Optimizing the Delivery of Self-Disseminating Vaccines in Fluctuating Wildlife Populations

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Courtney Schreiner

Approved by

Major Professor: Scott L. Nuismer, Ph.D.

Committee Members: Christopher H. Remien, Ph.D.; Jim Bull, Ph.D. ;

Terence Soule, Ph.D.

Department Administrator: Paul A. Hohenlohe, Ph.D.

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Abstract

Zoonotic pathogens spread by wildlife continue to spill over into human populations and threaten human lives. A potential way to reduce this threat is by vaccinating wildlife species that harbor infectious diseases of humans. Unfortunately, even in cases where vaccines can be distributed en masse as edible baits, achieving levels of vaccine coverage sufficient for pathogen elimination is rare. Developing vaccines that self-disseminate may help solve this problem by magnifying the impact of limited direct vaccination. Although models now exist that quantify how well these self-disseminating vaccines will work when introduced into temporally stable wildlife populations, how well they will perform when introduced into populations with pronounced seasonal dynamics remains unknown. Here we develop and analyze mathematical models of fluctuating wildlife populations that allow us to study how reservoir ecology, vaccine design, and vaccine delivery interact to influence vaccine coverage and opportunities for pathogen elimination. Our results demonstrate that the timing of vaccine delivery can make or break the success of vaccination programs, and that the importance of timing is greater for some types of vaccines than others. As a general rule, the effectiveness of self-disseminating vaccines is optimized by introducing after the peak of seasonal reproduction when the number of susceptible animals is near its maximum.

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Dedication

I want to first thank my significant other, Jackson Rieb for being so supportive throughout this experience and listening to me go on and on about the math involved. Additionally, I would like to thank my family, my Mom and my Dad who have been so supportive and encouraging throughout my education. I love these people dearly and I couldn't have got through this without their love and support.

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CHAPTER 1

Introduction

The majority of human infectious diseases are caused by pathogens with animal origins (Jones et al. 2008). As the human population continues to encroach on wildlife habitat, zoonotic pathogens such as Ebola virus, *Borrelia burgdorferi*, Lassa virus, Hantavirus, and Nipah virus pose an increasing threat of spillover into the human population (Gottdenker et al. 2014; Pongsiri et al. 2009; Keesing et al. 2010; Coltart et al. 2017; Jones et al. 2008). Several of these emerging infectious diseases have had devastating impacts on public health. The 2014 Ebola outbreak, for example, killed more than 11,000 people (Coltart et al. 2017), and the ongoing SARS-CoV-2 pandemic has killed millions (WHO 2021). The SARS-CoV-2 pandemic has made the perils of our current reactionary approach to managing emerging infectious disease clear and helped to focus attention on methods that proactively reduce the risk of spillover and emergence.

Vaccinating wildlife reservoir populations is a proven method for lowering pathogen prevalence and reducing the risk of spillover into the human population (Hampson et al. 2007; Velasco-Villa et al. 2017). For example, oral rabies vaccines that are distributed in bait-form have proven to be effective at controlling rabies in fox and raccoon populations (Freuling et al. 2013; Sidwa et al. 2005; MacInnes et al. 2001). However, even in these cases where an effective bait-deliverable vaccine exists, it remains difficult to achieve a level of vaccination coverage sufficient for pathogen elimination (Ramey et al. 2008; Sattler et al. 2009). The key obstacles are the cost and logistical difficulty of distributing vaccine into inaccessible wildlife populations. For zoonotic infectious diseases with short-lived reservoirs

(e.g., rodents), the challenge is compounded by the rapid dilution of immunity established through traditional vaccination. These challenges suggest that distributing traditional vaccines as baits is unlikely to provide a general solution (Nuismer et al. 2020; Mariën et al. 2019).

Recent developments in vaccine design offer fresh solutions to this long-standing problem by creating vaccines that are capable of some degree of self-dissemination. Self-disseminating vaccines can be either transferable or transmissible. Development of transferable vaccines has focused on applying topical vaccine-laced gels to individual animals (Bakker et al. 2019). When other individuals engage in natural allogrooming behaviors common in some reservoir species (e.g., bats), they ingest the vaccine and become vaccinated. As a result, the number of animals that can be vaccinated is substantially multiplied (Bakker et al. 2019). In contrast to transferable vaccines which do not generate sustained chains of self-dissemination, transmissible vaccines are engineered to be contagious, and are potentially capable of indefinite self-dissemination within the reservoir population (Nuismer and Bull 2020). A diverse range of modeling studies have demonstrated that both types of self-disseminating vaccines reduce the effort required to achieve herd immunity within wildlife reservoir populations (Nuismer and Bull 2020; Bakker et al. 2019; Nuismer et al. 2016; Layman et al. 2021; Varrelman et al. 2019; Basinski et al. 2018, 2019). We do not yet know, however, how the introduction of these vaccines can be best timed to maximize their impact when used in reservoir species that have pronounced seasonal dynamics.

Previous modeling work has demonstrated that the success of traditional wildlife vaccination campaigns can be improved by timing vaccine introduction to coincide with seasonal

birth pulses in short-lived animal species (Schreiner et al. 2020). Although intuition suggests similar results should hold for self-disseminating vaccines, the quantitative details remain unknown and important questions remain unanswered. For instance, is timing vaccine introduction more important in transferable than transmissible vaccines? Do the detailed transmission dynamics of the vaccine (e.g., transmission rate and duration) influence the optimal timing of introduction? Does timing matter more for some reservoir species than others? Here we develop a general mathematical modeling framework for transmissible and transferable vaccines and use it to quantify the consequences of introducing self-disseminating vaccines at different times. We then apply our model to two specific reservoir species of important humans pathogens *Mastomys natalensis*, the multimammete rat (Lassa virus) and *Desmodus rotundus*, the common vampire bat (rabies virus) to provide clear examples of potential applications of these new vaccines. The specific questions we address are: 1) What is the optimal time of year to distribute a self-disseminating vaccine? 2) In which situations is optimal timing critical for success? 3) How does the duration of self-dissemination affect the optimal implementation of vaccines?

CHAPTER 2

Methods

Methods

We use a SIR (Susceptible-Infected-Recovered) modeling framework to study how the timing of vaccination influences the ability of a self-disseminating vaccine to protect a population from a pathogen. We focus our efforts on populations that undergo seasonal fluctuations in population density driven by a well-defined seasonal pattern of reproduction. Our models assume vaccines are introduced into relatively small geographic areas within which the reservoir population is well mixed and of modest size (e.g., 2000 individuals). These assumptions are motivated by rodent species such as *Mastomys natalensis* and *Peromyscus maniculatis* that harbor important human pathogens such as Lassa virus and Sin Nombre virus, respectively (Leirs et al. 1994; Luis et al. 2010).

In the model, we use a time-dependent birth function that is a variation of the periodic Gaussian function developed by Peel et al. (2014). To help facilitate the analysis of a stably cycling population, we use this functional form to describe a density-independent rate of births. We also adjusted this birth function to be in units of days rather than years, and added a variable to adjust the day that the function reaches its maximum (t_p):

$$b(t) = k \cdot e^{-s \cdot \cos^2\left(\frac{\pi}{365} \cdot (t - (t_p + \frac{365}{2}))\right)} \tag{2.1}$$

where s tunes the synchrony of births, and k is set so that the average annual population size is equal to $\bar{N}$ (see appendix).

Direct vaccination is assumed to occur each year beginning t_v days after the start of the reproductive season and continue for V_l days. Assuming N_v vaccine-laced baits are distributed each year (transmissible vaccine) or N_v animals are painted with vaccine-laced gel (transferable vaccine) at a rate $\sigma(t)$, the rate at which individuals are vaccinated is given by:

$$\sigma(t) = \begin{cases} \frac{N_v}{V_l} & t_v \leq \text{mod}(t, 365) < t_v + V_l \\ 0 & \text{Otherwise} \end{cases}. \tag{2.2}$$

2.0.1 Transmissible Vaccine Model

Our transmissible vaccine model contains four classes: individuals that are susceptible to both the pathogen and the vaccine (S), individuals that are infected with the pathogen (P), vaccinated individuals that are immune to the pathogen and capable of transmitting vaccine to susceptible individuals (V), and individuals that have immunity due to recovery from pathogen infection or from vaccination (R). For simplicity, we assume individuals that have recovered from either the pathogen or the vaccine maintain lifelong immunity to both, and that co-infection with vaccine and pathogen does not occur. Individuals that are infected with the pathogen recover at rate γ_P, and individuals infected with the vaccine recover at rate γ_V. We assume density-dependent transmission of the pathogen and the vaccine, with transmission coefficients β_P and β_V respectively. Individuals may also be lost from the system due to pathogen-induced mortality at rate v. Setting the transmission rate of the vaccine β_V equal to zero (more on R_0 below) yields a model for a traditional

vaccination campaign.

Susceptible individuals can be vaccinated directly or by coming into contact with vaccine-infected individuals. Because vaccine-laced baits can be consumed by any individual in the population, including individuals already immune to the pathogen, waste is inevitable. We model this feature of vaccine distribution by multiplying the the rate of vaccines deployed at time t ($\sigma(t)$) by the fraction of susceptible individuals ($\frac{S}{N}$) in the population. Thus, if the entire population is susceptible, vaccination efficiency is high and waste is low. In contrast, if the population contains a large proportion of immune individuals, vaccination efficiency is low and waste is high. Here, N denotes the total population size. See table 2.1 for a description of parameters. Together, these assumptions lead to the following system of differential equations:

$$\frac{dS}{dt} = b(t) - \beta_P\, S\, P - \beta_V\, S\, V - \sigma(t)\,\frac{S}{N} - d\, S \tag{2.3a}$$

$$\frac{dP}{dt} = \beta_P\, S\, P - \gamma_P\, P - v\, P - d\, P \tag{2.3b}$$

$$\frac{dV}{dt} = \beta_V\, S\, V + \sigma(t)\,\frac{S}{N} - \gamma_V\, V - d\, V \tag{2.3c}$$

$$\frac{dR}{dt} = \gamma_P\, P + \gamma_V\, V - d\, R. \tag{2.3d}$$

2.0.2 Transferable Vaccine Model

Our transferable vaccine model contains five classes: individuals that are susceptible to the pathogen (S), Individuals that are currently infected by the pathogen (P), individuals that are immune to the pathogen (R), individuals that are currently infected by the pathogen and also carrying the vaccine laced topical gel (P_g), and individuals that are immune to the pathogen and also carrying the vaccine laced topical gel (R_g). We assume vaccine laced gel is applied topically to captured animals at rate $\sigma(t)$. These captured animals are also assumed to be directly vaccinated and to immediately transition to the R_g class. In contrast to the transmissible vaccine model, the rate of vaccination is multiplied by $\frac{1}{S+P+R}$ rather than $\frac{1}{N}$. This is because we assume that if individuals have gel on them, we will be able to recognize these individuals and will not apply more gel to them. Allogrooming behavior allows an individual to become vaccinated at rate β_g if it encounters an individual carrying the vaccine laced gel. At the same time, however, allogrooming behavior also depletes the quantity of vaccine-laced gel an individual carries. We model this phenomenon by assuming the topical gel is lost at rate αN which implies gel is lost more rapidly in densely populated animal populations. Additionally, we assume the topical gel loses its ability to serve as a vaccine at rate γ_g.

We assume that transfer of the vaccine can occur only from an individual to which vaccine laced gel has been directly applied and that vaccine transfer is density dependent. Pathogen transmission is also assumed to be density dependent and to occur at rate β_P from contact with either a pathogen-infected individual (P) or a gelled and pathogen-infected individual (P_g). Together, these assumptions lead to the following system of differential

equations. Parameter descriptions and values can be found in table 2.1.

$$\frac{dS}{dt} = b(t) - \beta_P\, S\,(P + P_g) - \beta_g\, S\,(P_g + R_g) - \sigma(t)\,\frac{S}{S+P+R} - d\,S \tag{2.4a}$$

$$\frac{dP}{dt} = \beta_P\, S\,(P + P_g) - \sigma(t)\,\frac{P}{S+P+R} + \alpha\, N\, P_g - \gamma_P\, P + \gamma_g\, P_g - v\, P - d\, P \tag{2.4b}$$

$$\frac{dP_g}{dt} = \sigma(t)\,\frac{P}{S+P+R} - \alpha\, N\, P_g - \gamma_P\, P_g - \gamma_g\, P_g - v\, P_g - d\, P_g \tag{2.4c}$$

$$\frac{dR}{dt} = \beta_g\, S\,(P_g + R_g) - \sigma(t)\,\frac{R}{S+P+R} + \alpha\, N\, R_g + \gamma_P\, P + \gamma_g\, R_g - d\, R \tag{2.4d}$$

$$\frac{dR_g}{dt} = \sigma(t)\,\frac{S+R}{S+P+R} - \alpha\, N\, R_g + \gamma_P\, P_g - \gamma_g\, R_g - d\, R_g \tag{2.4e}$$

$$\tag{2.4f}$$

2.0.3 Assessment of Vaccination Strategy

We evaluate the success of a vaccination campaign by comparing the reduction of pathogen-infected individuals it achieves relative to the situation where no vaccination occurs. For each type of vaccine and distribution strategy, we use the deSolve package in R to numerically solve the corresponding system of differential equations (Soetaert et al. 2010). For each combination of parameters we solve the system of differential equations twice: once with vaccination and once without vaccination. Initial conditions are identical for these two cases and both are burned in for 15 years, allowing the system to settle into stable seasonal cycles. One numerical solution is continued from this point for ten years

with no vaccination occurring and the other is run with vaccination for ten years after the first day of vaccination. We then extract from each of the numerical solutions the average number of pathogen-infected hosts over the ten year period following the burn-in. Specifically, we calculate the fractional reduction of pathogen-infected individuals (average level of pathogen reduction) provided by vaccination as:

$$\frac{\overline{x}_0 - \overline{x}_v}{\overline{x}_0} \tag{2.5}$$

where $\overline{x}_0$ is the average number of pathogen-infected individuals in the scenario without vaccination and $\overline{x}_v$ is the average number of pathogen-infected individuals with vaccination. We use this comparative approach to explore how the benefits of vaccination change as a function of vaccine properties, reservoir properties, and the timing of vaccine introduction.

2.0.4 Case Studies

Up to this point we have used quite general models to explore a wide range of parameter space. Our goal was to develop a general understanding of the performance of self-disseminating vaccines as a function of reservoir biology, vaccine properties, and introduction protocol. Here we take a much more focused approach to the problem and tune our models to the biology of two specific systems where self-disseminating vaccines have been broadly proposed as a useful tool and for which vaccine development is currently underway. Specifically, we focus on the primary rodent reservoir of Lassa virus, *Mastomys natalensis* and a bat reservoir of rabies virus *Desmodus rotundus*. A list of parameters used in both the general simulations and specific case studies can be found in Table 2.1.

Table 2.1: List of parameters used. Values for α were chosen by first exploring a range, and then deciding on an intermediate value. For most simulations, this value reflects that on average, individuals with gel lose gel due to grooming in 8 days. We explored a range of values that are not represented in the figures in the general results section. However these parameters did not change the qualitative results discussed. For parameters where a range of values were used, an asterisk in the general values column indicates the default parameters presented in the general results section. Parameter values in figures are also indicated in the figure caption. The values used for the case studies are also presented here with the Rodent values and Bat values columns.

Parameter list					
Parameter	Description	General values	Rodent values	Bat values	Citation
t_v	day in year of vaccine initiation	(1–365)	(1–365)	(1–365)	See text

Parameter list					
Parameter	Description	General values	Rodent values	Bat values	Citation
v_l	Duration of the vaccination campaign	(1–365)	(1–365)	(1–365)	See text
s	Synchrony of births	$(1, 5, 10^*)$	2.48	2.11	Leirs et al. (1997); Blackwood et al. (2013)
t_p	Day in year of peak birth rate	100	100	100	see text
d	Natural mortality rate	($1/365^*$, $1/(365/2)$, $1/(365*5)$)	$1/365$	$1/(365*3.5)$	Nuismer et al. (2020); Lord et al. (1976)
$\bar{N}$	Average population size	2000	2000	240	Mari Saez et al. (2018); Bakker et al. (2019)

Parameter list					
Parameter	Description	General values	Rodent values	Bat values	Citation
$R_{0,V}$	R_0 of the vaccine	(0,0.75, 1.5, 2.5)	(0, 0.75, 1, 1.5, 2)	(0, 0.75, 1, 1.5, 2)	Varrelman et al. (2019); Bakker et al. (2019); Griffiths et al. (2020)
$R_{0,P}$	R_0 of the pathogen	(0,0.75, 1.5, 2*)	1.5	1.5	Nuismer et al. (2020); Blackwood et al. (2013); Hampson et al. (2009)
γ_P	Recovery rate of the pathogen	(1/21*, 1/182.5, 1/365)	1/21	1/21	Nuismer et al. (2020); Bakker et al. (2019)
γ_V	Recovery rate of the transmissible vaccine	(1/21*, 1/182.5, 1/365)	1/365	1/365	Varrelman et al. (2022); Griffiths et al. (2020)

Parameter list					
Parameter	Description	General values	Rodent values	Bat values	Citation
γ_g	Recovery rate of the transferable vaccine	($1/21^*$, $1/182.5$, $1/365$)	$1/7$	$1/2$	Nuismer et al. (2020); Bakker et al. (2019)
β_P	Rate of pathogen transmission	-	-	-	See appendix
β_V	Rate of transmissible vaccine transmission	-	-	-	See appendix

Parameter list					
Parameter	Description	General values	Rodent values	Bat values	Citation
β_g	Rate of transferable vaccine transmission	-	-	-	See appendix
v	Virulence of pathogen	(0*,1/30, 1/100, 1/365)	0	10% of the number infected	Blackwood et al. (2013); Bakker et al. (2019)
α	Rate at which individuals remove gel	($\frac{1}{1.0\times10^4}$, $\frac{1}{1.5\times10^4}$*, $\frac{1}{2.0\times10^4}$)	$\frac{1}{1.5\times10^4}$	$\frac{1}{1.5\times10^4}$	See caption

CHAPTER 3

Results

3.1 General Results

3.1.1 Temporal Dynamics of Immunity Depends on the Type of Self-Disseminating Vaccine

Previous work has demonstrated that self-dissemination increases vaccine coverage and reduces the effort required for disease eradication (Nuismer and Bull 2020). However it remains unclear how self-disseminating vaccines will perform in fluctuating populations. To establish baseline expectations for the performance of self-disseminating vaccines in fluctuating reservoir populations we begin by studying the dynamics of immunity in the absence of the pathogen. Numerical analyses performed over a wide range of parameters demonstrate that the temporal dynamics of immunity differ across vaccine types in characteristic ways (Figure 3.1). For conventional vaccines that lack the ability to self-disseminate, vaccination results in a rapid increase in the number of vaccinated individuals, followed by a decrease due to the continued influx of susceptible individuals during the birthing season. Transferable vaccines result in similar temporal dynamics but show a transient increase in immunity from self-dissemination following vaccine introduction. In contrast, transmissible vaccines with an $R_0 > 1$ can continue to increase the number of immune individuals long after vaccine introduction due to their ability to generate self-sustaining chains of transmission. Because all individuals die at a constant rate d, the number of immune individuals decreases until the next vaccination campaign for each type of vaccine. We

use the concept of the basic reproductive number, denoted as R_0, to compare the relative transmissibility of the vaccine and the pathogen. R_0 represents the average number of new infections caused by a single infected individual that is introduced into a fully susceptible population (Keeling and Rohani 2011). More details on the R_0 derived for this work can be found in the appendix. With self-disseminating vaccines, the level of increase in the number of immune individuals in the population is dependent on the vaccine R_0 (Figure 3.1).

3.1.2 Timing is Critical for Most Self-Disseminating Vaccines

Previous work has shown that the timing of delivery for conventional vaccines matters in short-lived animals with distinct reproductive seasons (Schreiner et al. 2020). Here, our goal is to evaluate whether timing is more important for transmissible or transferable vaccines and under what conditions is timing critical. To this end, we compared the reduction in pathogen prevalence achieved for vaccination campaigns that are initiated at different times of year and last for various lengths of time. Our results demonstrate that distributing self-disseminating vaccines a few days after the peak of the birthing season will substantially reduce pathogen prevalence (Figure 3.2). This is when the population density is near its seasonal maximum, and contains the greatest proportion of susceptible individuals.

For both types of self-disseminating vaccine, opportunity for pathogen reduction is greater with a larger vaccine R_0. In addition to facilitating pathogen eradication, increasing the transmissible vaccine's R_0 also increases the range of times over which a vaccine

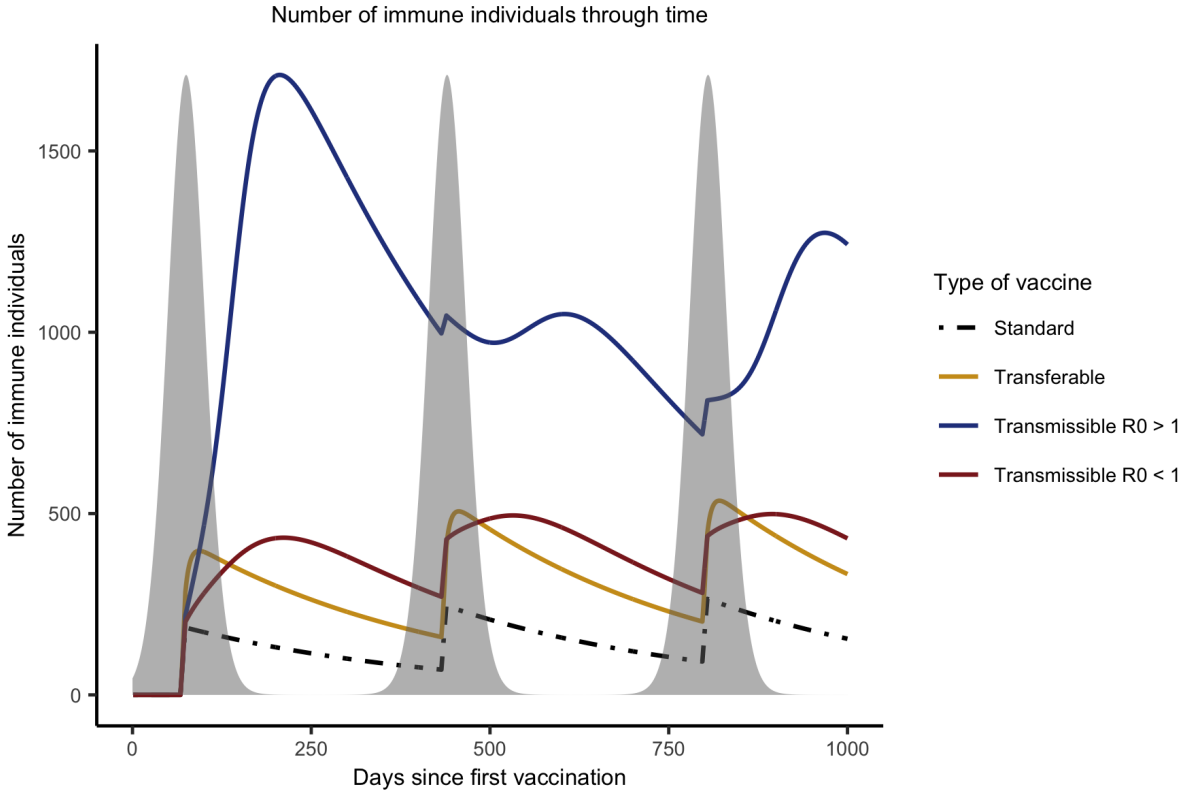

Figure 3.1: The temporal dynamics of immunity for standard, transferable, and transmissible vaccines in the absence of a pathogen. For each type of vaccine, 200 vaccines are distributed on day 50, which corresponds to the mid-point of the 100 day birthing season (gray region). The lines show the number of immune individuals in the population over three years of repeated vaccination. R_0 of the standard, transferable, strongly transmissible, and weakly transmissible are: $(0, 1.5, 1.5, 0.75)$ respectively. The remaining parameters are: $s = 10, t_p = 100, d = 1/365, \bar{N} = 2000, \gamma_P = 1/21, \gamma_V = 1/21, \alpha = 6.6 \cdot 10^{-5}, V_l = 1$ day.

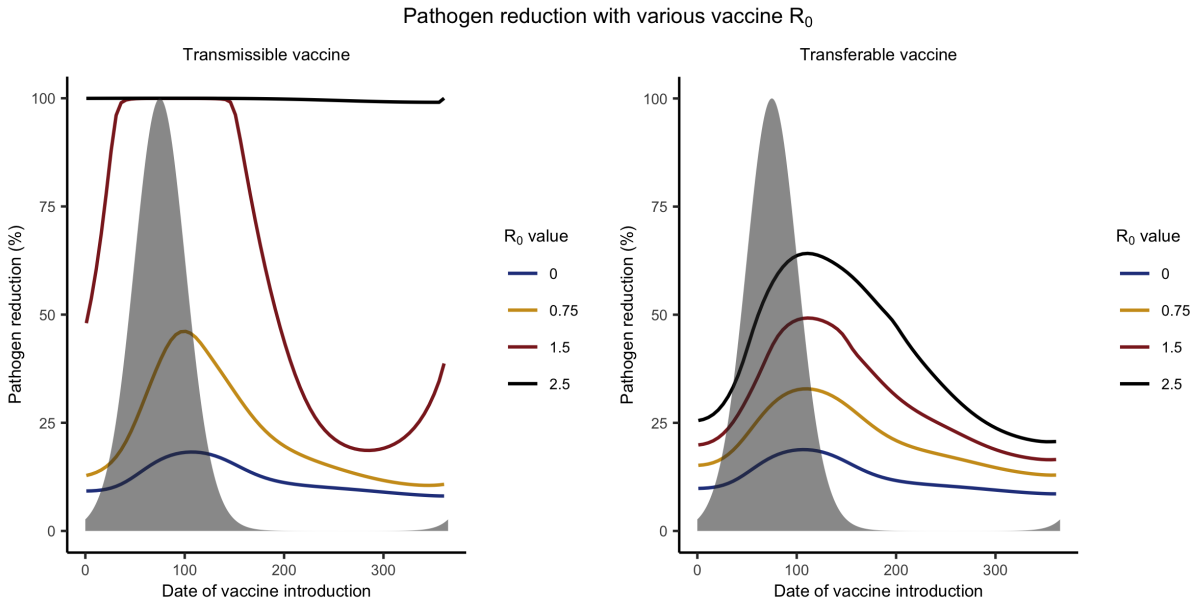

Figure 3.2: Optimal timing for self-disseminating vaccines as a function of vaccine R_0. Here the vaccination campaign lasts 1 week. R_0 refers to the vaccine R_0. Pathogen R_0 is fixed at 2. Both the transmissible and transferable vaccine disseminate for an average of 21 days ($\gamma_v = 1/21$) and infection with the pathogen has a mean duration of 21 days ($\gamma_p = 1/21$). Grey region represents the reproductive season. The remaining parameters are: $s = 10, t_p = 100, d = 1/365, \bar{N} = 2000, \alpha = 6.6 \cdot 10^{-5}, N_V = 200$.

can be introduced and still substantially reduce the pathogen's prevalence (Figure 3.2). This occurs because increased transmission allows the vaccine to be introduced earlier in the reproductive season and yet still reach individuals that will be born later through downstream transmission. In contrast, with reduced transmission (lower R_0), if a transmissible vaccine is introduced too early, chains of transmission are generally too short to reach individuals born later in the season resulting in wasted vaccine. Once the R_0 of the transmissible vaccine exceeds that of the pathogen R_0, timing matters little and significant pathogen reductions can be accomplished for a broad range of introduction times (Figure 3.2). This is because a vaccine more transmissible than the target pathogen can out-compete the pathogen and will inevitably displace it from the population over time (Nuismer et al. 2016). A fundamental difference for transferable vaccines is that they never reach this same level of insensitivity to the timing of introduction. The reason for this is that they are (by definition) capable of spreading only from individuals that have been directly vaccinated and thus generate chains of transmission only one step long. Because of this limited spread an increased R_0 of the transferable vaccine results in higher levels of pathogen reduction, but not an increase in the range of times for high pathogen reduction (Figure 3.2).

As mentioned above, transmissible vaccines with an $R_0 > 1$ but less than the R_0 of the pathogen have a wide range of times of which $> 90\%$ pathogen reduction can be achieved. This range corresponds to when the birthing seasons has begun. Distributing vaccine during the birthing season allows for the transmissible vaccine to infect susceptible individuals as they are introduced to the population. However for lower R_0 values, optimal timing (highest level of pathogen reduction) is slightly after the peak of the birthing season. Sim-

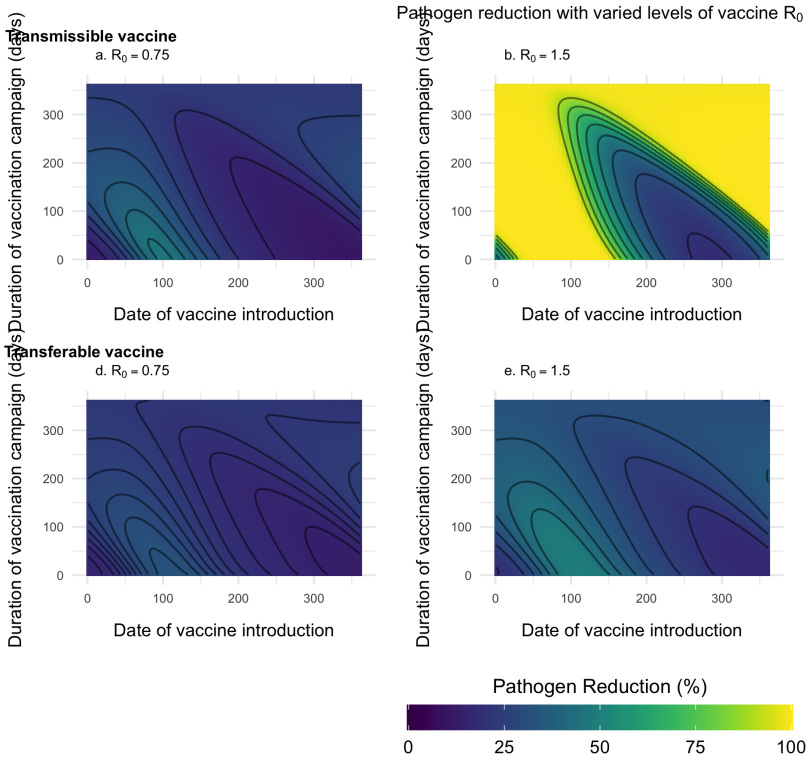

Figure 3.3: Level of pathogen reduction achieved for both transmissible vaccines and transferable vaccines at different times and for different durations of a vaccination campaign. The R_0 in the figure refers to the vaccine R_0. The pathogen R_0 is set to 2. The remaining parameters are set to the values described in Figure 3.1.

ilar to the transmissible vaccine, the optimal time for the implementation of a transferable vaccine is slightly after the peak of the host birthing season and over a short period of time (Figure 3.2). This ensures a large number of susceptible individuals in the population and thus allows for the highest level of vaccination to be achieved leading to higher levels of pathogen reduction. In addition, for transferable vaccines or transmissible vaccines that are unable to displace a pathogen autonomously, pathogen reduction is not achieved if they are administered after the birthing season when newly born individuals have already been infected.

For vaccination campaigns of feasible duration (one week - 2 months) and using the same total amount of vaccine, the duration of the vaccination campaign matters little. This insensitivity arises primarily because birth rates change little over such short periods of time in most systems. In special cases where it is possible to distribute vaccine over greater periods of time, differences do begin to develop (Figure 3.3 vertical axis). Generally a longer vaccination campaign results in a lower overall vaccination rate because vaccines are distributed when few susceptible individuals exist within the reservoir population and are thus wasted. If, however, the vaccination campaign begins at the wrong time (i.e., after the birthing season), extending the duration of vaccine-delivery can compensate to some degree (Figure 3.3). If the timing of birthing within the reservoir population is known, however, the best solution for maximizing the reduction in pathogen prevalence is to distribute vaccines shortly after the peak of the birthing season and over a relatively short amount of time.

3.1.3 Short Durations of Self-Dissemination Lead to More Effective Vaccines

Because vaccines may differ widely in the period of time over which they self-disseminate, we explored how this property influenced the optimal timing of delivery. For both types of vaccines, we considered scenarios where the vaccine self-disseminated for 21, 182, and 365 days on average. In these scenarios individuals had an average lifespan of one year, these infectious periods model vaccines that generate short-lived acute infections as well as vaccines that generate lifelong chronic infections. To evaluate the specific affect of the duration of self-dissemination we held the vaccine $R_0 = 1.5$ and evaluated the level of pathogen reduction that was achieved. A necessary consequence of holding R_0 constant is that changing γ_V also changes the transmission rate of the vaccine β_V. Thus vaccines with a short duration of self-dissemination also have a high transmission rate and vaccines with a lengthy period of self-dissemination have a low transmission rate.

Our results indicate that short durations of self-dissemination lead to more effective vaccines and more opportunity for substantial pathogen reduction (Figure 3.4). Transferable vaccines achieve the highest level of pathogen reduction with acute durations of self-dissemination. This is because with long durations of self-dissemination, β_V is weaker and thus it takes longer to infect the slow dynamics of the vaccine cause transferable vaccines to miss the peak of the birthing season. However, since the transferable vaccine is groomed off of individuals at rate ($alpha$), the lengths of self-dissemination that are longer than the average duration gel remains on individuals, show no difference 3.4. In contrast, the transmissible vaccine can continue to spread and increase protection even into the

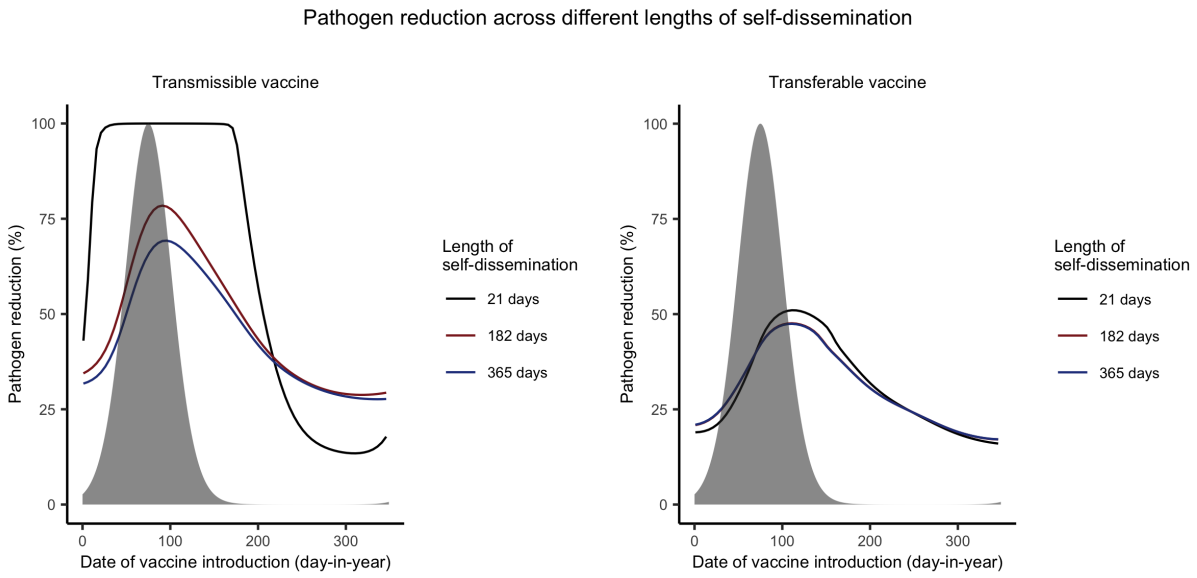

Figure 3.4: Effect of the duration of self-dissemination on pathogen reduction. In each of these simulations the vaccine R_0 is held at 1.5 and the pathogen R_0 is held at 2. The duration of transmission is varied across each pane by changing the value of γ_V. The duration of pathogen infection is held at 21 days ($\gamma_p = 1/21$).The remaining parameters are set to the values described in Figure 3.1.

subsequent birthing season, and so is less sensitive than the transferable vaccine. Overall, we find that although the duration of self-dissemination influences the effectiveness of self-disseminating vaccines, it has little impact on the optimal timing of vaccine introduction: it is generally best to distribute the transmissible vaccine during the birthing season and the transferable vaccine slightly after the peak of the birthing season.

3.2 Case Study Results

3.2.1 Rodents (*Mastomys natalensis*)

Rodents are a prime example of hosts that experience large fluctuations in population size due to seasonal reproduction. For instance, population sizes of the primary rodent reservoir of Lassa virus, *Mastomys natalensis*, have been shown to fluctuate seasonally in East Africa in response to seasonal birth pulses coinciding with wet season and an increase in the availability of green grass (Leirs et al. 1997; McCormick et al. 1987). We used data from this well-studied system (Leirs et al. 1997) to parameterize our model of seasonal birth rates. An important caveat is that the data from Leirs et al. (1997) comes from outside of the range of Lassa virus and thus may overestimate the extent of seasonality in populations where Lassa virus is endemic. We use a population size of 2000 (Mariën et al. 2019). Parameters estimated from Nuismer et al. (2020) suggest a lifespan of one year for the rodent reservoir.

Lassa virus commonly spills over into the human population through rodent droppings and leads to the development of Lassa fever (McCormick et al. 1987). Lassa fever is a hemorrhagic fever that can be fatal (Dan-Nwafor et al. 2019). Infection from rodents

occurs typically from rodents living in households (McCormick et al. 1987). The WHO considers Lassa virus to be a pertinent threat to public health, and is of wide concern (WHO 2018). Although infection in humans can be fatal, Lassa virus is not known to cause much illness within the rodent population. To simulate the pathogen dynamics of Lassa Virus we use a rate of recovery from Lassa virus infection equal to 1/21, and a Lassa virus $R_{0,P} = 1.5$ these values were estimated in Nuismer et al. (2020). We are then able to solve for the transmission coefficient β_P based on γ_p and $R_{0,P}$.

Previous efforts to combat Lassa Virus have been insufficient to successfully eliminate Lassa Virus in the rodent population (Mari Saez et al. 2018). Vaccinating these rodents could reduce the prevalence of Lassa virus in the rodents which then could potentially reduce both the rate of spillover into the human population and the number of deaths due to Lassa fever. We base the transmissible vaccine parameters on a recent study (Varrelman et al. 2022) which suggests that the rodents would be infectious with the vaccine for their entire life ($\gamma_v = 1/365$). Due to self-disseminating vaccines currently being developed we consider a range of values for the vaccine reproductive number. However, (Varrelman et al. 2022) suggests $R_{0,P}$ to be between 1.2 and 11. We determine $\beta_{V,g}$ similar to how we determined β_P.

We studied simulated vaccination campaigns targeting Lassa virus using the parameters described above. Our results indicate that both transmissible and transferable vaccines have the potential to significantly reduce the prevalence of Lassa virus within the rodent population. Similar to our general results above, the level of pathogen reduction achieved largely depends on the R_0 of the vaccine (Figure 3.5). If the vaccine is incapable of spreading to additional individuals ($R_{0,V} = 0$) timing of vaccine does not have much affect.

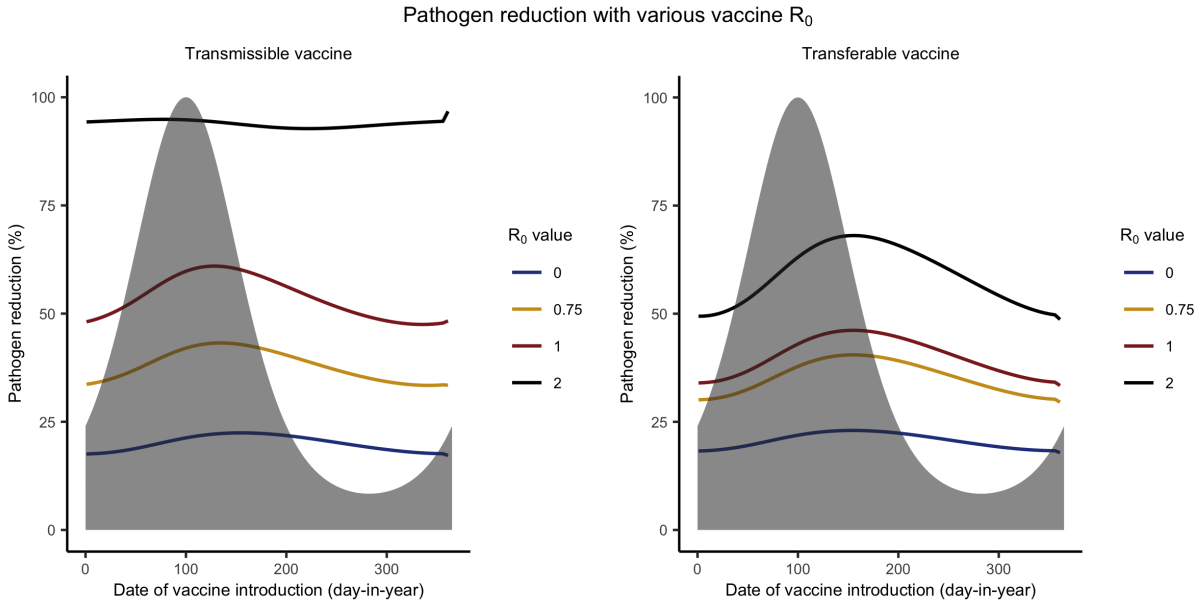

Figure 3.5: The level of pathogen reduction achieved for administering either a transmissible vaccine or transferable vaccine into a rodent (*Mastomys natalensis*) population against Lassa virus in West Africa at different times of year and for various Vaccine R_0's. The parameters are: $s = 2.48, t_p = 100, d = 1/365, \bar{N} = 2000, R_{0,P} = 1.5, \gamma_P = 1/21, \gamma_V = 1/7, \alpha = 6.6 \cdot 10^{-5}, V_l = 1$ week, $N_V = 200$.

When the transmissible vaccine is capable of spreading to additional individuals but not more than the pathogen ($0 < R_{0,V} < 1.5$) timing the implementation of the vaccination campaign to be slightly after the peak of the birth pulse results in the highest level of pathogen reduction. If the implementation of the vaccine does not occur at this time, the level of pathogen reduction achieved will be substantially lower. Once the transmissible vaccine can spread more than the pathogen, timing becomes irrelevant. However, for the transferable vaccine, timing remains critical for any vaccine that is capable of spreading to additional individuals. The results here appear to be less influenced by the timing in comparison with the results demonstrated in Figure 3.2. This is likely due to the differing levels of seasonality that is being simulated in these scenarios. Here in Figure 3.5 the seasonality is much lower than in Figure 3.2 and so seasonality has less of an effect. For either a transmissible or transferable vaccine that is implemented into the *M. natalensis* population, the initiation of the vaccination campaign should occur slightly after the peak of the birth pulse.

Our results for *M. natalensis* supports our general results for the optimal timing of vaccine introduction. Specifically, our results show that pathogen reduction is maximized by initiating the vaccination campaign slightly after the peak of the birthing season, and that timing matters most for self-disseminating vaccines that cannot transmit more than the pathogen ($R_{0,V} < R_{0,P}$).

3.2.2 Vampire Bats (*Desmodus rotundus*)

Desmodus rotundus are another animal that experiences seasonal reproduction, however these animals tend to be longer lived than *M. natalensis*. It has been estimated that *D. rotundus* live for three and a half years (Lord et al. 1976). Recent studies use lactation rates to estimate the reproductive seasonality in these populations. We tailor our birth function to data on lactation from Lord (1992). It is unclear what the overall population size of *D. rotundus* is, however, estimates for colony size do exist. For this example we assume vaccination to be occurring for a single colony and therefore use a population of 240 individuals as estimated by Bakker et al. (2019).

Bats harbor various viruses that pose a threat to the human population (Calisher et al. 2006; Luis et al. 2013). One that is a current threat in the Americas is rabies (Schneider et al. 2009). Rabies is a disease caused by a virus commonly spread by bats and is fatal in most mammals, including humans (Fisher et al. 2018). Rabies frequently spills over into livestock from vampire bats (*D. rotundus)* in South America and can end up causing dramatic losses for farmers (Benavides et al. 2017). To simulate the pathogen dynamics of rabies we use a pathogen R_0 of 1.5 and a recovery rate of 1/21 (Blackwood et al. 2013; Hampson et al. 2009; Moreno and Baer 1980). In addition, it is thought that roughly 10% of bats that are exposed to rabies end up developing a lethal infection (Blackwood et al. 2013; Bakker et al. 2019). Our model does not incorporate an exposed class, instead we incorporate this by defining the virulence parameter to reflect that on average 10% of infections should result in mortality. With these parameters we then back solve to find the transmission rate β_p.

Previous efforts to control vampire-bat rabies has focused on culling, but has yet to be successful. However, there are ongoing efforts to try and reduce the prevalence of rabies within the vampire-bat population through self-disseminating vaccines rather than culling (Bakker et al. 2019; Griffiths et al. 2020). We use parameters from these studies to demonstrate the vaccine dynamics. Specifically, Bakker et al. (2019) suggests that the transferable gel stays on for approximately two days for the transferable vaccine ($\gamma_v = 1/2$). As the proposed transmissible vaccine vector for bats is a betaherpes virus which is likely to induce lifelong infection (Griffiths et al. 2020, 2022), we use a recovery rate of $1/(365 \times 3.5)$ for the transmissible vaccine. Similar to the rodent example, it is unclear what R_0 the self-disseminating vaccines will have, thus, we explore a range of vaccine R_0 values. Bakker et al. (2019) demonstrates the potential of transferable vaccines to be effective within vampire bat populations. However this was only over one year of vaccination and did not include the seasonality of the bats. Here we provide an example of the outcome of self-disseminating vaccines in vampire-bat populations against rabies, for both a transmissible and transferable vaccine.

Figure 3.6 demonstrates that vaccination in the bat population could prove to be immensely successful, even with vaccines with no transmission capabilities. This is likely due to bats having longer lifespans than the previously mentioned *M. natalensis*. Due to bats having longer lifespans and there being repeated vaccination, there is not much turnover in the number of immune individuals in the population. This allows for the proportion of vaccinated individuals in the population to continually be boosted by yearly vaccination. Our results indicate that seasonal reproduction would not have a major effect on the outcome of a vaccination campaign. Additionally, a self-disseminating vaccine with at least some

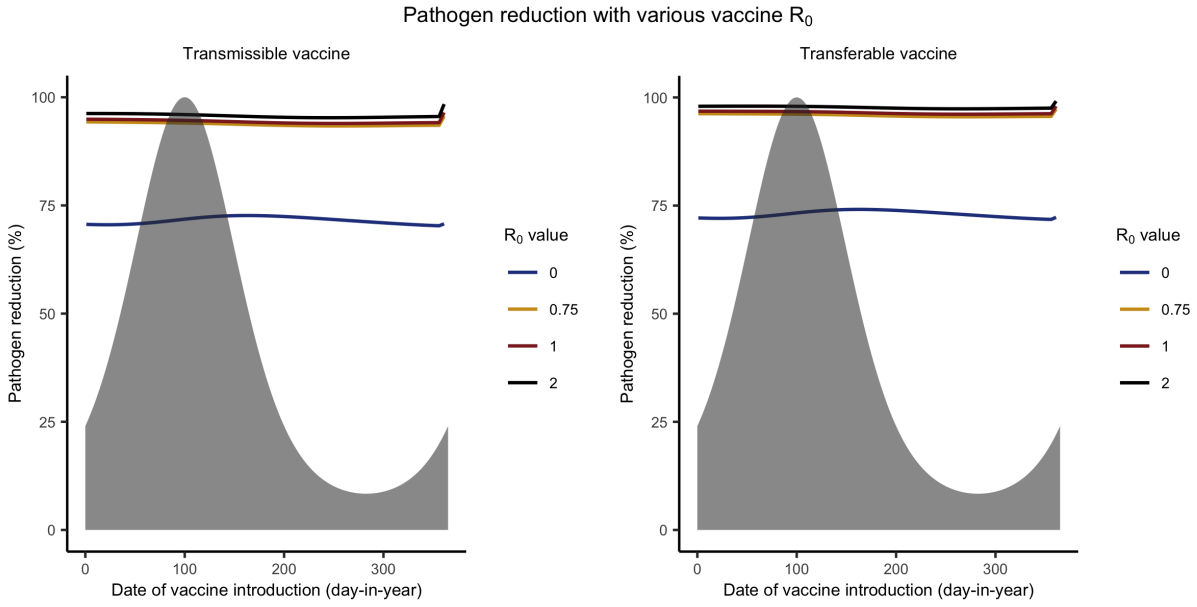

Figure 3.6: The level of pathogen reduction achieved for administering either a transmissible vaccine or transferable vaccine into a bat (*Desmodus rotundus*) population against Rabies virus in a small bat colony at different times of year and for various Vaccine R_0's. The parameters are: $s = 2.11, t_p = 100, d = 1/(365 \cdot 3.5), \bar{N} = 2000, R_{0,P} = 1.5, \gamma_P = 1/21, \gamma_V = 1/7, \alpha = 6.6 \cdot 10^{-5}, V_l = 1$ week, $N_V = 200$.

spreadable capabilities should achieve a major level of pathogen reduction (>90%)(Figure 3.6). The sensitivity to timing of a self-disseminating vaccine into the bat population is minimal. Again this is likely due to the lower seasonality and longer lifespan.

CHAPTER 4

Discussion

4.1 Discussion

We have used mathematical models of self-disseminating vaccines to evaluate how the timing and duration of vaccine distribution influences the impact of vaccination campaigns targeting seasonally fluctuating wildlife populations. Our results demonstrate that self-disseminating vaccines increase protection relative to traditional vaccines but that the magnitude of this increase depends on the mechanism of self-dissemination and the timing of vaccine distribution. Specifically, for both types of self-disseminating vaccines, introduction should be timed relative to seasonal reproduction. Introducing the vaccine during the birthing season generally increases the success of vaccination campaigns. Vaccines introduced far past the seasonal reproduction period are generally less effective. The importance of timing arises because the number of susceptible individuals available for vaccination fluctuates seasonally, reaching a maximum slightly after the peak of the birthing season.

Our results demonstrate that transferable vaccines are more sensitive to timing than transmissible vaccines. This occurs primarily because transmissible vaccines can generate self-sustaining chains of transmission whereas transferable vaccines cannot. Thus, transferable vaccines can spread only to susceptible individuals at the time of vaccine introduction. This also holds true but to a lesser extent for weakly transmissible vaccines that generate only short chains of transmission. With proper timing, however, our results indicate that highly transferable and weakly transmissible vaccines can be nearly as effective as highly transmissible vaccines, at least in some cases.

The importance of our results for real world applications rests upon the extent to which reproduction shows strong patterns of seasonality within a target reservoir species as well as how much population turnover there is. As demonstrated by our case studies with comparable levels of seasonality, the lifespan of hosts has a large effect on the sensitivity to seasonality. The rodent population demonstrated higher levels of sensitivity to the timing of vaccine introduction. This is likely due to the combination of their seasonal reproduction and their short lifespans. Due to high population turnover in the rodent population, the individuals vaccinated in the prior year will not be present in subsequent years. This reinforces the importance of vaccinating the newly introduced and susceptible individuals in the population.

Our results are highly relevant to pathogens such as Lassa virus and Rabies virus. Other pathogens that our results could be important for are, Sin Nombre virus and hantavirus. Our results suggest that vaccination efforts targeting these pathogens will need to be well-timed and carefully planned to achieve maximum effectiveness (Mills et al. 1999). Our results demonstrate that campaigns with self-disseminating vaccines will need to be well timed in host populations with distinct seasonal reproduction and short lifespans.

Our model makes three important assumptions. First, we have ignored age structure. This could be important in cases where vaccines rely upon the natural behavior of the animal in order to spread. For instance, if vaccines are initially distributed as edible baits, most may be consumed by actively foraging adults rather than susceptible juveniles. In such a case, optimal timing of vaccine introduction may matter less and vaccine self-dissemination may be less effective. Second, we do not take maternal antibodies into consideration. Maternal antibodies may interfere with juveniles to surmount an immune response to the

vaccine, and therefore alter the optimal time for vaccination (Zhi Q. and Hildegund C.J. 1992). Third, we assume a constant rate of mortality. There are wildlife that experience seasonally forced population sizes due to mortality rather than reproduction. For such wildlife we expect our results may be heightened if seasonal mortality occurred after the birthing season. However, if there was no seasonality due to reproduction, and instead fluctuations were driven predominantly by seasonal mortality, we expect our results to differ slightly due to mortality affecting all individuals rather than only susceptible individuals.

Here our goal was to gain both general understanding of the affects of seasonality and the time of vaccine distribution as well as an idea of the affects within certain hosts. We recognize that our model does not perfectly describe the dynamics of rabies in vampire bat populations, nor the spread of Lassa virus in rodents, but we believe it generates a basic understanding of self-disseminating vaccines in these hosts and provides a good foundation for future studies to build from.

Self-disseminating vaccines make vaccinating hard to reach wildlife populations more feasible. Our results show that optimizing the timing and duration of vaccine delivery can make or break the success of a vaccination program in fluctuating wildlife populations with high levels of population turnover. These results further demonstrate the importance of understanding the population ecology of wildlife species prior to implementing vaccination campaigns using self-disseminating vaccines.

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4.2 Appendix

4.2.1 Setting the Birth Scaling Constant k

In our simulations, the scaling constant k in the birthing function is set by the user-specified values d, s, t_p, and $\bar{N}$. To solve for the value of k, we first rewrite the birthing function as

$$b(t) = k \cdot e^{-s \cdot \cos^2\left(\frac{\pi}{365} \cdot (t - (t_p + \frac{365}{2}))\right)} \tag{4.1}$$

$$= k\,\bar{b}(t). \tag{4.2}$$

The differential equation that describes the population size in the absence of any infectious agent is

$$\frac{dN}{dt} = b(t) - d\,N. \tag{4.3}$$

Let $N^*(t)$ denote the T-periodic solution of Eq (4.3) with mean value $\bar{N}$. Then

$$\frac{1}{T}\int_0^T N^*(t)\,dt = \bar{N}. \tag{4.4}$$

This implies

$$\frac{dN^*}{dt} = b(t) - d\,N^* \tag{4.5}$$

$$\int_0^T \frac{dN^*}{dt}\,dt = \int_0^T b(t)\,dt - d\int_0^T N^*\,dt \tag{4.6}$$

$$0 = k\int_0^T \bar{b}(t)\,dt - d\,T\,\bar{N}. \tag{4.7}$$

The left hand side of Eq (4.7) is zero because N^* is T-periodic. Thus, we have

$$k = \frac{dT\bar{N}}{\int_0^T \bar{b}(t)\,dt} \tag{4.8}$$

Thus, for a specified d, s, T, and $\bar{N}$, Eq (4.8) can be numerically integrated to solve for the implied value of k. Note that the value of t_p only shifts the birthing function in time; namely, it does not change the integral of $\bar{b}(t)$ over a single period.

4.2.2 Derivation of R_0

In this section, we derive an expression for the basic reproduction number, notated R_0, that describes the average number of new infections that result when a single infected individual is introduced into a stably cycling population of susceptible hosts. We keep our derivation broad so as to simultaneously derive the relevant R_0 for the pathogen, transmissible vaccine, and transferable vaccine.

Let $N^*(t)$ denote the T-periodic limit cycle that describes a population of susceptible hosts in the absence of infection and vaccination. We assume that $N^*(t) >> 1$ so that

the susceptible population is not significantly depleted by the infection process. Let β, γ, v denote the transmission rate, recovery rate, and the virulence rate of the infectious agent. In addition, for the transferable vaccine, let $\alpha\, N^*(t)$ denote the rate at which vaccine is groomed off gelled individuals. When a single infected host is introduced into the population, the rate of new infections that are caused by the infected host at time t is $\beta N^*(t)$. This infection rate continues until the initial infected dies due to natural mortality (at rate d), dies due to virulence (at rate v), recovers from infection (at rate γ), or in the transferable vaccine case, leaves the infectious class due to grooming of gel at rate $\alpha\, N^*(t)$. Note that $\alpha = 0$ in the case of the pathogen or transmissible vaccine.

Let t_0 denote the time at which the infected individual is introduced. The total number of new infections caused by the infected individual is obtained by integrating the infection rate multiplied by the probability that the individual has not recovered or died from time $t = t_0$ to time $t = \infty$:

$$\int_{t_0}^{\infty} \beta N^*(t)\, e^{-(d+\gamma+v+\alpha N^*(t))(t-t_0)}\, \mathrm{d}t. \tag{4.9}$$

Eq (4.9) shows that, because the population size $N^*(t)$ is non-constant, the number of new infections is a function of the time t_0 at which the infected individual is introduced. In order to find the average number of new infections generated by an infected that is introduced at a randomly chosen time, we integrate Eq (4.9) with respect to t_0 over the interval $[0, T]$, and divide by $\frac{1}{T}$. Note that because $N^*(t)$ is T-periodic, averaging over introduction times that are outside the interval $[0, T]$ is redundant. Consequently, we have

$$R_0 = \frac{1}{T} \int_0^T \int_{t_0}^{\infty} \beta N^*(t)\, e^{-(d+\gamma+v+\alpha N^*(t))(t-t_0)} \mathrm{d}t\, \mathrm{d}t_0. \tag{4.10}$$

Transferable Vaccine

In the case of the transferable vaccine virulence is absent so we set $v = 0$. In addition, $\alpha \neq 0$, and the integral described by Eq 4.10 is made difficult to simplify by the presence of $N^*(t)$ in an exponent. However, it is possible to rewrite this expression for R_0 as a single integral by changing the order of integration. Let $k(t) = d + \gamma + \alpha N^*(t)$ and let $w(t, t_0) = \beta N^*(t) e^{k(t)(t-t_0)}$. Then

$$R_0 = \frac{1}{T} \int_0^T \int_{t_0}^{\infty} \beta N^*(t)\, e^{-(d+\gamma+\alpha N^*(t))(t-t_0)} \mathrm{d}t\, \mathrm{d}t_0 \tag{4.11}$$

$$= \frac{1}{T} \int_0^T \int_0^t w(t, t_0)\, \mathrm{d}t_0\, \mathrm{d}t + \frac{1}{T} \int_T^{\infty} \int_0^T w(t, t_0)\, \mathrm{d}t_0\, \mathrm{d}t \tag{4.12}$$

$$= \frac{1}{T} \int_0^T \frac{\beta\, N^*(t)}{k(t)} (1 - e^{-k(t)\, t})\, \mathrm{d}\, t + \frac{1}{T} \int_T^{\infty} \frac{\beta\, N^*(t)}{k(t)} (e^{-k(t)(t-T)} - e^{-k(t)\, t})\, \mathrm{d}\, t \tag{4.13}$$

$$= \frac{\beta}{T} \int_0^{\infty} \frac{N^*(t)}{k(t)} (e^{-k(t)\max(0, t-T)} - e^{-k(t)\, t}). \tag{4.14}$$

Here, we changed the order of integration so that integration with respect to $\mathrm{d}t_0$ is performed first (Eq (4.12)). The limits of integration are changed accordingly so that the region that is integrated over (Figure 4.1a) remains the same. The resulting inner integral with respect to dt_0 is straightforward to evaluate, leading to Eq (4.13). Finally, Eq (4.13) can be written in the more compact form of Eq (4.14).

Transmissible Vaccine and Pathogen

In the case of the transmissible vaccine and the pathogen, $\alpha = 0$, and as a consequence the expression for R_0 in Eq (4.10) can be simplified. Specifically, the double integral described by Eq (4.10) can be simplified by using the change of coordinates $u = t$, $w = t - t_0$. This change of coordinates needs to be applied to three terms in the above integral: the area differential $\mathrm{d}t\,\mathrm{d}t_0$, the limits of integration, and the integrand (Stewart 2012).

Let $T(u, w) = (u, u - w)$ denote the vector-valued function that converts (u, w) coordinates into (t, t_0) coordinates. Then the area differential $\mathrm{d}t\,\mathrm{d}t_0$ is equal to $|DT|\,\mathrm{d}u\,\mathrm{d}w$, where D denotes the Jacobian operator with respect to u and w, and $|\cdot|$ denotes the determinant. Because $|DT| = 1$, we have $\mathrm{d}t\,\mathrm{d}t_0 = \mathrm{d}u\,\mathrm{d}w$. The region of integration in the (u, w) plane can be found by drawing the region of integration in the (t, t_0) plane, and identifying boundary lines with their analogue in the (u, w) plane (Figure 4.1). Finally, the integrand is transformed by the substitution $t \to u$ and $t - t_0 \to w$.

These substitutions allow us to transform the integral in Eq. (4.10) and evaluate as follows:

$$R_0 = \frac{1}{T}\int_0^\infty \int_w^{w+T} \beta N^*(u)\, e^{-(d+\gamma+v)w}\mathrm{d}u\,\mathrm{d}w \tag{4.15}$$

$$R_0 = \frac{\beta}{T}\int_0^\infty \left(\int_w^{w+T} N^*(u)\,\mathrm{d}u\right) e^{-(d+\gamma+v)w}\mathrm{d}w \tag{4.16}$$

$$= \beta\bar{N^*}\int_0^\infty e^{-(d+\gamma+v)w}\mathrm{d}w \tag{4.17}$$

$$= \frac{\beta\bar{N}^*}{d+\gamma+v}. \tag{4.18}$$

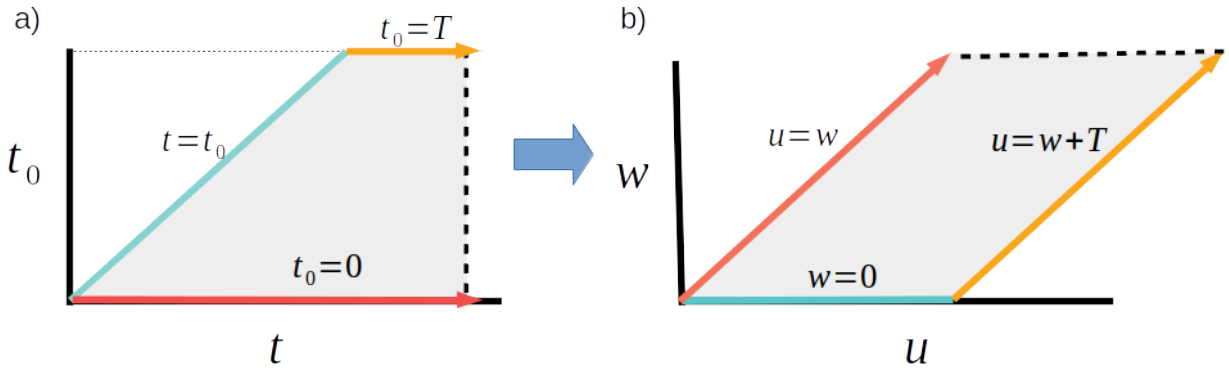

Figure 4.1: Region of integration (gray) of Eq (4.10) in the (t, t_0) plane (a). When $\alpha = 0$, the calculation of R_0 is simplified by transforming the region into the (u, w) plane (b). The dashed boundary lines indicate that the region continues out to infinity. Boundary lines and their transforms are identified by the same color.

Here, $\bar{N}^*$ denotes the average population size over a single period T. Virulence v is possibly nonzero in the case of the pathogen and is set to zero in the case of a transmissible vaccine.

4.2.3 Setting transmission rate β

Equations (4.14) and (4.18) are used to define the transmission rate β that corresponds to specific values of R_0 in our simulations. For a given simulation and infectious agent, we define an average population size $\bar{N}$, death rate d, virulence v, recovery rate γ, and R_0. In the case of a transmissible vaccine or pathogen, Eq (4.18) can then be used to solve for the value of β that is implied by the user-defined parameters.

The transferable vaccine case is more difficult because we need the solution of $N^*(t)$ to evaluate Eq (4.14). To this end, we first solve for the value of k using Eq (4.8) and parameters specified by the user. k, in turn, is used to define the birthing rate $b(t)$. Next,

we obtain a numerical approximation of $N^*(t)$ by simulating the population equation Eq (4.3). Specifically, we simulate Eq (4.3) for 10 years to allow the solution to converge to the stable limit cycle $N^*(t)$. Next, we use the function "approxfun" in R to approximate the stable limit cycle $N^*(t)$ over a single period. Finally, we use this approximation in the integral of Eq (4.14) to solve for the value of β that is implied by a user specified R_0. All integration was performed in the statistical language R using the deSolve package (Soetaert et al. 2010).