accessing PEP are likely to be major contributors (Sudarshan et al., 2007). Targeting this group at increased risk through lessons on rabies in schools have been shown to have a positive effect on knowledge and understanding of rabies in other low- and middle- income countries and formed the initial basis of community awareness in the current programme (Burdon Bailey et al., 2018; A. A. Dzikwi et al., 2015; Matibag et al., 2009). This chapter includes a description and outcomes from the school and community education programme to provide context to the wider activities of mass dog vaccination and surveillance.

Here, I report how the operational challenges were overcome in Goa through a collaboration between local government, non-governmental organisations, and academic partners, culminating in the elimination of human rabies, for the first time, at the state level in India and providing a compelling case for the expanded development of mass dog vaccination programmes elsewhere in South Asia. This study aims to evaluate the impact of the rabies control intervention in Goa from 2013 to 2022, providing evidence for the use of mass dog vaccination and community education as a control strategy in India and context to support the translation of relevant methods to other settings.

4.3 Materials and methods

The study site of Goa state is described in Chapter 1 and the development of dog vaccination methods are reported in detail in Chapters 2 and 3. The period of study was between 10/09/2013 to 31/12/2022, which coincides with the launch of the first pilot dog vaccination and education initiative and the end of the eighth year of large-scale vaccination activities. The Government of Goa Department for Animal Husbandry oversaw the project protocols and methods for mass dog vaccination and animal rabies surveillance, with input from the Goa Veterinary Association to adhere to all relevant local regulations.

4.3.1 Evaluation of human rabies incidence

All suspect human rabies cases in Goa state were routinely transferred to Goa Medical College (GMC), a tertiary medical hospital. Human rabies incidence was monitored through GMC records. Data on annual human rabies deaths were provided by the Directorate of Health Services (DHS) (DHS/IDSP/19-20/26/346), as submitted to the India National Rabies Control Program. Diagnosis was based on the DFA test using brain samples at NIMHANS, Bangalore.

The launch of the National Rabies Control Program (NRCP) by the National Centre for Disease Control in December 2016 brought renewed funding for training in human rabies diagnosis and PEP to medical practitioners throughout government hospitals in Goa. State-level rabies engagements with the medical profession included a sampling and diagnosis workshop conducted at GMC in December 2017 through a collaboration between the DHS, GMC, Mission Rabies and NIMHANS. The workshop was attended by residents and faculty of the Department of Medicine, Pathology, Paediatrics, Psychiatry, Forensics and Neurology. GMC also hosted the Association for the Prevention and Control of Rabies in India (APCRI) national rabies Conference in GMC in July 2017. In April 2018 the Department of Animal Husbandry and Veterinary Services hosted the state level Stepwise Approach to Rabies Elimination (SARE) Workshop in collaboration with the U.S. Centers for Disease Control and Prevention (CDC), bringing together human and animal health stakeholders and emphasising the importance of human rabies diagnosis.

PEP was available free of charge to those presenting for treatment of dog bites at government medical facilities throughout the state, however shortages of rabies vaccine and immunoglobulin were periodically reported during the project period (Bindiya Chari, 2015). Data on the number of people presenting to health services for treatment following a dog bite were provided by the Department of Health, Government of Goa, for the period 2010 - 2019.

4.3.2 Animal rabies surveillance

A central public rabies reporting and response service was established in March 2014, prior to which there was no structured process for the reporting of suspect rabid animals. The service was coordinated through the ‘Rabies Hotline’ a phone number which was widely publicised to the public, government, and private sectors for the reporting of suspect rabid animals 24 hours a day, 7 days a week. The only period in which rabies reporting and response were not active was from October 2014 to September 2015.

Pocket cards with details of the Rabies Hotline were distributed by vaccination and education teams to the public, human and animal health facilities, schools, and local government administrative offices (panchayats) (Figure 4.1). Calls were screened to evaluate the history and presenting signs for risk of rabies in the dog, including aggression, hypersalivation, ataxia, neurological signs, collapse, and sudden death. The digital recording of call records began in October 2017 through customised forms in the WVS App.

Figure 4.1 - Rabies hotline cards distributed widely across Goa state during the Rabies Control Campaign, the size of a business card for people to retain for easy reference (5.1cm x 8.9cm).

Notification of a suspect rabies case to the Rabies Hotline triggered a field investigation to assess the situation. Initially the response teams consisted of a veterinarian and a dog catching team, however the protocol was adjusted in 2018 with the introduction of integrated bite case management (IBCM) methods (Etheart et al., 2017; Wallace et al., 2015). The investigations were conducted by trained, full-time Rabies Surveillance Officers who called for additional support if a net-catching team was required to restrain a rabid animal (Figure 4.2). Throughout the project, teams would respond to reports of rabid dogs in regions immediately adjacent to Goa due to the risk posed by these animals to the public, however active promotion of the Rabies Hotline and investigation of suspected rabid dogs in districts beyond Goa's borders began in 2022.

Figure 4.2 - Photos showing the key elements of rabies surveillance. A) Notification to a central Rabies Hotline. B) Timely investigation and assessment of suspect rabid animals. C) Sample collection in animals where animals die or have been euthanised. D) Rapid field screening through lateral flow assays, E) Timely laboratory rabies diagnosis.

Each investigation included assessment of the animal and interviews with community members to identify exposed people and animals (Figure 4.2). Animals showing signs of rabies were removed from the community and isolated in quarantine facilities for further care and monitoring in cases with equivocal signs. Where deemed appropriate by a registered veterinarian, humane euthanasia was performed in accordance with the Animal Welfare Board of India advisory and the Prevention of Cruelty to Animals Act 1960 and veterinary guidance from the Department of Animal Husbandry & Veterinary Services (Animal Welfare Board of India, 2013).

Investigations were coordinated through the REACT App, a custom-built system designed on the IBCM protocol developed in Haiti, and formed a part of the wider WVS App platform for programme management (Chapter 3). Details recorded in the app for each investigation included the date, time, and location of activities, signalment and clinical signs of the suspect animal, details of human and animal exposures, case progression, and outcomes of diagnostic tests.

Historically, rabies diagnosis was performed at the Goa Disease Investigation Unit by identification of Negri bodies in Sellers-stained brain tissue. From March 2014, Anigen lateral flow assay (LFA) tests (Anigen Rapid Rabies Ag Test Kit, Bionote, Hwaseong-si, Korea) were performed in the field at the time of post-mortem examination (Yale et al., 2019). Frozen brain samples were batched for transportation to the National Institute for Mental Health and Neurosciences (NIMHANS) some 600km away, for diagnosis using the direct fluorescent antibody (DFA) test approximately once a fortnight. State diagnostic capacity for rabies case detection was established in December 2016 through the donation of a fluorescent microscope to the Disease Investigation Unit (DIU) in the Department of Animal Husbandry and Veterinary Services, enabling more timely rabies diagnosis. NIMHANS provided DFA proficiency testing on an annual basis from 2017 to 2019 on 10 randomly selected stored samples from throughout the year to evaluate concordance with DFA test results from the Goa DIU. The rabies surveillance programme in Goa, Rabies Hotline and response team, and development of laboratory diagnostic capacity at DIU was project managed by Dr Gowri Yale from September 2016 to present.

The WHO animal rabies case definitions for ‘Suspected’, ‘Probable’, ‘Confirmed’, and ‘Non-case’ were assigned to animal case investigations based on case records. Suspected cases were any animal presenting with any of the following signs: abnormal vocalisation, lethargy, paralysis, hypersalivation, abnormal aggression (biting two or more people and/or inanimate objects). Probable cases met the ‘suspected’ case definition and had a history of contact with a suspected, probable, or confirmed rabid animal, or a ‘suspected’ animal that was lost, killed, or died within 4-5 days of showing signs of illness. Confirmed cases were any animal that was diagnosed with rabies by DFA. A non-case was one that was confirmed as being alive after 10 days of illness onset, or that tested negative by DFA. Only ‘confirmed’ cases were included in analysis and reporting of canine rabies incidence during the period of enhanced surveillance (2014 onwards). Dog rabies incidence reported for 2012 and 2013 are from data provided by the Department of Animal Husbandry and Veterinary Services diagnosed by identification of Negri bodies in brain tissue.

The use of novel MinION sequencing technology (Oxford Nanopore Technologies) was explored in July 2018 to build capacity for rabies virus sequencing at the Disease Investigation Unit (Department of Animal Husbandry & Veterinary Services). Phylogenetic analysis would provide valuable insights into viral movements within Goa to inform the dog vaccination strategy. Sequencing of the rabies virus nucleoprotein (N) and glycoprotein (G) genes was performed by Dr Crystal Gigante to evaluate similarity between samples and to compare with historic references from across India (Gigante et al., 2020). Ongoing viral sequencing capacity was established in 2020 through donation of equipment and training, with resources provided by Mission Rabies, University of Edinburgh, the Government of Goa, and National Centre for Disease Control (NCDC).

4.3.3 Rabies education and awareness

Alongside the state-wide systematic mass dog vaccination program, Mission Rabies implemented a concurrent education initiative focused on delivery of structured lessons to children in schools in collaboration with the Department of Education, Government of Goa, and educational sessions to community groups (Figure 4.3). Typically, the education program was implemented through three rabies education officers who moved systematically across the state ahead of the vaccination schedule, delivering rabies lessons in schools and sessions to community (A. D. Gibson et al., 2018). Rabies lessons were 15-30 minutes in duration, were adjusted to the age-group and fell under the following headings: Rabies is serious; Stopping dog bites; Rabies first aid; and Rabies is preventable (Burdon Bailey et al., 2018). School rabies lessons comprised a presentation in the local language, incorporating visual, auditory, and kinaesthetic teaching styles through theatre, demonstration, and question-answer activities. Lessons were delivered to groups, from the class level to the entire school, dependent on the school's preference, schedule, and facilities. In later stages of the project, events to train schoolteachers in rabies lesson delivery were also conducted. Data about schools attended, teacher-training sessions, and community events were recorded in the WVS App following delivery, including time, date and GPS location of the entry, the number of children, adults or teachers educated and the type of lesson. The rabies education programme in Goa was project managed by Dr Murugan Appapillai from 2013 to present and directed by Gareth Thomas.

Figure 4.3 - Components of community rabies education. A) School classes and teacher training on rabies education. B) Assemblies and large group presentations. C) Education sessions to community groups. D) Large community rallies and awareness events.

4.3.4 Data analysis

Data for dog vaccinations, educational events, post-vaccination dog surveys, notifications of suspect animal rabies cases, and suspect animal rabies case investigations were exported from the WVS App database in CSV format as outlined in Chapter 2. Analysis was performed using R (version 3.6.2) (R Core Team, 2018). Data on human rabies deaths provided by the Directorate of Health Services was imported in CSV format. Canine rabies incidence (mean cases per month) was calculated using individual case records from the REACT App, including date and GPS location of the case investigation. Data for vaccinations, post-vaccination surveys, and dog rabies cases were spatially paired with vector map files of Working Zones, village, and taluka boundaries for region-wise analysis and reporting. Manual reports and field records were used to verify App data. Post-vaccination surveys and dog vaccination data were used to calculate mean dog vaccination coverage and month-wise vaccination coverage by taluka. Where stated, confidence intervals were calculated at the 95% level using t-tests.

4.3.4.1 Taluka-wise evaluation of rabies control

The taluka month-wise point vaccination coverage was approximated as the monthly estimated number of immune dogs in the population divided by the taluka total dog population estimate. The month-wise number of immune dogs in the population was estimated as either the number of immune dogs from the previous month reduced by a factor of population turnover, or in months in which a vaccination campaign took place, the total number of dogs vaccinated during the campaign. Where campaigns covered a campaign over numerous months, the month of maximum vaccination was considered the mid-point of the campaign. Each campaign vaccinated the population as an independent effort, without consideration of the previous vaccination status for individual dogs. Therefore, in months where the campaign vaccination output was greater than the estimated number of remaining immune dogs, the campaign vaccination total became the estimated total immune dogs in the population, as described in the following equations:

$$R_m = 0.94(I_{m-1}) \quad (1)$$

$$I_m = \begin{cases} C_m\,, & if\ C_m \geq R_m \\ R_m\,, & if\ C_m < R_m \end{cases} \quad (2)$$

$$Prop_m = \frac{I_m}{N} \quad (3)$$

R_m was the estimated remaining number of immune dogs in the population calculated from the number of immune dogs the previous month after application of a decay factor to account for estimated monthly population turnover (0.94). I_m was the estimated number of immune dogs in the population for a particular month (m). C_m was the number of new dogs vaccinated in a campaign centred on the campaign month of maximum vaccinations. $Prop_m$ was the estimated vaccination coverage in the population for a particular month. N was the estimated dog population for each taluka. As outlined in equation 2, where the number of campaign vaccinations did not exceed R_m, the campaign was not included in calculation, as these were erroneous vaccination entries not under a particular campaign. Taluka-wise dog rabies cases per month were plotted with monthly estimated proportion of immune dogs and 12-month mean coverage.

4.3.5 Programme cost and evaluation of cost-effectiveness

The calculated cost per dog vaccinated in Chapter 3 considered the operational costs for direct comparison of vaccination methodologies (field salaries, vehicle costs etc.), however here I considered all in-country annual program expenditure and total dog vaccination output to estimate the cost per dog vaccinated for each year of the programme, including aspects of administration and management. This expenditure was determined from account records reporting on Goa expenditure on all sources of income, including government and charitable grants, and the estimated value of donated vaccine. A breakdown of dog vaccination program expenditures, within total program expenditures, was only available for 2018 and 2019 (Appendix C). Mean annual US dollar exchange rates were calculated from the International Monetary Fund country database records (International Monetary Fund, 2021).

The RabiesEcon model, developed by the US Centers for Disease Control and Prevention, was used to estimate the impact and cost-effectiveness of the intervention (Borse et al., 2018; Jeon et al., 2019; Kunkel et al., 2021). Goa values were inputted into the RabiesEcon version used by Kunkel et al. (2021) to assess the additional costs and benefits of the Goa rabies control program as compared to no intervention (Kunkel et al., 2021). Input values from Goa, including human and dog population data, cost of dog vaccination and PEP, annual dog vaccination output and estimated rates of access to PEP during and after the program. Predicted outcomes such as estimated human exposures and human rabies deaths were cross-checked with real-world data. The RabiesEcon model published by Kunkel et. al was modified to account for costs associated with PEP administration resulting from exposures to animals that were unavailable for diagnostic testing. This adjustment was made by including a feature to allow the user to estimate the reduction in PEP after implementation of the rabies control program. As part of the data inputs to the model, it was assumed that there was no reduction in PEP administration during or after the intervention. All annual costs were discounted at 3%. The costs associated with surgical sterilization of dogs by non-governmental organisations were not considered in the model.

4.4 Results

4.4.1 Overview

As dog vaccinations and number of children educated increased during the project period, there was a concurrent decrease in the number of human and dog rabies deaths in Goa state (Figure 4.4). There were 17 reported human rabies deaths in 2014, representing 1.15 deaths per 100,000 capita, but falling to zero in 2018, with the last human rabies death occurring in September 2017 (Figure 4.4). As a result of the progress made toward dog rabies elimination under the leadership of the Government of Goa, the state was declared a ‘Rabies Controlled Area’ through the Prevention and Control of Infectious and Contagious Diseases in Animals Act, 2009 (14-9-AH/Rabies Control/2021-22 Rabies Disease Control in the State of Goa, 2021).

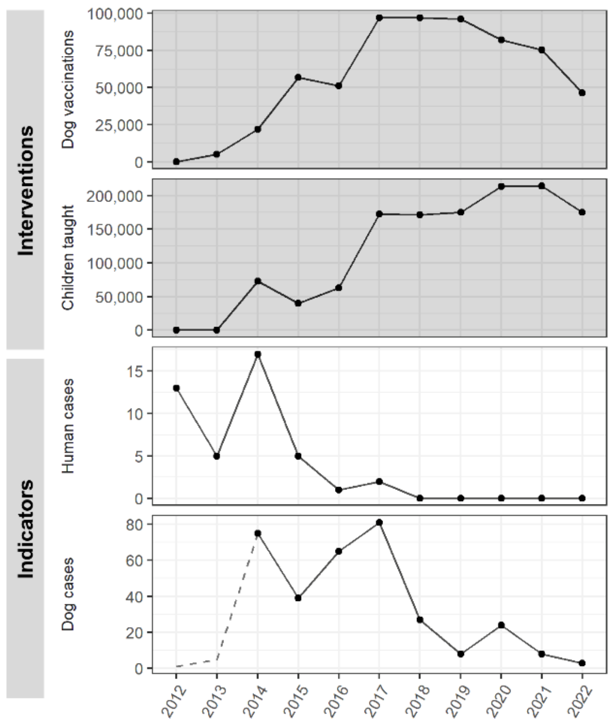


Figure 4.4 - Year-wise graphs of intervention outputs and indicators of rabies control from 2012 - 2022. The dotted line in canine cases indicates a period prior to the enhancement of animal rabies surveillance activities. The decrease in canine rabies cases in 2015 is due to cessation of canine rabies surveillance activities between October 2014 and September 2015.

4.4.1.1 Reporting and investigation of suspected rabid animals

Details of phone calls to the Rabies Hotline were available from October 2017 to August 2022, totalling 17,579 and increasing from an average of 49.9 calls per week in 2018 (95% CI: 42.6 – 57.1) to 78.4 calls per week in 2019 (CI: 69.3 – 87.4) (Figure 4.5A, Appendix C). Mapping the origin of calls showed wide-spread engagement with the Rabies Hotline throughout the state (Figure 4.5B). The most common reasons for contacting the Rabies Hotline were requests for vaccination of dogs (45.0%), reporting sick or injured dogs (without typical signs of rabies) (30.9%) and dog nuisance (4.82%). Despite increasing total calls, the rate of calls reporting suspect rabid animals reduced from a mean of 4.83 (CI: 1.8 – 7.9) per month in 2018 to 2.9 (CI: 1.5 – 4.3) in 2022 (Figure 4.5).

Of 364 investigations of confirmed rabid animals from Goa and surrounding regions, the number of people exposed was recorded for 69%. For investigations reporting the number of people bitten, 47.9% reported at least one human exposure, representing a total of 235 people bitten by dogs that were subsequently tested positive for rabies (Appendix C). The overall mean number of people bitten per investigation of dogs later testing positive was 1.1 (95% CI: 0.9– 1.4) and of investigations where at least one bite was reported, the mean number of people bitten was 2.30 (CI: 1.9 – 2.7, range 1 – 15).

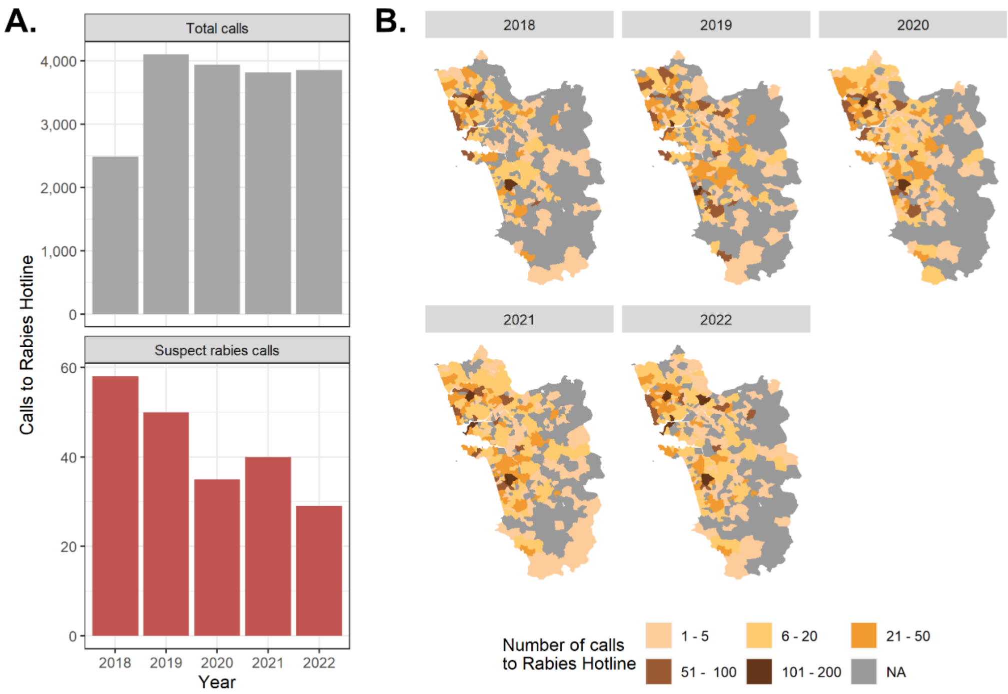


Figure 4.5 - Rabies hotline calls. A) Total annual calls and calls reporting suspect rabid dogs. B) Maps of Goa showing the distribution of villages from which calls originated by year.

4.4.2 Evaluation of dog rabies incidence

The number of confirmed rabies cases rose from 5 in 2013, to 73 in the first 6 months of intensified surveillance following the launch of the Rabies Hotline in 2014 (Figure 4.6). The highest month incidence of rabies of any month in the project was in July 2014, when 21 dogs were confirmed rabid. The mean state-wide occurrence of canine rabies cases remained high through the early stages of programme development, starting at 10.6 cases per month in 2014 and dropping to 6.8 per month in 2017, which marked the first year of intensive state-wide dog vaccination.

Cases then declined to a mean of 2.4 per month in 2018 and 0.67 in 2019 (Appendix C). There was an increase in confirmed rabies cases in 2020 likely due to the disruption caused by the COVID-19 pandemic (Figure 4.7). This prompted re-vaccination of affected areas and a subsequent decline in rabies incidence to an all-time low of 0.25 per month in 2022, a decrease of 98% since the project began (Figure 4.6).

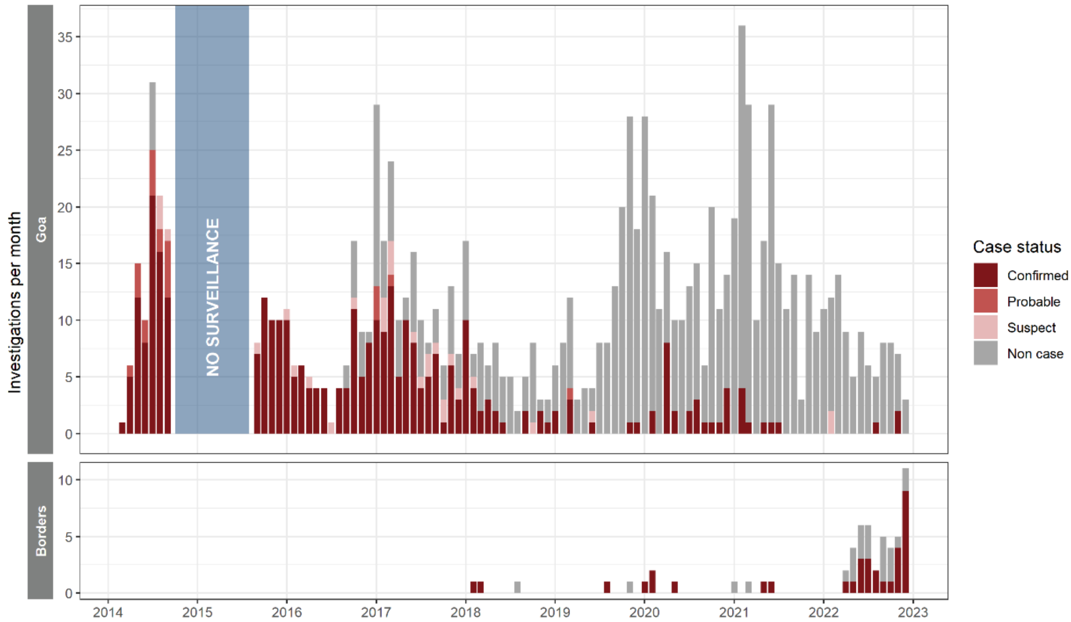


Figure 4.6 - Monthly canine rabies case incidence in Goa and bordering regions (2014 – 2022). Chart showing the outcome of laboratory tests of suspect animal rabies cases by month, coloured by outcome status. The blue box denotes a period where surveillance systems were not active in Goa.

The regional distribution of cases also changed significantly during the project. Figure 4.7 shows the geographic extent of vaccination activity and confirmed rabid dogs over the project period and Figure 4.8 shows the taluka-wise rabies cases, estimated monthly vaccination coverage, and 12-month mean coverage. Rabies persisted throughout the state during campaign scale-up from 2014 to 2017, followed by a decline in cases in south Goa in 2018, and absence of rabies in southern talukas thereafter. In 2019 rabies was only detected in the northernmost taluka of Pernem, which borders unvaccinated dog populations in Maharashtra (Figure 4.7).

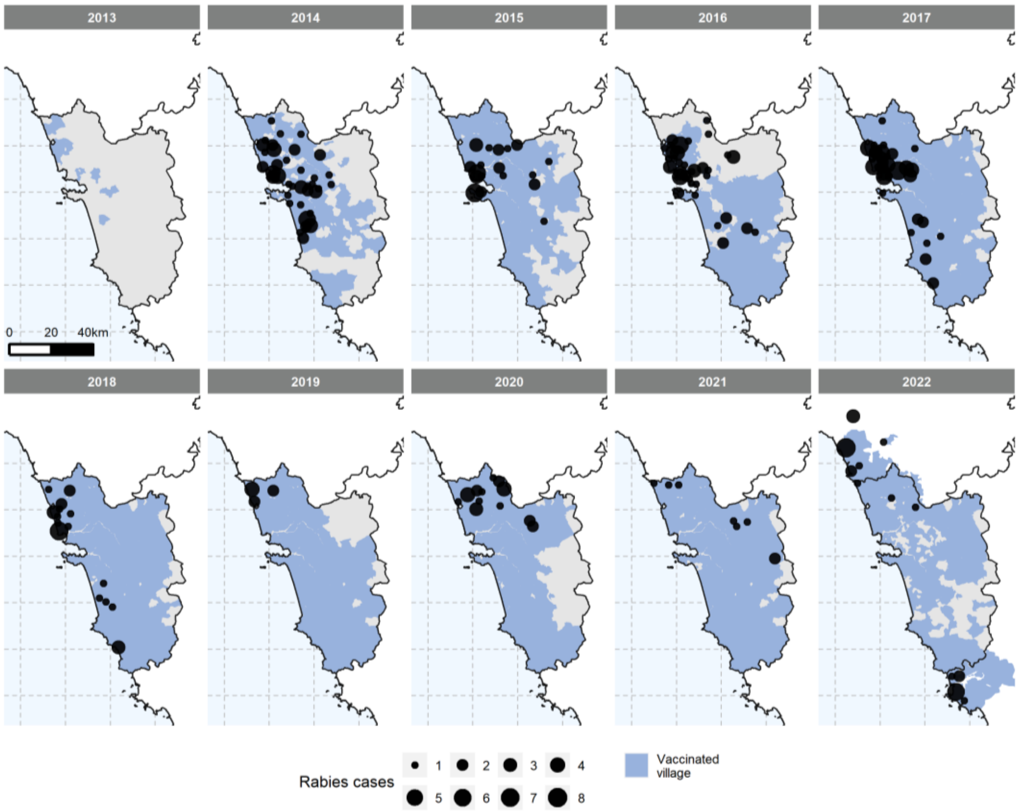


Figure 4.7 - Year-wise maps of Goa state showing canine rabies cases (black dots) and the extent of dog vaccination by village (blue shading). Surveillance was not active in 2013.

There was a notable increase in cases in Pernem coinciding with the COVID-19 lockdown restrictions from March 24th, 2020, with 4 confirmed cases in April and a further 2 in May (Figure 4.8). Lockdowns and movement restrictions, anecdotally impacting on roaming dog behaviour, continued over the next year and a resurgence of rabies was also seen in the three talukas directly adjacent to Pernem (Bardez, Bicholim and Satari); regions in which rabies had been absent for over 18 months previously (Figure 4.8). Three rabid dogs were confirmed in Bardez in April, Bicholim had cases from April through to August, and Satari had an outbreak starting in September 2020 through until March 2021 (Figure 4.8). After the second round of lockdowns in April 2021, rabid dogs were detected for the first time in the project period in Dharbandora, with two cases in June and July 2021.

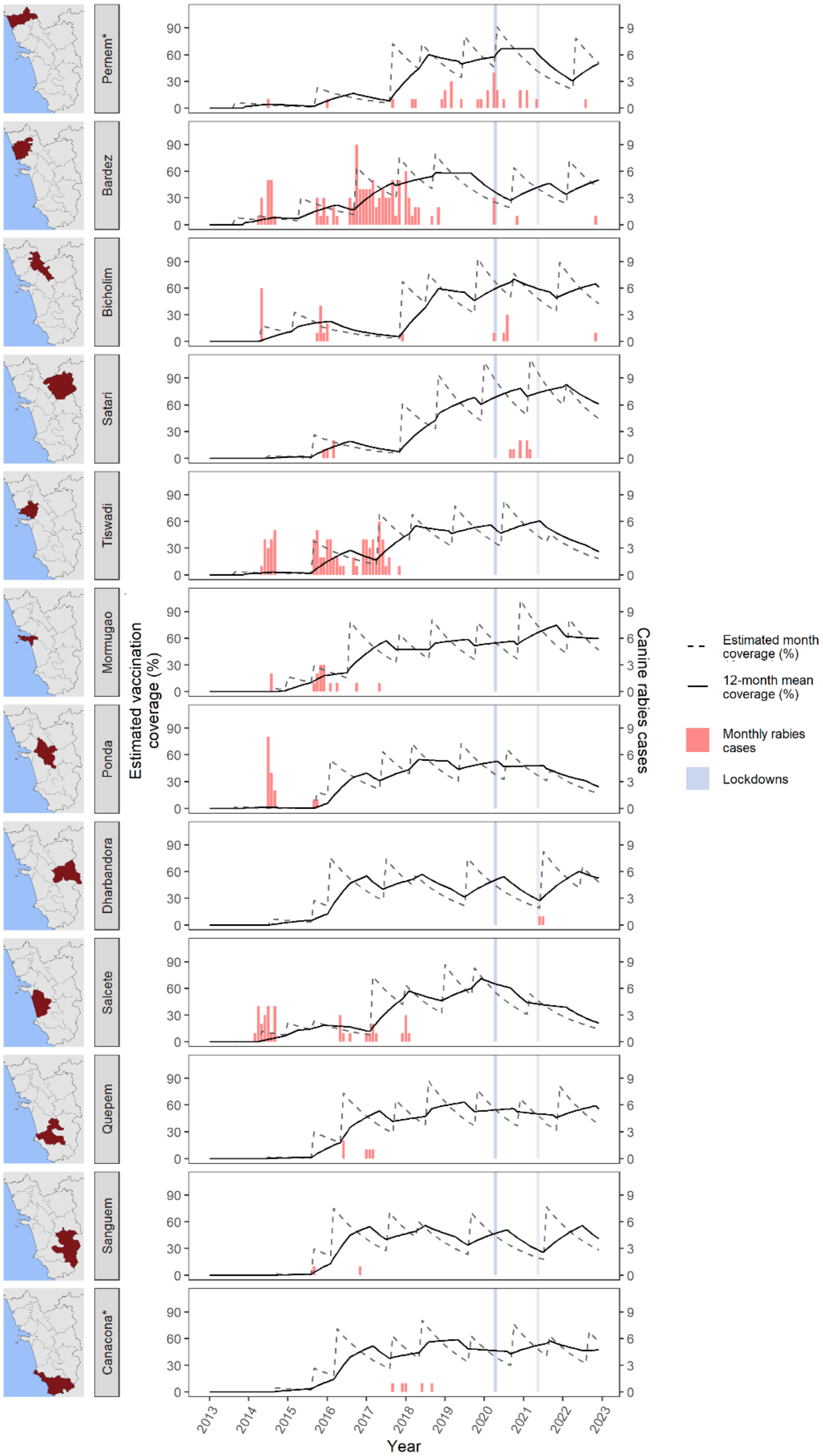


Figure 4.8 - Graph of month-wise estimated vaccination coverage (dotted line), rolling mean 12-month vaccination coverage (solid line) and monthly animal rabies cases (red bars) from 2014 to 2022 for each taluka region of Goa (shown in maps). Asterisk denotes talukas that border areas of high dog density in other states in which rabies remains endemic.

No canine rabies cases were detected in seven of Goa’s 12 taluka regions for over four years from December 2018 to the end of the study period (Figure 4.8) (Appendix C). The eight southern talukas’ rabies cases diminished after an average of 1.4 campaigns exceeding an estimated 50% vaccination coverage corresponding with the increase in mean 12-month rolling mean coverage in each taluka (Figure 4.8). Cases ceased after a single high-coverage vaccination campaign in Mormugao, Ponda, Quepem, and Sanguem (Figure 4.8). Occurrence of cases in the four northern talukas continues in the face of sustained high-coverage vaccination, indicating recurring reintroduction of the virus.

As vaccination extended beyond Goa into neighbouring states to the north and south in 2022, so did awareness of the Rabies Hotline reporting and response service operating in Goa. The absence of historic surveillance data from these regions resulted in the same revelation of rabies burden as had been seen in Goa in 2014, with a sudden increase in cases detected in these areas. Mapping these cases shows the close proximity of rabid dogs to Goa’s north and south borders (Figure 4.7 – 2022 facet). As vaccination intensifies in these regions, we hope to see a decline in incidence and cessation of rabies transmission in north Goa. The piloting of portable viral sequencing technology in 2018 gave insights into movement of rabies virus within Goa and has subsequently been established to routinely monitor rabies transmission dynamics in the region to aid vaccination strategy decision making.

Tracking the rolling 12-month mean coverage in Figure 4.8 shows the diminishing herd immunity across many talukas following cessation of intensive DD-CVR methods in 2022. This will continue to decline and highlights the importance of sustaining sensitive surveillance in these regions as the populations become increasingly susceptible to rabies.

4.4.3 Rabies awareness and post-bite presentations

In total, school-based rabies education classes were delivered to 1,297,677 school children and 59,282 teachers between 2014 and 2022 (Figure 4.4). The scale of the school education program increased from 2014, plateauing from 2017 onwards with the delivery of educational lessons to approximately 170,000 children per year across 1,400 schools in Goa. Activities to distribute rabies educational messages throughout communities intensified along a similar timeframe which resulted in the delivery of rabies lessons to 244,590 people through community groups, local authorities, and public events (Table 4.1).

Data on the number of people presenting to health centres for treatment of dog bites was available from 2012 to 2019. There was an increasing trend in presentations from 0.79 per capita in 2012 to 1.43 per capita in 2019, whilst the incidence of rabies in dogs fell (Table 4.1, Figure 4.9A, Appendix C). This increase may reflect a true increase in the incidence of dog bites, however, it may have also been influenced by increasing awareness of the risk of rabies and the need to seek post-bite treatment because of educational activities conducted through this period. Bites predominated in regions of high density, which have also shown the greatest increases over recent years (Figure 4.9B).

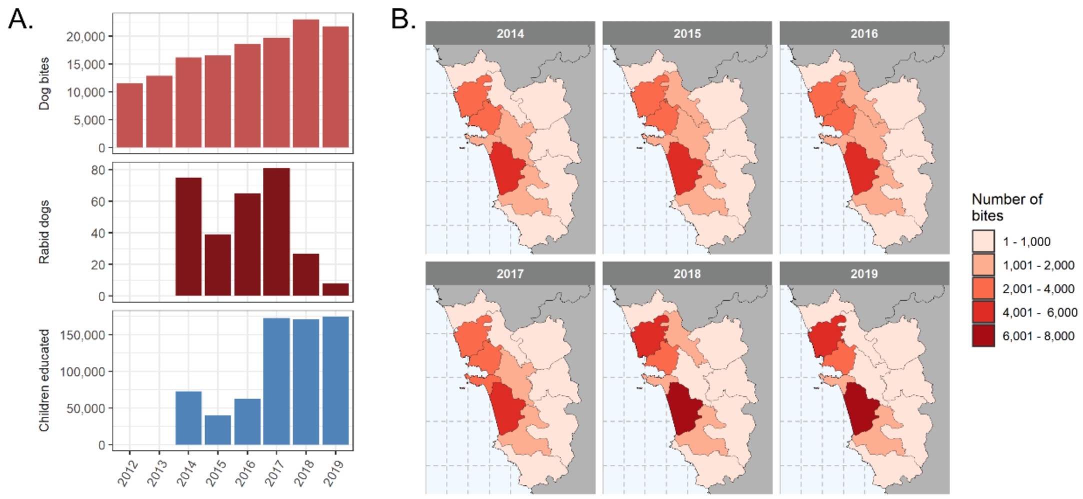


Figure 4.9 - Dog bite cases in Goa. A) Bar chart of dog bite presentations to health centres from 2012 – 2019, with dog rabies incidence and children taught for comparison. B) Maps of dog bite presentations by taluka for the years 2014 – 2019.

Table 4.1 - Table of community awareness activities and post-bite presentations at health centres (2012 - 2019).

Year	Children taught	Teachers taught	Number of schools	Community education (in-person attendance)	Total bites	Bites per capita
2012	-	-	-	-	11,515	0.79
2013	-	-	-	-	12,857	0.87
2014	72,744	3,024	-	1,122	16,136	1.09
2015	40,070	2,589	-	25,205	16,478	1.11
2016	62,782	3,054	-	23,012	18,585	1.24
2017	172,728	7,162	1,368	22,293	19,655	1.31
2018	171,097	7,339	1,427	52,503	22,955	1.52
2019	174,850	8,083	1,456	30,944	21,662	1.43
2020	213,735	10,265	1,461	17,624	-	-
2021	214,379	10,636	1,426	17,743	-	-
2022	175,292	7,130	1,349	54,144	-	-

4.4.4 Programme cost and evaluation of cost-effectiveness

Project funding sources and expenditure were analysed for the period 2015 – 2019. Considering only the dog vaccination component of the project, the mean cost per dog vaccinated was 3.45 USD (239 INR), increasing to 3.93 USD (267 INR) with the inclusion of education and surveillance activities. These figures are higher than that estimated in Chapter 3, as they account for the additional managerial and administrative costs of project implementation.

The government of Goa progressively increased funding to the programme from 2015 to 2019 (Appendix C), which has continued through 2020 to 2022. In 2018, government funding represented 32% of the mass dog vaccination campaign in-country expenditure, rising to 47% in 2019. The proportion of government funding for vaccination within Goa has further increased from 2020 to 2022, with non-governmental donated funds enabling vaccination outside of Goa's borders to establish the cordon sanitaire, something that would not be possible within the bounds of Goa's state government funding structures.

The cost-effectiveness model estimated that the mean cost per death averted and cost per DALY averted from 2013 to 2022 was 16,020 USD and 567 USD respectively. During this period the program was estimated to result in a total of 3,467 DALYS averted, and 121 deaths averted as compared to no intervention. The model predictions of human rabies deaths, human rabies exposures and total estimated intervention cost were concordant with empirical values from the program area.

4.5 Discussion

This project is the first to report the impact of dog vaccination on rabies incidence in dogs and people at the state scale in India, providing evidence to support the use of dog vaccination to address this One Health issue. Insights gained at the taluka scale can support the planning of focal campaigns elsewhere and challenges encountered at the boundaries of the intervention provide important learnings for strategizing rabies control across larger areas of the Indian sub-continent. The success of this collaborative project in Goa was underpinned by a focus on three core areas of activity; mass dog vaccination, education, and rabies surveillance, and leveraged innovation in mobile technology to improve the timely recording and transmission of project data from the field. Rabies virus reintroduction through the direct movement of dogs at state borders and via human-mediated transport of dogs remains a continued threat.

This decade-long effort to progress rabies control in Goa has only been possible through strong collaboration between many governmental, non-governmental, and academic partners, and its united commitment to a common objective. The leadership and resolve of the government to progress rabies control mobilised resources and legislation, whilst funding through Mission Rabies made it possible to invest in research and development of vaccination strategies that had yet to be proved effective in the Indian context. The collaborative structure of the Goa program drove rapid innovation and expansion of activities, making it possible to rapidly adjust the programme structure in response to the epidemiological situation, such as in the expansion of vaccination beyond Goa's borders in 2022. Similar collaborative approaches were central to the global effort to eradicate polio (Aylward & Tangermann, 2011) and have been beneficial in rabies control initiatives elsewhere (Léchenne et al., 2021; Taylor, 2013).

Intensification of surveillance activities in both dogs and people was of crucial importance in revealing the true burden of rabies and monitoring areas of success and failure. Ensuring broad engagement on the issue of rabies across the human medical sector gave confidence to stakeholders that the early decline in human rabies cases was a true reflection of progress as opposed to absence of data. This decline occurred predominantly between 2014 and 2016, during a period when the dog vaccination campaign was still developing, and dog rabies cases were being detected throughout the state. However, rabies was also more prominent in mass media through the government's announcement of the 'Goa Rabies Control Programme' in 2015, increasing coverage of dog vaccination activities, and the expansion of the rabies education programme in schools and so it is likely that knowledge for the importance of seeking post-exposure prophylaxis was increasing during this time. Intensification of rabies surveillance activities themselves can also serve to prevent human rabies deaths by providing counselling to people at high risk of rabies exposure and ensuring that they access timely PEP (Etheart et al., 2017). Despite the lack of data during the early project about counselling of people with high-risk exposures, this was standard practice and over 230 people with confirmed bites from rabid dogs were recorded as having been offered guidance over the project period.

'Enhanced rabies surveillance' through intensifying the processes of centralised reporting, timely response, and accurate diagnosis in animals suspected of rabies was also of paramount importance to the success of the programme. Engaging the public, veterinary and medical sectors to report suspect rabid animals and capacitating a central Rabies Hotline to screen calls, give advice, and coordinate a response was a crucial first stage. In wildlife rabies surveillance systems, where significant effort is placed on active surveillance processes, the most rabies cases are still found through citizen notification (Rees et al., 2011; R. Rosatte et al., 2001). Continued monitoring of the origin of calls to the Rabies Hotline aims to identify regions of reducing public engagement and the risk of epidemiological silence from focal regions (Figure 4.9) (R. C. Rosatte, 2013). Rabies Surveillance Officers, who were available to immediately deploy to the field to investigate suspect cases, were also a pivotal to the detection and retrieval of rabid animals (Wallace et al., 2015). It was clear that without this dedicated human resource, field investigation by individuals with other veterinary responsibilities is invariably too slow to yield high rates of success. Timely investigation and active removal of rabid dogs has the added benefit of interrupting onward viral transmission within the dog population and thereby contributing to the objective of rabies elimination (Laager et al., 2019; T. N. Leung & Davis, 2014; Wallace et al., 2015).

Improving state capacity for laboratory rabies diagnosis was an early priority for the programme. Shipping of biohazardous samples over 500km from Goa to Bengaluru not only placed considerable logistical strain on the project, but it also meant a lag of weeks or months between investigation and diagnosis. One-time donations of equipment made it possible to rapidly advance methods that otherwise may have taken years to establish through government channels of proposal, finance, and approval. For example, three-way support from non-government, academic, and government partners made it possible to capacitate the Goa government veterinary Disease Investigation Unit laboratory with WOAH approved rabies diagnostic testing capacity in 2016: Mission Rabies donated a fluorescent microscope; the National Institute for Mental Health and Neurosciences (NIMHANS) provided laboratory training to staff in direct fluorescent antibody test protocol; and the India National Centre for Disease Control (NCDC) provided ongoing funding for conjugate and reagents.

Employing lateral flow assays as a cadaver-side research tool for rabies diagnosis generated early data on rabies incidence in the absence of timely state rabies diagnostic services. The tests motivated veterinarians to retrieve samples from suspect rabid animals under difficult field conditions and demonstrated the urgent need for in-state laboratory rabies diagnostic capabilities (Yale et al., 2019). Reports of poor quality-control and low sensitivity of these tests meant that negative results could not be considered valid and guidelines for their use should be a point of consideration in the development of national programs (Eggerbauer et al., 2016). Exploration of applying modern portable rabies virus sequencing technology to the relatively austere laboratory environment of the DIU in 2018 was another example of pushing boundaries to discover scalable solutions for robust rabies surveillance at the Indian state scale. In-state sequencing and phylogenetic analysis by Gigante et al. identified three distinct groups of co-circulating rabies viruses in Goa, two of which had appeared to have been eliminated, whilst the remaining group spanned the border region between north Goa and Maharashtra (A. D. Gibson et al., 2022; Gigante et al., 2020). Identification of an importation of rabies virus originating from Rajasthan in North India highlighted the risk posed by inter-state human-mediated transport of infected dogs (Hampson et al., 2007; Talbi et al., 2010; Tohma et al., 2016). Insights from these analyses informed the expansion of vaccination efforts into neighbouring states and strengthened the conviction that dog vaccination has eliminated the virus from much of the state. Further academic collaboration has enabled routine viral sequencing to be established at DIU in 2022, providing ongoing insights into rabies virus transmission in the region and setting an example for establishing comprehensive capacity for state-level rabies surveillance in India.

Sustaining vigilance for reintroduction of rabies into talukas that have achieved freedom will determine the extent to which the virus is able to circulate undetected and the ease with which it can again be eliminated (Townsend, Lembo, et al., 2013). Whilst the intensive vaccination of dog populations at Goa's borders aims to control direct spread of the virus through movement of free-roaming dogs, human-mediated dog transport will likely introduce the virus into central Goa over the coming years (Hampson et al., 2007; Rinchen et al., 2020; Talbi et al., 2010; Tohma et al., 2016). The decision to cease intensive vaccination in regions where no rabid dogs have been confirmed from more than two years will inevitably result in the gradual loss of herd immunity, however this is an important stage in the progression of any elimination initiative (Brunker et al., 2020; Roeder et al., 2013). The time to detection of viral reintroduction, and speed of response, directly relates to the ease with which elimination can be achieved (Gilbert & Chipman, 2020; Kotzé et al., 2021; Townsend, Lembo, et al., 2013). The passive surveillance approach employed in Goa relies on the active reporting of suspect rabid dogs by veterinarians, physicians, civil services, and the public and so its success hinges on broad awareness of the signs of rabies and the need to report cases to state rabies surveillance services. In 2022 we began to develop systems to incorporate elements of active surveillance by soliciting animal welfare organisations, private veterinarians, and public services to submit all dogs to have died of unknown reasons from anywhere in the State. Whilst we expect public reporting to continue to be the primary route of identifying rabid dogs in the community, a mixed methods approach is likely to be required to maximise the chances of early detection in regions with low prevalence (Gilbert & Chipman, 2020).

Robust data on dog rabies incidence enabled the programme to be tailored to the epidemiological situation, intensifying efforts in regions where rabies persisted and avoiding wasted resources where the objective had been achieved (LeRoux et al., 2018). The decline in dog rabies cases in many talukas following a single round of intensive vaccination is encouraging and further research into the factors that contributed to this rapid success has the potential to benefit planning of programmes elsewhere. Aspects of population density, the effect of landscape barriers to dog movement such as rivers, overall population size, and limited rates of reintroduction all may have played a role (Brunker et al., 2018; Kotzé et al., 2021). The development of accessible tools that support population mapping and visualisation of factors likely to impact on rabies transmission have the potential to aid in large-scale campaign planning (Kanankege et al., 2022).

The high cost of advanced vaccination techniques required to access a high proportion of roaming dogs in India is a major barrier to scaling rabies control interventions. Despite most dogs being handled manually for vaccination, advanced vaccination techniques were necessary to achieve vaccination coverages approaching 70% (Chapter 3). The mean cost of 3.45 USD per dog vaccinated was higher than reports of global averages (2.18 USD), but within the range reported by other mass dog vaccination interventions (1.13 – 15.62 USD) (Elser et al., 2018; Undurraga et al., 2020). This appears reasonable given the large free-roaming dog population in Goa and reliance on net-capture to reach adequate vaccination coverages. Exploration of the use of oral rabies vaccination (ORV) of dogs to improve access to roaming dogs for immunisation in such settings has intensified over recent years (Bonwitt et al., 2020; Chanachai et al., 2021; T. G. Smith et al., 2017). Inclusion of ORVs, in combination with parenteral vaccination methods, has the potential to improve cost-efficiency and was identified as an area of further research progressed through Chapters 5 and 6 (A. D. Gibson, Mazeri, et al., 2019; A. D. Gibson, Yale, et al., 2019; Wallace et al., 2019).

Many studies have reported rabies control as an attractive proposition in terms of cost-effectiveness (Anothaisintawee et al., 2019; Borse et al., 2018; Shim et al., 2009; Tenzin et al., 2012; Wera et al., 2017). Cost-effectiveness thresholds (CET) of 1 to 3× gross-domestic product (GDP) per capita are most frequently used in the evaluation of population health interventions, however, concerns that these thresholds are likely to be too high and risk the misallocation of public funds in settings with significant budget constraints are increasingly raised (Anothaisintawee et al., 2019; Kazibwe et al., 2022). The Goa rabies control programme remained cost-effective even at the more stringent 'health opportunity cost threshold' of 0.5× GDP per capita (Ochalek et al., 2018; Woods et al., 2016). The estimated cost per DALY averted of 567 USD was 0.27× India's GDP per capita (2,100 USD), and 0.08× that of Goa in 2019 (7,029 USD) (Statistics Times, 2021; The World Bank, 2019). As such, under the WHO criteria of cost-effectiveness the intervention can be considered 'very cost-effective' (World Health Organisation, 2003). The estimated cost per DALY averted from the Goa program of 567 USD was lower than the estimated cost-effectiveness of simulated rabies interventions in India and Sri Lanka at 1,064 USD and 1,401 USD per DALYs respectively (Fitzpatrick et al., 2016; Häsler et al., 2014), but higher than a recent report in Rajasthan at 40 USD per DALY averted (Larkins et al., 2020). This variability is likely a reflection of non-standardisation of economic modelling methodologies. However, unlike many assessments based on secondary estimated values (Ozawa et al., 2012), the current programme was implemented through a single government collaborator which enabled model inputs to be based on primary operational and surveillance data and expenditures. In the current analysis, I assumed that rates of PEP administration would not change until policies were updated to reflect the reduced risk and limited need for PEP following successful elimination of rabies from many areas. Assuming these changes are made in the lifetime of this program, the interventions would be even more cost-effective (Hampson, Ventura, et al., 2019).

The state-wide education initiative in schools directed rabies awareness towards children, the demographic at disproportionate risk of death from rabies (D. L. Knobel et al., 2005). Similar class structures, combining presentation, theatre and question-answer methods have been demonstrated to be effective in other settings (Burdon Bailey et al., 2018). Rabies educational content was integrated into the Government of Goa school science curriculum for children aged 11 to 12 years in 2020, helping to ensure sustained awareness of the disease whilst regional control efforts grow. The progressive increase in dog-bite presentations at bite clinics during the project period may reflect the increasing widespread community awareness of rabies brought about by the community education program and mass-media attention on rabies, however this counters the traditional view that dog bite incidence falls following successful the control of rabies (Cleaveland et al., 2003). Rabies was attributed to 3% of biting dogs in Haiti, a figure which would be even lower in Goa (Medley et al., 2017). Concurrent development of integrated bite case management (IBCM) systems to reduce unnecessary PEP in people bitten by healthy dogs would maintain cost-effective use of PEP in the face of this increase (Etheart et al., 2017; Hampson, Ventura, et al., 2019; Undurraga et al., 2017). The increasing rate of dog bite presentation warrants further investigation and speaks to the wider societal discourse on dog overpopulation discussed in Chapters 1 and 7. Operational research prioritising the development of impactful approaches to dog population management are urgently needed.

4.6 Conclusion

Whilst the Goa project is currently a unique example in India, demonstrating the construction of a comprehensive One Health approach to dog rabies elimination, the learnings and insights gained provide opportunities for other states to begin to advance rapidly through the earliest stages of programme development. Beyond the implementation of sustained, high-coverage annual dog vaccination campaigns, robust surveillance and mass engagement through community awareness were of central importance. Heterogeneity in the speed and ease of viral elimination from different areas highlight the importance of evaluating the barriers and facilitators of rabies spread during campaign planning. I hope that the data generated through this programme, and greater access to phylogenetic techniques, will enable further research into rabies transmission and elimination to support the wider objectives of rabies control in India. Prospects for translating Goa's achievements to other larger geographies of India are dependent on scaling the dog vaccination effort by orders of magnitude, whilst sustaining high coverage in the roaming dog population. Through the coming chapters I turn our attention to oral rabies vaccines and the benefits they may bring to solving this part of the puzzle.

Chapter 5 Comparing the effectiveness of Oral-Bait-Handout and Capture-Vaccinate-Release methods

5.1 Abstract

The Goa Rabies Control programme has demonstrated that dog and human rabies elimination can be achieved using parenteral mass dog vaccination approaches and that such programmes can be cost-effective. Scaling these methods would be theoretically possible, however the advanced skill, considerable human resource, and expanded infrastructure that would be required of the capture-vaccinate-release method presents a barrier to replication in many austere environments. Oral rabies vaccines have been used extensively in the control of wildlife rabies, however their application in the control of dog rabies has been limited to date. In this chapter I explore the potential for oral rabies vaccination approaches to improve vaccination coverage and reduce operational complexity for the vaccination of free-roaming dogs.

Two methods were compared in Goa; the oral bait handout (OBH) method, where teams of two travelled by scooter offering dogs an empty oral bait construct, and the conventional catch-vaccinate-release (CVR) method, where teams of seven travel by supply vehicle and used nets to catch dogs for parenteral vaccination. Both groups parenterally vaccinated any dogs that could be held for vaccination.

The OBH method was more efficient on human resources, accessing 35 dogs per person per day, compared to 9 dogs per person per day through CVR. OBH accessed 80% of sighted dogs, compared to 63% by CVR teams, with OBH accessing a significantly higher proportion of inaccessible dogs in all land types. All staff reported that they believed OBH would be more successful in accessing dogs for vaccination. The fixed operational cost of running a CVR team was four times higher than OBH, at 127 USD and 34 USD per day respectively. The mean per dog vaccination cost of CVR was 2.53 USD, whilst OBH was 2.29 USD. A considerable proportion of the OBH cost was attributed to the estimated cost of oral rabies vaccines, which are expected to be high during initial implementation. Extrapolation to a two-week national Indian campaign, estimated that 1.1 million staff would be

required using CVR, however only 293,000 staff would be needed to implement an OBH based campaign.

OBH was operationally feasible, economical, and effective at accessing the free roaming dog population. This study provides evidence for the continued expansion of research into the use of OBH as an additional method for difficult to access roaming dogs, alongside parenteral mass dog vaccination activities in India.

5.2 Introduction

The Goa Rabies Control programme demonstrates the feasibility of dog rabies elimination in an Indian state using existing parenteral vaccination methods, with enhanced programme coordination using smartphone technology, however we must confront the limitations in applying these methods at the scale required to impact on dog rabies across the region. India is diverse in terms of population density, ecology, and culture and it is therefore likely that dog vaccination campaign strategies will be equally diverse in their composition and methods. Nevertheless, the predominance of free-roaming dogs that are not readily amenable to handling has been reported in many settings across India and efficiently accessing these dogs for immunisation will inevitably form a critical part of India's journey to dog rabies freedom.

As described in Chapter 1, dog vaccination methods have been limited to three options for decades; Central Point (CP), Door-to-Door (DD), and Capture-Vaccinate-Release (CVR). The initial focus of the rabies control campaign in Goa was to apply these existing approaches in the India field context, with Chapter 3 describing the evolution of the combined DD-CVR approach and Chapter 4 reporting the resulting success in eliminating dog rabies from large areas of Goa. During this process, however, several methodological limitations were identified that impact on the wider application of these findings. The large, skilled human resource required to implement the CVR method presents a considerable barrier to the rapid development of campaigns of a scale required to eliminate rabies from larger states of India. Furthermore, the net catching approach is inherently one that dogs will try to evade, risking that the dog population becomes increasingly difficult to catch over time as reported in Bali, Indonesia (Widyastuti et al., 2015), and indicated by the diminishing daily team vaccination output over consecutive campaigns in Goa (Chapter 3). These concerns prompted us to explore the potential addition of a fourth dog vaccination method to the menu; oral rabies vaccination (ORV) of dogs.

Methods using ORVs offer an opportunity to immunise dogs without the need for direct handling and have the potential to circumvent CVR methods. Oral vaccination of dogs, as a supplementary tool to parenteral vaccination, has been shown to increase dog vaccination coverage in various field studies, especially of ownerless and poorly supervised owned dogs (Bonwitt et al., 2020; Chanachai et al., 2021; Estrada, Vos, De Leon, et al., 2001a; Freuling et al., 2022; Guzel et al., 1998; T. G. Smith et al., 2017; Vos et al., 2003). The Oral Bait Handout (OBH) method involves offering ORV baits to owned and unowned dogs that cannot be held for parenteral vaccination. Any bait or remnants that are not consumed are recollected by the vaccination staff and disposed of safely (World Organisation for Animal Health, 2018). Studies to assess OBH have been conducted in settings in the Americas, Africa, Europe, and Asia (Bender et al., 2017; Corn et al., 2003; Darkaoui et al., 2014; Estrada, Vos, De Leon, et al., 2001a; Freuling et al., 2022; Schuster et al., 1998; T. G. Smith et al., 2017), however its use has not been studied in India. WHO and WOAH advocate for the evaluation of this approach as a supplementary measure to increase vaccination coverage in areas where a sufficient proportion of dogs cannot be accessed for parenteral vaccination (Wallace et al., 2020; World Health Organization, 2018; World Organisation for Animal Health, 2018).

This study compares two vaccination approaches for inaccessible dogs, CVR and OBH, based on population access, operational feasibility, and cost. Both approaches were used in conjunction with parenteral vaccination of dogs that could be held for vaccination. There are no oral rabies vaccines (ORVs) currently licensed for use in India and so no ORV was used in this study, instead a prototype bait containing an empty PVC sachet was used to assess the OBH method. This study aimed to explore the proportion of dogs that could be accessed by each method, with further optimisation of the bait construct required.

5.3 Materials and methods

5.3.1 Study site

The study was conducted over two weeks in February 2018. The sampling frame was dogs within Ponda taluka due to it being a convenient location alongside the ongoing vaccination schedule at the time of the study and away from the coast, where dog populations are influenced by fluctuations in tourism throughout the year. The taluka was stratified by land type (urban, sub-urban, village housing, sparse housing, and forest-agriculture) according to its appearance on Google satellite images (Figure 5.1**Error! Reference source not found.**) (A. D. Gibson et al., 2016). Forest areas were omitted from the study due to the absence of dogs (known from previous campaigns). The remaining strata were divided into Working Zones based on subjective assessment of the Google satellite images to produce an area that would take the vaccination teams 1-3 days to vaccinate. Working Zones were randomly assigned to either CVR or OBH study arms within each stratum.

Permission for the study was granted by the Department of Animal Husbandry & Veterinary Services, Government of Goa. Dogs were parenterally vaccinated in accordance with the Memorandum of Understanding between Mission Rabies and the Government of Goa as part of a non-research public health campaign. Ethics approval was provided by University of Edinburgh R(D)SVS Veterinary Ethical Review Committee (Reference number 113.18).

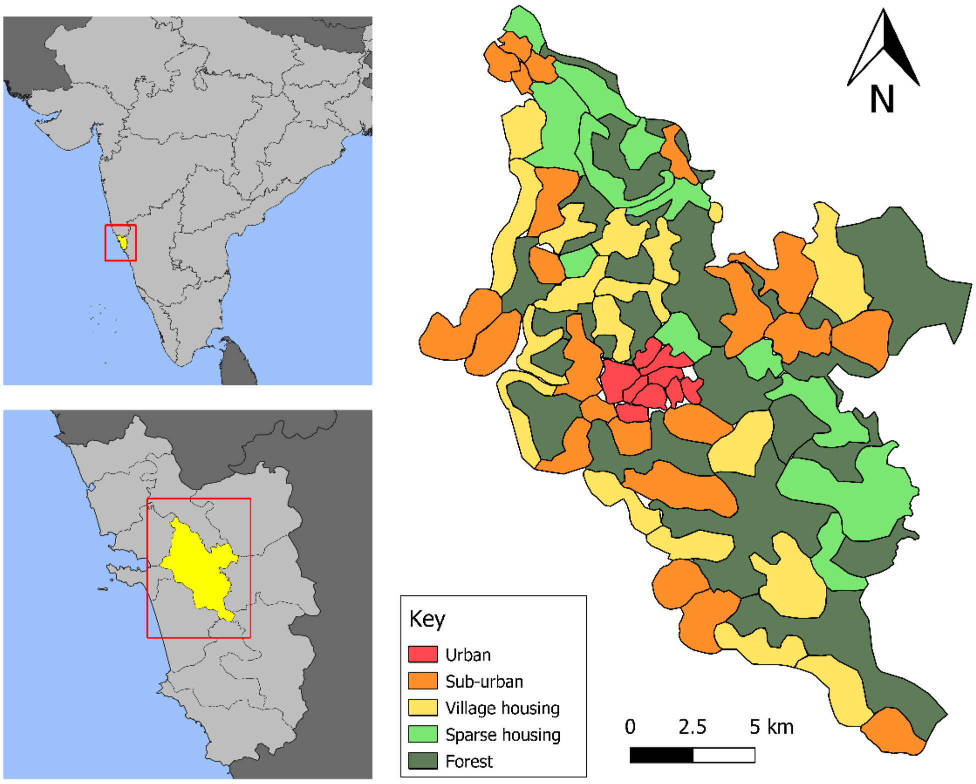


Figure 5.1 - Map of the Ponda taluka showing Working Zones coloured by land type. Inserts show maps of India and Goa state indicating region of Ponda taluka (red boxes).

5.3.2 Comparison of CVR and OBH

Four vaccination teams were included in the study (uniquely identified as Elephants, Leopards, Cobras, and Vishnu), with all teams having approximately the same levels of experience and ability. Two teams performed CVR for the first week, followed by OBH the second week and the other two teams performed OBH in the first week followed by CVR in the second week. All staff had received pre-exposure rabies vaccination.

Because no ORV was used, all OBH regions were revisited immediately following the study to catch, vaccinate and mark roaming dogs that were not already marked as parenterally vaccinated in accordance with the standard campaign protocol.

For both study arms, dogs that could be handled either by an owner or by the team were manually held and vaccinated parenterally. An inaccessible dog was defined as any dog which could not be readily handled and restrained for parenteral injection of vaccine. In the CVR study arm, an attempt was made to catch inaccessible dogs using nets, to enable parenteral vaccination. In the OBH study arm, inaccessible dogs were offered a bait (Figure 5.2**Error! Reference source not found.**). An information leaflet containing an explanation of the study in English and Hindi, with contact details for further information, were distributed to members of the public by all teams (Appendix D). In cases where owners refused vaccination, were not available to give consent or reported that the dog was already vaccinated, the dogs were recorded as sighted, but were removed from analysis in both arms as they were not available to attempt vaccination in either group.

Existing methods of estimating coverage in CVR, by marking all vaccinated dogs and conducing post-vaccination dog sight surveys to count the proportion of marked sighted dogs could not be used to assess OBH because it was not possible to physically mark all dogs consuming baits. The use of biomarkers within baits has been described to evaluate coverage (Algeo et al., 2013; Cagnacci et al., 2006; Fernandez & Rocke, 2011), however this was not considered acceptable for use in the dogs of unknown ownership status in this study.

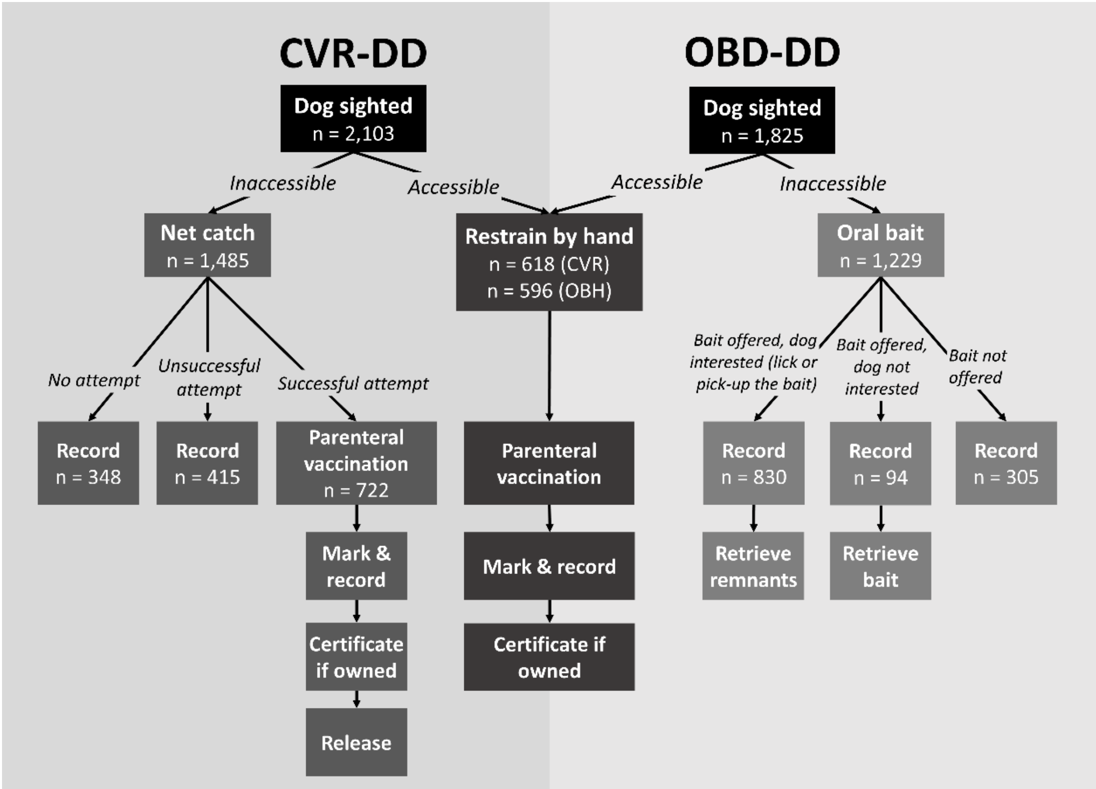


Figure 5.2 - Flow diagram for action taken for sighted dogs in each intervention arm. CVR = Catch-vaccinate-release, DD = Door-to-door, OBH = oral bait handout. Dogs which were reported by the owner as already vaccinated or refused vaccination were not included in the counts or analysis for either group.

5.3.3 Oral bait handout method (OBH)

Empty vaccine capsules made of PVC (3cm x 6.5cm) and sealed with aluminium foil were used to replicate the mechanical presence of the capsule in the bait. The capsule was placed inside a collagen casing with a section of blanched pig skin to encourage chewing (Appendix D). The capsule was tied at both ends and frozen until the morning of distribution. Each morning baits were packaged into zip-lock bags and transported in cooler boxes. At the start of the vaccination session, a sachet of commercial meat dog food and gravy (Chicken & Vegetable 100g pouches) was poured into each zip-lock bag to coat all 15 baits in each bag.

OBH teams were comprised of two people riding a two-wheel scooter. Roles within the OBH teams were a team leader, responsible for vaccinating dogs parenterally and distributing baits, and one assistant, who was responsible for navigation, data entry and public communication. The total training period was a full day the day before beginning OBH vaccination which consisted of a verbal training and afternoon supervised practical session. Where an owned dog could not be held for vaccination, verbal consent was requested to offer a bait. They were informed that their dog had not been vaccinated and that teams would return with equipment to help vaccinate their dog within the same week. Where accessible, all puppies were parenterally vaccinated, however puppies under approximately 5kg that could not be caught were not offered a bait.

5.3.4 Catch Vaccinate Release method (CVR)

CVR teams contained seven people travelling in a supply vehicle (A. D. Gibson et al., 2015). Roles within the team were one team leader, one assistant, one driver and four animal handlers/ butterfly-net catchers (Appendix D). The CVR method requires at least four catchers working as a team to capture dogs in nets. The process is dynamic and requires physical strength, agility, and teamwork as well as an understanding of dog behaviour and movement. All four teams were experienced in the CVR method and are employed by Mission Rabies to conduct this method across Goa state throughout the year. The mean number of months working experience in the CVR method per team member was 14 months. CVR teams received the same briefing as in the OBH training and were given training on the study data collection protocol, followed by an afternoon of supervised vaccination.

5.3.5 Data collection

Both study arms entered data about every dog sighted in the WVS App, a tailor-made smartphone-web system designed to direct vaccination teams and monitor campaign outputs (Chapter 2) (A. D. Gibson et al., 2018). All data points automatically recorded the time, date, team name, and GPS location of the entry, in addition to information entered by the user through forms containing logic dependencies in the app. The data structure for every dog sighted is summarised in Appendix D, however in brief, this included i) whether the dog was vaccinated and if not, why, ii) for dogs not parenterally vaccinated by hand, whether the alternative method was attempted, iii) where the alternative method was attempted, whether this was successful. For OBH, information about bait acceptance, swallowing and capsule/bait retrieval were also recorded. For the evaluation of the OBH method's potential, a dog was considered to have been 'mock vaccinated' by the bait if the dog made direct contact through licking or consuming the bait, with the assumption that the rudimentary bait used in this study would be optimised for palatability to achieve vaccination of these dogs. Throughout the study references to the number of dogs `vaccinated` includes those which were mock vaccinated using the bait constructs. The ownership status, confinement, sex, neuter status, age, and health of every dog vaccinated was also recorded.

5.3.6 Spatial analysis

Convex hull polygons were drawn around the GPS locations within each Working Zone recorded in each vaccination session using QGIS (version 3.20.3). Anomalous GPS locations outside of the general working area resulting from variation in GPS signal were removed based upon time stamp and GPS accuracy records available for each entry. The polygon boundaries were adjusted to the nearest border of the assigned Working Zone so that the final polygon represented the proportion of the Working Zone that had been covered (Figure 5.3). The area of polygons was used to calculate the density of dog vaccinations and sightings by each team and land type.

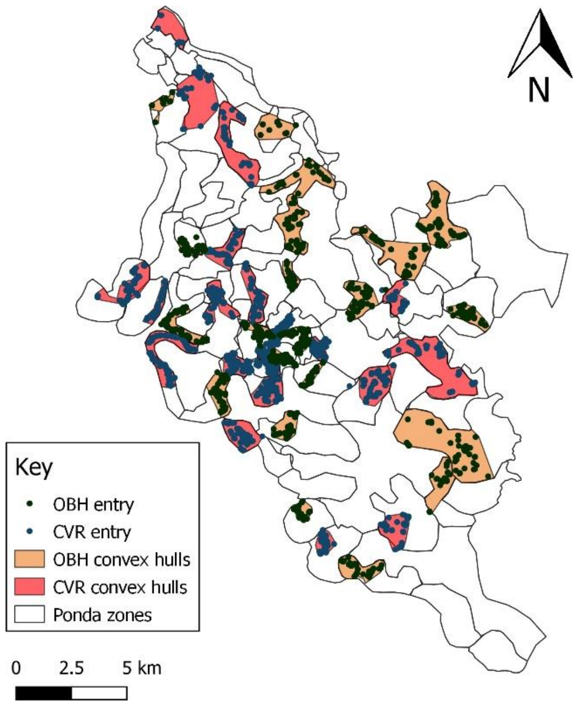


Figure 5.3 - Map of study area, showing the GPS location of all data entry points by OBH and CVR teams, in addition to the convex hull regions used to calculate 'vaccination' area and density.

5.3.7 Statistical analysis

Data were exported from the WVS app database in CSV format. Further analysis was then performed in the R statistical software environment (version 3.6.2) (R Core Team, 2018). Confidence intervals are reported from regression analyses at the 95% level using a profile log likelihood.

Multivariable logistic regression was used to estimate the difference in vaccination coverage achieved by each vaccination method (CVR / OBV), adjusting for factors of land type (urban / sub-urban/ village / sparse housing) and team (Elephants/ Leopards/ Cobras/ Vishnu). Three different models were built; the first estimating overall vaccination coverage in sighted dogs (dogs vaccinated as a proportion of all sighted dogs); the second estimating vaccination coverage in inaccessible dogs (dogs vaccinated as a proportion of all dogs seen that could not be vaccinated by hand); and the third estimating vaccination coverage by hand vaccination alone (dogs held for parenteral vaccination as a proportion of all dogs sighted). All predictors (vaccination method, land type, team), and possible combinations of interactions between predictors, were considered for inclusion in the model. The model with lowest Akaike information criterion (AIC) was chosen as the final model (Appendix D). The estimated marginal means (also known as least-squares means) (Searl et al., 1980) of the overall predicted vaccination coverage by each vaccination method, and for each land type, were calculated using the *emmeans* package (Lenth, 2018). Estimated marginal means provide predictions of the outcome variable whilst adjusting for the effects of other covariates included in the model. This helps to isolate the average effect of interest while holding other variables constant at their observed values (Searl et al., 1980).

A multivariable Poisson regression model was initially used to examine the influence of vaccination method (CVR / OBV), land type (urban / sub-urban/ village / sparse housing), and team (Elephants/ Leopards/ Cobras/ Vishnu) on vaccination rate (dogs vaccinated per hour). Vaccination count data were expressed as rate within the model by incorporating the log of hours as an offset. Overdispersion of the resulting model was tested for, and confirmed, using the *AER* package (Kleiber & Zeileis, 2008) indicating a larger variance than could be accounted for by a simple Poisson model. Therefore, analysis was repeated with the same predictors using a multivariable quasi-Poisson model. All combinations of predictor variables and interactions were considered using the model averaging approaches implemented in the package *MuMIn* (Bartoń, 2019). The model with the lowest quasi-likelihood AIC (QAIC) was chosen as the final model (Appendix D). Estimated marginal means of the overall predicted vaccination rate by vaccination method and land type were calculated using the *emmeans* package (Lenth, 2018). Estimated coefficients were exponentiated to calculate the rate ratio (Appendix D). Results were plotted using package *ggplot2* (Wickham, 2016).

Recent studies had reported variable rates of seroconversion in dogs consuming ORV (Cliquet et al., 2007; T. G. Smith et al., 2017). Therefore estimates were calculated to compare the proportion of sighted dogs expected to seroconvert following the two vaccination methods. The proportion of dogs estimated to seroconvert from parenteral vaccination was 98% (Lankester et al., 2016), whilst scenarios for seroconversion in 60, 70, 80 and 90% of dogs that accessed bait by the OBH method were included (Cliquet et al., 2007; T. G. Smith et al., 2017).

5.3.8 Cost Comparison

All operational costs associated with implementing each method were recorded based on expenditure during the study or review of monthly project expenditure. This figure does not include costs of post-exposure rabies prophylaxis for staff, training, publicity, community awareness activities, bite surveillance, cold chain storage or vaccine transport. Costs reported in this chapter are stated in US dollars at a currency exchange rate of 72.2 rupees per dollar. Operational costs were defined as either fixed or variable costs. Fixed costs were constant regardless of the number of dogs vaccinated (e.g. salaries, staff pre-exposure vaccination, vehicle purchase, equipment). In contrast, variable costs changed with the number of dogs vaccinated (e.g., vaccine cost, needles, syringes). Itemised fixed costs that span months or years were converted into a daily operational cost (Appendix D). Variable costs were calculated per vaccine administered, at a parenteral vaccine dose cost of 0.45 USD (32 Rupees), 0.05 USD Per parenteral dose for consumable equipment (needle, syringe, vaccine certificate) and 2.77 USD (200 Rupees) per oral bait dose delivered. The mean daily variable cost was calculated for each method using the parenteral and oral cost per vaccine dose, multiplied by the mean daily doses of each vaccine type administered. The cost per vaccine administered was then calculated for each approach using the following formula:

$$\text{Cost per vaccine administered} = \left(\frac{\text{Fixed daily cost} + \text{Mean variable daily costs}}{Mean\ total\ vaccinations\ administered\ per\ team\ per\ day}\right)$$

5.3.9 Staff Survey

A survey to explore the opinions of staff members was conducted immediately following completion of the field study, consisting of a face-to-face questionnaire with each Team Leader and Assistant (Appendix D)

5.3.10 Estimation of scalability

The approximate number of teams and staff that would be required to vaccinate 50,000 dogs (district level estimate from historic data) and 100 million dogs (national level estimate used in previous studies (D. L. Knobel et al., 2005; Wallace et al., 2017)) was estimated for two campaign durations; a two-week period (10 working days) or a one-year period (288 working days). The number of team-days required was calculated by dividing the number of dogs to be vaccinated by the mean vaccinations per team per day for each method. This was divided by the number of working days in the campaign duration to give the number of teams that would be required. The total number of staff required was calculated by multiplying the number of teams by the number of staff in each method (2 per team for OBH, 7 per team for CVR). The estimate was compared with current project structure in Goa (three CVR teams, approximately 21 staff vaccinating over a 12-month period) to assess reliability at the district level.

5.4 Results

In total 45 Working Zones were included in the study (23 CVR, 22 OBH) in which teams sighted a total of 3,928 available dogs (Table 5.1). A further 467 dogs were sighted but were not eligible for attempted vaccination. The mean estimated by the regression model was 10.43 and 11.48 vaccinations per team per hour for CVR and OBH respectively, equating to 1.5 vaccinations per person per hour for CVR and 5.7 vaccinations per person per hour for OBH. For a working day consisting of 6 hours of vaccination time (1 hour travel to/from vaccination site), the CVR teams vaccinated 63 dogs per day as compared to OBH teams vaccinating 69 dogs per day. Given the difference in team size for each approach, the CVR method results in nine dog vaccinations per person per day, compared to 35 dogs per person per day for OBH.

The multivariable logistic regression model for overall vaccination coverage included the explanatory variables vaccination method, team, land type, the interaction between vaccination method and team, and the interaction between vaccination method and land type (Appendix D). OBH teams were able to access a significantly higher proportion of sighted dogs for vaccination than CVR teams. The predicted overall vaccination coverage in dogs sighted was 63% (CI: 61-66) for CVR and 80% (CI: 78 – 82) for OBH (P <0.001) (Figure 5.4A).

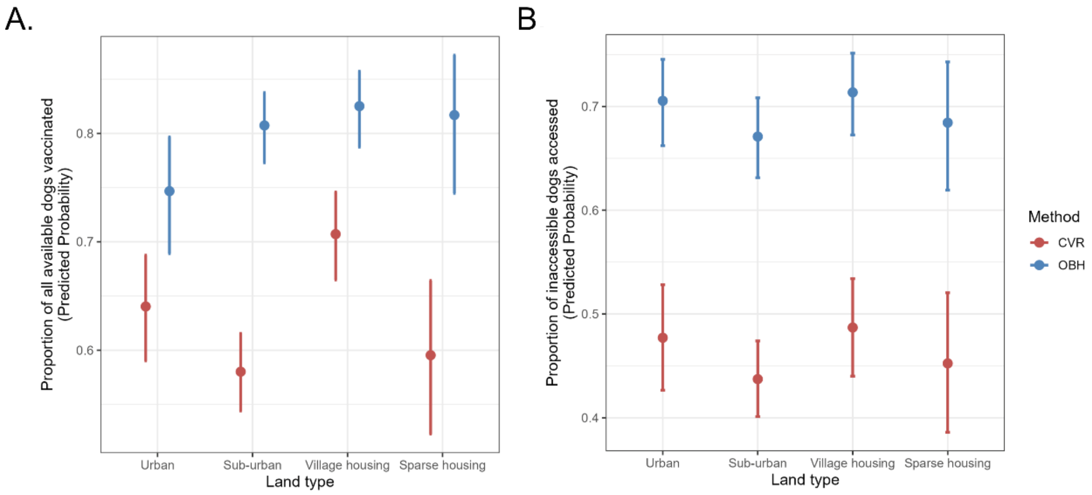


Figure 5.4 - Predicted coverage of CVR and ORV methods by land type in (A) all available dogs and (B) inaccessible dogs. Error bars show 95% confidence intervals.

The second logistic regression model considered the proportion of inaccessible dogs that could be vaccinated. The final model included vaccination method, land type, and team, and the interaction between method and team (Appendix D). Of dogs that could not be restrained by hand for parenteral vaccination (inaccessible dogs), OBH was able to access 69% (CI: 66 - 72) through baits, as compared to 46% (CI: 43 - 49) by CVR. The difference between the proportion of inaccessible dogs 'vaccinated' was significantly different between methods (odds ratio: 2.27, CI: 1.59 – 3.27, P-value: <0.001) (Figure 5.4**Error! Reference source not found.**B).

The third logistic regression model examined the proportion of all dogs sighted that could be manually restrained for parenteral vaccination (i.e. 'hand-vaccinated'). The final model included predictive variables of vaccination method, team, and land type, and interactions between method and team, and between method and land type (Appendix D). The model prediction of the proportion of dogs that could be hand-vaccinated, when adjusting for other predictive variables, was similar for both methods at 30% (CI: 27 - 32) for CVR and 31% (CI: 29 - 34) for OBH, however OBH had significant effect on reducing the odds of hand vaccination occurring (odds ratio 0.61, CI: 0.39 – 0.95, P-value: 0.03) (Appendix D). Therefore, the model indicates a lower likelihood of hand vaccination using OBH as compared to CVR.

Overall OBH teams vaccinated a larger area than CVR at 1.47km^2 compared to 1.39km^2 and at a higher vaccination density at 85 dogs per km^2 compared to 75 dogs per km^2 by CVR (Table 5.1). The final quasi-Poisson model for vaccination rate included vaccination method, land type, and team. The rate of vaccination was significantly lower in village housing (rate ratio 0.84, CI: 0.72 - 0.99, P-value 0.040) and sparse housing areas (rate ratio 0.61, CI: 0.50 - 0.75, P-value <0.001) as compared to urban areas.

In total, 924 baits were dropped during the study. Of the 94 baits that were not picked up by dogs, only one (0.1% of all baits) could not be retrieved. Of the 830 baits that were picked up by dogs, the capsules of 133 could not be retrieved because the dog carried it away, of which the perforation status of 124 baits was unknown. This represents 13% of all baits distributed that were carried away by dogs to an unknown location and it is unknown whether the capsule was perforated or swallowed. The number of people bitten per day was recorded for 17 of 22 vaccination sessions for CVR and 19 of 22 sessions for OBH. Three staff members were bitten during CVR work, and there were no bites reported from OBH teams.

Table 5.1 - Table of aggregate and means from team-day data by method and land type. The mean figures refer to the proportions for each team-vaccination-day averaged over method and land type. Calculations of the total row refer to the proportions for each team day averaged by method. Numbers in brackets indicate 95% confidence intervals.

Land type	Method	Team vacc days	Total available dogs sighted	Total dogs vacc*	Total dogs hand vacc	Total dogs alternate method vacc (bait/net)*	Mean daily output (vacc/ team/ day)*	Mean proportion sighted dogs vacc (%)*	Mean sighted dogs vacc by hand (%)	Mean area covered (km^2)	Mean sighting density (dogs/ km^2)	Mean vacc density (vacc/ km^2)*	Mean vacc rate (vacc/ hour)*
Urban	CVR	5	523	342	134	208	68	64	24	0.38	345	189	13
	OBH	4	407	319	71	248	80	79	18	0.45	259	187	13
Sub-urban	CVR	8	793	453	209	244	57	59	27	1.39	94	51	12
	OBH	8	722	548	261	287	69	79	40	1.19	121	80	14
Village housing	CVR	7	563	408	221	187	58	72	41	1.46	65	43	11
	OBH	6	521	410	193	217	68	81	38	1.48	98	67	12
Sparse housing	CVR	3	224	137	54	83	46	61	25	2.95	36	21	9
	OBH	4	175	149	71	78	37	85	42	3.07	25	18	7
Total (95% CI)	**CVR**	**23**	**2,103**	**1,340**	**618**	**722**	**58 (49 – 67)**	**64 (60 – 68)**	**30 (26 – 35)**	**1.39 (0.95 – 1.84)**	**132 (76 – 188)**	**75 (43 – 106)**	**11 (10 – 13)**
	OBH	**22**	**1,825**	**1,426**	**596**	**830**	**65 (56 – 74)**	**80 (76 – 85)**	**35 (27 – 44)**	**1.47 (0.83 – 2.13)**	**123 (80 – 166)**	**85 (55 – 115)**	**12 (11 – 13)**

**Vaccination figures include dogs that were 'mock vaccinated' by accepting a bait, however no oral rabies vaccine was used in the study.*

5.4.1 Staff Survey

Eight staff (team leader and data collector for each of the four teams) were interviewed. The full responses to questions are included in Appendix D. All eight staff responded that they believed that the OBH method could reach more dogs than CVR. Seven staff responded that they preferred the OBH approach, with all seven giving the reason that more dogs can be reached and three additionally reporting the method is easier. The one staff member who preferred the CVR method gave the reason that there is less fear of dog bite when using the nets.

5.4.2 Cost

The costs associated with the two methods are summarised in Table 5.2. The itemised breakdown of fixed costs is provided in Appendix D. The mean cost per vaccine delivered through CVR teams was 2.53 USD, whilst per dog vaccinated through OBH teams was 2.29 USD (Table 5.2). The CVR method had high fixed costs at 127 USD per day, representing 80% of the mean cost per dog vaccinated, but low variable vaccine costs (Figure 5.5A). The fixed cost of running an OBH team was 34 USD per team per day, almost a quarter of the cost of CVR, however variable costs were considerably higher due to the cost of ORV (Figure 5.5A). The high fixed cost of CVR resulted in increasing per dog vaccinated costs in lower density areas where fewer dogs were vaccinated each day, whereas OBH costs rose in areas with a greater number of inaccessible dogs (Figure 5.5B).

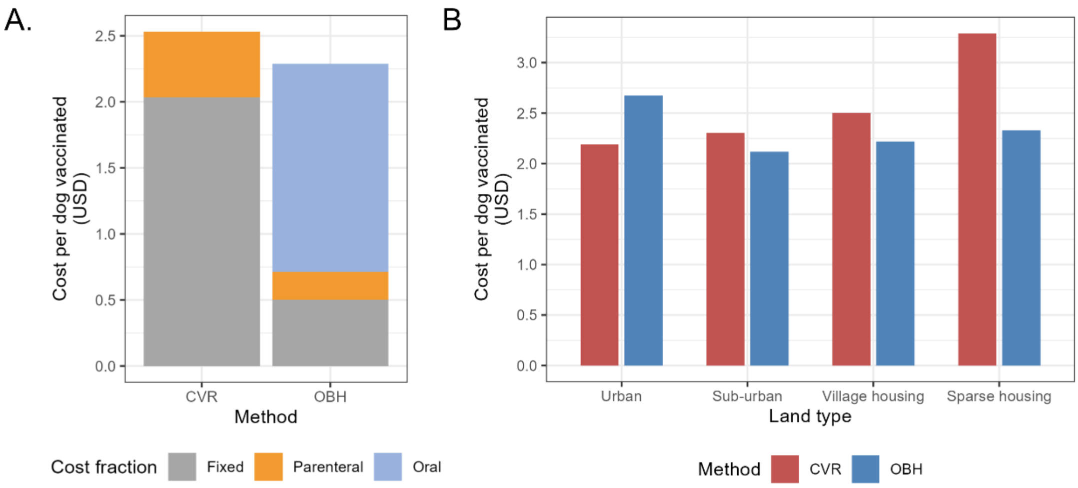


Figure 5.5 – Cost per dog vaccinated by method. A) Graph showing a breakdown of mean fixed and variable (oral/parenteral) cost per dog 'vaccinated' based on the mean number of dogs vaccinated per team per day in each method. B) Bar graph of cost per dog 'vaccinated' by land type and method in USD.

5.4.3 Extrapolation of resources to district and national vaccination campaign scale

Extrapolating the pilot study vaccination efficiencies for each method to district and national dog vaccination campaign sizes revealed large differences in the manpower and vehicle requirements (Table 5.3). To vaccinate 50,000 dogs in two weeks using CVR would require 560 staff, compared to 146 staff using OBH, whereas at the estimated national level would require 1.1 million staff using CVR and 293,000 staff for OBH. The extrapolation accurately estimated the current campaign structure at district level.

Table 5.2- Table showing calculation of cost per dog 'vaccinated' by land type (USD). Numbers in brackets for totals are the confidence interval calculated using the 95% confidence limits for the rate of vaccination for each method.

		Parenteral			Oral							
Land type	**Method**	**Parenteral cost/ dose**	**Parenteral doses/ day**	**Total parenteral cost/ team/ day**	**Oral cost/ dose**	**Oral doses/ team/ day**	**Total oral cost/ team/ day**	**Total variable cost / team**	**Fixed cost**	**Total cost/ team/ day**	**Total vacc/ day**	**Per dog cost**
Urban	**CVR**	0.5	75.23	37.57	2.77	0.00	0.00	37.57	127.113	164.67	75.23	2.19
	OBH	0.5	18.80	9.39	2.77	64.04	177.40	186.78	34.41	221.19	82.84	2.67
Sub-urban	CVR	0.5	70.49	35.20	2.77	0.00	0.00	35.20	127.11	162.31	70.49	2.30
	OBH	0.5	37.54	18.75	2.77	40.08	111.02	129.77	34.41	164.18	77.62	2.12
Village housing	CVR	0.5	63.50	31.71	2.77	0.00	0.00	31.71	127.11	158.82	63.50	2.50
	OBH	0.5	32.14	16.05	2.77	37.79	104.68	120.73	34.41	155.14	69.93	2.22
Sparse housing	CVR	0.5	45.53	22.74	2.77	0.00	0.00	22.74	127.113	149.84	45.53	3.29
	OBH	0.5	24.93	12.45	2.77	25.20	69.82	82.27	34.41	116.67	50.13	2.33
TOTAL	**CVR**	**0.5**	**62.57 (57.3 - 68.3)**	**31.25 (28.6 - 34.1)**	**2.77**	**0**	**0**	**31.25 (28.6 - 34.1)**	**127.11**	**158.36 (155.7 - 161.2)**	**62.57 (57.3 - 68.3)**	**2.53 (2.36 - 2.72)**
	OBH	**0.5**	**29.83 (27.5 - 32.4)**	**14.90 (13.7 - 16.1)**	**2.77**	**39.08**	**108.24**	**123.14 (113.3 - 133.7)**	**34.41**	**157.55 (147.7 - 168.1)**	**68.90 (63.4 - 74.8)**	**2.29 (2.25 - 2.33)**

Table 5.3 - Extrapolation of mean team 'vaccination' output for CVR and OBH methods to the district level in Goa and nationally in India.

Approx. Scale	Method	Campaign duration	Dog vacc	Number staff per team	Vacc/ team/ day	Working days	Number of team days	Number of teams	Number teams (LCI)	Number teams (UCI)	Total staff	Total Staff (LCI)	Total Staff (UCI)
District	CVR	2 weeks	50,000	7	62.6	10	799	80	74	88	560	518	616
District	ORV	2 weeks	50,000	2	68.9	10	726	73	67	79	146	134	158
District*	CVR*	1 year*	50,000*	7*	62.6*	286*	799*	3*	3*	4*	21*	21*	28*
District	ORV	1 year	50,000	2	68.9	286	726	3	3	3	6	6	6
National	CVR	2 weeks	101,067,346	7	62.6	10	1,615,157	161,516	147,975	176,297	1,130,610	1,035,825	1,234,079
National	ORV	2 weeks	101,067,346	2	68.9	10	1,466,815	146,682	135,034	159,334	293,363	270,068	318,668
National	CVR	1 year	101,067,346	7	62.6	286	1,615,157	5,647	5,174	6,165	39,532	36,218	43,155
National	ORV	1 year	101,067,346	2	68.9	286	1,466,815	5,129	4,722	5,572	10,257	9,444	11,144

**Indicates the estimated number of teams and manpower requirement for the method and timeframe that is currently being conducted in Goa across two districts (therefore double the capacity stated here).*

5.5 Discussion

This study reports the first field evaluation of the oral bait handout (OBH) method for accessing dogs on a large scale for rabies vaccination in India. OBH was superior to CVR in terms of the proportion of roaming dogs accessed for vaccination, mean cost per dog vaccinated and human resource efficiency.

Under the direction of the Government of Goa, there has been success through the current state-wide mass dog vaccination campaign using catch-vaccinate release and door to door vaccination, however the method has limited potential for sustained national implementation. The large team sizes required in the CVR method resulted in low per-person vaccination efficiencies (9 vaccinations/person/day), in contrast to the OBH method, which was able to vaccine three times as many dogs per person per day (35 dogs/person/day). When extrapolating these methods to the district and national scale this would result in a dramatic difference in the human resource requirement of the campaign (Wallace et al., 2017). A national two-week campaign using CVR would require 1.1 million staff and 160,000 trucks, compared to 300,000 staff and 150,000 scooters using OBH. In 2015 there were reported to be 70,767 veterinarians and veterinary paraprofessionals in India, highlighting that an intensive campaign using either method would need additional staff to be trained (World Organization for Animal Health (OIE), 2018). Experience from multi-national dog vaccination efforts in Latin America demonstrate several benefits to synchronising large campaigns over short timeframes, such as combining resources from multiple government and NGO sectors and in maximising public/political awareness through mass media (Vigilato et al., 2013), however this would be infeasible with the CVR method. From a logistical and human resource perspective, OBH would be a more feasible approach for conducting mass dog vaccination over a short timeframe at the national scale.

The mean operational cost per vaccine delivered for the CVR and OBH methods was 2.53 USD and 2.29 USD respectively, however this varied with land type. The high fixed daily operating cost of each CVR team at 127 USD meant that acceptable cost-efficiency relied on a high number of dogs being vaccinated every day. In low density areas the CVR cost per dog vaccinated rose to 3.29 USD in contrast to 2.33 USD for OBH. The higher vaccine cost of ORV in comparison to high quality parenteral vaccine increases the cost of OBH in regions where large numbers of inaccessible dogs require vaccination by ORV. The only other study evaluating the cost of different methods was conducted in Tunisia, comparing door to door or central point distribution of bait to dog owners and transect line distribution (Ben Youssef et al., 1998), which would not be considered acceptable methods of bait distribution in Goa. The cost per dog vaccinated for both methods here are comparable to reports from other mass dog vaccination campaigns in Africa ranging from to 1.73 to 7.3 USD, however these campaigns only accessed owned dogs that could be handled for parenteral vaccination (Hatch et al., 2017; Kaare et al., 2009; Kayali et al., 2006). A limitation of the present study is that only field delivery costs were considered in the estimated cost per dog 'vaccinated' and that the cold-chain transport and storage costs of ORV, which require freezing, will be considerably higher than for inactivated parenteral vaccines. The current study also assumed an ORV unit cost of 2.77 USD, and that the true cost per vaccine may differ from this once ORVs become available.

The OBH method of bait distribution has several advantages to public safety and campaign efficiency over other methods such as distributing to dog owners to administer and the wildlife-immunisation model (WIM). A study in Tunisia distributed baits to dog owners at central collection points (Ben Youssef et al., 1998), however this approach could not be applied in most countries due to the unacceptable risk of human exposure to the vaccine and parenteral vaccination should be prioritised for these owned dogs whose owners can hold them for injection (World Health Organization, 2018; World Organisation for Animal Health, 2018). The use of WIM may be of use for vaccination of dogs that cannot be approached, which is often the case in garbage dumps (Darkaoui et al., 2014;

Matter et al., 1998; OIE, 2015). The widespread use of the WIM would be unfavourable in residential areas, particularly due to the risk of children encountering baits and the increased risk of uptake or re-distribution by non-target species such as crows, rats, and cats (Vos & Sanli, 1998). Coverage achieved by OBH in this study is comparable with studies conducted elsewhere (Bender et al., 2017; Corn et al., 2003; Estrada, Vos, De Leon, et al., 2001a; Schuster et al., 1998), likely due to roaming dogs generally being accustomed to the presence of humans, albeit not comfortable enough to be held.

Estimation of vaccination coverage using oral bait approaches is challenging because the dogs cannot be easily marked and therefore conventional post-vaccination surveys counting marked dogs are not possible (A. D. Gibson et al., 2015; Sambo et al., 2017). In the current study the recording of all dogs sighted enabled estimation of the proportion of all dogs sighted that could be vaccinated, however this does not equate to the vaccination coverage in the population. The proportion of sighted dogs vaccinated may be influenced by the likelihood of sighting dogs between the two methods. Many staff reported that dogs are more likely to run away from the net catching teams and alert dogs in the area by barking, therefore potentially making it less likely for the team to sight dogs that could not be vaccinated. This may have resulted in over-estimating the proportion of vaccinated dogs in the CVR group in contrast to OBH teams which did not carry nets and so were less likely to alert dogs before sighting. OBH teams also reported that dogs were often attracted to the baits and would gather around them. This not only has benefits in the chances of vaccinating dogs but would also be of benefit to the sustainability of repeat vaccination campaigns.

Parenteral vaccination will continue to be the primary choice for animals that can be readily handled because of the greater control over the certainty of administration and high rates of protection in dogs of different ages and immunocompetence (Morters et al., 2015). With the use of live-modified or live-attenuated oral rabies vaccines, lower rates of immunoconversion have been reported (Cliquet et al., 2007). A field study of oral vaccination using the 3rd Generation ORV 'SPBN GASGAS' reported that 78% of dogs that consumed the bait had detectable rabies binding antibodies measured by blocking enzyme linked immunosorbent assay (ELISA) (T. G. Smith et al., 2017). A more recent evaluation of kennelled dogs in Thailand showed no significant difference in immunity between those consuming 3ml SPBN GASGAS (at a titre of $10^{8.2}$ FFU/mL), in boiled pig intestine baits, as compared to dogs vaccinated with inactivated parenteral vaccine (Leelahapongsathon et al., 2020). Therefore, should a widely acceptable bait construct be developed to effectively deliver the vaccine to the oral cavity, it is likely that high rates of seroconversion would be achieved with this vaccine. Challenge studies have shown high levels of protection using several oral rabies vaccines, including SPBN GASGAS (Bobe et al., 2023; Cliquet et al., 2007, 2008; Orciari et al., 2001; C. E. Rupprecht et al., 2005), and that evaluation of the presence of rabies binding antibodies using ELISA is likely to be a better predictor of immunity in vivo (Moore et al., 2017). Estimates of possible proportion of sighted dogs successfully seroconverting following the two methods in the present study remained comparable even at rates as low as 60% of dogs accessing ORV (Appendix D).

Ultimately the cost-effectiveness of a campaign hinges on the successful elimination of rabies, and for this to occur it must be feasible to achieve sustained, high vaccination coverage across land types (E. A. Ferguson et al., 2015). OBH was able to consistently access a higher proportion of inaccessible dogs for vaccination across land types in comparison to CVR (**Error! Reference source not found.**B). The c hallenges in catching dogs through CVR in open areas, as well as dogs becoming fearful of nets over time, creates the potential for pockets of low vaccination coverage and therefore regions where sustained endemic transmission may occur (Hampson et al., 2009). The rate of staff dog bites in this study was too low to evaluate significance between the two approaches, however, warrants further study.

The impact on the welfare and safety of the dogs, staff, and general public as a result of any intervention must be considered and weighed against the consequence of not conducting the intervention. Action to minimise the risk of injury or suffering to these groups should be taken at every opportunity. Both CVR and OBH methods present potential risks since dogs are often roaming freely in public areas and can behave unpredictably, however this must be weighed against the suffering that would be prevented for future generations through rabies virus elimination. The selection of an ORV that is safe in both target and non-target species, including humans, is essential (C. E. Rupprecht et al., 2019). More than 270 million doses of recombinant, modified-live and attenuated-live oral rabies vaccines have been used in wildlife in Europe and North America with minimal adverse events in target and non-target species (Cliquet et al., 2018; Mahl et al., 2014; Maki et al., 2017; Wallace et al., 2020), and the handout distribution method reduces the chances of human exposure to vaccine by removing a large proportion of the unconsumed bait and capsule material from the environment. In the current study it was possible to recover 99.9% of unconsumed intact baits, however the outcome of 13% of baits was unknown. This compares to a study in Haiti, where the fate of 4.8% of the baits offered was unknown (T. G. Smith et al., 2017). This may be because roaming dogs in Goa may be more likely to take the bait away to eat, however this higher rate in Goa may have also been influenced by the prototype bait construct used. The potential higher rate of non-retrieval will need to be considered when evaluating the chances of human exposure to vaccine material remaining in the environment. The lower staff bite rate for OBH suggests that there may be benefits to staff safety, project administration and cost.

The results of the staff opinion survey in this study indicate that staff preferred the OBH method and felt that they were able to ‘vaccinate’ more dogs with this as compared to the CVR method. The limitations of small sample size and possible bias for a novel method must be considered, however this survey found that experienced vaccination staff endorsed the OBH method as a feasible supplement to door-to-door parenteral vaccination to reach inaccessible dogs. Training of catchers using nets is difficult, requiring novice catchers to work within teams of experienced catchers for several weeks or months to become competent. This presents limitations to the rapid up-scaling of CVR in larger states. In the current study, the comparison was between teams highly experienced in CVR, compared to having had one day of field training using the OBH method. Despite this limitation, OBH was still comparable in the number of dogs 'vaccinated' per team per day with CVR. The OBH method still requires good training and strict adherence to standard operating procedure, however this study suggests that OBH can be successful, given good training over a short time.

There is no universally successful bait due to differences in local culture, dog ecology and food preference between countries (Berentsen et al., 2014, 2016; Guzel et al., 1998). The lack of a quality bait construct in this study is likely to have affected the proportion of dogs 'vaccinated' through the OBH approach. It is expected that more attractive baits will be developed with time, however there were limited options at the time of the study. It is important to note that the OBH 'vaccination coverage' in this study includes all dogs that were interested in the bait, as opposed to dogs that perforated the capsule. Studies using intestine baits in Haiti and Philippines both reported that 93% of baits offered to dogs resulted in the capsule being perforated (Estrada, Vos, De Leon, et al., 2001a; T. G. Smith et al., 2017) and so with bait optimisation for use in Goa, it is expected that similar outcomes could be achieved.

The development of efficient, scalable methods to repeatedly vaccinate a high proportion of the roaming dog population is the only way to avoid the indefinite provision of post-exposure prophylaxis, suffering caused by rabid dog bites and detrimental impact on tourism and agriculture industries in developing countries. The lack of a licenced ORV means that capture of dogs for parenteral vaccination is the only method of increasing coverage in inaccessible dog populations. This study indicates that should ORV be available, it would likely benefit both operation efficiency and vaccination coverage in the free roaming dog population and therefore may be of considerable benefit to rabies control activities in Goa and similar settings.

Chapter 6 Evaluation of bait constructs for oral rabies vaccination of dogs in South Asia

6.1 Abstract

Oral rabies vaccination may enable the vaccination of free-roaming dogs that are inaccessible to parenteral vaccination and is considered a promising complementary measure to parenteral mass dog vaccination campaigns. WHO and WOAH have published detailed minimum requirements for rabies vaccines and baits to be used for this purpose, requiring that baits must not only be well-accepted by the target population but must also efficiently release the vaccine in the oral cavity. For oral rabies vaccination approaches to be successful, it is necessary to develop baits which have a high uptake by the target population, are culturally accepted, and amenable to mass production. The aim of this study was to compare the interest and uptake rates of meat-based and a prototype egg-bait constructs by free roaming dogs in Goa, India.

Three teams randomly distributed two prototype baits; an egg-flavoured bait and a commercial meat dog food (gravy) flavoured bait. The outcomes of consumption were recorded and compared between baits and dog variables.

A total of 209 egg-bait and 195 gravy-bait distributions were recorded and analysed. No difference ($p = 0.99$) was found in the percentage of dogs interested in the baits when offered. However, significantly more dogs consumed the egg-bait than the gravy-bait; 77.5% versus 68.7% ($p = 0.04$). The release of the blue-dyed water inside the sachet in the oral cavity of the animals was significantly higher in the dogs consuming an egg-bait compared to the gravy-bait (73.4% versus 56.7%, $p = 0.001$).

The egg-bait had a high uptake amongst free roaming dogs and enabled efficient release of the bait fluid contents in the oral cavity, whilst also avoiding bovine or porcine meat products that would be of cultural concern in India.

6.2 Introduction

Oral rabies vaccines (ORVs) have the potential to improve the efficiency and sustainability of immunising dogs that cannot be easily accessed for parenteral vaccination (Chapter 5). The success of ORV in rabies control programmes relies on three components: an effective vaccine which is safe for target and non-target species; a bait construct that is attractive to the target species and optimised for release of the vaccine in the oral cavity; and a distribution system that maximises availability to the target species whist minimising non-target species contact. The acceptance of baits has not been previously reported in free-roaming dogs in India.

Currently available ORVs consist of modified live rabies virus or recombinant constructs, as opposed to modern parenteral vaccines which consist of inactivated rabies virus (World Health Organization, 2018). ORVs are delivered in liquid suspension within an impermeable sachet which is surrounded in a palatable material, together known as the bait construct. The bait construct promotes oral uptake and chewing by target species, at which point the vaccine sachet is perforated by the teeth and the vaccine suspension is released in the oral cavity. Subsequently, the vaccine enters the body, predominantly at the palatine tonsils, and after limited locally restricted replication, induces a protective immune response (Vos et al., 2017). This approach has been successfully developed for several rabies reservoir species including red fox (*Vulpes vulpes*), raccoon dog (*Nyctereutes viverrinus*), coyote (*Canis latrans*), grey fox (*Urocyon cinereoargenteus*), raccoon (*Procyon lotor*) and golden jackal (*Canis aureus*) (Elmore et al., 2017; T. Müller et al., 2015; Sidwa et al., 2005; Yakobson et al., 2005). For example, in Germany, the number of rabies cases in animals fell from 10,487 in 1983 to 83 cases in 1997 and ultimately led to 'rabies-free' status in 2008 following sustained systematic vaccination of the reservoir fox population using ORV (European Commission, 2002). The European Union continues to work to eliminate fox-mediated rabies from its member states through passive surveillance and systematic distribution of ORV (European Commission, 2017; European Food Safety Authority & European Centre for Disease Prevention and Control, 2023).

Studies in recent decades have indicated that ORV of dogs may be of considerable benefit to increasing vaccination coverage within inaccessible dog populations

(Cliquet et al., 2018), however there is yet to be a large-scale example of its implementation. WOAH and WHO have advocated for its incorporation into mass dog vaccination initiatives, following evaluation in settings where they could be of benefit to rabies control (World Health Organization, 2018; World Organisation for Animal Health, 2018). In the evaluation of the oral bait handout method (OBH) in Chapter 5, the OBH method was combined with the DD parenteral vaccination of accessible dogs. When compared with the existing CVR vaccination protocol, the OBH method was more efficient both in terms of human resource and estimated cost per dog vaccinated.

Identifying a bait that is well accepted by the local dog population is crucial to the success of ORV of dogs. The smell, palatability, texture, shape, and size of the bait construct is critical to ensuring uptake of the vaccine sachet into the dog's mouth and chewing to ensure perforation and release of the liquid contents into the oral cavity before the remnants are swallowed or discarded. If the bait construct is swallowed whole, without perforation of the vaccine sachet in the oral cavity, the dog will not be immunised (Langguth et al., 2021; Leelahapongsathon et al., 2020). Many studies have demonstrated wide variation in bait preferences between dog populations of different countries, however, comparison of results between studies is challenging due to variation in study design and bait type (Corn et al., 2003; Estrada, Vos, & De Leon, 2001; Estrada, Vos, De Leon, et al., 2001b; Frontini et al., 1992; Langguth et al., 2021; Linhart et al., 1997; Matter et al., 1995; Schuster et al., 1998).

Previous studies in the Philippines, Turkey, the Navajo Nation, Haiti, and Thailand showed that baits made by placing the vaccine sachet inside locally available bovine or porcine intestine were not only very attractive for dogs but were also efficient in delivery of the vaccine in the oral cavity (Aylan & Vos, 2000; Bender et al., 2017; Estrada, Vos, & De Leon, 2001; Estrada, Vos, De Leon, et al., 2001b; Kasemsuwan et al., 2018; T. G. Smith et al., 2017). This intestine bait is not suitable for use at scale in India due to difficulty in mass production as well as the need to avoid bovine and porcine meat products for its use to be broadly acceptable in Hindu and Islamic communities (Bonne & Verbeke, 2008). Therefore, alternative solutions for mass producible bait constructs have been explored, which have included fish, commercial pet food and egg-baits (Bender et al., 2017; Kasemsuwan et al., 2018). Pet food-based and egg-baits were considered most feasible for mass production and so were selected for use in this study.

This study aimed to compare the acceptance, perforation, and swallowing rates of two bait constructs by free-roaming dogs in Goa, India. The study design is comparable to that used in previous studies conducted in the Navajo Nation and in Thailand (Bender et al., 2017; Kasemsuwan et al., 2018).

6.3 Materials and methods

6.3.1 Study Area

The study was conducted in Goa State, India as part of the ongoing rabies control activities being conducted by the Mission Rabies charity in partnership with the Government of Goa to investigate alternative methods for accessing dogs for rabies vaccination. Locations were chosen at random within two urban regions: Panjim and Goa Velha.

6.3.2 Bait Constructs

The highly attractive baits made from porcine or bovine intestine used in previous studies would likely not be culturally accepted across India and hence were not evaluated. Two bait constructs were tested; the placebo vaccine sachet was incorporated in an egg-flavoured bait matrix (‘egg-bait) or coated with a commercially available pet food gravy (‘gravy-bait’) (Figure 6.1).

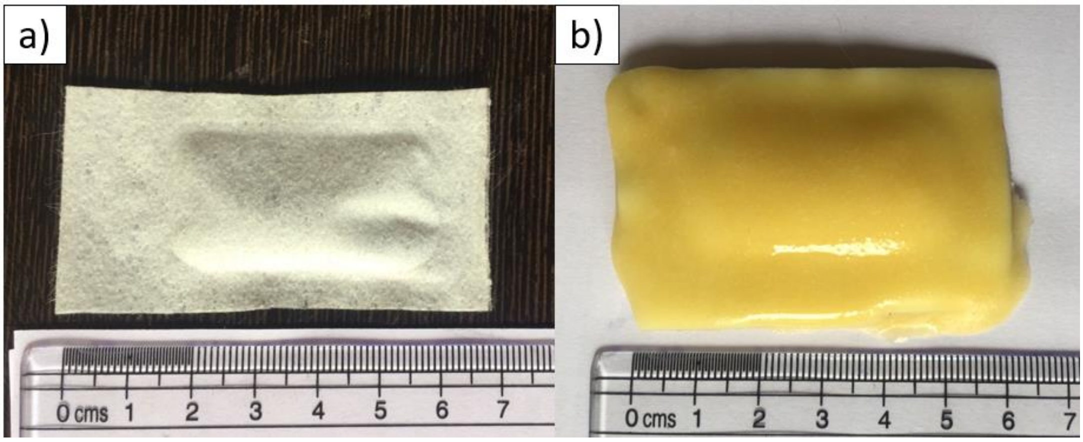


Figure 6.1 - Photographs of the two bait construct types; (A) gravy-bait (before being dipped in dog food gravy) and (B) egg bait.

6.3.2.1 Capsule

A soft blister sachet made of biodegradable foil covered with an absorbent fleece was used as the base of the bait construct (70 × 35 × 5 mm) (Figure 6.1A). The sachets contained a food colorant (Patent Blue V, Thermo Fischer Scientific, Geel, Belgium) and sucrose dissolved in water (3 mL) and no active ingredients. The colorant was added to increase detectability if the contents of the sachet were released in the oral cavity.

6.3.2.2 Egg-Bait

The industrial manufactured egg-flavoured bait was almost identical to the baits used in previous studies (proprietary to IDT Biologika, Dessau-Rosslau, Germany) (Bender et al., 2017; Kasemsuwan et al., 2018). Due to import restrictions, the egg-baits were manufactured in India using locally available materials that partially deviated from the original ingredients and method, meaning that the egg matrix coating differed in thickness and flavour to previous baits. After preparation, batches of 15 egg-baits were placed in a foil zip-bag and stored frozen until used.

6.3.2.3 Gravy-Bait

The outer layer of the sachet used in this study was absorptive to liquid. Therefore, batches of 15 sachets were placed in a zip-bag and at the beginning of each distribution session shortly before use, 100 g of commercially available pet food gravy (chicken flavour) was poured into the zip-bag, coating the sachets, and soaking into the outer layer of the sachet.

6.3.3 Study Design and Bait Distribution

The field study took place on the 11th and 12th of July 2018. Three teams (named 'Leopards', 'Tigers', 'Anmesh'), each consisting of two people, travelled by moped distributing baits in randomly allocated sections of the study area between 07:00 and 17:00. Baits were defrosted shortly before each vaccination session and carried by the teams in separate bags within portable cool boxes. One person was responsible for offering the bait to the dog and the other for data collection. The type of bait offered to each dog was randomly pre-determined and free-roaming stray dogs were the target population for bait administration.

Staff were trained in bait distribution methods as in a previous study of OBH methods in Goa State (Chapter 3, (A. D. Gibson, Yale, et al., 2019)). Briefly, staff were trained to approach dogs indirectly, avoiding eye-contact, dropping the bait in front of the dog whilst continuing to walk on and having the data collector watch the dog inconspicuously from a distance, recording their observations. The training consisted of a classroom-based session, entering dummy data under supervision into the forms after watching a video footage of bait administrations, followed by a supervised field session. The whole training was no more than three hours in duration. When dogs were in a group, baits were distributed individually to spread out the dogs and minimise competition, with the dominant animal being offered first. Any remnants of baits discarded by dogs were recollected by the observer and not left behind. A project contact number was distributed for members of the public to contact for any questions about the study.

6.3.4 Data Collection

Data about every bait dispensed were recorded in customised forms in the WVS App (Chapter 2, (A. D. Gibson et al., 2018)). This automatically captured the GPS location, time, date, and user of each data point. Compulsory fields were then displayed for entering information about the bait interaction and about the dog. These fields were comparable to data recorded during the field studies in Thailand and the Navajo Nation (Bender et al., 2017; Kasemsuwan et al., 2018).

Data recorded about the bait interaction included the type of bait (egg/gravy), acceptance, consumption, sachet perforation, bait handling time, bait outcome and bait efficacy. Bait acceptance was defined as whether the dog showed interest with direct oral/nasal contact with the bait through sniffing or licking ('interested') or ignored or did not acknowledge the bait ('ignored'). Consumption was recorded as whether the dog took the bait into the mouth or not and for egg-baits what proportion of the egg casing was consumed (<50%, >50%, 100%). Perforation was recorded on whether the sachet was observed to be perforated by the teeth of the dog. Bait handling time was estimated based on the observed time that the dog manipulated (chewed) the bait (very short (<10 seconds), short (10–30 seconds), medium (30–60 seconds), or long (>60 seconds)) and the outcome of whether the sachet remnants were swallowed or discarded was also recorded. Finally, bait efficacy was recorded as the staff member's assessment of whether the dog would have been effectively vaccinated if the sachet contained active oral rabies vaccine, based on observing release of the blue dyed water in the oral cavity. For all answers an "Unknown" field was available if the outcome was not observed, for example if the dog took the bait out of sight.

Data recorded about each dog offered bait included whether the dog was alone ('single') or with other dogs ('multiple') and if so, how many other dogs were present, age (adult/juvenile/puppy), sex (male/female) and size (small/medium/large). For analysis, a 'time of day' variable was defined according to which vaccination session each record was created in: 'early morning' (before 09:30), 'morning' (09:30 – 13:00), or afternoon (after 13:00).

6.3.5 Statistical Analysis

The data from the WVS App were downloaded in comma-separated values (CSV) format. Further analysis was then performed in R statistical software environment (version 3.6.2). Confidence intervals for proportions were calculated using the exact binomial test of the R *stats* package (Clopper & Pearson, 1934; R Core Team, 2018). Confidence intervals are reported from regression analyses at the 95% level using a profile log likelihood. Chi squared test was used to identify association between individual variables.

Multivariable logistic regression was used to estimate the difference in bait acceptance between the egg-bait and the gravy-bait, adjusting for other factors including dog size, presence of multiple dogs, age, time of day, sex, and team. Two different models were built. The outcome variable of the first model was whether, according to the data collector, blue dyed liquid was released in the oral cavity, i.e., likely theoretical “vaccination” if ORV had been present. The outcome variable of the second model was possible “vaccination”, i.e., dogs who were seen to release the blue-dyed liquid in the oral cavity as well as those where the bait was seen to have been taken in the mouth of the dog, but the perforation status of the capsule was not confirmed within the oral cavity were both classed as “vaccinated”. All predictors were considered for inclusion in the model. All possible variable combinations were considered using the package MuMIn (Bartoń, 2018). The model with lowest Akaike information criterion (AIC) was chosen as the final model (Appendix E). Ordinal logistic regression was used to evaluate the effect of presence of multiple dogs and team on bait handling time, using the *MASS* package (Venables & Ripley, 2002). Bait handling time groupings are defined above in Section 6.3.4. Model outcomes for combinations of predictor variables of bait type, presence of multiple dogs, and team were compared (Appendix E). Bait type and team were as defined above, and the presence of multiple dogs was defined as dogs being alone (single). Akaike information criterion (AIC) was used to assess goodness of model fit and the significance of the effect of the presence of multiple dogs on bait handling time was compared between models.

6.3.6 Ethical Statement

Permission for the study was granted by the Department of Animal Husbandry and Veterinary Services, Government of Goa. Ethics approval was provided by University of Edinburgh R(D)SVS Veterinary Ethical Review Committee (Reference number 113.18).

6.4 Results

A total of 406 bait offerings were recorded, however two were removed, one because it was recorded as bait type ‘unknown’ and one bait was taken by birds, leaving a total of 404 observations (209 egg-bait, 195 gravy-bait). Eight records reported bait acceptance as ‘ignored’, but the bait was also recorded as ‘consumed’ with subsequent information about vaccine release and chewing time, therefore, bait acceptance was corrected to ‘interested’. One record was recorded as ‘not consumed’, but also the theoretical vaccination status as ‘vaccinated’ and so this record was amended to ‘not vaccinated’. In six cases (two egg-bait and four gravy-bait), the perforation status was recorded as ‘unknown’, whilst the theoretical vaccination status was ‘vaccinated’, so the vaccination status was amended to ‘unconfirmed’.

Overall, a high proportion of dogs showed an interest in both bait types, with 81.3% (CI: 75.4 - 86.4%) of dogs making oral or nasal contact when offered the bait compared to 81.0% (CI 74.8 - 86.3%) of dogs offered gravy-baits (Appendix E). A statistically significantly higher proportion of dogs consumed (i.e. took the bait into the oral cavity) the egg-bait (77.5%, CI: 71.2 - 83.0%) than did for those offered the gravy-bait (68.7%, CI: 61.7 - 75.2%) (Appendix E); Chi2 = 3.94, df = 1, p = 0.047 (Figure 6.2).

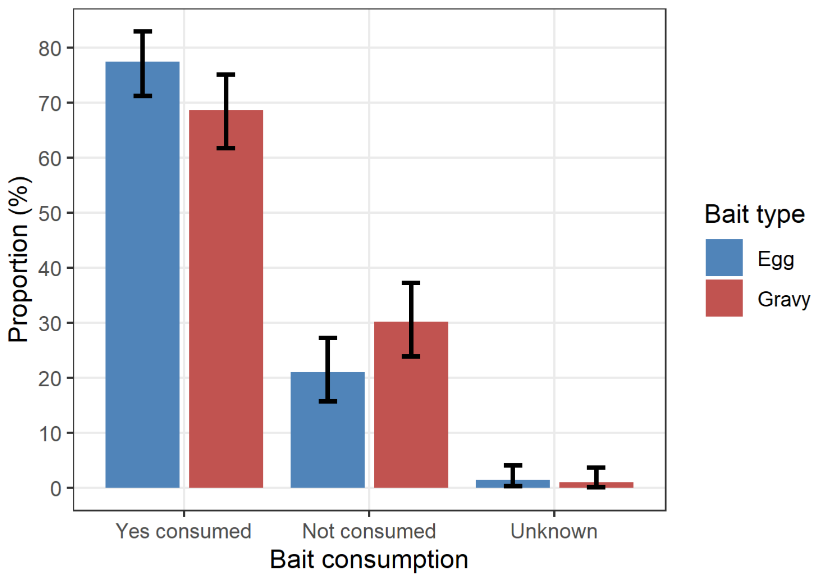


Figure 6.2 - Chart showing the proportion of all dogs offered baits which took the bait into the oral cavity (consumed).

Of the 296 baits consumed, the perforation status of 269 sachets was observed. Of baits where the outcome was observed, the sachet within the egg-bait (91.1%; CI: 86.4–95.7%) was significantly more often perforated than with the gravy-bait (72.4%; CI: 64.4–80.2%); Chi2 = 14.98, df = 1, $p < 0.001$ (Appendix E).

Theoretical 'vaccination' success as indicated by observation of release of the blue-dyed liquid in the oral cavity was more likely in dogs offered an egg-bait than dogs offered a gravy-bait and this effect was significant when adjusting for sex of the dog and team (OR 2.25, CI 1.47–3.43) (Appendix E). Blue-dye liquid was observed as released in the oral cavity in 73.4% of dogs consuming the egg-bait and 56.7% of dogs offered gravy-bait, representing 56.9% and 39.0% of all dogs offered egg- and gravy-baits respectively (Table 6.1, Figure 6.3). The outcome of 30 egg-baits and 24 gravy-baits was recorded as 'unknown' and were considered as 'vaccination' failures in the estimates above. Oral release may have occurred in these cases and so if they were included, the proportion of all dogs that may have been 'vaccinated' was 71.3% of dogs offered egg-baits and 51.3% of dogs offered gravy-baits (Table 6.1).

Table 6.1 - Table of bait consumption, perforation, and oral release of blue-dyed liquid. Percentages in brackets are the percentage of total baits for that bait type.

	Not Consumed		Bait Consumed				
Bait Type	**Not Interested**	**Interested, Not Consumed**	**Not Perforated**	**Perforation Unconfirmed***	**Perforation Seen, Oral Contact Unconfirmed***	**Perforation Seen, Oral Contact Confirmed**	**Total**
Egg	37 (17.7%)	10 (4.8%)	13 (6.2%)	16 (7.7%)	14 (6.7%)	119 (56.9%)	209
Gravy	36 (18.5%)	25 (12.8%)	34 (17.4%)	11 (5.6%)	13 (6.7%)	76 (39.0%)	195

** Fields where oral release of liquid was not observed, but may have occurred.*

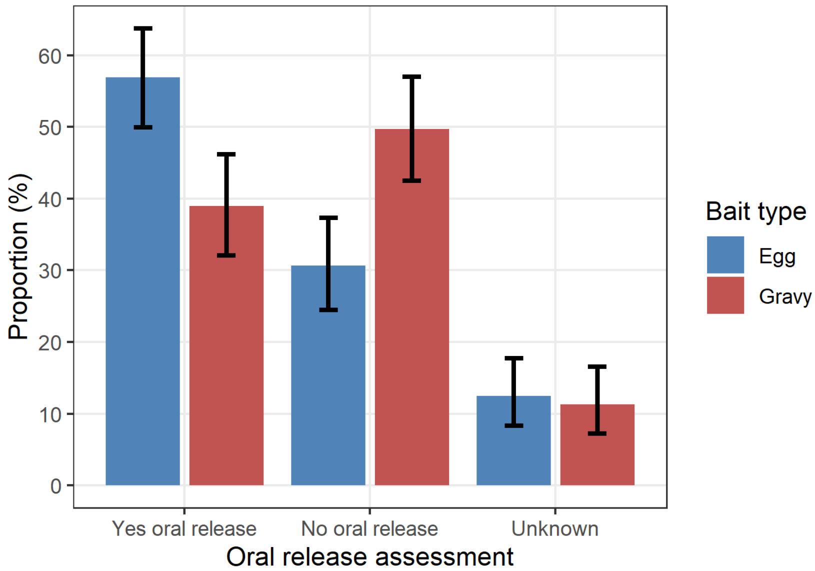


Figure 6.3 - Chart showing the proportion of all dogs offered baits which were observed to release the blue-dye liquid sachet contents in the oral cavity, therefore likely 'vaccination' if vaccine had been present in the liquid.

The multivariable logistic regression model showed no association between dog age, dog size or time of day with bait consumption. Significant differences were observed between the three teams in the proportion of dogs interested, consuming, and considered vaccinated after being offered a bait (Appendix E).

Whether or not the sachet was ingested or discarded was observed for 286 of the 296 consumed baits. Significantly more sachets were swallowed for the egg-bait (59.9% CI 51.9–67.5%) than were for the gravy-bait (35.1% CI 27.0–43.8%) (Chi2 =

20.2, df = 1, p < 0.001), with the gravy-bait sachet being more likely to be discarded (Figure 6.4, Appendix E).

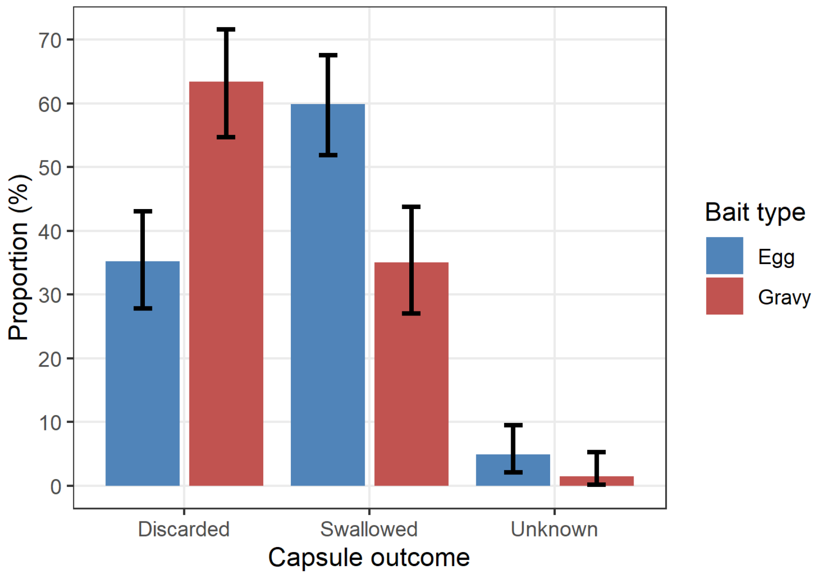


Figure 6.4 - Chart showing the proportion of bait sachets swallowed and discarded for each bait type.

The duration of bait handling did not differ significantly between the two bait types; Chi2 = 4.840, df = 3, p = 0.183 (Appendix E). Single dogs took significantly longer to consume the bait than dogs who were offered a bait when the animals were together with other dogs (Chi2 = 12.566, df = 3, p = 0.0056). Ordinal logistic regression indicated a difference between chewing time for single dogs versus dogs in a group, however when the team was added as a variable, this effect is not seen, indicating a potential user bias in the recording of bait handling time (Appendix E). Of baits that were consumed, all of the egg-bait material was eaten in 54.8% (CI: 46.4–63.0%) of cases.

6.5 Discussion

This study investigated the acceptance rates of oral bait constructs in free roaming local breed dogs. The egg-bait was found to be a better candidate than the gravy-bait as a potential vehicle for delivering ORV in the roaming dog population in India.

Just as a safe and efficacious vaccine is important, the identification of a bait that is widely consumed by the target population and releases the vaccine in the oral cavity is prerequisite to the success of ORV. WOAH has listed detailed requirements and characteristics of baits to be used for ORV, among others; (1) it should be designed specifically for the target species, (2) it should be attractive to the targeted population (local food preferences), (3) it should remain stable under a wide range of temperatures and weather conditions, (4) it should optimise the release of the vaccine into the targeted tissues (in the oral cavity), (5) its ingredients should be safe for target and non-target species and should comply with animal feed standards and not interfere with vaccine activity, (6) it should allow the incorporation of a biomarker, and (7) it should feature a labelling system, including public warning and identification of the product (Wallace et al., 2020).

Previous studies have used PVC-based vaccine sachets (Bender et al., 2017; Estrada, Vos, & De Leon, 2001; Schuster et al., 1998), however, there would be concern using such sachets at scale in conjunction with bait constructs that result in high rates of swallowing due to the risk of gastrointestinal tract irritation or obstruction. Therefore, a soft sachet was developed which reduces any risk of gastrointestinal tract obstruction if swallowed. The absorbent outer layer of the soft sachet made it possible to effectively coat the sachet in commercially available pet food gravy, to make the sachet palatable in the case of the gravy-bait and to attach the egg casing for the egg-bait.

Although the egg-bait ingredients, sachet type and bait sizes varied between studies, there were considerable differences in the swallowing rate of the sachets in the egg-bait between India (63%), Thailand (2%) and the Navajo Nation (59%) studies. The Navajo Nation study compared ‘hard’ and ‘soft’ sachet types in numerous bait constructs, with soft sachet type baits having significantly higher swallow rates than those containing the hard PVC sachets, however this was 42.2% and 80.4% in hard and soft egg-baits respectively (Bender et al., 2017). Locality also seems to play a role and may be related to access to or competition for food. In the

Navajo Nation, 42.2% of dogs offered an egg-bait swallowed the hard capsule, as compared to just 1.5% in Thailand. The dogs in Thailand were fed on a regular basis in contrast to the dogs in the Navajo Nation who devour baits offered without much chewing. In the current study, bait handling times were considerably shorter than both studies, which may relate to the use of the soft rather than hard sachet or potentially a consequence of estimating the time the dogs spent chewing as opposed to timing with a stop clock. Unmanaged food waste and feeding by community members are common food sources for free roaming dogs in India (Tiwari, Robertson, O'Dea, & Vanak, 2019b) and further investigation is required to investigate the impact that this may have on bait consumption and handling time.

Dogs consumed the egg-bait (77.5%) more often than the gravy-bait (68.7%). Interestingly, very similar consumption rates for the egg-bait were reported in the Navajo Nation (77.4%) and Thailand (78.8%) (Bender et al., 2017; Kasemsuwan et al., 2018). However, only 54.8% of the dogs in India consumed the whole bait compared to 88.3% and 81.2% in the Navajo Nation and Thailand, which was thought have been due to variation in the ingredients used between the studies and should be possible to overcome with further refinement.

The most important record was whether the data collector observed release of the blue-dyed liquid in the oral cavity, indicating whether the dog would likely have been vaccinated if the sachet had contained ORV. Of dogs that consumed the bait, at least 73.4% were observed to release liquid in the oral cavity in the current study, as compared to 84.5% in Thailand and 89.9% in the Navajo Nation (Bender et al., 2017; Kasemsuwan et al., 2018). Of all dogs offered an egg-bait where an outcome was recorded, 64.3% were observed with blue-dyed liquid released in the oral cavity in the present study. This clearly underscores the potential of ORV for dogs in India but also emphasises that ORV is a complementary tool to parenteral vaccination since not all dogs offered a bait will accept it and not all dogs that consume a bait can be considered vaccinated (T. G. Smith et al., 2017). Evaluation of vaccination coverage subsequently achieved is difficult due to the lower rates of seroconversion as detected by conventional tests, e.g., seroneutralisation tests (Rapid Fluorescent Focus Inhibition Test - RFFIT, Fluorescent Antibody Virus Neutralization - FAVN), used to evaluate parenteral vaccination (Moore et al., 2017), however, ORV of dogs can increase the vaccination coverage of the dog population above the level needed to achieve the required herd immunity and therefore interrupt the rabies virus transmission cycle among dogs (T. G. Smith et al., 2017; Vos et al., 2003).

In the current study, there was considerable variation between teams, indicating an inconsistency in the method of bait distribution. The chances of a dog approaching and consuming a bait is highly influenced by the way that the team approach the dog and how they drop/toss the bait. All the field staff in the study were experienced in CVR methods and data capture using the WVS App however they had comparatively limited experience with the OBH method, which may account for the variation in bait acceptance seen between teams. This finding underscores the need for the development of comprehensive and effective training resources that achieve consistency between teams. The half day training described in this study would need to be followed by a period of field supervision and evaluation to ensure that competence in the distribution method is reached. One of the main advantages of the OBH method as practiced in this study is that even if baits are not accepted, the risk of direct human contact with the vaccine is reduced to negligible levels through recollection of unconsumed baits (Head et al., 2019).

The contribution of ORV will be a crucial tool in the elimination of dog rabies, especially in areas with a high proportion of free-roaming dogs inaccessible for parenteral vaccination. For example, in Bali, Indonesia, free-roaming owned dogs outnumber the restricted owned dogs as 66% to 79% of the owned dogs are free-roaming (Arief et al., 2017; Widyastuti et al., 2015). Furthermore, free-roaming owned dogs in Bali were 2–3 times more likely to be unvaccinated compared to those confined (Arief et al., 2017) and the majority of dogs were vaccinated by dog catching teams using nets, since most dogs resisted handling even by their owners (Widyastuti et al., 2015). Another concern reported from repeated use of net-catching methods was that it can become increasingly difficult to catch free-roaming dogs during subsequent vaccination campaigns (Widyastuti et al., 2015). Challenges in accessing dogs for parenteral vaccination were also encountered during mass dog vaccination campaigns in Flores, Indonesia (Wera et al., 2015). One of the main reasons identified for owned dogs not being vaccinated was the lack of resources to catch and restrain them by their owners. Intensive vaccination of 70% of the dog population has been demonstrated in focal projects in India, however the challenge of how to efficiently vaccinate large numbers of inaccessible dogs to achieve herd immunity remains. Combining parenteral and ORV methods may help to increase the feasibility of conducting mass dog vaccination at scale in such settings (Chapter 3, (A. D. Gibson, Yale, et al., 2019)). The egg-bait investigated in this study could provide an effective delivery vehicle for use in these approaches to finally break the deadlock and eliminate dog rabies from large areas.

For a bait to be of potential use for ORV delivery across large areas of India, it must be both possible to produce efficiently in large quantities and it must be widely culturally accepted in both Hindu and Islamic communities. The use of bovine meat products would not be acceptable to the Hindu community, neither would porcine meat products in Islamic communities. Therefore, a non-meat-based bait which can be mass produced locally would be preferable. The egg-bait evaluated in this study could feasibly be produced at mass-scale using local products and is therefore a candidate for further optimisation. Given the slight difference in ingredients used in previous studies, the author is confident that continued refinement of the egg construct will increase palatability and rate of likely vaccination above those reported in this study.

6.5.1 Conclusion

This study reports potential bait types for use in delivery of ORV to dogs in India and other settings of South Asia. The use of an effective, well accepted ORV, alongside parenteral vaccination methods may make it possible to more rapidly scale-up mass dog vaccination activities in India, which is urgently needed to reduce the canine rabies burden. The high acceptance rates of the non-meat-based egg-bait indicates the potential for ORV to access a high proportion of free roaming dogs which cannot be readily accessed for parenteral vaccination.

Chapter 7 Discussion

Dog-mediated rabies represents a generational opportunity to combat a disease that epitomises many deeply intrenched health inequities in the modern world. This research began with the objective to implement mass dog vaccination in Goa, India and evaluate the impact on rabies incidence in humans and dogs. I quickly identified the need to explore the use of technology to improve the quality and availability of campaign data, which unfolded into several other advantages for programme implementation. Challenges in achieving and sustaining high vaccination coverage in a large roaming dog population spurred research into variations on campaign structure and vaccination methodology. Enhancement of state-level surveillance processes revealed insights into the impact of control measures on rabies incidence in dogs and people and review of programme expenditure identified the intervention as highly cost-effective. New research priorities emerged from recognition of the limitations of existing dog vaccination methods, prompting the evaluation of oral rabies vaccines and bait constructs that would be suitable for mass deployment in South Asia.

We arrive at a waypoint on the journey for rabies control in Goa state and in the wider odyssey for the control of dog rabies in India. This work is an unapologetic spotlight on the importance of operational research into the nuts and bolts of implementing rabies control interventions in endemic settings. The new insights gained, in terms of smartphone technology, vaccination methods, dog demography, One Health impact, and use of ORVs, lower the barriers to progressing effective rabies control interventions elsewhere in India and contribute to the wider body of experience and learning on the subject of dog rabies elimination. Further research of this nature is needed to illuminate a better understanding of the strengths and limitations of existing field processes, advance innovation in programme refinement, and promote the adoption of evidence-based government policies.

7.1.1 Key findings

Review of the literature of dog rabies control globally showcased the significant weight of evidence for the efficacy of mass dog vaccination in eliminating rabies at relatively low vaccination coverages (**Chapter 1**). However, with a dearth of examples reporting attempts, let alone success, from most rabies endemic settings, key opinion leaders were increasingly vociferous of the urgent need for applied research into the mechanisms of dog vaccination delivery at scale (Bagcchi, 2015; Cleaveland et al., 2017; Kakkar et al., 2012; Zinsstag, 2013).

My early exploration of the use of smartphone technology in dog vaccination was driven by a need to improve the quality of operational data from which to understand unfolding field activities (**Chapter 2**). I led a team of colleagues and collaborators to develop a smartphone app-based platform to support the planning, implementation, and evaluation of mass dog vaccination campaigns. The superiority of electronic data entry forms over paper records opened new horizons for gathering high-resolution spatiotemporal data from which to evaluate operations and study the dog population being vaccinated. Campaign oversight was drastically improved through the ability of vaccinators to upload these data via cellular connectivity, enabling project managers to review maps of vaccination activity through a simple website interface and rapidly adapt the campaign strategy accordingly. Providing project managers with simple digital cartographic functionality through the platform created an opportunity to build additional features to support efficient vaccination team direction. The system enabled them to define the geographic region they wanted the remote vaccination workforce to deploy to, and send this spatial instruction directly through maps displayed in the smartphone app. As the number of active vaccination teams increased, this technology transformed the spatial coordination of vaccination effort across a population. Research conducted by others, in collaboration with the author, demonstrated that use of the system significantly increased vaccination coverage in comparison to traditional vaccination methods when implemented by a government workforce in Haiti (Monroe et al., 2021). It provided an implementable solution for the theoretical importance of homogenous vaccination effort (E. A. Ferguson et al., 2015; Suseno et al., 2019). Use of the WVS App platform by independent organisations and governments has continued to increase and has been used to record the delivery of over 3 million dog vaccination events to date (**Chapter 2**) (Adrien et al., 2019). The functionalities developed to support rabies control have relevance to other mass immunisation programmes and have potential to benefit the efficient control of other diseases (DEFRA, 2022).

The iterative process of developing dog vaccination methods began with an understanding that a high proportion of the roaming dog population in Goa were not readily amendable to handling for parenteral vaccination (**Chapter 3**). This fuelled an initial campaign structure grounded in the capture-vaccinate-release (CVR) method, where teams of seven or more people moved through communities using aluminium-framed butterfly-nets to catch dogs for vaccination as had been reported in the large campaigns in Bali (Putra et al., 2013). I initially hoped to harness the benefits brought by short-duration pulse vaccination campaign structures that had been the cornerstone of the Global Polio Eradication Initiative and in the enormous dog vaccination campaigns of Latin America (Andrus et al., 2001; Velasco-Villa et al., 2017). Whilst the implementation of a one-month state-wide campaign in 2015 vaccinated over 30,000 dogs, it highlighted the limitations of scaling the CVR method whilst maintaining high vaccination coverage. Effective CVR implementation required a large, specialist workforce; something that was not readily available on a temporary basis for a short period of the year. The subsequent expansion of a more protracted campaign structure enabled the retention of a highly skilled, permanent workforce that achieved high vaccination coverages in a region-by-region 12-month rotation. Field experience revealed inefficiencies in a CVR-only approach, as the high proportion of dogs that could be held by an owner or guardian for vaccination created redundancy for the large team of skilled net-catching staff. The workforce was restructured to establish small, two-person, door-to-door (DD) hand-catching teams, to first target the vaccination of dogs that could be restrained by hand for vaccination, before CVR teams deployed to increase coverage through vaccination of dogs less amenable to handling. This combined DD-CVR method increased the campaign output and workforce efficiency, with similar reliance on hand-catching reported in other vaccination campaigns in rural settings of Sikkim and Tamil Nadu (Airikkala-Otter et al., 2022; Byrnes et al., 2017).

As the campaign scaled, using smartphone technology to record over 97,000 vaccinations annually, vast amounts of information were amassed from a large cross-section of the dog population. This created a cornucopia of spatiotemporal data from which to explore operational outputs and population structure (Chapter 3). I used open-access high-resolution human data to map Goa's urban-rural continuum, and overlayed GPS campaign data to explore aspects of dog population demography and vaccination methodology. The insights gained into the heterogeneities of dog ownership and accessibility across the urban-rural gradient can help to inform the creation of tools aimed at supporting the design of efficient high-coverage vaccination programmes (Wallace et al., 2019).

Robust surveillance to monitor rabies incidence in dogs and people was central to evaluating the impact of control efforts (**Chapter 4**). I described the development of a state reporting channel to screen notifications of suspect rabid animals, provide advice, and coordinate a response, which became the core to the identification of rabid animals. Laboratory capacity for rabies diagnosis underpins effective rabies surveillance and was initially lacking in Goa, as is the case across much of Asia (Banyard et al., 2013). State-laboratory rabies diagnostic capacity was built through multi-agency collaboration and the government veterinary laboratory serves as an example for establishing sustained high-throughput testing of suspect rabid animals at the state-level. The use of lateral flow assays and portable viral sequencing and demonstration of their benefit to the programme are of relevance to expanding rabies surveillance systems across larger areas of India (Gigante et al., 2020; Yale et al., 2019).

Review of the spatiotemporal distribution of rabies cases across the project showed the progressive control of human and dog rabies as dog vaccination and community awareness activities scaled-up (**Chapter 4**). After five years without a human death from rabies and elimination of the virus from many regions of the state, the programme demonstrated dog vaccination as an effective solution for rabies control in dog populations in India. Cost-effectiveness analysis estimated that the intervention was highly cost effective at 0.27× India's gross domestic product per capita, positioning rabies control as a clear political opportunity to improve public health in India and comparable to evaluations of simulated interventions in India and Sri Lanka (Fitzpatrick et al., 2016; Häsler et al., 2014). The intervention was estimated to have prevented the death of 121 people in Goa, many of whom would have been children (Sudarshan et al., 2006).

As Goa approaches the milestone of dog rabies freedom it is imperative that the project continues to evolve. Stakeholders must remain clear-sighted about ongoing priorities of maintaining rabies freedom and the risks that lay ahead should rabies surveillance and awareness become neglected (Townsend, Sumantra, et al., 2013). Sustained widespread public awareness for the need to report animals showing possible signs of rabies is needed to ensure early detection of rabies virus introduction to previously free regions (Layan et al., 2021). To this end, I and others produced a short educational video using footage of rabid animals in Goa to communicate the signs of rabies in English, Hindi, and Kannada (Worldwide Veterinary Service, Gibson, Yale, et al., 2021). It is equally important that funders and government partners understand that reintroduction of the rabies virus is likely to occur, and that provision is made to ensure that capacity for remedial vaccination is available when required (Hampson et al., 2007). Furthermore, Mission Rabies and our collaborators continue to explore the use of annual Central Point vaccination campaigns as a mechanism for maintaining public and political attention on the issue of rabies and to promote a culture of responsible dog ownership through owner-presentation of dogs.

During project implementation several fundamental limitations of the CVR method for rabies control in India were forecasted, both in terms of their sustained deployment in the dog population and in the exponential growth of vaccination campaigns required to achieve elimination at scale. Experience and data from Goa indicate that dogs become progressively harder to catch with repeated deployment of the CVR method, risking diminishing efficiency over consecutive campaigns. Furthermore, the highly skilled nature and large human resource requirement of the CVR approach presents a challenge in establishing a workforce of sufficient scale to vaccinate a population of millions of dogs every year. The evaluation of methods incorporating ORVs into mass dog vaccination programmes offered possible benefits in both aspects (**Chapters 5 and 6**). The ease with which staff can be rapidly trained, as outlined in a training video produced from this research (Worldwide Veterinary Service, Gibson, Bell, et al., 2021), offers the possibility of recruiting a large workforce covering entire districts during a short campaign period (**Chapter 4**) (A. D. Gibson et al., 2020). The broadly positive vaccination experience through ORV, even in timid dogs, as compared to capture in a net, would likely result in increasing vaccination coverage in consecutive campaigns as compared to dogs becoming progressively more difficult to catch through CVR (**Chapter 3**).

Hesitancy for the use of ORVs to vaccinate dogs in settings of high human density stem from concerns of the risk of modified live rabies virus vaccines to revert to pathogenic forms and the risk this poses to human health (Cliquet et al., 2018). Third generation ORVs, such as the vaccine SPBN GASGAS (CEVA Animal Health, France), have been developed through targeted site-specific mutations of first-generation rabies virus vaccines, which has further improved the vaccine safety profile (Chanachai et al., 2021; Head et al., 2019; Kamp et al., 2021; Wallace et al., 2020). The simulation of a hypothetical vaccination campaign delivering 10 million baits containing the SPBN GASGAS via the oral bait handout method estimated no human deaths through exposure to the vaccine (Yale et al., 2022). Field trials deploying ORVs for dog vaccination in Thailand, Haiti, and Namibia, as well as vocal advocacy from global health institutions including WHO, WOAH and FAO, indicate momentum towards their expanded use (Chanachai et al., 2021; Freuling et al., 2022; T. G. Smith et al., 2017).

Whilst authorisation for the use of ORVs in South Asian countries would define a new horizon of opportunities for optimising rabies control strategies, it should be recognised that they will not be a panacea for the challenges of mass dog vaccination in South Asia. Questions remain about the cost of high-quality, effective ORVs, realistic timelines for their mass production and availability at scale, and availability of infrastructure to maintain cold chain (Yale et al., 2022). Further research is needed into methods of ORV distribution, rates of human contact, and social acceptance, and the pathway for regulatory approval, policy recommendation, and programme introduction can be complex (Giersing et al., 2017). It will likely be several years before the incorporation of ORVs into state-wide dog vaccination campaigns is a consideration, during which time people continue to be exposed to the rabies virus via bites from rabid dogs. Therefore, it is imperative that parenteral approaches to mass dog vaccination are advanced without delay as regardless of prospects for ORVs, they will always form the core foundation of rabies control as the vaccine of choice for dogs that can be handled (Wallace et al., 2020; World Health Organization, 2018).

There were several limitations to the research into rabies control in Goa. Monitoring of rabies incidence in both humans and dogs is impacted by the sensitivity of surveillance systems in the detection of rabies cases. Even with enhanced surveillance for dog and human rabies established during the project it is possible that rabies virus circulation below the detection threshold occurred during the study period. The likelihood of elimination of rabies from Goa may have been increased by several local factors. Goa's geographic isolation and the further physical separation of dog populations by rivers were likely to be advantageous to rabies elimination and are not typical of many areas of India (Brunker et al., 2018). Smaller population size was also identified as increasing the probability of rabies elimination at wide ranges of vaccination coverage by Kotzé et al. and Goa's dog population of approximately 150,000 dogs is far less than many contiguous dog populations in India (Kotzé et al., 2021).

7.1.2 Prospects for rabies elimination beyond Goa

Debate on the merits and drawbacks of global disease elimination / eradication initiatives continues at the very heart of the global public health discourse. Whilst such visions can align activities around specific aims, energise action, and mobilise resources, many cite issues in drawing attention and investment away from broader development goals and creating silos of activity which duplicate efforts (MacDonald et al., 2020). These endeavours risk becoming an all-or-nothing gambit; front-loading massive investment toward disease elimination, justified by the ultimate long-term pay-off of disease freedom for future generations. Whilst the success of smallpox and rinderpest eradication left the world looking for the next pathogen to wipe from the planet, the Global Polio Eradication Initiative (GPEI) has been a telling case of the difficult situation that arises when unforeseen issues hamper eradication in the final mile (Chumakov et al., 2021; Kew & Pallansch, 2018). After an investment of 17 billion US dollars over three decades, the leadership of GPEI now finds itself in a bind; whether to double-down on a disease which no longer presents an immediate public health concern, and accept the misalignment this creates with national health priorities, or capitulate on the goal of eradication and pivot to broader health objectives (Abraham, 2018; Fortner, 2021).

National implementation of effective canine rabies control in India would represent the greatest achievement by a single country in the endeavour to eliminate dog-mediated human rabies by 2030 and would generate huge momentum towards this objective globally (Thumbi et al., 2022). Although the outputs of the Goa project would need to be amplified several hundred times over to be applied at national scale, it showcases the feasibility, cost-effectiveness, and considerable public health impacts of One Health interventions for rabies control at the state level. Many of the areas of progress support priorities laid out in the National Action Plan for Dog

Mediated Rabies Elimination from India by 2030 (NAPRE) and the Goa government's announcement of legislation through Goa becoming a 'Rabies Controlled Area' set a precedent for other states to follow (National Centre for Disease Control et al., 2021).However the prospects for the wider advancement of rabies control in India must consider rabies within a complex political landscape of growing public antipathy for free roaming dogs and the disruption they cause in peoples' everyday lives (Radhakrishnan et al., 2020). Large-scale dog vaccination programmes, however, reach every community at a scale that would be infeasible for reproductive management interventions focused on surgical sterilization of dogs. This research into dog rabies control in Goa speaks to both narratives, offering rabies control as an opportunity for government to deliver benefit to all people, whilst at the same time serving to gather data from which to plan focal interventions addressing dog overpopulation. The annual delivery of rabies vaccination to every village creates a valuable point of engagement between the dog-owning public and Departments of Veterinary Services on matters relating to dog health. Interventions promoting reproductive management and responsible dog ownership can then be built on this field experience and expertise of working with dogs.

A compelling case can also be made for political prioritisation of rabies control as the primary objective, even where elimination may not be feasible in the near-term. A staged approach to campaign development enables project planners to strive towards objectives at the city level that are achievable within a timespan of years as opposed to decades at the national level. This was the kernel of early efforts to address dog rabies in Latin America, where dog vaccination programme development was prioritised in urban centres during the 1970s (Schneider et al., 1996; Velasco-Villa et al., 2017). Not only was the rabies burden greatest in cities due to the large dog population size, but rapid campaign expansion was possible through the operational advantages of workforce availability, infrastructure, and communications. These regions were also weighted in their political significance, with the high-profile urban successes sparking political appetite for expansion elsewhere. In the 1980s the gains made in reducing rabies burden, operational experience, and robust collaborative networks had placed regional rabies elimination within reach and a coordinated drive led by the Pan American Health Organisation was agreed (A. J. Belotto, 2004). Progressive expansion of the campaign saw expansion into small villages by 1991, reporting a decline in dog rabies cases from 23,000 in 1979 to 316 in 2015 (Velasco-Villa et al., 2017). Goa may be seen as a similar early success in India, in a location which was politically, operationally, and epidemiologically favourable, but providing a platform from which to develop methods (Chapters 2, 3, 5, 6) and showcase the benefits of dog rabies control (Chapter 4).

An approach prioritising metropolis settings in India is already showing success. In 2019, the work in Goa resulted in engagement with the municipal government of Bengaluru, the capital city of Karnataka state, with a population of approximately 11 million people. The objective of a Memorandum of Understanding between the government, Bruhat Bengaluru Mahanagara Palike (BBMP), and Mission Rabies was to provide the technical experience, tools, and methods developed in Goa to support the intensification of rabies control in the city. The work of BBMP from 2020 to 2022 has showcased the rapid progress that can be achieved through government resource. Annual vaccination output in Bengaluru increased from 26,000 doses in 2019 to over 100,000 doses in 2021 through technology-aided campaign management outlined in Chapter 3 and rabies cases have decreased significantly (unpublished data).

The Karnataka state government subsequently picked up on the progress in Bengaluru and implemented a state-wide vaccination campaign in 2022 through a workforce of over 4,000 that vaccinated over 200,000 dogs in the month of September using Central Point and Door-to-Door methods (Hindustan Times, 2022). Whilst vaccination coverage is unlikely to be sufficient to eliminate the dog rabies virus, the exercise was an incredible mobilisation of the government veterinary workforce and provided valuable experience in developing processes for campaign coordination and implementation whilst generating widespread local publicity on the issue of rabies. Wallace et al. (2017) advocate for an approach of progressive intensification and expansion of vaccination efforts during early campaigns, rather than seeing 70% coverage as the primary objective. Experience from the expansion of rabies control activities in South Africa reported the need for a similarly pragmatic approach of starting vaccination at whatever intensity and frequency is feasible within resource constraints and using rabies surveillance data as the measure of campaign efficacy rather than vaccination coverage (LeRoux et al., 2018).

7.1.3 Future research priorities

Research into opportunities to interrupt rabies transmission cycles more efficiently through targeted vaccination efforts at specific populations, or subpopulations, have the potential to reduce the cost and resource requirement of rabies control programmes. There is strong evidence for the importance of homogenous vaccination coverage in achieving rabies elimination, with patches of unvaccinated population rapidly undermining success, however much is yet to be learnt about the thresholds for elimination across populations at higher scales (E. A. Ferguson et al., 2015; P. M. Kitala et al., 2002; Townsend, Lembo, et al., 2013; Townsend, Sumantra, et al., 2013). Experience from the successful Global Rinderpest Eradication Programme advocated for the identification of transmission hubs and prioritising vaccination efforts in these areas as opposed to mass area-wide (blanket) vaccination (Jeggo & Roeder, 2021; Roeder et al., 2013). There have been several studies questioning the long held sweeping guidance to dog rabies control programmes for 70% vaccination coverage across all populations (Beyer et al., 2012; Kotzé et al., 2021; Layan et al., 2021). Initial suggestions that urban centres act as hubs that sustain rabies endemicity have been disproven in several African settings and point to the need for a more nuanced understanding of population distribution, and barriers and facilitators to transmission across the urban-rural gradient (Bourhy et al., 2016; Laager et al., 2019; Zinsstag et al., 2017). The strong association between dog and human populations creates the potential to leverage new high-resolution mapping of global human populations, generated through machine learning techniques in feature extraction from satellite imagery, as was used in Chapter 3 (Facebook Connectivity Lab and Center for International Earth Science Information Network - CIESIN - Columbia University, 2016). Combining these maps with road networks, landscape mapping, human:dog ratios, rabies surveillance data, and landscape epigenetics signals a new frontier in predicting the weighted risk of rabies transmission across vast geographies (Brunker et al., 2018). As in the eradication of rinderpest, the omission of populations at lowest risk of sustaining viral transmission from vaccination has the potential to dramatically reduce the cost and operational complexity of rabies elimination (Roeder et al., 2013).

The possibility of developing a more facetted strategy to vaccination presents an immediate dichotomy; homogenous vaccination coverage is critical for elimination from a contiguous population, but vaccination may not be required at the same intensity in all populations. The spatial definition of populations and the targeted deployment of vaccination effort based on modelled disease risk, distinct of political boundaries, is going to be of central importance in advancing this area of research (Utazi et al., 2019). Functionalities of smartphone technology described in Chapter 2 could play a crucial role in the implementation of this more spatially prescriptive approach to vaccination through the targeted direction of vaccination resource.

7.2 Conclusion

The hype for global dog rabies elimination conjures excitement for a mountain summit far in the distance, but we must equally confront the brutal reality that the route ahead is yet uncharted. The work in Goa represents a pioneering expedition by a small group of organisations in what we hope will become a far more audacious ascent by a far larger community. This research highlighted the foundational importance of strong collaboration and clear communication between core stakeholders to weather the vicissitudes that can be expected of any population health campaign. The exercise also put many of the existing tools and approaches into practice, identified what to keep for the journey, what can be adapted, and where an entirely new perspective is needed to stand a chance of success. Innovation in mobile technology to improve spatial vaccination team direction and support rapid data-driven campaign refinement offers an opportunity to drive research in efficiency-saving through resource prioritisation. The potential of ORV as a vehicle to efficiently immunise difficult-to-reach dogs and the demonstration of scalable ORV methods provide way marks on a new path for mass dog vaccination. There is no doubt that the global endeavour toward dog rabies elimination is in its nascency, and the wider priorities of roaming dog population management in India loom, but the risk of a rabid dog attacking a child on the streets of Goa are diminished and the same can be true across India through prioritisation of mass dog vaccination.

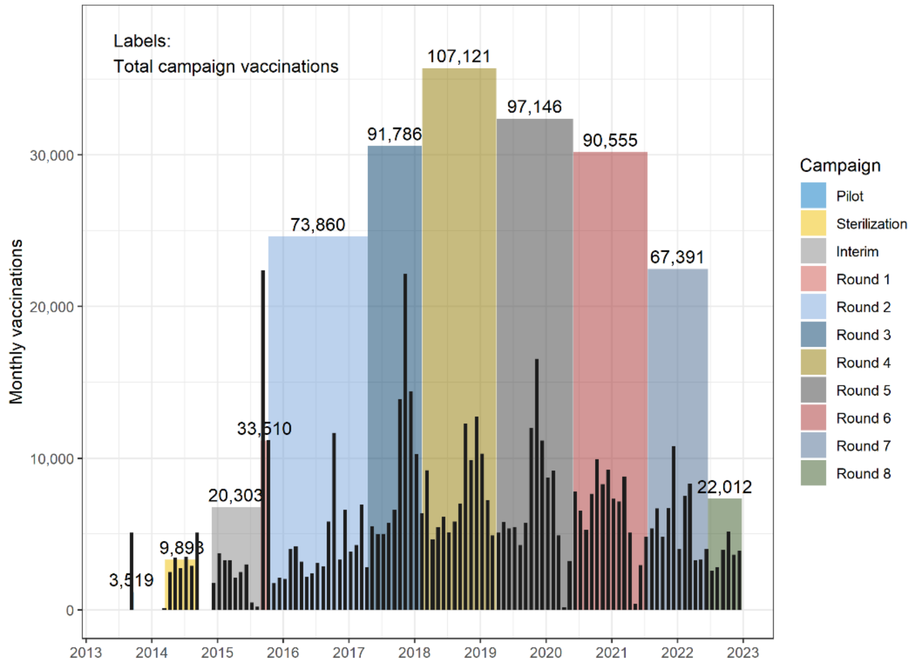
Appendix A – Chapter 1

Supplementary Table A1 - Table of articles reporting outcomes of dog vaccination campaigns identified in literature review. Location, vaccination method, peak annual vaccination output, peak vaccination coverage and reported cost per dog vaccinated are included. Vaccination methods: CP = Central Point, DD = Door-to-Door, CVR = Capture-Vaccinate-Release, CAHW = Community animal health workers, Govt = government, ORV = oral rabies vaccination.

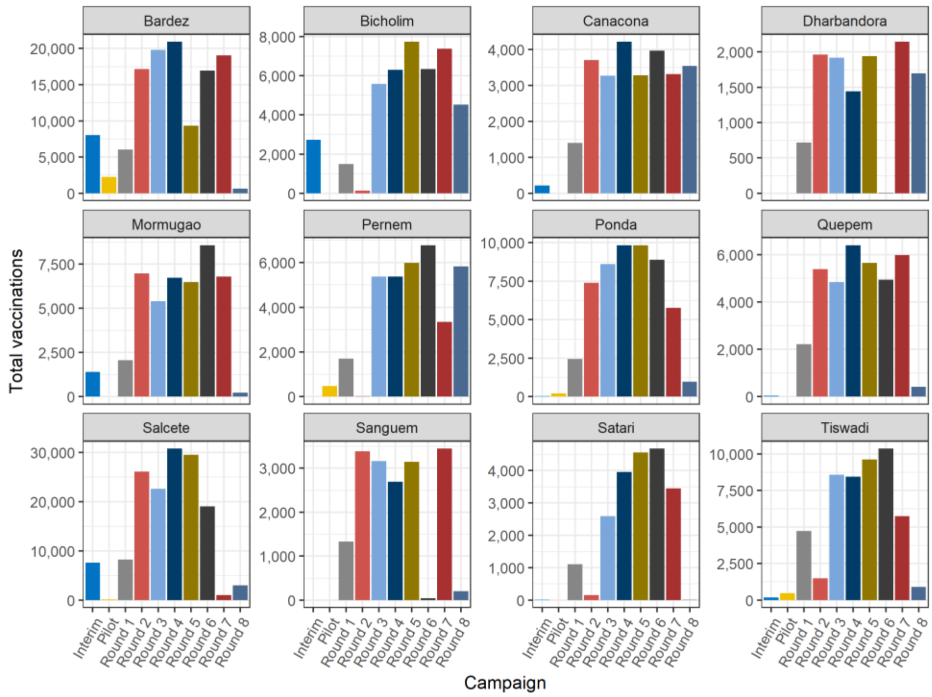
Ref	Continent	Country	State/District	Method(s)	Peak annual doses	Peak vacc cov (%)	Cost/ dog (USD)
Lechenne 2016	Africa	Chad	N'Djamena	CP	22,306	71	
Kayali 2003	Africa	Chad	N'Djamena	CP	1,219	87	3.8
(Durr et al., 2009)	Africa	Chad	N'Djamena	CP	352	23	19.4
(Yimer et al., 2012)	Africa	Ethiopia	Addis Ababa	Unknown	1	33.3	
Belcher 1976	Africa	Ghana	Accr	CP	12,308	25	
Ferguson 2020	Africa	Kenya	Laikipia	CP-DD	8,332	24	3.44
(Perry et al., 1995)	Africa	Kenya	Nairobi	DD	433	68 - 75%	
Filla 2021	Africa	Madagascar	Moramanga	CP	3,137	60%	1.8
Filla 2021	Africa	Madagascar	Moramanga	CP-decentalised	2,385	5 - 60%	1.39
Sanchez-Soriano 2020	Africa	Malawi	Blantyre, Zom, Chirad	CP-DD	89,032	83.4	
Gibson 2016	Africa	Malawi	Blantyre	CP-DD	35,216	79.3	
Traore 2020	Africa	Mali		CP	9,087		
Mosimann 2017	Africa	Mali	Bamako	CP	1,623	27	
Muthiani 2015	Africa	Mali	Bamako	CP	658	17.6	
(Athingo et al., 2020)	Africa	Namibia	Northern	CP	13,219	16.64	
(Ameh et al., 2014)	Africa	Nigeria	Taraba	CP	200		
(Adeyemi & Zessin, 2000)	Africa	Nigeria	Ibadan	CP	176		
(A. Dzikwi et al., 2011)	Africa	Nigeria	Zaria	Unknown	1	16.9	
Shwiff 2014	Africa	South Africa	Kwazulu-Natal	Unknown	638,392		6.61
LeRoux 2018	Africa	South Africa	KwaZulu-Natal	CP-DD	395,000		
(Van Sittert et al., 2010)	Africa	South Africa	Chris Hani	Unknown	1	56	
Mpolya 2017	Africa	Tanzania		Unknown	55,000		7.3
Kaare 2009	Africa	Tanzania	Serengeti	CP	27,400	80.1	1.73
Lugelo 2022	Africa	Tanzania	Marra	CP-decentalised	17,571	64.1	
Cleaveland 2003	Africa	Tanzania	Serengeti	CP	7,552	67.8	
Kaare 2009	Africa	Tanzania	Serengeti	CP-DD	1,165	80.3	5.55
Kaare 2009	Africa	Tanzania	Serengeti	CP-decentalised	1,165	86.3	4.07
(Touihri et al., 2011)	Africa	Tunisia		CP-DD		59	
Evans 2019	Africa	Uganda	Nwoya	CP-DD	4,172	88.4	
(De Balogh et al., 1993)	Africa	Zambia	Lusaka	CP	9,000		
De Balogh 1993	Africa	Zambia	Lusaka	DD-CP	189		

De Balogh 1993	Africa	Zambia	Lusaka	DD	87		
Ghosh 2020	Asia	Bangladesh		Unknown	365,316	42	
Tenzin 2015	Asia	Bangladesh	Dhaka	CVR	6,665	79.3	
Byrnes 2017	Asia	India	Sikkim	DD-CVR	24,571	85	3.69
Gibson 2015	Asia	India	Jharkhand	CVR	6,904	70	
Reece 2006	Asia	India	Rajasthan	CVR	3,522		
Belsare 2013	Asia	India	Maharashtra	CP-DD	277	42	
Evans 2022	Asia	India	Jharkhand	CVR	9,790	70.1	
Airikkala-Otter 2022	Asia	India	Tamil Nadu	DD	1,083	79	
Putra 2013	Asia	Indonesia	Bali	DD-CVR	249,429	70	
Wera 2013	Asia	Indonesia	Flores Islands	DD	172,763	53	2.49
Windiyaningsih 2004	Asia	Indonesia	Flores Islands	Unknown	28,043	50	
Miranda 2015	Asia	Philippines	Cebu	DD	59,731	88.5	1.28
Lapiz 2012	Asia	Philippines	Bohol	DD	53,739	70	
Valenzuela 2017	Asia	Philippines	Ilocos Norte	CP-DD	38,276	38.8	3.09
(Robinson et al., 1996)	Asia	Philippines	Sorsogon	CP	5,700	73	
Yang 2018	Asia	South Korea		Unknown	1,450,000		
Lee 2001	Asia	South Korea		Unknown	661,277	70	
Harischandra 2016	Asia	Sri Lanka		CP	1,500,000		
Sanchez-Soriano 2019	Asia	Sri Lanka	Negombo	CP-DD-CVR	7,804	75.8	
Matter 2000	Asia	Sri Lanka	Gampaha	CP	387	57.6	
Kumarapeli 2009	Asia	Sri Lanka		CP	1	49.3	
(Kongkaew et al., 2004)	Asia	Thailand	Thungsong	CP-DD	22,000	70	
Shwiff 2018	Asia	Vietnam		Unknown	3,850,391	47	
Suzuki 2008	South America	Bolivia	Santa Cruz de la Sierra	CP	250,000	85	
(A. J. Belotto, 1988)	South America	Brazil		CP	8,383,563		
Undurraga 2020	South America	Haiti	West Dept	CP-DD-CVR-ORV	7,065	80	
Vigilato 2013	South America	Latin America		Unknown	51,000,000	81	
Fishbein 1992	South America	Mexico		CP-DD	1,237	78.4	
Flores-Ibarra 2004	South America	Mexico	Baja California	CP-DD		73	
Chomel 1988	South America	Peru		CP	273,000	65	

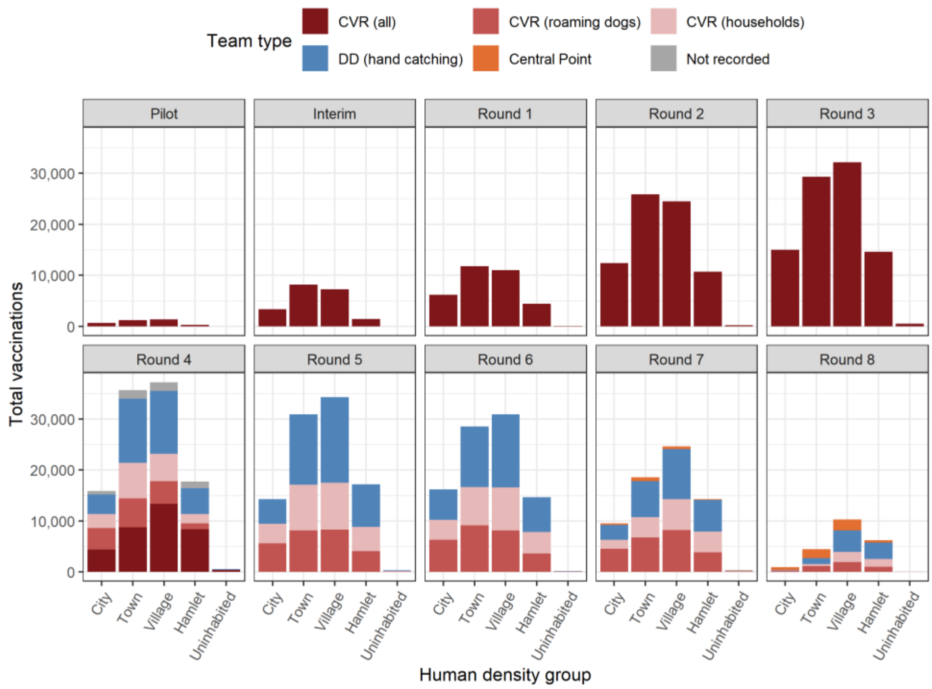
Appendix B – Chapter 3



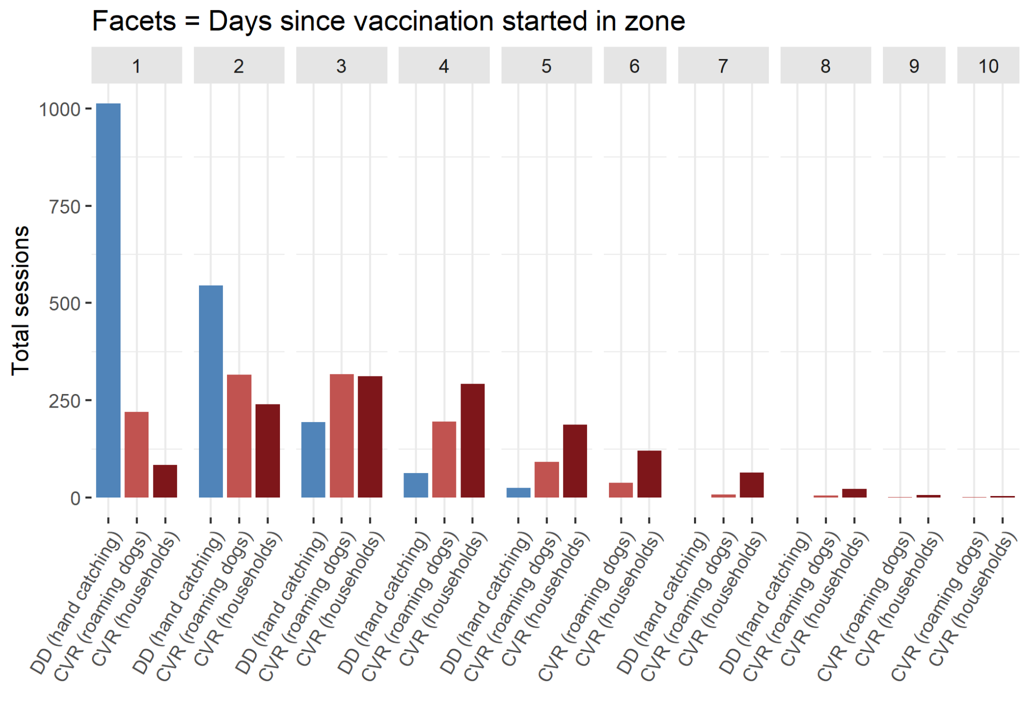
Supplementary Figure B1 - Vaccinations by month (black bars) and campaign total vaccinations (coloured bars labelled with total campaign vaccination output).



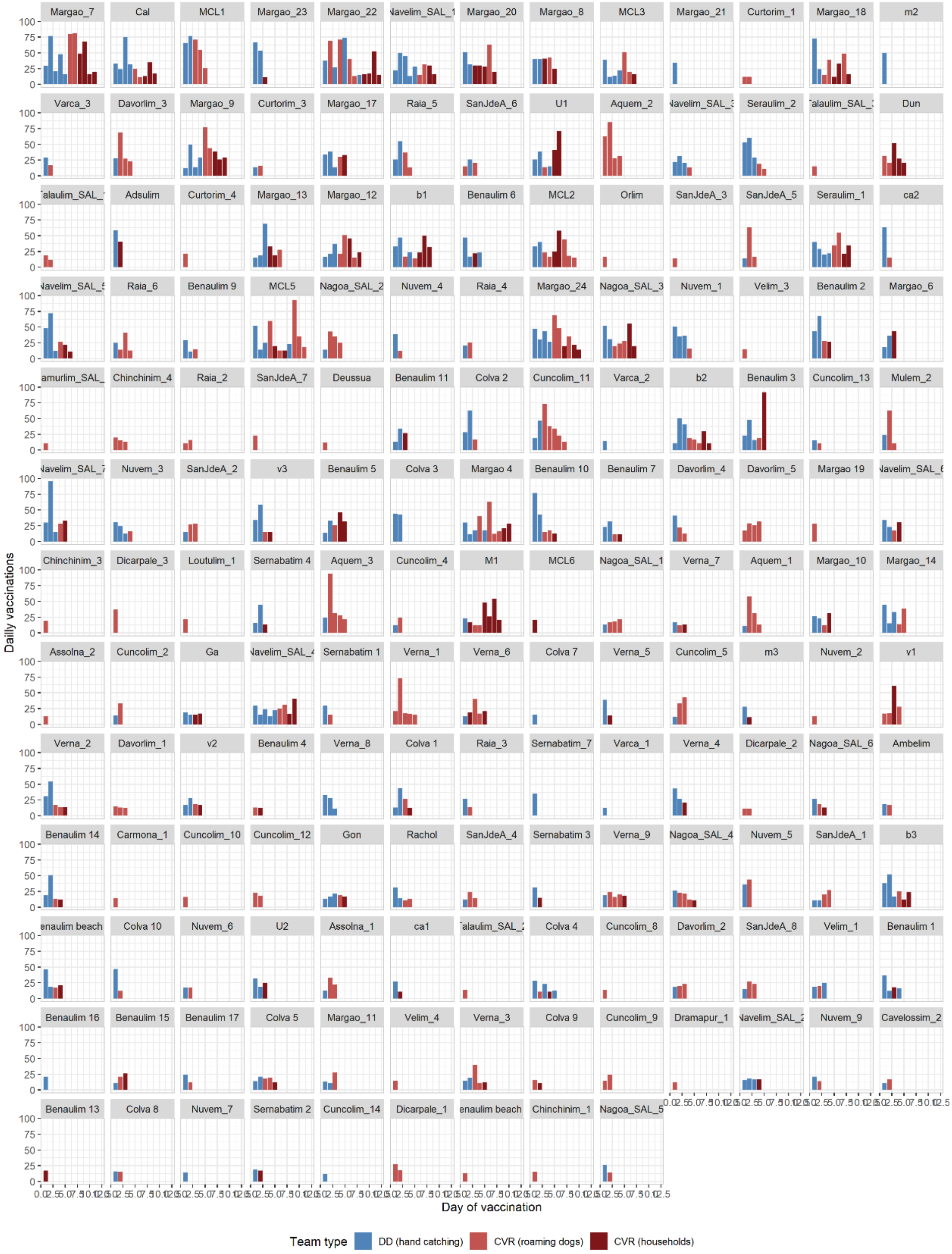
Supplementary Figure B2 - Total vaccinations by campaign and taluka.



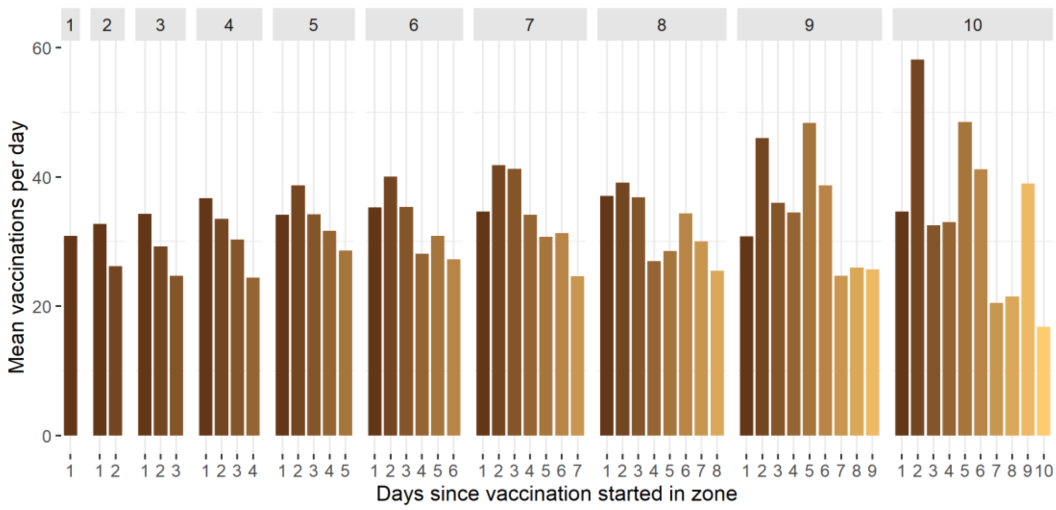
Supplementary Figure B3 - Bar chart of total vaccinations by human density group, faceted by campaign. Colour shows the team type.



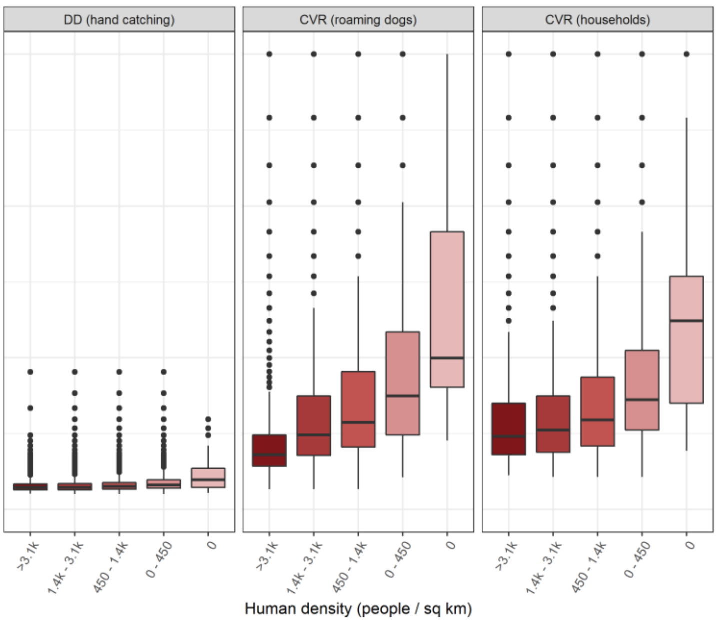
Supplementary Figure B4 - Method sequence of Working Zone vaccination by DD-CVR method. On day 1 the predominant method was DD, transitioning to CVR-roaming dogs and finally CVR-households.



Supplementary Figure B5 - Example Working Zone-wise data of daily vaccination output and method. Data from Salcete region in 2018 campaign.



Supplementary Figure B6 - Plot of mean vaccinations per day in Working Zone for the DD-CVR method, faceted by total number of days in Working Zone.



Supplementary Figure B7 - Plot of cost per dog vaccinated by method within DD-CVR method by human population density grouping.

Supplementary Table B1 - Mean and median daily team vaccinations by method (colours) and campaign period.

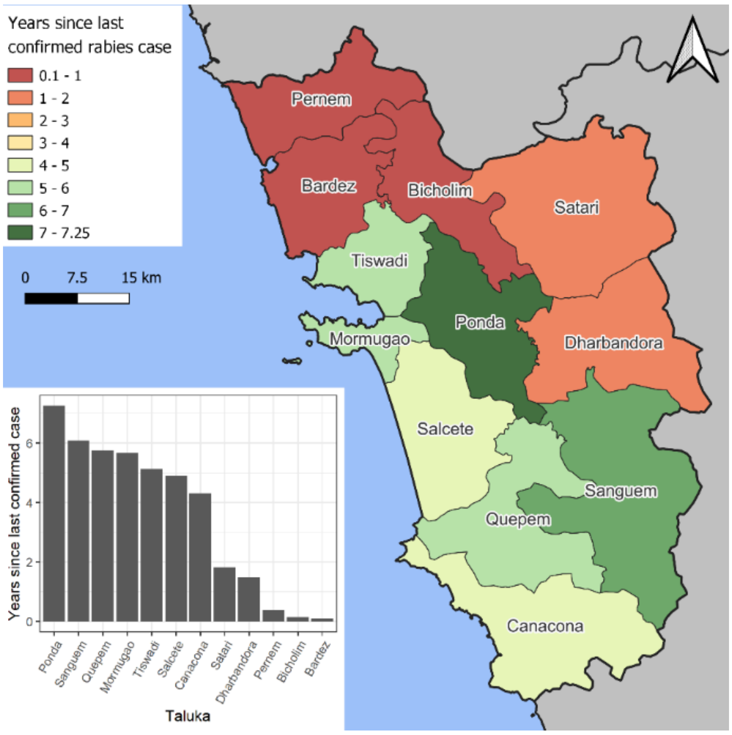
Methods phase	Campaign	Method	Team type	Total vacc	Mean team daily vaccinations (CI)	Median team daily vaccinations (OQR)
Pilot	Pilot	CVR	CVR	4,628	84 (69-99)	80 (41-118)
Sterilization	Sterilization	CVR	CVR	17,413	28 (27-29)	24 (16-37)
dev	Interim	CVR	CVR	20,288	69 (65-74)	71 (39-102)
Pulse	Round 1	CVR	CVR	33,502	71 (68-74)	68 (46-89)
CVR	Round 2	CVR	CVR	73,831	62 (60-64)	60 (38-82)
	Round 3	CVR	CVR	91,725	59 (57-61)	55 (35-77)
	Round 4	CVR	CVR	15,530	49 (46-52)	46 (29-65)
dev	Round 4	dev	DD	9,079	28 (27-30)	27 (18-36)
	Round 4	dev	CVR	19,742	34 (33-36)	32.5 (20-45)
DD-CVR	Round 4	DD-CVR	DD	24,863	48 (46-50)	47 (32-60)
	Round 4	DD-CVR	CVR (households)	16,971	32 (31-34)	28 (17-44)
	Round 4	DD-CVR	CVR (roaming-dogs)	15,401	35 (32-38)	28 (15-46.75)
	Round 5	DD-CVR	DD	41,881	45 (43-46)	42 (28-58)
	Round 5	DD-CVR	CVR (households)	24,351	24 (23-25)	20 (12-32)
	Round 5	DD-CVR	CVR (roaming-dogs)	24,553	26 (25-27)	20 (11-35.25)
COVID	Round 5	DD-CVR	DD	2,104	38 (33-44)	38 (26-47)
	Round 5	DD-CVR	CVR (households)	2,360	26 (22-29)	22 (14-35.5)
	Round 5	DD-CVR	CVR (roaming-dogs)	1,527	22 (18-25)	17 (10.5-26.5)
	Round 6	DD-CVR	DD	38,932	33 (32-34)	31 (20-44.75)
	Round 6	DD-CVR	CVR (households)	23,942	23 (22-24)	20 (12-30)
	Round 6	DD-CVR	CVR (roaming-dogs)	27,161	22 (22-23)	18 (10-30)
	Round 7	DD-CVR	CP	1,815	17 (14-19)	13 (8-20.25)
	Round 7	DD-CVR	DD	15,866	27 (26-28)	25.5 (14-36)
	Round 7	DD-CVR	CVR (households)	7,773	20 (18-21)	17 (10-26)
	Round 7	DD-CVR	CVR (roaming-dogs)	17,115	21 (20-22)	17 (10-28)
Borders	Round 7	DD-CVR	DD	10,024	34 (32-37)	32.5 (21-43)
	Round 7	DD-CVR	CVR (households)	8,184	24 (22-26)	18 (12-32)
	Round 7	DD-CVR	CVR (roaming-dogs)	6,133	20 (18-22)	16 (9-26)
	Round 8	DD-CVR	CP	4,837	35 (30-40)	24.5 (14.25-50)
	Round 8	DD-CVR	DD	8,677	22 (20-23)	19 (11-29)
	Round 8	DD-CVR	CVR (households)	3,958	16 (14-17)	13 (8-19.5)
	Round 8	DD-CVR	CVR (roaming-dogs)	4,286	15 (14-16)	13 (8-19)

Supplementary Table B2 - Table of vaccination event data from a single state-wide vaccination cycle using the DD-CVR vaccination approach. Numbers in parentheses represent the proportion of vaccinations within each group (%) (further clarification provided below).

		Dog ownership & confinement**				Vaccination team type**			Handling method**		Dogs within each vaccination method handled manually***		
Human density strata (people / km^2)	**Total vaccinat-ions***	**Owned always confined**	**Owned sometimes roaming**	**Owned always roaming**	**Stray roaming**	**DD (hand catching)**	**CVR (roaming dogs)**	**CVR (houses)**	**Hand**	**Net**	**DD by hand**	**CVR roaming by hand**	**CVR houses by hand**
Density 1 (>3157)	**21,006 (16.1)**	1,316 (6.3)	4,701 (22.4)	306 (1.5)	14,683 (69.9)	6,260 (29.8)	8,593 (40.9)	6,153 (29.3)	10,237 (48.7)	10,769 (51.3)	6,205 (99.1)	1,868 (21.7)	2,164 (35.2)
Density 2 (1425 – 3156)	**42,195 (32.3)**	5,904 (14)	13,375 (31.7)	1,136 (2.7)	21,780 (51.6)	15,592 (37)	13,046 (30.9)	13,557 (32.1)	24,666 (58.5)	17,529 (41.5)	15,312 (98.2)	3,466 (26.6)	5,888 (43.4)
Density 3 (452 – 1424)	**45,428 (34.8)**	5,454 (12)	17,730 (39)	1,402 (3.1)	20,842 (45.9)	17,999 (39.6)	13,587 (29.9)	13,842 (30.5)	27,925 (61.5)	17,503 (38.5)	17,806 (98.9)	3,897 (28.7)	6,222 (45)
Density 4 (1 - 451)	**21,561 (16.5)**	2,663 (12.4)	9,016 (41.8)	1,216 (5.6)	8,666 (40.2)	8,860 (41.1)	6,141 (28.5)	6,560 (30.4)	13,338 (61.9)	8,223 (38.1)	8,800 (99.3)	1,693 (27.6)	2,845 (43.4)
Density 5 (0)	**362 (0.3)**	77 (21.3)	129 (35.6)	31 (8.6)	125 (34.5)	197 (54.4)	92 (25.4)	73 (20.2)	232 (64.1)	130 (35.9)	197 (100)	18 (19.6)	17 (23.3)
Total	**130,552 (100)**	**15,414 (11.8)**	**44,950 (34.4)**	**4,091 (3.1)**	**66,096 (50.6)**	**48,908 (37.5)**	**41,459 (31.8)**	**40,185 (30.8)**	**76,398 (58.5)**	**54,154 (41.5)**	**48,320 (98.8)**	**10,942 (26.4)**	**17,136 (42.6)**

** Numbers in parentheses indicate dogs vaccinated in each human density strata as a proportion of total vaccinations in all human density strata.*
*** Numbers in parentheses indicate the number of dogs vaccinated as a proportion of total vaccinations in that human density strata.*
**** Numbers in parentheses indicate the proportion of dogs vaccinated by hand as a proportion of all dogs vaccinated (by hand and net) for that method and human density strata (number of dogs vaccinated by net for each method are not included in this table).*

Appendix C – Chapter 4



Supplementary Figure C1 – Map of Goa talukas, coloured by years since last confirmed rabies case. Inset chart of time since last rabies case, in years, from 30/12/2022.

Supplementary Table C1 - Table of dog vaccination and animal rabies surveillance data in Goa from 2012 to 2022.

Year	**Total dogs vacc** (Goa only)	**Total calls to rabies hotline**	**Mean calls/ week**	**Prop'n calls rabies susp (%)**	**Total tested**	**Canine +ve cases (Goa)**	**Tested prop'n +ve (%)**	**Total months active**	**Mean +ve/ month**	**Human bites from pos dog**	**Cases where bites known**
2014	22,059	-	-	-	94	74	78.7	7	10.6		
2015	56,780	-	-	-	45	39	86.7	4	9.8	52	32
2016	51,291	-	-	-	78	64	82.1	12	5.3	57	59
2017	96,899	628	57.1	3.2	132	81	61.4	12	6.8	80	69
2018	97,032	2,544	49.9	2.3	73	29	39.7	12	2.4	25	16
2019	96,036	4,153	78.4	1.2	132	8	6.1	12	0.67	4	5
2020	82,001	3,975	75	0.9	175	24	13.7	12	2	13	22
2021	75,390	3,875	74.2	1	206	8	3.9	12	0.67	4	5
2022	46,479	388	76.1	0.7	97	3	3.1	12	0.25	0	5

Cost per dog vaccinated

Supplementary Table C2 - Table of granted amounts allocated and received from the Government of Goa for implementation of rabies control activities during the study period (2013 – 2019).

Block	Grant ID	Grant period	Instalment allocated (INR)	Total received (INR)	Months covered	Amount per month (INR)
Grant 1	**g1_1**	Sep 15 - Feb 16	2,700,000	2,783,000	6	463,833
	g1_2	Mar 16 - Aug 16	2,700,000	2,028,240	6	338,040
Grant 2	**g2_1**	Sep 16 - Feb 17	2,700,000	1,902,739	6	317,123
	g2_2	Mar 17 - Aug 17	2,700,000	2,262,200	6	377,033
Grant 3	**g3_1**	Sep 17 - Feb 18	2,700,000	3,075,800	6	512,633
	g3_2	Mar 18 - Aug 18	2,700,000	2,553,800	6	425,633
Grant 4	**g4_1**	Sept 18 - Aug 19	9,198,600	8,688,600	12	724,050
Grant 5	**g5_1**	Sept 19 - Aug 20	9,198,600	9,198,600	12	766,550

Supplementary Table C3 - Calculation of annual (Jan - Dec) Goa Government grant allocation. The funding allocation from the Government of Goa grant spanned different timeframes and so needed to standardise to the Jan – Dec cycle for inclusion in other calculations. This table provides the calculations for grant expenditure by month to calculate annual (Jan – Dec) granted expenditure during the study period.

Year	Grant ID	Grant monthly amount (INR)	Months covered	Number of months	Year instalment amount (INR)	Year total (INR)
2015	g1_1	463,833	Sep 15 - Dec 15	4	1,855,333	1,855,333
2016	g1_1	463,833	Jan 16 - Feb 16	2	927,667	4,224,399
2016	g1_2	338,040	Mar 16 - Aug 16	6	2,028,240	
2016	g2_1	317,123	Sep 16 - Dec 16	4	1,268,493	
2017	g2_1	317,123	Jan 17 - Feb 17	2	634,246	4,946,980
2017	g2_2	377,033	Mar 17 - Aug 17	6	2,262,200	
2017	g3_1	512,633	Sep 17 - Dec 17	4	2,050,533	
2018	g3_1	512,633	Jan 18 - Feb 18	2	1,025,267	6,475,267
2018	g3_2	425,633	Mar 18 - Aug 18	6	2,553,800	
2018	g4_1	724,050	Sep 18 - Dec 18	4	2,896,200	
2019	g4_1	724,050	Jan 19 - Aug 19	8	5,792,400	8,858,600
2019	g5_1	766,550	Sep 19 - Dec 19	4	3,066,200	

Supplementary Table C4 - Table of campaign expenditure and estimated vaccine value for the calculation of annual estimated campaign value and mean cost per dog vaccinated.

		2015	2016	2017	2018	2019
US exchange rate*		64.15	67.20	65.07	68.30	70.40
Vaccine contribution	Total dog vaccinations	56,954	51,302	97,277	97,248	96,187
	Estimated value per vaccine (USD)	0.53	0.53	0.53	0.53	0.53
	Estimated value per vaccine (INR)	34	36	34	36	37
	Estimated total vaccine value (INR)	**1,936,381**	**1,827,095**	**3,354,844**	**3,520,462**	**3,588,978**
FULL PROGRAMME EXPENDITURE (dog vaccination / education / surveillance)**						
Total Expenditure**	Donated fund domestic expenditure (INR)***	7,067,842	8,725,573	18,934,887	15,346,996	12,471,346
	Goa Government funding expenditure (INR)	1,855,333	4,224,399	4,946,980	6,475,267	8,858,600
	Total Goa expenditure (INR)	**8,923,175**	**12,949,973**	**23,881,867**	**21,822,263**	**21,329,946**
Total programme cost (vaccine value + expenditure)	**Total estimated campaign value (INR)**	**10,859,556**	**14,777,068**	**27,236,711**	**25,342,725**	**24,918,925**
	Total estimated campaign value (USD)	**169,286**	**219,906**	**418,570**	**371,031**	**353,957**
Cost per dog vaccinated (total programme)	**INR**	**191**	**288**	**280**	**261**	**259**
	USD	**2.97**	**4.29**	**4.30**	**3.82**	**3.68**
DOG VACCINATION CAMPAIGN EXPENDITURE						
Dog vaccination Expenditure	Donated fund domestic expenditure (INR)				13,833,503	9,952,588
	Goa Government funding expenditure (INR)				6,475,267	8,858,600
	Goa dog vaccination expenditure (INR)				**20,308,770**	**18,811,188**
Dog vaccination campaign cost (vaccine value + expenditure)	**Total estimated campaign value (INR)**				**23,829,232**	**22,400,167**
	Total estimated campaign value (USD)				**348,873**	**318,180**
Cost per dog vaccinated (dog vaccination campaign)	**INR**				**245**	**233**
	USD				**3.59**	**3.31**

* Mean annual US dollar exchange rates were calculated from the International Monetary Fund country database records:

https://www.imf.org/external/np/fin/ert/GUI/Pages/CountryDataBase.aspx

** Expenditure values were only available throughout 2015 – 2019 at the campaign level and therefore include the cost of dog vaccination, education and rabies surveillance activities.

*** Donated expenditure constitutes only campaign implementation expenditure in Goa. International expenditure from Mission Rabies in project administration, data analysis and smartphone technology development were not included as these would not be associated with routine vaccination campaign implementation.

Cost effectiveness model

The following parameters were used to populate the RabieEcon cost effectiveness model. Grey shaded fields denote parameters estimated by the model. The final model tool can be found in the supplementary files of Gibson et al. (2022) DOI: 10.1038/s41467-022-30371-y.

Project parameters

Supplementary Table C5 - Table of Goa population model inputs.

Program Area	Goa
Square kilometres (km^2) of program area	3,702
Human population	1,817,000
Humans per km^2	491
Human birth rate (per 1,000 population)	17.00
Human life expectancy	74
Number of humans per dog (Human:Dog ratio)	13.2
Dog population	137,350
Dogs per km^2	37.1
Dog birth rate (per 1,000 dogs)	750
Dog life expectancy, years	3.0
Rabies R_0 Dog to Dog	1.500
Dog-Human transmission rate	0.000034

Supplementary Table C6 - Table of project parameters for intervention and non-intervention scenarios.

Vaccination Campaign	No vaccination	Annual
Mass vaccination campaign coverage levels	0%	Use "Vax_cover"
Frequency of vaccination*	Single/one time	Annual
Proportion of adult female dogs spayed, annually	5.0%	10.0%
Proportion of adult male dogs neutered, annually	0.0%	10.0%
Probability of receiving PEP, post-exposure	80.0%	85.0%
Total number of dog rabies cases during 1st year	16,229	15,481
Total number of human deaths during 1st year	16	13
Discount rate (health and economic outcomes)	3%	
Number of rabid dogs at the end of year 20	271	0
Total number of rabid dogs during years 20 through 30	140,091	0
Total number of dog rabies cases during 20 years	282,969	30,308
Total number of human deaths during 20 years	358	31
Inflation factor for the suspect exposure (>=1)	40	
Post-Elimination PEP Reduction (%)	0%	

Supplementary Table C7 - Table of estimated vaccination coverage by year.

Year	Target coverage	Weekly target coverage	Human Deaths during the year	Rabid Dogs during the year
2013	4%	0.38%	13	15,074
2014	15%	1.61%	12	10,399
2015	41%	5.36%	5	3,772
2016	37%	4.68%	1	554
2017	71%	12.32%	0	99
2018	71%	12.31%	0	3
2019	70%	12.05%	0	0
2020	66%	10.65%	0	0
2021	66%	10.65%	0	0
2022	58%	8.73%	0	0
2023	10%	1.05%	0	0

Probability of a dog to human bite by location, exposure type, and incubation period

Supplementary Table C8 - Probability of a dog to human bite by location, exposure type, and incubation period.

Probability of a dog to human bite to the:	**Probability of exposure by location (1,2):**	**Probability of developing rabies from exposure (1,2):**	**Length of human incubation after bite (weeks)**
Head or neck	0.070	0.450	3.14
Upper extremity (arm or hand)	0.384	0.275	8.57
Trunk of the body	0.060	0.050	6.43
Lower extremity (leg or foot)	0.486	0.050	10.71
Rates of not developing rabies from exposure (bites), per week			0.097
Rates of developing rabies from exposure (bites), per week			0.025
Dog rabies infective period, life expectancy (days)			10.00
Risk of clinical outcome per bite (rabid dog-dog)			0.45
Dog rabies incubation period (days) (3)			45.00
Efficacy of dog rabies vaccine			0.95
Human rabies infective period (days)			7.00
Efficacy of human rabies post exposure vaccine (PEP)			0.93

Supplementary Table C9 - Table of parameters used in the calculation of disability adjusted life years.

Parameters for Disability Adjusted Life Years (DALY (YLL)) estimates at a 3% discount rate, r	
a, Average age of death (human) due to rabies exposure (years)	15.00
b, Life expectancy	74.00
L, standard expectation of life at age a	59.00
K, age weighting modulation factor	1
β, parameter from the age weighting function	0.02
C, Constant	0.0634
Most productive years	27.2 - 83.1
Years of Life Lost (YLL) per death	**28.26**

Vaccination cost

Supplementary Table C10 - Fixed cost values.

Fixed costs		Units	Work Days	Price/ Unit	Total Cost
Workers @ Vaccination Sites (per diem):	Training Supervisor (project manager)	1	286	32.20	9,209
	Informational Supervisor (education)	3	286	14.80	12,698
	Vaccination (CVR team lead)	6	286	11.62	19,940
	Training Technician (DD lead)	6	286	11.62	19,940
	Informational Technician (data collector)	12	286	9.60	32,947
	Vaccination Technician (animal handler)	30	286	7.70	66,066
	Driver	6	286	11.60	19,906
	Other Personnel (veterinary)	3	286	19.00	16,302
Transportation:	CVR vehicle (including gasoline)	6	286	21.00	36,036
	DD Vehicle (2-wheelers inc. gasoline)	6	286	4.00	6,864
	Management cars	2	286	10.00	5,720
Other Vaccination Campaign Information:	Media (e.g. posters, leaflets)	100000	N/A	0.15	15,000
	Additional expenses (e.g., radio)	0	N/A	0.00	0
Total fixed costs					**260,628**

Supplementary Table C11 - Variable costs.

Percent vaccine wastage	10%		
Variable costs	**Units**	**Price/ Unit**	**Total**
Vaccines	89,277	0.53	47,317
Syringes & Needles	89,277	0.01	893
Vaccination Certificates	89,277	0.01	946
Dog marking	89,277	0.02	1,425
Total variable costs			55,639
Average variable cost per dog vaccinated			0.62
Average cost per dog vaccinated when vaccinating			**3.54**
	89,277	**dogs**	

PEP costs

Supplementary Table C12 - Table of PEP costs.

PEP efficacy	0.93
Material costs per injections (includes needles, syringes, swabs, etc.)	0.43
Overhead costs per PEP visit (includes anti-rabies clinic staff salaries and administration costs)	2.22
Cost per vaccine dose	3.96
Number of vaccine doses/visit	1.00
Number of visits	5.00
Average cost of eRIG	7.00
Proportion of PEP recipients receiving RIG	15%
PEP cost & Other Costs	**34.10**

Supplementary Table C13 - Table of animal rabies investigations.

Probabilities and costs of suspect animals	**Probability:**	**Cost per animal:**
Quarantined animal	0.0008	140.00
Lab test	0.011333333	26.49
Bite investigation	0.466666667	3.25
Vaccinated Dog	N/A	3.38

Appendix D – Chapter 5

Vaccination methods outline

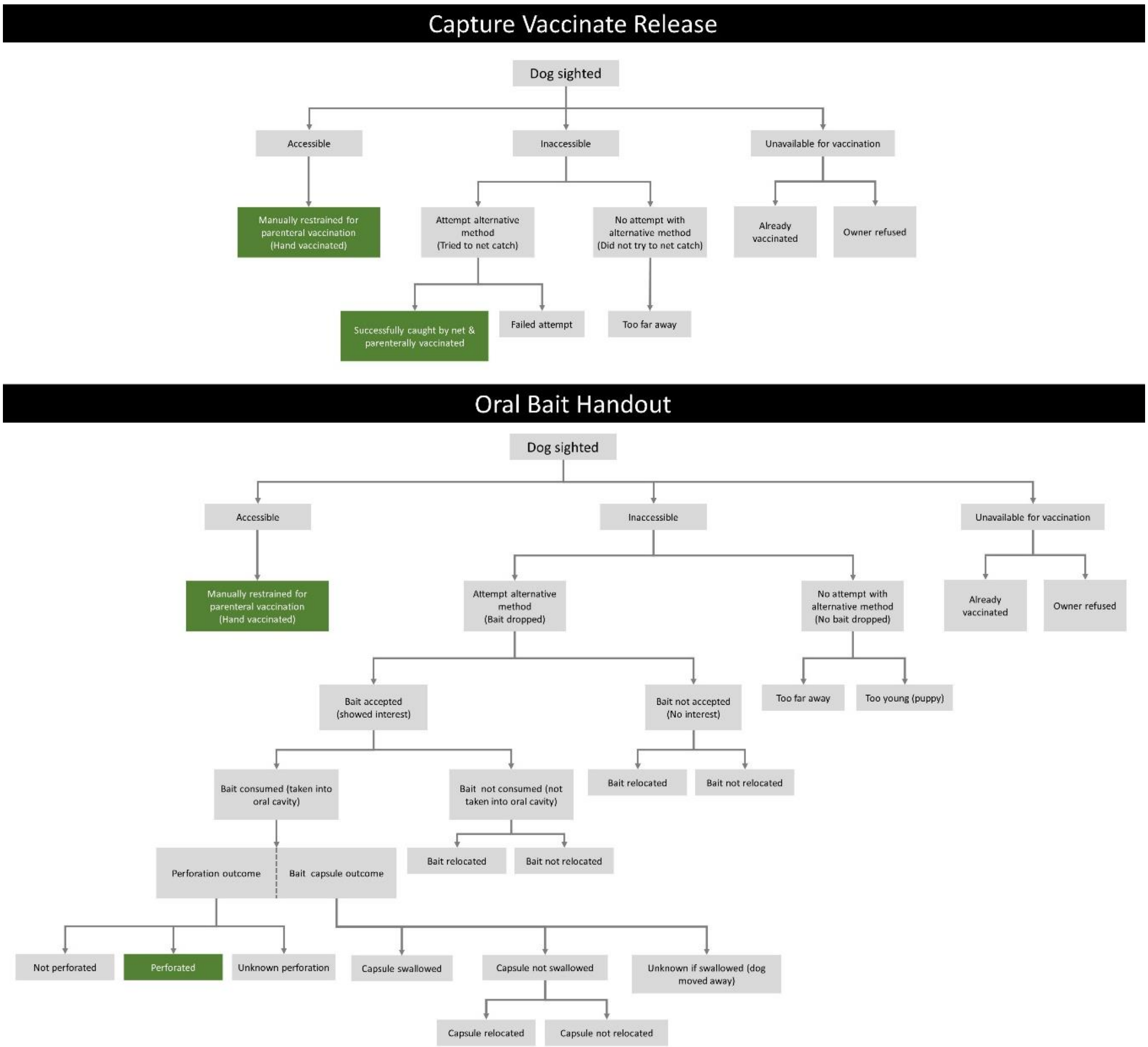
Oral-Bait-Handout (OBH) method

a) OBH teams travelling by scooter (2 people per team).
b) Nobivac® Rabies parenteral vaccine given to dogs that can be manually restrained.
c) Oral bait given to dogs that could not be handled. Consists of an empty capsule and boiled pig skin within collagen casing, which is then coated in dog food gravy.

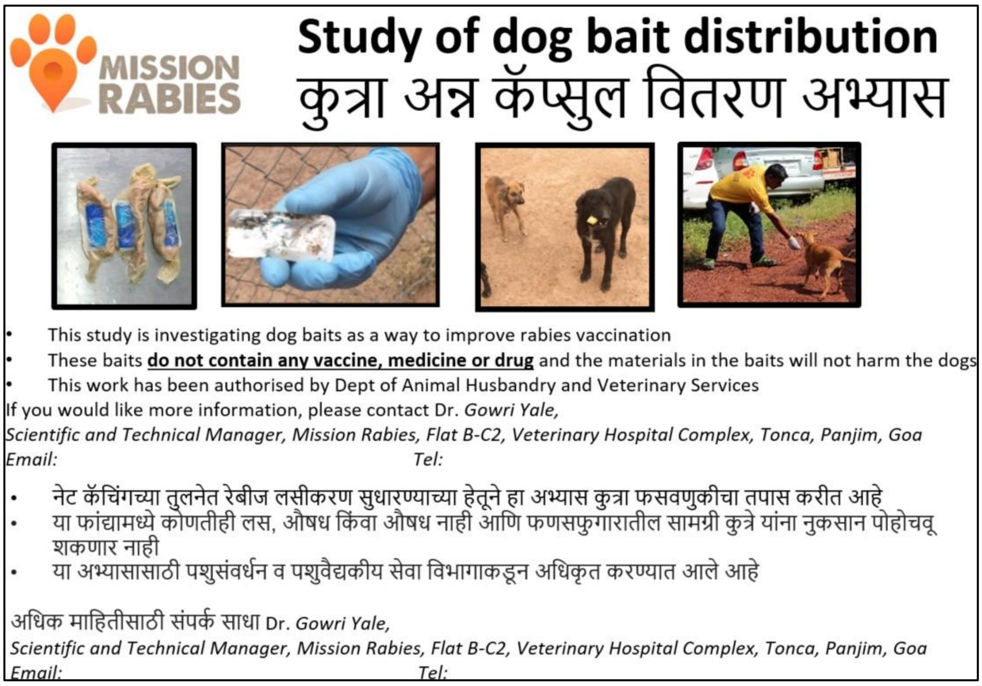
Capture-Vaccinate-Release (CVR) method

a) CVR teams travelling by supply vehicle (7 people per team).
b) Nobivac® Rabies parenteral vaccine given to dogs that can be manually restrained and dogs caught in nets.

Supplementary Figure D1 - Description of the Oral bait handout (OBH) and Capture vaccinate release (CVR) methods.



Supplementary Figure D2 - Flow diagram of Capture Vaccinate Release and Oral Bait Handout method dataset structures.



Supplementary Figure D3 - Leaflet distributed by OBH teams on A5 paper.

Multivariable logistic regression analyses

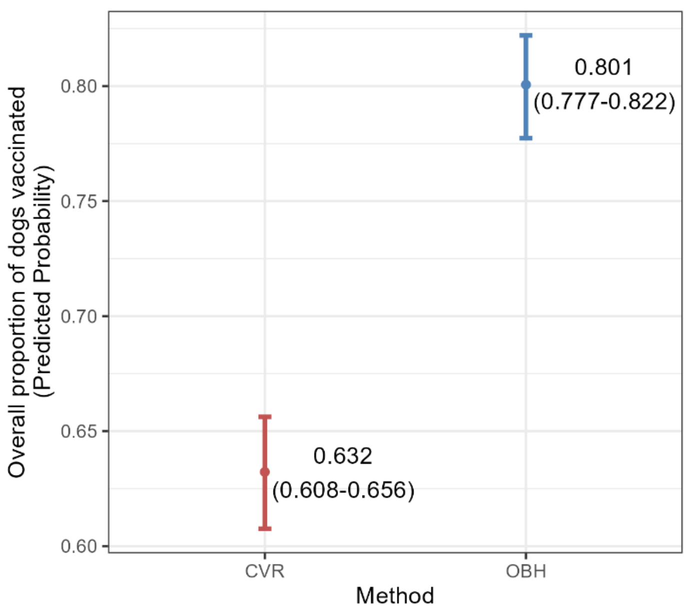
MODEL 1 - Overall vaccination proportion

Supplementary Table D1 – Summary table of multivariable logistic regression model selection for the evaluation of overall vaccination coverage. The dependent variable was dog vaccinations as a proportion of all available dogs. Combinations of independent variables vaccination method, land type, team, and their interactions were compared. Model 5 was selected with the lowest AIC (independent variables vaccination method, land type, team, interaction between method and land type, and interaction between method and team).

	Dependent variable:				
	n_vacc, n_failedavailable)				
	(1)	(2)	(3)	(4)	(5)
methodOBH	0.7862***	0.5749***	0.9366***	0.7821***	0.5946**
	(0.0747)	(0.1775)	(0.1697)	(0.0964)	(0.2564)
UserElephant Vet 2	-0.4534***	-0.3618***	-0.6387***	-0.3438	-0.5036***
	(0.1091)	(0.1219)	(0.1413)	(0.2354)	(0.1480)
UserLeopards Fernandes	-0.6851***	-0.6515***	-0.4251***	-0.4219**	-0.3989***
	(0.0956)	(0.0977)	(0.1197)	(0.1850)	(0.1211)
UserVishnu	-0.1934*	-0.0969	-0.2106	-0.3077	-0.0704
	(0.1098)	(0.1197)	(0.1447)	(0.2321)	(0.1542)
DescriptioSub-urban	-0.2231**	-0.3849***	-0.0146	0.0526	-0.2533*
	(0.0932)	(0.1313)	(0.1106)	(0.1862)	(0.1375)
DescriptioVillage housing	0.1728*	0.2268*	0.3322***	0.1485	0.3045**
	(0.1037)	(0.1354)	(0.1132)	(0.1699)	(0.1363)
DescriptioSparse housing	0.0238	-0.2117	0.0594	0.2778	-0.1905
	(0.1398)	(0.1822)	(0.1509)	(0.4117)	(0.1923)
methodOBH:DescriptioSub-urban		0.3906*			0.6049**
		(0.2289)			(0.2406)
methodOBH:DescriptioVillage housing		-0.0755			0.1658
		(0.2308)			(0.2513)
methodOBH:DescriptioSparse housing		0.6217**			0.6049*
		(0.3148)			(0.3178)
methodOBH:UserElephant Vet 2			0.3645		0.3805
			(0.2589)		(0.2730)
methodOBH:UserLeopards Fernandes			-0.6482***		-0.6815***
			(0.2105)		(0.2119)
methodOBH:UserVishnu			-0.0216		-0.0596
			(0.2462)		(0.2590)
UserElephant Vet 2:DescriptioSub-urban				-0.4726	
				(0.3001)	
UserLeopards Fernandes:DescriptioSub-urban				-0.5135**	
				(0.2481)	
UserVishnu:DescriptioSub-urban				0.0344	
				(0.2914)	
UserElephant Vet 2:DescriptioVillage housing				0.4925	
				(0.3473)	
UserLeopards Fernandes:DescriptioVillage housing				-0.2024	
				(0.2479)	
UserVishnu:DescriptioVillage housing				0.2750	
				(0.3317)	
UserElephant Vet 2:DescriptioSparse housing				-0.0344	
				(0.5414)	
UserLeopards Fernandes:DescriptioSparse housing				-0.5150	
				(0.4949)	
UserVishnu:DescriptioSparse housing				-0.1287	
				(0.4944)	
Constant	0.9099***	0.9424***	0.7506***	0.8309***	0.8200***
	(0.0943)	(0.1048)	(0.1003)	(0.1277)	(0.1088)
Observations	45	45	45	45	45
Log Likelihood	-151.0511	-146.0684	-140.6819	-142.6397	-135.6815
Akaike Inf. Crit.	318.1023	314.1369	303.3638	319.2795	299.3629
Note:	*p<0.1; **p<0.05; ***p<0.01				

Supplementary Table D2 – Table of outputs for multivariable logistic regression model evaluating overall vaccination proportion. Table shows Odds Ratios with 95% confidence intervals, standard error, and p-values. *P-values lower than 0.05.

Variable	**Odds Ratio (95% CI)**	**Std. Error**	**P-value**
(Intercept)	2.270 (1.838 - 2.817)	0.1088	<0.001*
Method OBH	1.812 (1.098 - 3.002)	0.2564	0.020*
Team Elephants	0.604 (0.452 - 0.808)	0.1480	<0.001*
Team Leopards	0.671 (0.529 - 0.851)	0.1211	<0.001*
Team Vishnu	0.932 (0.69 - 1.263)	0.1542	0.648
Land type Suburban	0.776 (0.593 - 1.016)	0.1375	0.065
Land type Village housing	1.356 (1.038 - 1.772)	0.1363	0.025*
Land type Sparse housing	0.827 (0.567 - 1.206)	0.1923	0.322
Method ORV : **Team** Elephants	1.463 (0.857 - 2.502)	0.2730	0.163
Method ORV : **Team** Leopards	0.506 (0.332 - 0.763)	0.2119	0.001*
Method ORV : **Team** Vishnu	0.942 (0.566 - 1.564)	0.2590	0.818
Method ORV : **Land type** Suburban	1.831 (1.144 - 2.941)	0.2406	0.012*
Method ORV : **Land type** Village housing	1.180 (0.723 - 1.936)	0.2513	0.509
Method ORV : **Land type** Sparse housing	1.831 (0.99 - 3.446)	0.3178	0.057



Supplementary Figure D4 – Graph showing multivariable logistic regression model estimated overall vaccination proportion by vaccination method (averaged over factors of land type and team). Points show estimated marginal means, error bars show 95% confidence intervals. Labels give numeric values of the same.

Supplementary Table D3 – Estimated overall vaccination proportion by vaccination method and land type (averaged over team). Confidence intervals are for 95% level.

Land type	Method	Proportion (95% CI)
Urban	CVR	64 (59-68.8)
Urban	OBH	74.7 (68.9-79.7)
Sub-urban	CVR	58 (54.4-61.6)
Sub-urban	OBH	80.7 (77.3-83.8)
Village housing	CVR	70.7 (66.5-74.6)
Village housing	OBH	82.5 (78.7-85.7)
Sparse housing	CVR	59.5 (52.3-66.4)
Sparse housing	OBH	81.7 (74.5-87.2)

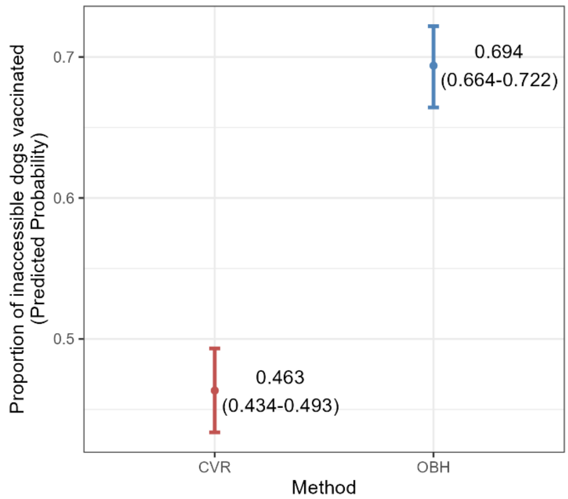
MODEL 2 – Proportion of inaccessible dogs vaccinated

Supplementary Table D4 – Summary table of multivariable logistic regression model selection for evaluation of the proportion of inaccessible dogs vaccinated. The dependent variable was dog vaccinations as a proportion of inaccessible dogs. Combinations of independent variables vaccination method, land type, team, and their interactions were compared. Model 3 was selected with the lowest AIC (independent variables vaccination method, land type, team, interaction between method and team).

	Dependent variable:				
	n_failedinaccessible)				
	(1)	(2)	(3)	(4)	(5)
methodOBH	0.8647***	1.0088***	0.8178***	0.7897***	0.7805***
	(0.0840)	(0.1944)	(0.1837)	(0.1089)	(0.2772)
UserElephant Vet 2	-0.6926***	-0.7411***	-1.1103***	-0.1495	-1.0757***
	(0.1284)	(0.1454)	(0.1786)	(0.2518)	(0.1865)
UserLeopards Fernandes	-0.6468***	-0.6030***	-0.4241***	-0.4248**	-0.4097***
	(0.1075)	(0.1100)	(0.1343)	(0.2050)	(0.1354)
UserVishnu	-0.0283	-0.0262	-0.1072	-0.0334	-0.0521
	(0.1203)	(0.1309)	(0.1601)	(0.2471)	(0.1711)
DescriptioSub-urban	-0.4492***	-0.3870***	-0.1607	-0.0203	-0.2127
	(0.1023)	(0.1478)	(0.1221)	(0.2030)	(0.1547)
DescriptioVillage housing	-0.1820	-0.0187	0.0394	-0.1265	0.0536
	(0.1153)	(0.1526)	(0.1269)	(0.1890)	(0.1536)
DescriptioSparse housing	-0.1970	-0.2575	-0.0994	0.2300	-0.2098
	(0.1539)	(0.2038)	(0.1664)	(0.4343)	(0.2155)
methodOBH:DescriptioSub-urban		-0.1593			0.0900
		(0.2533)			(0.2612)
methodOBH:DescriptioVillage housing		-0.3990			-0.0394
		(0.2555)			(0.2763)
methodOBH:DescriptioSparse housing		0.2156			0.2606
		(0.3422)			(0.3456)
methodOBH:UserElephant Vet 2			0.8670***		0.8346***
			(0.2970)		(0.3157)
methodOBH:UserLeopards Fernandes			-0.4666**		-0.4661**
			(0.2319)		(0.2339)
methodOBH:UserVishnu			0.1877		0.1401
			(0.2668)		(0.2782)
UserElephant Vet 2:DescriptioSub-urban				-1.0072***	
				(0.3288)	
UserLeopards Fernandes:DescriptioSub-urban				-0.5497**	
				(0.2779)	
UserVishnu:DescriptioSub-urban				-0.1683	
				(0.3107)	
UserElephant Vet 2:DescriptioVillage housing				-0.6045	
				(0.4292)	
UserLeopards Fernandes:DescriptioVillage housing				-0.0046	
				(0.2756)	
UserVishnu:DescriptioVillage housing				0.3317	
				(0.3519)	
UserElephant Vet 2:DescriptioSparse housing				-0.6789	
				(0.5857)	
UserLeopards Fernandes:DescriptioSparse housing				-0.5147	
				(0.5365)	
UserVishnu:DescriptioSparse housing				-0.3214	
				(0.5245)	
Constant	0.4780***	0.4177***	0.3188***	0.3348**	0.3278***
	(0.1034)	(0.1149)	(0.1110)	(0.1396)	(0.1199)
Observations	45	45	45	45	45
Log Likelihood	-139.4668	-137.2498	-128.3167	-131.4471	-127.8379
Akaike Inf. Crit.	294.9337	296.4996	278.6334	296.8941	283.6759
Note:	*p<0.1; **p<0.05; ***p<0.01				

Supplementary Table D5 – Table of outputs for multivariable logistic regression model evaluating proportion of inaccessible dogs vaccinated. Table shows Odds Ratios with 95% confidence intervals, standard error, and p-values. *P-values lower than 0.05.

Variable	Odds Ratio (95% CI)	Std. Error	P-value
(Intercept)	1.375 (1.107 - 1.712)	0.1110	0.004*
Method OBH	2.265 (1.588 - 3.266)	0.1837	<0.001*
Team Elephants	0.329 (0.231 - 0.466)	0.1786	<0.001*
Team Leopards	0.654 (0.503 - 0.851)	0.1343	0.002*
Team Vishnu	0.898 (0.656 - 1.23)	0.1601	0.503
Land type Suburban	0.852 (0.67 - 1.082)	0.1221	0.188
Land type Village housing	1.040 (0.811 - 1.334)	0.1269	0.756
Land type Sparse housing	0.905 (0.654 - 1.256)	0.1664	0.550
Method ORV : **Team** Elephants	2.380 (1.33 - 4.265)	0.2970	0.004*
Method ORV : **Team** Leopards	0.627 (0.397 - 0.985)	0.2319	0.044
Method ORV : **Team** Vishnu	1.206 (0.714 - 2.033)	0.2668	0.482



Supplementary Figure D5 – Graph showing multivariable logistic regression model estimated proportion of inaccessible dogs vaccinated by vaccination method (averaged over factors of land type and team). Points show estimated marginal means, error bars show 95% confidence intervals. Labels give numeric values of the same.

Supplementary Table D6 – Estimated proportion of inaccessible dogs vaccinated by vaccination method and land type (averaged over team). Confidence intervals are for 95% level.

Land type	Method	Proportion (95% CI)
Urban	CVR	47.71 (42.66-52.81)
Urban	OBH	70.54 (66.21-74.53)
Sub-urban	CVR	43.73 (40.12-47.4)
Sub-urban	OBH	67.1 (63.13-70.83)
Village housing	CVR	48.69 (44.01-53.4)
Village housing	OBH	71.35 (67.26-75.13)
Sparse housing	CVR	45.24 (38.61-52.05)
Sparse housing	OBH	68.43 (61.94-74.28)

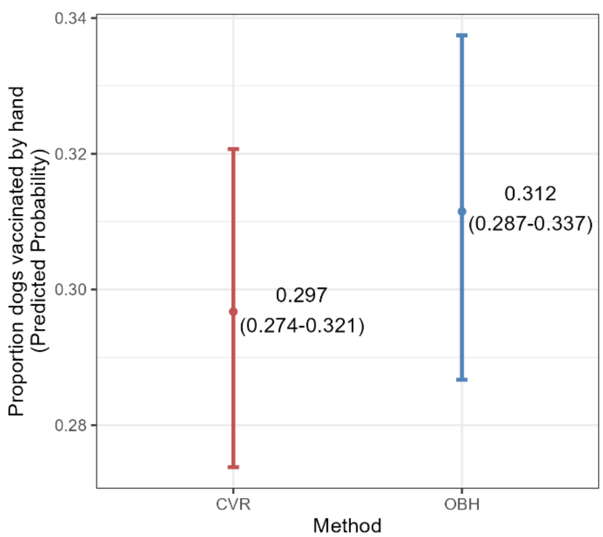
MODEL 3 – Proportion of dogs vaccinated by hand

Supplementary Table D7 – Summary table of multivariable logistic regression model selection for evaluation of proportion of dogs manually restrained for parenteral vaccination. The dependent variable was the proportion of dogs vaccinated by hand. Combinations of independent variables vaccination method, land type, team, and their interactions were compared. Model 5 was selected with the lowest AIC (independent variables vaccination method, land type, team, interaction between method and land type, and interaction between method and team).

	Dependent variable:				
	n_hand, n_handfailedavailable)				
	(1)	(2)	(3)	(4)	(5)
methodOBH	0.2027***	-0.7386***	0.4196***	0.3457***	-0.4970**
	(0.0712)	(0.1883)	(0.1318)	(0.0895)	(0.2297)
UserElephant Vet 2	0.0665	0.4074***	0.0872	-0.7559***	0.4416***
	(0.1012)	(0.1156)	(0.1425)	(0.2396)	(0.1551)
UserLeopards Fernandes	-0.4393***	-0.4481***	-0.2263*	-0.1920	-0.1913
	(0.0931)	(0.0953)	(0.1286)	(0.2030)	(0.1296)
UserVishnu	-0.5568***	-0.3471***	-0.3811**	-1.0849***	-0.0903
	(0.1043)	(0.1134)	(0.1486)	(0.2495)	(0.1635)
DescriptioSub-urban	0.4939***	-0.1868	0.5174***	0.2727	-0.1820
	(0.0976)	(0.1428)	(0.1131)	(0.1791)	(0.1525)
DescriptioVillage housing	0.7627***	0.5249***	0.7781***	0.4776***	0.5440***
	(0.1030)	(0.1350)	(0.1117)	(0.1645)	(0.1368)
DescriptioSparse housing	0.5932***	0.1096	0.5147***	0.0642	-0.0428
	(0.1373)	(0.2008)	(0.1467)	(0.3106)	(0.2155)
methodOBH:DescriptioSub-urban		1.5033***			1.5569***
		(0.2376)			(0.2402)
methodOBH:DescriptioVillage housing		0.7425***			0.7382***
		(0.2278)			(0.2359)
methodOBH:DescriptioSparse housing		1.0324***			1.1292***
		(0.2957)			(0.3019)
methodOBH:UserElephant Vet 2			-0.0854		-0.0998
			(0.2210)		(0.2340)
methodOBH:UserLeopards Fernandes			-0.4572**		-0.5472***
			(0.1898)		(0.1902)
methodOBH:UserVishnu			-0.3673*		-0.5102**
			(0.2172)		(0.2277)
UserElephant Vet 2:DescriptioSub-urban				0.6664**	
				(0.3010)	
UserLeopards Fernandes:DescriptioSub-urban				-0.3098	
				(0.2549)	
UserVishnu:DescriptioSub-urban				0.7139**	
				(0.2973)	
UserElephant Vet 2:DescriptioVillage housing				1.8085***	
				(0.3202)	
UserLeopards Fernandes:DescriptioVillage housing				-0.3888	
				(0.2539)	
UserVishnu:DescriptioVillage housing				0.2693	
				(0.3343)	
UserElephant Vet 2:DescriptioSparse housing				1.3840***	
				(0.4291)	
UserLeopards Fernandes:DescriptioSparse housing				-0.1062	
				(0.4487)	
UserVishnu:DescriptioSparse housing				0.8526**	
				(0.4208)	
Constant	-1.1502***	-0.8783***	-1.2409***	-0.9824***	-0.9827***
	(0.0980)	(0.1073)	(0.1063)	(0.1319)	(0.1142)
Observations	45	45	45	45	45
Log Likelihood	-210.3542	-187.7366	-206.8590	-180.2426	-182.3525
Akaike Inf. Crit.	436.7083	397.4732	435.7180	394.4852	392.7049
Note:	*p<0.1; **p<0.05; ***p<0.01				

Supplementary Table D8 – Table of outputs for multivariable logistic regression model evaluating proportion of dogs vaccinated by hand. Table shows Odds Ratios with 95% confidence intervals, standard error, and p-values. *P-values lower than 0.05.

Variable	**Odds Ratio (95% CI)**	**Std. Error**	**P-value**
(Intercept)	0.374 (0.298 - 0.467)	0.1142	<0.001*
Method OBH	0.608 (0.387 - 0.952)	0.2297	0.030*
Team: Elephants	1.555 (1.148 - 2.109)	0.1551	0.004*
Team: Leopards	0.826 (0.64 - 1.064)	0.1296	0.140
Team: Vishnu	0.914 (0.662 - 1.257)	0.1635	0.581
Land type: Suburban	0.834 (0.618 - 1.124)	0.1525	0.233
Land type: Village housing	1.723 (1.319 - 2.256)	0.1368	<0.001*
Land type: Sparse housing	0.958 (0.625 - 1.456)	0.2155	0.843
Method ORV : **Team** Elephants	0.905 (0.572 - 1.432)	0.2340	0.670
Method ORV : **Team** Leopards	0.579 (0.399 - 0.84)	0.1902	0.004*
Method ORV : **Team** Vishnu	0.600 (0.384 - 0.938)	0.2277	0.025*
Method ORV : **Land type** Suburban	4.744 (2.971 - 7.62)	0.2402	<0.001*
Method ORV : **Land type** Village housing	2.092 (1.32 - 3.33)	0.2359	0.002*
Method ORV : **Land type** Sparse housing	3.093 (1.716 - 5.608)	0.3019	<0.001*



Supplementary Figure D6 – Graph showing multivariable logistic regression model estimated proportion of dogs vaccinated by hand by vaccination method (averaged over factors of land type and team). Points show estimated marginal means, error bars show 95% confidence intervals. Labels give numeric values of the same.

Supplementary Table D9 – Estimated proportion of dogs vaccinated by hand by vaccination method and land type (averaged over team). Confidence intervals are for 95% level.

Land type	Method	Proportion (95% CI)
Urban	CVR	28.03 (23.64-32.9)
Urban	OBH	15.07 (11.68-19.24)
Sub-urban	CVR	24.51 (21.53-27.77)
Sub-urban	OBH	41.24 (37.22-45.38)
Village housing	CVR	40.16 (35.82-44.67)
Village housing	OBH	39.01 (34.51-43.71)
Sparse housing	CVR	27.18 (21.07-34.29)
Sparse housing	OBH	34.47 (27.72-41.9)

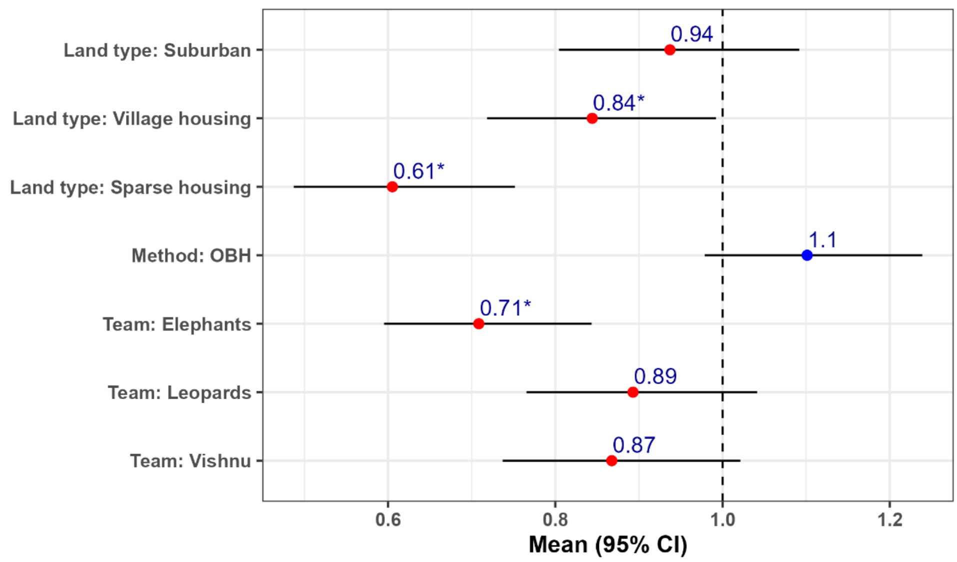
MODEL 4 - Quasi-Poisson regression model of vaccination rate

Supplementary Table D10 – Table of summarised quasi-Poisson regression models considered for selection, with vaccination rate as the response variable and vaccination method, land type, and team as predictor variables. The model with the lowest QAIC was selected.

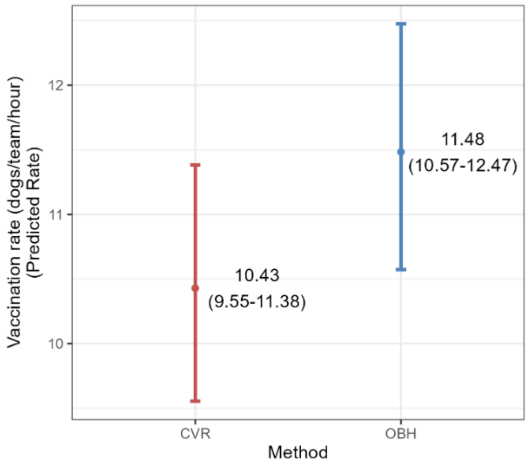
Intercept	Land type	method	Team	Land type: method	Land type: User	method: User	Landtype: method: User	offset(log(hours))	QAIC
2.68	+	+	+					+	162.0
2.71	+		+					+	162.6
2.74	+	+	+			+		+	163.8
2.65	+	+	+	+				+	166.0
2.71	+	+	+	+		+		+	168.2
2.58	+							+	170.6
2.55	+	+						+	171.5
2.78	+		+		+			+	172.1
2.78	+	+	+		+			+	173.0
2.59	+	+		+				+	174.4
2.78	+	+	+	+	+			+	175.2
2.78	+	+	+		+	+		+	177.8
2.78	+	+	+	+	+	+		+	180.3
2.61		+	+			+		+	180.8
2.55		+	+					+	180.9
2.59			+					+	181.0
2.78	+	+	+	+	+	+	+	+	182.2
2.46								+	191.0
2.44		+						+	192.3
4.62	+		+		+				198.1
4.62	+	+	+		+				198.9
4.62	+	+	+	+	+				201.1
4.62	+	+	+		+	+			201.2
4.62	+	+	+	+	+	+			203.4
4.62	+	+	+	+	+	+	+		205.4
4.44	+	+	+			+			209.4
4.36	+	+	+						210.9
4.38	+	+	+	+		+			211.4
4.29	+	+	+	+					211.7
4.41	+		+						216.7
4.24	+	+							220.1
4.23	+	+		+					222.3
4.30	+								223.0
4.23		+	+			+			234.0
4.17		+	+						234.5
4.23			+						238.6
4.06		+							247.1
4.12									248.4

Supplementary Table D11 – Table of outputs for multivariable quasi-Poisson regression model evaluating vaccination rate by vaccination method, land type, and team. *P-values lower than 0.05.

Variable	**Rate Ratio (95% CI)**	**Std. Error**	**P-value**
(Intercept)	14.567 (12.515 - 16.878)	0.0763	<0.001*
Land type Suburban	0.937 (0.809 - 1.087)	0.0753	0.394
Land type Village housing	0.844 (0.722 - 0.987)	0.0797	0.040*
Land type Sparse housing	0.605 (0.489 - 0.745)	0.1071	<0.001*
Method OBH	1.101 (0.983 - 1.234)	0.0582	0.106
Team Elephants	0.709 (0.598 - 0.838)	0.0860	<0.001*
Team Leopards	0.893 (0.769 - 1.036)	0.0759	0.144
Team Vishnu	0.868 (0.741 - 1.015)	0.0805	0.086



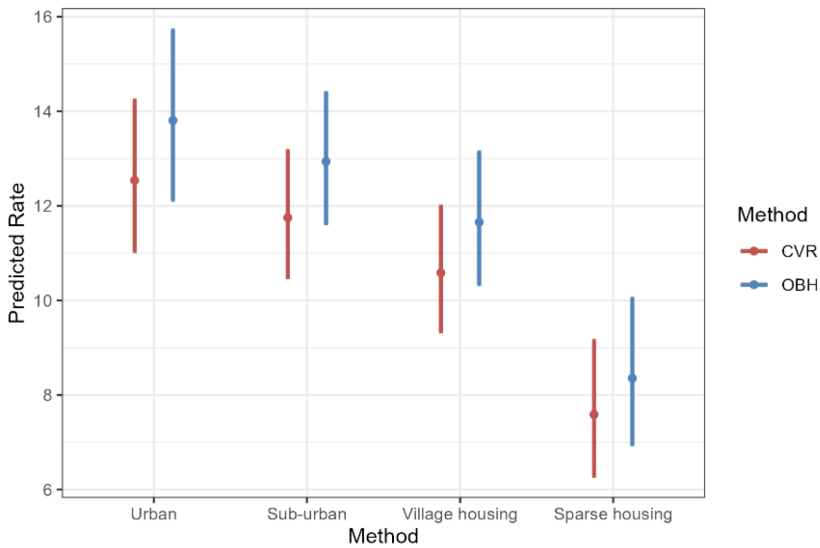
Supplementary Figure D7 – Quasi-Poisson regression model predicting rate of vaccination (dogs / team / hour).



Supplementary Figure D8 – Graph showing quasi-Poisson regression model predicted rate of dogs vaccinated (dogs/team/hour) by vaccination method (averaged over factors of land type and team). Points show estimated marginal means, error bars show 95% confidence intervals. Labels give numeric values of the same.

Supplementary Table D12 – Estimated marginal means of the predicted rate of dogs vaccinated (dogs/team/hour) by land type (averaged over team and method). Confidence intervals are for 95% level.

Land type	Rate (95% CI)
Urban	13.16 (11.74-14.75)
Sub-urban	12.33 (11.23-13.54)
Village housing	11.11 (9.97-12.37)
Sparse housing	7.96 (6.68-9.49)



Supplementary Figure D9 – Plot of mean 'vaccination' rate (dogs accessed/team/hour) by land type as predicted using a multivariable quasi-Poisson model (averaged over the factor of Team). Error bars show 95% confidence intervals.

Supplementary Table D13 – Table showing estimated serocoverage by method and land type with variable rates of seroconversion following consumption of ORV (60%, 70%, 80%, or 90%). Land type 'ALL' represents mean across land types.

Land type	Method	(60% OBH) Mean sero-coverage	(70% OBH) Mean sero-coverage	(80% OBH) Mean sero-coverage	(90% OBH) Mean sero-coverage
Urban	CVR	0.63 (0.55 - 0.7)	0.63 (0.55 - 0.7)	0.63 (0.55 - 0.7)	0.63 (0.55 - 0.7)
Urban	OBH	0.54 (0.44 - 0.63)	0.6 (0.49 - 0.71)	0.66 (0.53 - 0.79)	0.72 (0.58 - 0.86)
Sub-urban	CVR	0.58 (0.49 - 0.67)	0.58 (0.49 - 0.67)	0.58 (0.49 - 0.67)	0.58 (0.49 - 0.67)
Sub-urban	OBH	0.63 (0.51 - 0.74)	0.67 (0.56 - 0.77)	0.71 (0.6 - 0.81)	0.75 (0.64 - 0.85)
Village housing	CVR	0.7 (0.65 - 0.75)	0.7 (0.65 - 0.75)	0.7 (0.65 - 0.75)	0.7 (0.65 - 0.75)
Village housing	OBH	0.63 (0.49 - 0.76)	0.67 (0.55 - 0.79)	0.71 (0.6 - 0.82)	0.76 (0.65 - 0.86)
Sparse housing	CVR	0.59 (0.5 - 0.67)	0.59 (0.5 - 0.67)	0.59 (0.5 - 0.67)	0.59 (0.5 - 0.67)
Sparse housing	OBH	0.67 (0.61 - 0.73)	0.71 (0.67 - 0.75)	0.75 (0.73 - 0.77)	0.8 (0.76 - 0.83)
(ALL)	CVR	0.63 (0.59 - 0.67)	0.63 (0.59 - 0.67)	0.63 (0.59 - 0.67)	0.63 (0.59 - 0.67)
(ALL)	OBH	0.62 (0.57 - 0.67)	0.66 (0.62 - 0.71)	0.71 (0.66 - 0.75)	0.75 (0.71 - 0.79)

Cost calculations

Supplementary Table D14 - Fixed operational costs. Units in bold represent the input value which is then estimated as a daily cost. All costs are in Indian Rupees.

	Fixed	Seven years	Year	Month	Week	Day	CVR units per team	CVR team day cost	OBH units per team	OBH team day cost
Vehicles	Purchase goods vehicle	**800,000**	114,286	9,524	2,381	433	**1**	**433**	**0**	**0**
	Servicing goods vehicle	-	**100,000**	8,333	2,083	379	**1**	**379**	**0**	**0**
	Fuel goods vehicle	-	-	-	**6,000**	1,091	**1**	**1,091**	**0**	**0**
	Purchase moped	**67,000**	9,571	798	199	36	**0**	**0**	**1**	**36**
	Servicing moped	-	**3,000**	250	63	11	**0**	**0**	**1**	**11**
	Fuel moped	-	-	-	**600**	109	**0**	**0**	**1**	**109**
Salaries	Team leader	-	-	**15,000**	3,750	938	**1**	**938**	**1**	**938**
	Driver salary	-	-	**12,000**	3,000	750	**1**	**750**	**0**	**0**
	Assistant salary	-	-	**8,500**	2,125	531	**1**	**531**	**1**	**531**
	Catcher salary	-	-	**8,500**	2,125	531	**4**	**2,125**	**0**	**0**
Staff care	Food	-	-	-	-	**250**	**7**	**1,750**	**2**	**500**
	Accommodation	-	-	-	-	**150**	**7**	**1,050**	**2**	**300**
Equipment	Nets	-	**3,000**	250	63	11	**4**	**45**	**0**	**0**
	Cool box	-	**1,000**	83	21	4	**1**	**4**	**1**	**4**
	Back packs	-	**1,000**	83	21	4	**1**	**4**	**1**	**4**
	Smartphone	-	**4,000**	333	83	15	**1**	**15**	**1**	**15**
	Phone bill	-	-	**500**	125	23	**1**	**23**	**1**	**23**
	Helmets	-	**500**	42	10	2	**0**	**0**	**1**	**2**
Total								**9,137**		**2,473**

Supplementary Table D15 - Variable costs per vaccine dose. All costs are in Indian Rupees.

Item	Cost per unit	Parenteral		Oral	
		Units per dose	Cost per dose	Units per dose	Cost per dose
Syringe	2	0.03	**0.07**	0	**0**
Needle	0.5	1	**0.5**	0	**0**
Vaccination card	3	1	**3**	0	**0**
Parenteral vaccine procurement	40	1	**40**	0	**0**
Oral vaccine procurement	200	0	**0**	1	**200**
TOTAL COST PER DOSE			**44**		**200**

Staff survey

Staff Questionnaire questions

1) What do you like about the ORV method?
2) What do you dislike about the ORV method?
3) What improvements could you suggest for ORV method?
4) What do you like about the CRV method?
5) What do you dislike about the CRV method?
6) What improvements could you suggest for CVR method?
7) Which method do you prefer to use?
8) Why do you prefer this method?
9) Which method do you think can reach more dogs?
10) Which method do you think is better for the dogs' welfare?

Supplementary Table D16 – Individual responses to questionnaire to vaccination staff involved in the study. All staff were experienced in capture vaccination release vaccination method prior to the study.

Question	Staff 1 responses
01	When we give bait more dogs start coming and becomes friendly, so I like this part
02	I don't like to use Mobile phone While on highway
03	Other types of baits, and also after getting out from the Fridge the bait becomes too hard, it makes difficult to the dogs.
04	Handling is better because more boys are there
05	More walking
06	No Co-ordination among boys
07	Oral Bait
08	More dogs can be vaccinated
09	Oral Bait
10	Oral Bait

Question	Staff 2 responses
01	Good for stray dog. More dogs gets escaped in CRV. More dogs gets vaccinated compared to CRV
02	Lot of times get down from the vehicle, Owner Dogs can't be handled
03	One Net can help get those difficult dogs
04	Good for owner dogs for handling because Large Group helps
05	Difficult to catch stray dogs
06	Both Oral and Catching if combined, more dogs can be vaccinated
07	Oral Bait
08	Owner dogs can be vaccinated and more dogs can be vaccinated in less time
09	Oral Bait
10	CVR

Question	Staff 3 responses
01	Everything is Good – lot of dogs don't run here and there
02	Dogs use to run by looking at us, sometimes dogs use to run away from us when we gave baits. There is a fear of dog bite while handling
03	We don't get to know whether the dog has already been vaccinated or not. Sometimes if there is a Net, it is good to get difficult dogs.
04	This is also good, In Town areas stray dogs can be caught easily
05	Difficult to catch stray dogs in open areas
06	In open areas, bait can be used
07	Net Catching
08	There is no fear of dog bite in the Net Method
09	Oral Bait
10	Oral Bait

Question	Staff 4 responses
01	Lot of boys don't require to vaccinate large number of dogs, Good for stray dogs
02	Sleeping dogs are bit difficult, some dogs they pick up the bait and take it away, we don't get to know about those baits whether the dog has chewed the bait or not.
03	No improvements
04	Owner dogs can be caught with the help of net which are difficult to handle
05	More dogs run away, dog can get harm
06	First Oral bait should be done and later dogs can be caught through Net – Both the method should be combined to get more numbers
07	Oral bait
08	More dogs can be vaccinated in less time
09	Oral bait
10	Oral Bait

Question	Staff 5 responses
01	When Bait is given, dogs are coming to us not running away
02	some dogs they pick up the bait and take it away, we don't get to know about those baits whether the dog has chewed the bait or not. Same dog eats couple of times, the one who is dominant
03	At times dogs take the meat, tear the wrapper using their feet and teeth, so the wrapper should be better which can get in their mouth.
04	Aggressive Dogs can be caught easily and there is no fear
05	If there is a group of stray dogs, only couple of them can be caught and rest run away.
06	Combination of Oral Bait
07	Oral bait
08	More dogs can be vaccinated
09	Oral bait
10	Oral Bait

Question	Staff 6 responses
01	More dogs can be vaccinated and also owner dogs can be handled well.
02	Flavour of meat should be taken care, at times bad smell comes out with hand.
03	Use the Garbage dumps – throw the Baits in the garbage for more number of dogs vaccination. Some Owners asks us, why there is no Net with you.
04	Owner Dogs are caught easily in the Net
05	If Net is used on Owner Dogs, they shout and abuse us. Most of the stray dogs can't be caught.
06	No Co-ordination among boys
07	Oral bait
08	More dogs can be vaccinated and is easy.
09	Oral bait
10	Oral Bait

Question	Staff 7 responses
01	More dogs can be vaccinated and I feel good to do this, out of 10 dogs 5 or 7 dogs are possible.
02	Flavour of meat should be taken care, at times bad smell comes out with hand.
03	At times dogs are scared of us
04	Owner Dogs are caught easily in the Net
05	Looking at the nets dogs run away.
06	No Co-ordination among boys
07	Oral bait
08	More dogs can be vaccinated and is easy. I enjoy working
09	Oral bait
10	Oral Bait

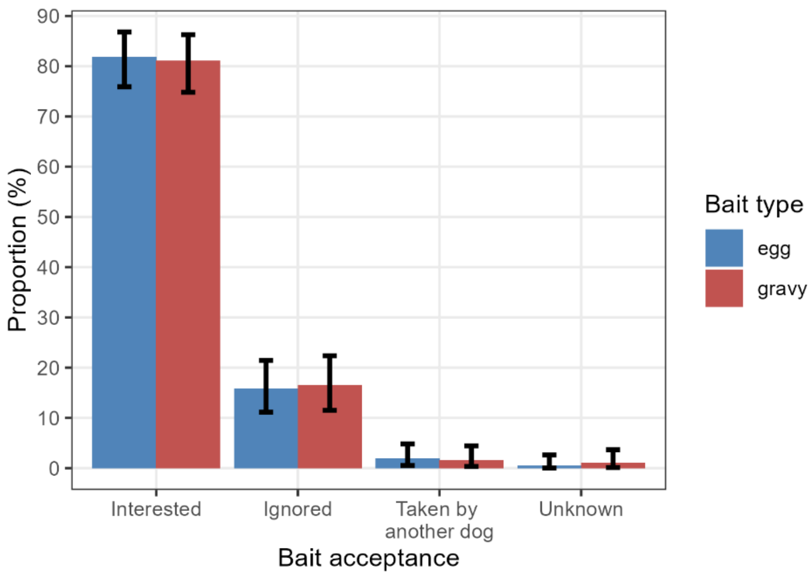
Question	Staff 8 responses
01	Better than Net, most of the stray dogs can be vaccinated
02	Getting Puppy is difficult,
03	No Idea on improvement
04	Owner dogs can be easily vaccinated
05	Looking at the nets dogs run away.
06	Change T-shirt
07	Oral bait
08	More dogs can be vaccinated and is easy. I enjoy working
09	Oral bait
10	Oral Bait

Appendix E – Chapter 6

Bait acceptance (showed interest in the bait by licking or sniffing)

Supplementary Table E1 - Table showing bait acceptance for each bait type (Count = number of baits by group, n = total number of baits distributed, Proportion within group with 95% confidence interval).

Bait type	Bait acceptance	Count	n	Proportion (95% CI)
Egg	Interested	171	209	81.82 (75.91-86.8)
Egg	Ignored	33	209	15.79 (11.12-21.45)
Egg	Taken by another dog	4	209	1.91 (0.52-4.83)
Egg	Unknown	1	209	0.48 (0.01-2.64)
Gravy	Interested	158	195	81.03 (74.81-86.27)
Gravy	Ignored	32	195	16.41 (11.5-22.37)
Gravy	Taken by another dog	3	195	1.54 (0.32-4.43)
Gravy	Unknown	2	195	1.03 (0.12-3.66)

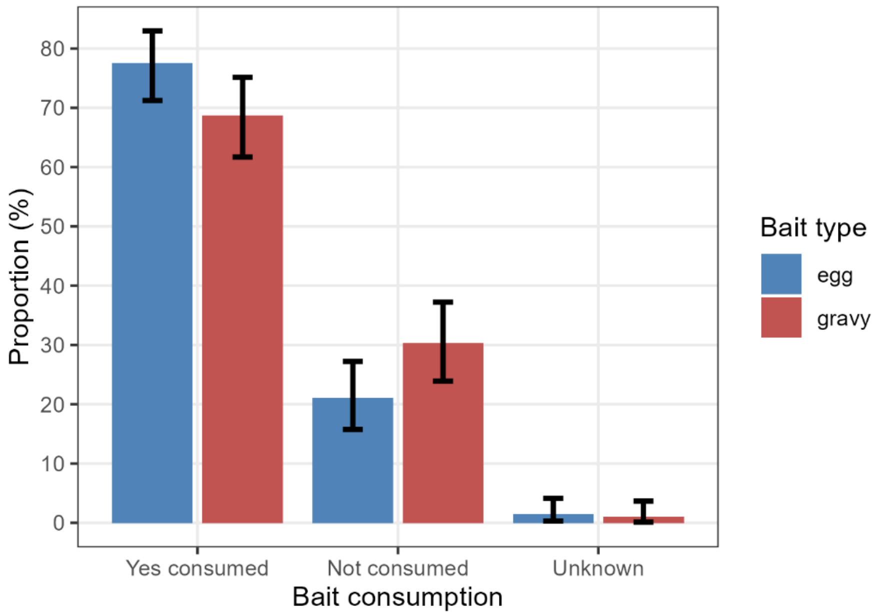


Supplementary Figure E1 - Chart showing the proportion of all dogs offered baits which made oral or nasal contact with the bait.

Bait consumption (took the bait into the oral cavity)

Supplementary Table E2 - Table showing bait consumption for each bait type (Count = number of baits by group, n = total number of baits distributed, Proportion within group with 95% confidence interval).

Bait type	Bait consumed	Count	n	Proportion (95% CI)
Egg	Yes consumed	162	209	77.51 (71.24-82.98)
Egg	Not consumed	44	209	21.05 (15.73-27.21)
Egg	Unknown	3	209	1.44 (0.3-4.14)
Gravy	Yes consumed	134	195	68.72 (61.7-75.15)
Gravy	Not consumed	59	195	30.26 (23.9-37.23)
Gravy	Unknown	2	195	1.03 (0.12-3.66)

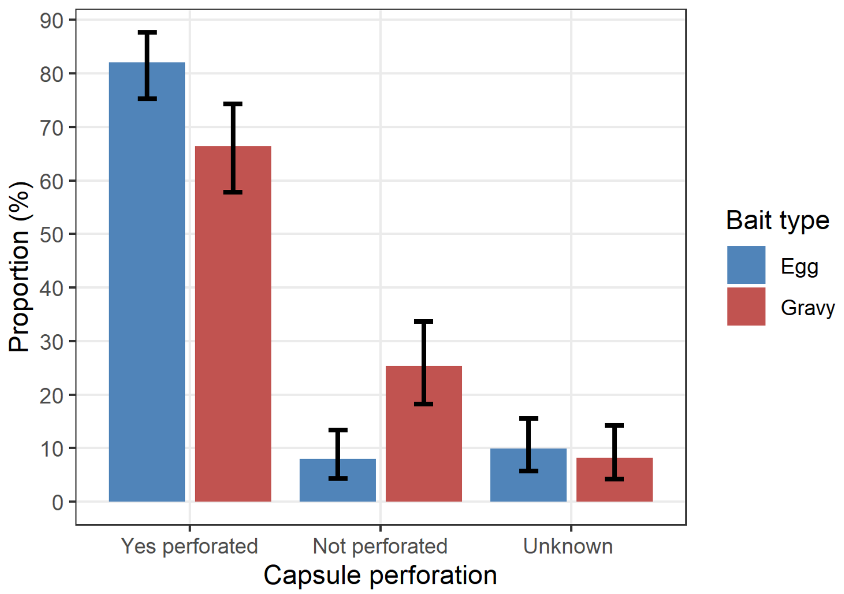


Supplementary Figure E2 - Chart showing the proportion of all dogs offered baits which took the bait into the oral cavity (consumed).

Capsule perforation

Supplementary Table E3 - Table showing capsule perforation outcome for each bait type (Count = number of baits by group, n = total number of baits distributed, Proportion within group with 95% confidence interval).

Bait type	Perforation status	Count	n	Proportion (95% CI)
Egg	Yes perforated	133	162	82.1 (75.31-87.67)
Egg	Unknown	16	162	9.88 (5.75-15.54)
Egg	Not perforated	13	162	8.02 (4.34-13.33)
Gravy	Yes perforated	89	134	66.42 (57.75-74.34)
Gravy	Not perforated	34	134	25.37 (18.26-33.61)
Gravy	Unknown	11	134	8.21 (4.17-14.21)

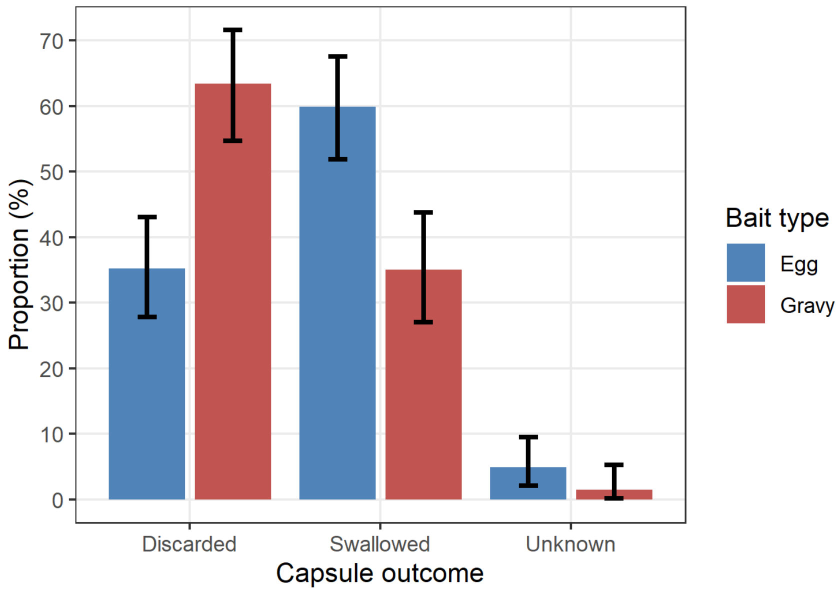


Supplementary Figure E3 - Chart showing the proportion of all dogs offered baits which perforated the sachet.

Bait outcome

Supplementary Table E4 - Table showing capsule outcome for each bait type (Count = number of baits by group, n = total number of baits distributed, Proportion within group with 95% confidence interval).

Bait type	Capsule status	Count	n	Proportion (95% CI)
Egg	Swallowed	97	162	59.88 (51.9-67.49)
Egg	Discarded	57	162	35.19 (27.86-43.07)
Egg	Unknown	8	162	4.94 (2.16-9.5)
Gravy	Discarded	85	134	63.43 (54.68-71.58)
Gravy	Swallowed	47	134	35.07 (27.04-43.79)
Gravy	Unknown	2	134	1.49 (0.18-5.29)

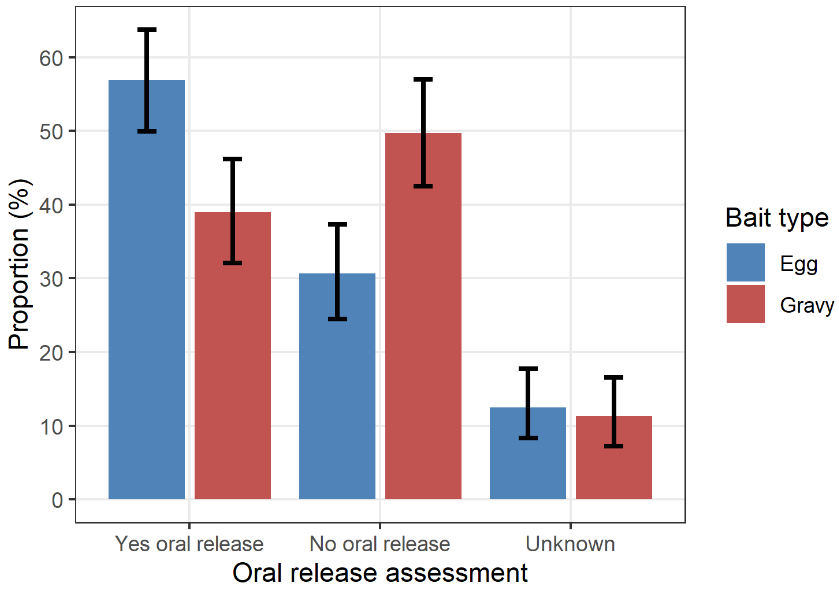


Supplementary Figure E4 – Chart showing the outcome status (discarded / consumed / unknown) for all dogs consuming baits.

Vaccination Assessment

Supplementary Table E5 - Table showing vaccination assessment outcome for each bait type (Count = number of baits by group, n = total number of baits distributed, Proportion within group with 95% confidence interval).

Bait type	Assessment	Count	n	Proportion (95% CI)
Egg	Yes oral release	119	209	56.94 (49.93-63.75)
Egg	No oral release	64	209	30.62 (24.45-37.35)
Egg	Unknown	26	209	12.44 (8.29-17.69)
Gravy	No oral release	97	195	49.74 (42.52-56.97)
Gravy	Yes oral release	76	195	38.97 (32.09-46.2)
Gravy	Unknown	22	195	11.28 (7.21-16.58)



Supplementary Figure E5 - Chart showing the vaccination outcome for all dogs offered baits.

Dog demographics

Supplementary Table E6 - Table showing demographic data for each bait type.

Variable	Egg	Gravy
Sex		
female	29	41
male	131	102
unknown	49	52
Age		
adult	182	170
juvenile	11	16
puppy	3	1
unknown	13	8
Size		
medium	167	156
large	5	5
small	17	19
unknown	20	15
Ownership		
owned	NA	1
stray	199	186
unknown	10	8
Confinement		
confined	4	1
roaming	200	190
unknown	5	4
Group		
multiple	73	62
single	119	118
unknown	17	15

Model outputs

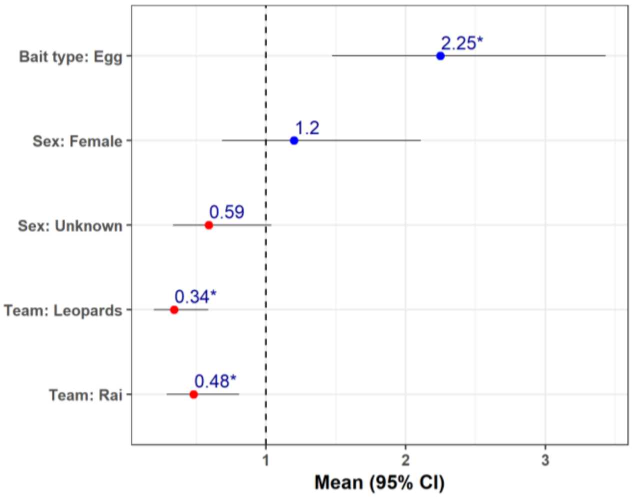
Model 1 - Confirmed 'vaccination' outcome

Supplementary Table E7 – Table of summarised logistic regression models considered for selection for evaluation of bait perforation. Confirmed bait perforation was the response variable and bait type, dog size, age, sex, time of day, team and whether multiple dogs were present (social) was predictor variables. Models are ordered by ascending AIC, and 50 of a total of a total 128 models are shown. The model with the lowest QAIC was selected.

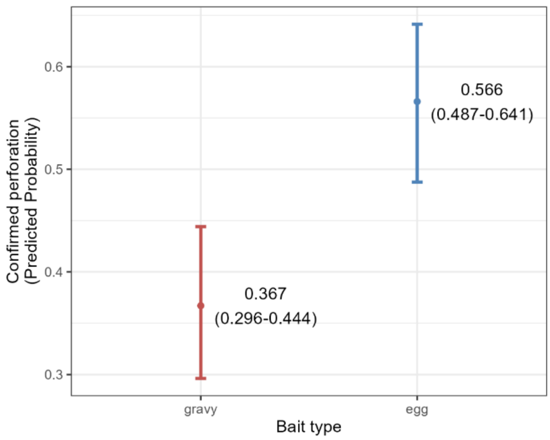
(Intercept)	age	bait_type	sex	dog_size	social	time_of_day	team	AICc
0.17		+	+				+	525.3
0.17		+					+	526
0.16		+	+			+	+	528.6
0.13	+	+	+				+	528.8
0.28		+	+		+		+	529
0.12	+	+					+	529.4
0.15		+				+	+	529.6
0.29		+			+		+	529.9
0.17		+		+			+	531
0.18		+	+	+			+	531.1
0.12	+	+	+			+	+	532.1
0.23		+	+		+	+	+	532.4
0.24	+	+	+		+		+	532.7
0.12	+	+				+	+	533
0.24	+	+			+		+	533.4
0.25		+			+	+	+	533.7
0.17		+	+	+		+	+	534.3
0.12	+	+		+			+	534.5
0.17		+		+		+	+	534.5
0.29		+	+	+	+		+	534.6
0.3		+		+	+		+	534.7
0.14	+	+	+	+			+	534.7
0.2	+	+	+		+	+	+	536.1
0.21	+	+			+	+	+	537.1
-0.58		+	+		+			537.4
0.57			+				+	537.8
0.26		+	+	+	+	+	+	537.9
0.14	+	+	+	+		+	+	538
-0.23		+	+					538.1
0.14	+	+		+		+	+	538.1
0.26	+	+		+	+		+	538.3
0.54							+	538.4
0.29		+		+	+	+	+	538.4
0.25	+	+	+	+	+		+	538.4
-0.62		+	+		+	+		539.6
-0.61	+	+	+		+			540.2
-0.24		+	+			+		540.4
-0.27	+	+	+					540.4
0.52			+			+	+	540.8
0.71			+		+		+	541.2
0.54	+		+				+	541.2
0.23	+	+	+	+	+	+	+	541.8
0.49						+	+	541.8
0.5	+						+	541.8
0.26	+	+		+	+	+	+	542
0.69					+		+	542.1
-0.63	+	+	+		+	+		542.5
-0.2		+	+	+				542.7
-0.27	+	+	+			+		542.9

Supplementary Table E8 – Multivariable logistic regression model which explored the factors that predicted confirmed 'vaccination' (observation of release of blue-dye liquid in the oral cavity). *P-values lower than 0.05.

Variable	Odds Ratio (95% CI)	Std. Error	P-value
(Intercept)	1.191 (0.794 - 1.792)	0.2072	0.400
Bait type Egg	2.249 (1.479 - 3.447)	0.2156	<0.001*
Sex Female	1.200 (0.685 - 2.12)	0.2876	0.526
Sex Unknown	0.588 (0.332 - 1.035)	0.2893	0.067
Team Leopards	0.34 (0.196 - 0.583)	0.2783	<0.001*
Team Tigers	0.482 (0.286 - 0.804)	0.2629	0.005*



Supplementary Figure E6 - Multivariable logistic regression model predicting confirmed 'vaccination'.



Supplementary Figure E7 – Graph showing multivariable logistic regression model estimated proportion of confirmed perforation by bait type (averaged over factors sex and team). Points show estimated marginal means, error bars show 95% confidence intervals. Labels give numeric values of the same.

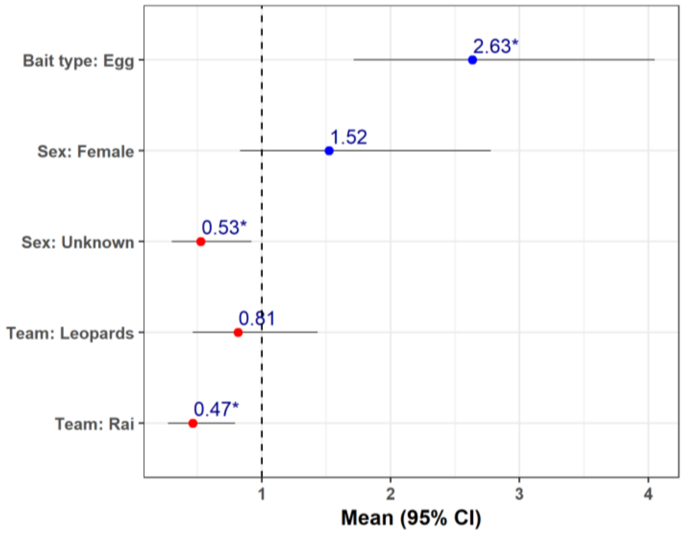
Model 2 - Possible 'vaccination' outcome

Supplementary Table E9 – Table of summarised logistic regression models considered for selection evaluating possible perforation. Possible bait perforation was the response variable and bait type, dog size, age, sex, time of day, team and whether multiple dogs were present (social) was predictor variables. Models are ordered by ascending AIC, and 50 of a total of a total 128 models are shown. The model with the lowest QAIC was selected.

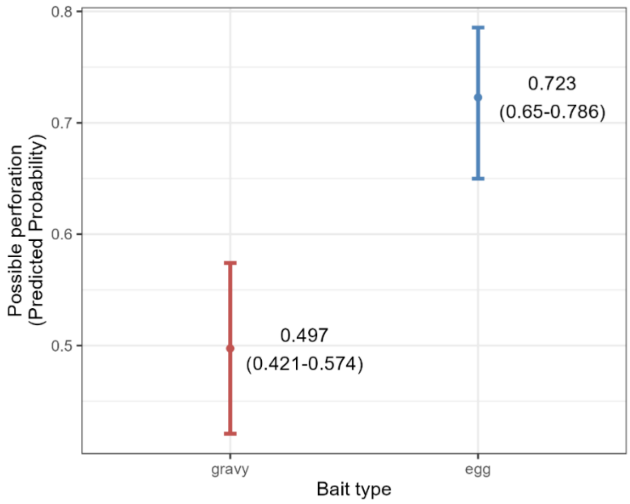
(Intercept)	age	bait_type	sex	dog_size	social	time_of_day	team	AICc
0.39		+	+				+	513.9
0.37		+	+	+			+	514.1
0.39	+	+	+				+	514.7
0.38	+	+	+	+			+	516.1
0.23		+	+		+		+	517.2
0.18		+	+	+	+		+	517.9
0.42		+	+			+	+	518
0.14		+	+					518.2
0.11	+	+	+					518.3
0.38		+	+	+		+	+	518.3
0.26	+	+	+		+		+	518.5
0.07		+	+	+				518.7
0.41	+	+	+			+	+	518.9
0.43		+					+	519.4
-0.1		+	+		+			519.7
-0.24		+	+	+	+			519.7
0.22	+	+	+	+	+		+	520
0.39	+	+	+	+		+	+	520.3
-0.12	+	+	+		+			520.4
0.05	+	+	+	+				520.5
0.42	+	+					+	521.3
0.26		+	+		+	+	+	521.4
0.4		+		+			+	521.5
-0.24	+	+	+	+	+			521.7
0.19		+	+	+	+	+	+	522.1
0.19		+	+			+		522.2
0.15	+	+	+			+		522.3
0.29	+	+	+		+	+	+	522.7
0.09		+	+	+		+		522.8
0.27		+			+		+	523.2
0.44		+				+	+	523.3
-0.05		+	+		+	+		523.8
0.41	+	+		+			+	523.8
-0.22		+	+	+	+	+		523.9
0.23	+	+	+	+	+	+	+	524.3
-0.08	+	+	+		+	+		524.5
0.07	+	+	+	+		+		524.7
0.05		+						524.8
0.24		+		+	+		+	525.1
0.43	+	+				+	+	525.2
0.3	+	+			+		+	525.2
0.41		+		+		+	+	525.4
-0.21		+			+			525.4
-0.24	+	+	+	+	+	+		526
0	+	+						526.9
-0.25	+	+			+			527.2
0.3		+			+	+	+	527.2
0.27	+	+		+	+		+	527.5
0.41	+	+		+		+	+	527.7
-0.35		+		+	+			527.8

Supplementary Table E10 - In addition to dogs which were observed to release blue dye liquid in the oral cavity, this group included dogs where the bait was seen to be consumed, but release of blue dye could not observed and yet may still have occurred. *P-values lower than 0.05.

Variable	Odds Ratio (95% CI)	Std. Error	P-value
(Intercept)	1.475 (0.976 - 2.25)	0.2126	0.067
Bait type Egg	2.634 (1.721 - 4.07)	0.2193	<0.001*
Sex Female	1.52 (0.841 - 2.823)	0.3077	0.173
Sex Unknown	0.525 (0.298 - 0.918)	0.2860	0.024*
Team Leopards	0.814 (0.463 - 1.436)	0.2883	0.475
Team Tigers	0.465 (0.271 - 0.79)	0.2721	0.005*



Supplementary Figure E8 - Multivariable logistic regression model predicting possible 'vaccination'.



Supplementary Figure E9 – Graph showing multivariable logistic regression model estimated proportion of possible 'vaccination' outcomes by bait type (averaged over factors sex and team). Points show estimated marginal means, error bars show 95% confidence intervals. Labels give numeric values of the same.

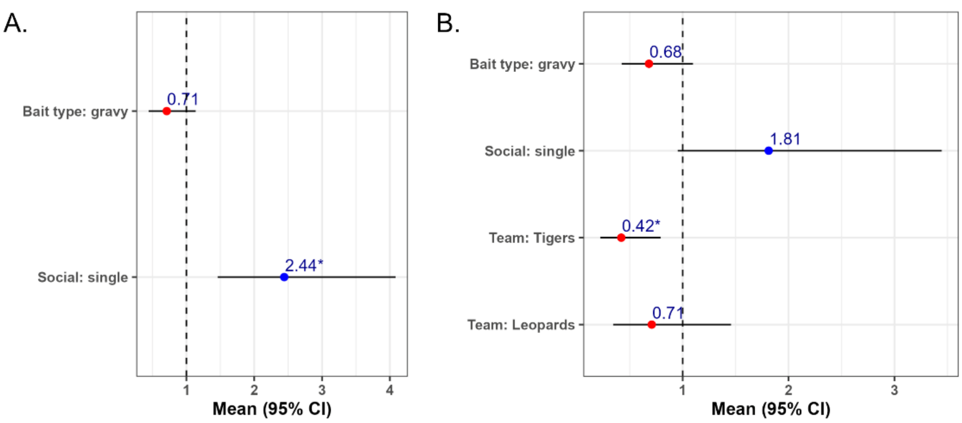
Model 3 – Ordinal logistic regression to evaluate bait handling time

Supplementary Table E11 – Summary table of coefficients for ordinal logistic regression model selection for bait handling time (very short, short, medium, long). Combinations of independent variables bait type, whether multiple dogs were present (social), and team were compared.

	Dependent variable:				
	chewing_time				
	(1)	(2)	(3)	(4)	(5)
Bait type: gravy	-0.3422				-0.3833
	(0.2390)				(0.2420)
Social: single	0.8929***	0.8516***	0.5390*		0.5945*
	(0.2609)	(0.2583)	(0.3243)		(0.3264)
Team: Leopards			-0.3734	-0.7317**	-0.3453
			(0.3677)	(0.2990)	(0.3663)
Team: Tigers			-0.8406***	-1.0666***	-0.8668***
			(0.3199)	(0.2912)	(0.3214)
Observations	260	260	260	260	260
Akaike Inf. Crit.	565.0038	565.0655	561.9161	562.6992	561.3890
Note:					*p<0.1; **p<0.05; ***p<0.01

Supplementary Table E12 – Table of model outputs for the first and fifth models summarised above. In the first model, where the predictor variable 'team' is not included, the presence of multiple dogs was a statistically significant predictor of bait handling time, however this effect was not seen when team was included in the fifth model, which also had a lower AIC.

Model	Variable	Odds Ratio (95% CI)	Std. Error	P-value
First model (bait type, social)	**Social** single	2.442 (1.461 - 4.083)	0.261	<0.001*
	Bait type gravy	0.710 (0.444 - 1.137)	0.239	0.153
Fifth model (bait type, social, team)	**Social** single	1.812 (0.953 - 3.446)	0.326	0.070
	Bait type gravy	0.682 (0.423 - 1.098)	0.242	0.114
	Team Leopards	0.708 (0.344 - 1.457)	0.366	0.347
	Team Tigers	0.420 (0.223 - 0.792)	0.321	0.007*



Supplementary Figure E10 – Ordinal logistic regression model outputs for the first (A) and fifth (B) models described above.

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