



Transmissible vaccines in heterogeneous populations: Implications for vaccine design

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ABSTRACT

Transmissible vaccines may provide a promising solution for improving the control of infectious disease, particularly zoonotic pathogens with wildlife reservoirs. Although it is well known that heterogeneity in pathogen transmission impacts the spread of infectious disease, the effects of heterogeneity on vaccine transmission are largely unknown. Here we develop and analyze a mathematical model that quantifies the potential benefits of a transmissible vaccine in a population where transmission is heterogeneous between two subgroups. Our results demonstrate that the effect of heterogeneity on the benefit of vaccine transmission largely depends on the vaccine design and the pattern of vaccine administration across subgroups. Specifically, our results show that in most cases a transmissible vaccine designed to mirror the transmission of the pathogen is optimal. If the vaccination effort can be preferentially biased towards a given subgroup, a vaccine with a pattern of transmission opposite to that of the pathogen can become optimal in some cases. To better understand the consequences of heterogeneity on the effectiveness of a transmissible vaccine in the real world, we parameterized our model using data from Sin Nombre virus in deer mice (*Peromyscus maniculatus*). The results of this analysis reveal that when a vaccination campaign is limited in vaccine availability, a traditional vaccine must be administered primarily to males for the spread of Sin Nombre virus to be prevented. In contrast, a transmissible vaccine remains effective even when it cannot be preferentially administered to males.

1. Introduction

Zoonoses, particularly those circulating in wildlife populations, are a primary source of pathogens that infect humans [1]. The burden of such pathogens on human populations can be profound, as demonstrated in the 2014–2015 West African Ebola virus epidemic. The virus was transmitted from wild animal populations such as fruit bats and apes [2], and resulted in over 11,000 human deaths and cost over 3.6 billion dollars [3]. Such outbreaks highlight the need to develop cost-effective strategies that mitigate zoonotic spillover into human populations. One strategy for reducing the spillover potential of zoonoses is to decrease the prevalence of infectious disease within wildlife reservoir populations. Both culling [4] and mass vaccination [4,5] have been used to control pathogens in wildlife reservoir populations. Though both strategies have been successful in some cases [4], the costs of implementation and the difficulties of delivering vaccine to wild animals limit their scope of applicability [6]. Transmissible vaccines are a

novel tool that might overcome some of these challenges, allowing for pathogen reduction or even the prevention of pathogen spread in wildlife reservoirs.

Transmissible vaccines, also known as self-disseminating vaccines, are live viral vaccines with the ability to transmit between hosts [7]. Mathematical models demonstrate that vaccine transmission reduces the vaccination effort required to protect a population [8], can reduce a pathogen's prevalence in a population, or facilitate pathogen eradication altogether [8–10]. Though insightful, these models simplify host biology by assuming that all hosts are identical in their capacity to transmit the vaccine and pathogen. In reality, of course, individual hosts differ in their transmission due to factors such as sex and age [11], and this heterogeneity in host populations has been shown to influence the outcome of vaccination campaigns as well as the optimal vaccination strategy [12]. For instance, if vaccine is delivered to a heterogeneous host population at random, pathogen control requires a greater rate of vaccination than in a uniform host population [12]. In contrast,

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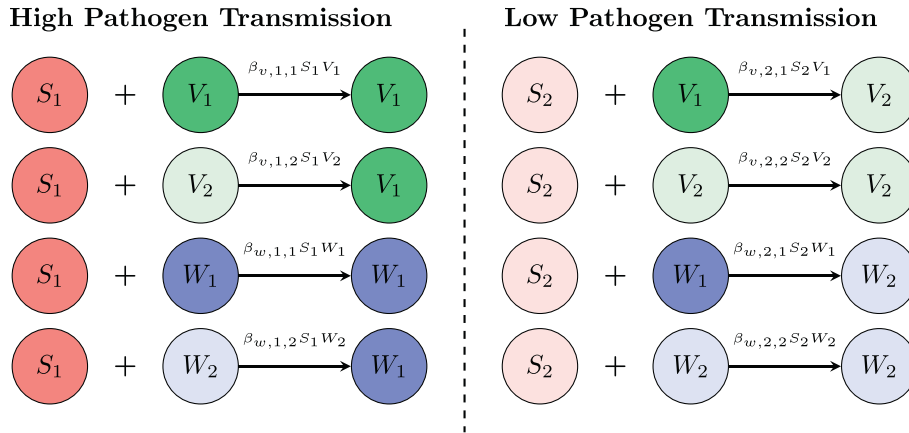


Fig. 1. Transmission events in the mathematical model. Subgroup one is assumed to maintain high within subgroup pathogen transmission (left), and subgroup two is assumed to maintain a low level of within subgroup pathogen transmission (right). High and low vaccine transmission is determined by the assumed vaccine design. Vaccine and pathogen infected individuals can infect susceptible individuals within their subgroup ($\beta_{v,1,1}$, $\beta_{v,2,2}$, $\beta_{w,1,1}$, $\beta_{w,2,2}$), as well as susceptible individuals in the other subgroup, at a reduced rate ($\beta_{v,1,2}$, $\beta_{v,2,1}$, $\beta_{w,1,2}$, $\beta_{w,2,1}$).

if it is possible to deliver vaccine selectively or optimally, the vaccination rate required for pathogen control can actually be less in a heterogeneous host population than a homogeneous host population [12]. Preferentially distributing a vaccine to a super-spreading class increases the overall effectiveness of a vaccination campaign [11]. Unfortunately, effectively identifying super-spreaders and selectively delivering vaccine to them is a formidable and unresolved public health challenge in many systems [13].

Mathematical models of another transmissible therapy, therapeutic interfering particles (TIPs), have demonstrated that heterogeneity in host transmission increases the effectiveness of TIPs by autonomously targeting super-spreaders [13]. TIPs replicate only in the presence of the pathogen, and naturally follow the same transmission pathways [13]. In a similar fashion, transmissible vaccines may benefit from following the same transmission pathways as the pathogen, thus increasing their effectiveness in heterogeneous populations. Although intuitively appealing, it is unknown whether the benefits demonstrated for TIPs in heterogeneous host populations also occur for transmissible vaccines. Here we explore the effects of vaccine transmission in a host population with heterogeneity in vaccine and pathogen transmission (i.e., some individuals spread the infectious agent to a higher degree than others). To this end, we develop mathematical models to quantify the effectiveness of a transmissible vaccine in a host population composed of subgroups that transmit a vaccine and pathogen at different rates. Our analyses address three specific questions: 1.) How sensitive are the benefits of vaccine transmission to population-level heterogeneity? 2.) Do certain patterns of heterogeneity favor the use of a vaccine that mimics the biased spread of a pathogen? 3) Do levels of heterogeneity observed in a natural reservoir population (Sin Nombre virus (SNV) in deer mice (*Peromyscus maniculatus*)) significantly influence the effectiveness of a transmissible vaccine?

2. Methods

We developed a model describing the spread of a pathogen and transmissible vaccine in a heterogeneous animal population. Hosts in the population fall into one of two subgroups. Each subgroup is defined by a unique set of parameters that reflect differences in the hosts' ability to transmit a pathogen and a transmissible vaccine. We assume that subgroup identity is a result of fixed differences in host biology (e.g., behavior, sex, genome), and as a consequence, hosts remain in the subgroup into which they were born. Based on the classic Susceptible-Infected-Recovered (SIR) model of disease spread [14], individuals in each subgroup i are further partitioned into classes that reflect their immunological status to a transmissible vaccine and pathogen: susceptible to both pathogen and vaccine (S_i), pathogen-infected (W_i), vaccine-infected (V_i), and recovered (R). New susceptible individuals are introduced into subgroup i at a constant rate b_i and all individuals

die at rate d . Although we refer to b_i as birth for simplicity, it more accurately describes the rate at which new susceptible individuals are added to the population through any mechanism. Susceptible individuals can be directly vaccinated as they are introduced into the susceptible class, or indirectly through infection with the vaccine. Although challenging in wildlife populations, direct vaccination of susceptible individuals may be possible in a number of ways. For instance, a captive colony could be used as a source of directly vaccinated juveniles, vaccine baits could be designed in a way that favors consumption by juvenile individuals more likely to be susceptible, or pregnant females could be targeted with vaccines capable of vertical transmission. In the model, a fraction σ_i of births into subgroup i are directly vaccinated and immediately enter the vaccine-infected class V_i .

The rate at which the vaccine and pathogen spread between susceptible and infected hosts depends on the subgroup identities of the hosts involved. The parameters $\beta_{v,i,j}$ and $\beta_{w,i,j}$ describe the rates of transmission from subgroup j to subgroup i for a transmissible vaccine and pathogen, respectively (Fig. 1). For example, pathogen-infected individuals within subgroup j transmit the infection to susceptible individuals in subgroup i according to the mass-action rate $\beta_{w,i,j} S_i W_j$. Because susceptible individuals of subgroup i can become pathogen-infected by members of either subgroup, the total rate of pathogen infection in subgroup i is $\sum_{j=1}^2 \beta_{w,i,j} S_i W_j$. Upon pathogen-infection, a susceptible in class S_i transitions to the pathogen-infected class W_i . Likewise, susceptible hosts in subgroup i become infected with the vaccine at rate $\sum_{j=1}^2 \beta_{v,i,j} S_i V_j$, and transition into class V_i . Because of the assumed immunological cross-reactivity between the vaccine and the pathogen, individuals who experience infection from one agent are immune to future infections from either agent. Individuals who are infected with either the vaccine or pathogen recover at rate γ . Because recovered hosts no longer contribute to the infection process, we combine the subgroups into a common R class. A list of model variables and parameters can be found in Table 1. The resulting system of ordinary differential equations is:

$$\begin{aligned} \frac{dS_i}{dt} &= b_i(1 - \sigma_i) - dS_i - \sum_{j=1}^2 (\beta_{v,i,j} S_i V_j + \beta_{w,i,j} S_i W_j) \\ \frac{dV_i}{dt} &= b_i \sigma_i - (\gamma + d)V_i + \sum_{j=1}^2 \beta_{v,i,j} S_i V_j \\ \frac{dW_i}{dt} &= -(\gamma + d)W_i + \sum_{j=1}^2 \beta_{w,i,j} S_i W_j \\ \frac{dR}{dt} &= -dR + \sum_{j=1}^2 (\gamma V_j + \gamma W_j). \end{aligned} \quad (1)$$

To simplify our model, we make several assumptions regarding the transmission coefficients, $\beta_{w,i,j}$ and $\beta_{v,i,j}$. First, we assume that for both infectious agents, within-group infectious contacts occur more frequently than between-group contacts. This assumption, known as assortative mixing [15], can be expressed mathematically for the pathogen as $\beta_{w,i,i} > \beta_{w,i,j}$ for $i \neq j$, and similarly for the vaccine. Without

Table 1
Model state variables and parameters. Subscript i specifies the subgroup of the population.

Name	Description	Units
S_i	Susceptible class	individuals
V_i	Vaccine-infected class	individuals
W_i	Disease infected individuals	individuals
R	Recovered individuals	individuals
$\beta_{v,i,j}$	Vaccine transmission rate from subgroup j to i	individual ⁻¹ day ⁻¹
$\beta_{w,i,j}$	Disease transmission rate from subgroup j to i	individual ⁻¹ day ⁻¹
γ	Recovery rate	day ⁻¹
b_i	Birth rates	day ⁻¹
D	Death rate	day ⁻¹
$R_{0,w}$	Disease reproductive number	nondimensional
$R_{0,v}$	Transmissible-vaccine reproductive number	nondimensional
σ_i	Proportion of newborns vaccinated directly	nondimensional
$\bar{\sigma}$	Average proportion of newborns that are directly vaccinated across groups	nondimensional
δ_σ	Difference in the proportion of directly vaccinated newborns across groups	nondimensional

loss of generality, we assume subgroup 1 of the population spreads the pathogen to a greater extent than subgroup 2, so that $\beta_{w,1,1} > \beta_{w,2,2}$. In addition, we assume equal cross transmission between groups: $\beta_{v,1,2} = \beta_{v,2,1}$ and $\beta_{w,1,2} = \beta_{w,2,1}$.

We focus on two possibilities of how the transmission rates of the vaccine relate to pathogen transmission between subgroups. In the first scenario, which we term positive correlation, the ordering of the vaccine transmission coefficients follows that of the pathogen, so that vaccine transmission is greatest in subgroup 1 ($\beta_{v,1,1} > \beta_{v,2,2}$). Because the heterogeneity in vaccine transmission mimics that of the pathogen, this scenario is likely relevant for transmissible vaccines produced through pathogen attenuation. Although unintentional, the best example of an attenuated transmissible vaccine is the Oral Polio Vaccine (OPV), which quite likely follows the transmission pathways of wild type Polio [16]. The second scenario, which we term negative correlation, describes a transmissible vaccine that spreads better in the subgroup with low pathogen transmission, so that $\beta_{v,1,1} < \beta_{v,2,2}$. Although unlikely for an attenuated vaccine, this scenario is in principle possible for recombinant vector vaccines whose transmission is determined by a vector that is unrelated to the pathogen. Recombinant vector transmissible vaccines targeting Lassa fever in *Mastomys natalensis* and Ebola virus in primates are currently being developed using a Cytomegalovirus vector, and are likely to fall in this category [7,17]. Focusing on these two potential vaccine characteristics, we evaluate the effectiveness of a transmissible vaccine in preventing pathogen invasion and in reducing pathogen incidence when vaccination prophylaxis cannot be achieved. We then parameterize our model using data from Sin Nombre virus to quantify the impact of vaccine transmission in a system that displays heterogeneity in pathogen transmission.

3. Results

3.1. Pathogen prophylaxis

A common goal of vaccination campaigns is to prevent a zoonotic pathogen from spreading to new populations that have not yet experienced infection. This is becoming particularly true for high impact zoonotic pathogens such as Ebola in great apes, rabies in a variety of reservoir species, and Lassa fever in rodent populations [7]. This goal is achieved by vaccinating the population to an extent that halts the spread of the targeted pathogen. In our model of a vaccination campaign, σ_1 and σ_2 denote the proportion of newborn individuals that are directly vaccinated in subgroups 1 and 2 respectively. We identify the threshold combinations of vaccination effort (σ_1, σ_2) that protect the entire population from pathogen invasion (Fig. 2, Appendix: Pathogen Prophylaxis). Each panel of Fig. 2 depicts the limiting combinations of

direct vaccination that result in prophylaxis when a non-transmissible (orange curve) or transmissible vaccine (blue curve) is used. Along each threshold curve, we characterize two vaccination strategies: random and optimal. The random strategy applies to many real-world vaccination campaigns that, due to limited host access, cannot preferentially target one subgroup over another. Instead, the total vaccination effort ($\sigma_1 + \sigma_2$) is distributed equally between the subgroups so that $\sigma_1 = \sigma_2$. In contrast, the optimal vaccination strategy is the combination (σ_1, σ_2) that prevents pathogen invasion with the minimal amount of total vaccination effort.

Our results indicate that, across different levels of heterogeneity in transmission between the subgroups, and for both positively and negatively correlated vaccine designs, the use of a transmissible vaccine reduces the minimal vaccination effort needed to prevent pathogen invasion. This can be seen in Fig. 2 by noting that the transmissible vaccination threshold (blue curve) is closer to the origin ($\sigma_1 = \sigma_2 = 0$) than the traditional vaccination threshold (orange curve). Consequently, the total amount of vaccination required for prophylaxis, is smaller when a transmissible vaccine is used. Comparing the optimal and random vaccination strategies along the prophylaxis curves shows that for a population with high heterogeneity between subgroups, the optimal vaccination strategy biases vaccine distribution to the subgroup in which pathogen transmission is greatest. This bias in the optimal strategy is present regardless of whether the vaccine and pathogen transmission coefficients are positively correlated between the subgroups or negatively correlated between subgroups.

Additionally, we evaluate which vaccine design is most beneficial when compared to a traditional vaccine, under both vaccination strategies (random and optimal) and across low and high levels of heterogeneity in transmission. To do so, we find the fractional reduction in the total vaccination relative a non-transmissible vaccine that is required for prophylaxis. Fig. 3 shows the fractional reductions for both vaccination strategies and designs, across low and high levels of heterogeneity, when facing a range of global pathogen R_0 values. Our results demonstrate that if a random vaccination strategy is applied, a positively correlated vaccine results in the greatest reduction in vaccination effort, relative to that of a non-transmissible vaccine (left column, Fig. 3). Furthermore, for a fixed, average pathogen R_0 , the fractional reduction from a positively correlated vaccine design remains relatively constant when heterogeneity is increased from low to high. In contrast, the benefit of a negatively correlated vaccine decreases as heterogeneity increases (Fig. 3). Generally, these results suggest that when a random vaccination strategy is implemented, the benefit of a positively correlated vaccine design is robust under different levels of population heterogeneity. Negatively correlated designs, in contrast, work best when population heterogeneity is small or absent.

In cases where it is feasible to deliver vaccines to subgroups optimally, vaccines that mimic the pathogen's patterns of transmission (positively correlated) are no longer guaranteed to be the best option. Specifically, if the local pathogen R_0 is greater than unity in only one subgroup, a positively correlated vaccine continues to be the best option. If, on the other hand, the local pathogen R_0 is greater than unity in both populations, a negatively correlated vaccine can become the most beneficial vaccine design (a specific example being Fig. 2). This reversal occurs because vaccination targets the subgroup of the population with highest pathogen transmission, reducing the susceptible population in that subgroup and effectively limiting the potential for vaccine transmission. Consequently, a vaccine with patterns of transmission negatively correlated with those of the pathogen spreads to a greater extent in the non-targeted subgroup, which in this case is the subgroup of the population that transmits the pathogen to a lesser degree. As a consequence, when both subgroups have local pathogen R_0 values greater than unity, a negatively correlated vaccine benefits an optimal vaccination strategy by spreading well in the subgroup that is less targeted by direct vaccination.

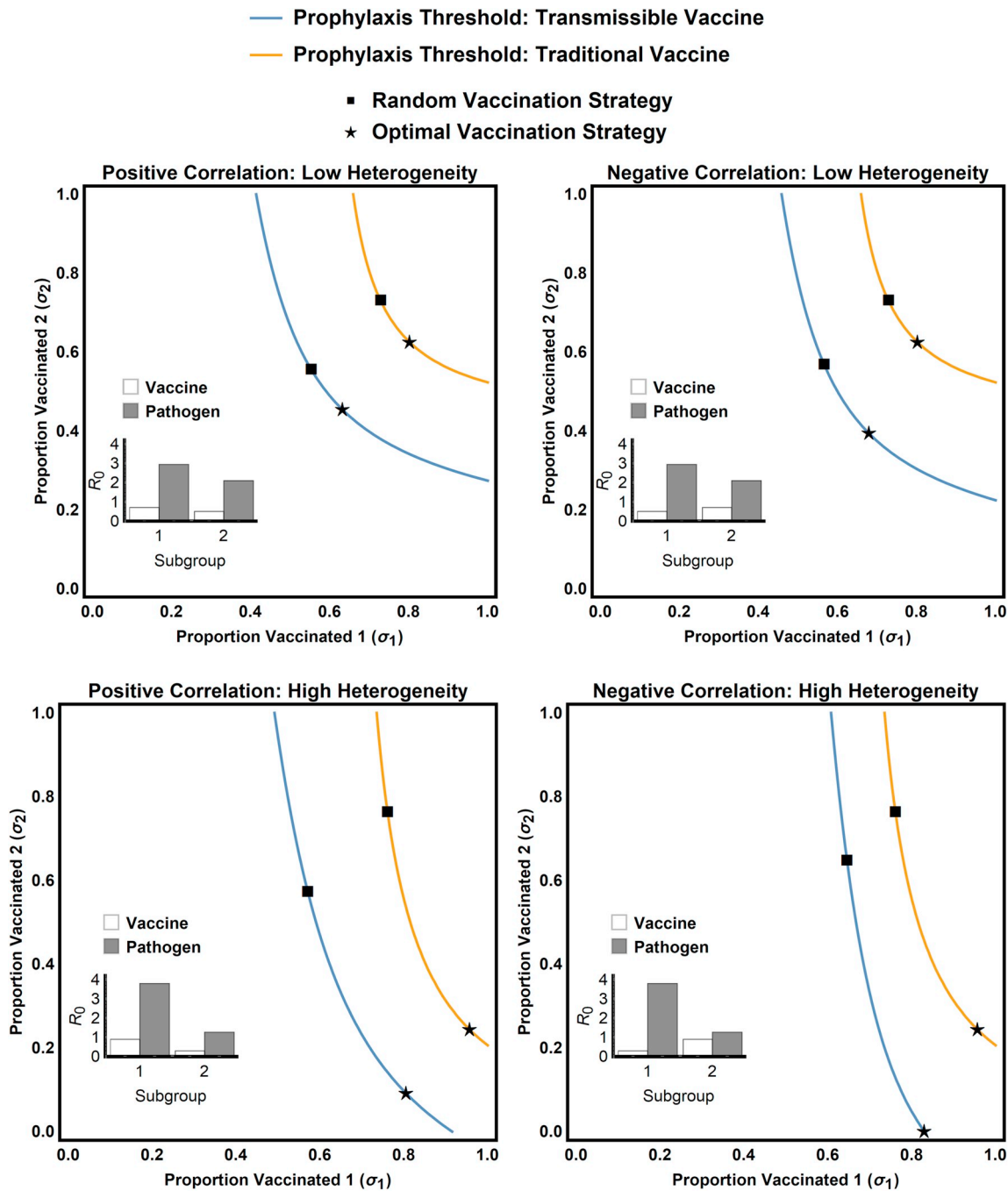


Fig. 2. Vaccination threshold required to prevent pathogen invasion when using a transmissible vaccine (shown by the blue line), and traditional vaccine (shown by the orange line). Each panel depicts the vaccination threshold, for low and high heterogeneity in transmission, and correlation in transmission. Within subgroup R_0 values of the vaccine and pathogen are depicted in the inset bar plot. Top panels: Global $R_{0,w} = 3.697$, global $R_{0,v} = 0.880$. Bottom panels: Global $R_{0,w} = 4.193$, global $R_{0,v} = 0.998$. Fractional reduction in vaccination effort afforded by a transmissible vaccine (clockwise, starting in the top left panel): a.) Optimal strat. = 0.24, Random strat. = 0.24 b.) Optimal strat. = 0.25, Random strat. = 0.22 c.) Optimal strat. = 0.31, Random strat. = 0.15 d.) Optimal strat. = 0.25, Random strat. = 0.25. Parameters varied across panels: a.) $R_{0,v,1,1} = 0.7$, $R_{0,v,2,2} = 0.5$, $R_{0,w,1,1} = 2.94$, $R_{0,w,2,2} = 2.1$, b.) $R_{0,v,1,1} = 0.5$, $R_{0,v,2,2} = 0.7$, $R_{0,w,1,1} = 2.94$, $R_{0,w,2,2} = 2.1$, c.) $R_{0,v,1,1} = 0.3$, $R_{0,v,2,2} = 0.9$, $R_{0,w,1,1} = 3.78$, $R_{0,w,2,2} = 1.26$, d.) $R_{0,v,1,1} = 0.9$, $R_{0,v,2,2} = 0.3$, $R_{0,w,1,1} = 3.78$, $R_{0,w,2,2} = 1.26$. Parameters conserved across panels: $\gamma = 0.02$, $d = 0.01$, $b_1 = 10$, $b_2 = 10$, $R_{0,v,1,2} = 0.26$, $R_{0,v,2,1} = 0.26$, $R_{0,w,1,2} = 1.1$, $R_{0,w,2,1} = 1.1$. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

3.2. Endemic pathogen reduction

If the pathogen is already endemic in a wildlife population and eradication is impossible, a transmissible vaccine may still be an effective tool for reducing pathogen incidence [8]. In this context, we use the proportional reduction in pathogen incidence relative to a non-transmissible vaccine to gauge the effectiveness of a transmissible

vaccine (Appendix: Endemic pathogen reduction). Fig. 4 shows the reduction in pathogen incidence across different levels of bias in vaccine distribution, defined as $\delta_\sigma = \sigma_1 - \sigma_2$. Our results show that a positively correlated vaccine generally outperforms a negatively correlated vaccine. Once more, when vaccination is random ($\delta_\sigma = 0$), the benefit of a positive vaccine design remains relatively constant as population heterogeneity increases. In contrast, the effectiveness of the

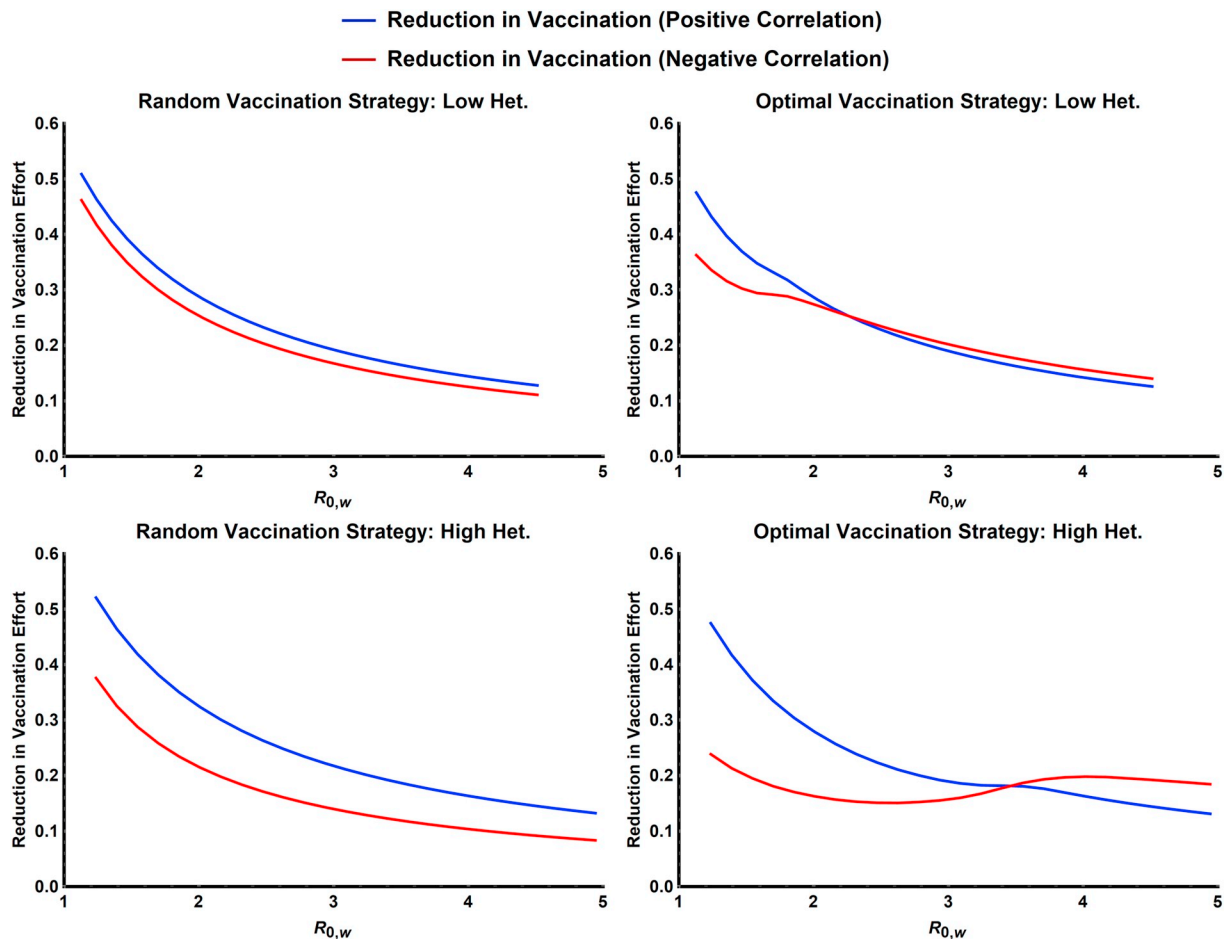


Fig. 3. The fractional reduction in prophylaxis vaccination effort for both vaccine designs and strategies. We hold the vaccine R_0 constant, and proportionally increase the pathogen transmission parameters, allowing us to look at a range of global $R_{0,w}$ values. Parameter values are as followed: (Top panels) Vacc. trans. Positive correlation: $R_{0,v,1,1} = 0.45$, $R_{0,v,2,2} = 0.27$, $R_{0,v,1,2} = 0.18$, $R_{0,v,2,1} = 0.18$, Vacc. trans. Negative correlation: $R_{0,v,1,1} = 0.27$, $R_{0,v,2,2} = 0.45$, $R_{0,v,1,2} = 0.18$, $R_{0,v,2,1} = 0.18$, Pathogen trans.: $R_{0,w,1,1} = \text{range } (0.91-3.63)$, $R_{0,w,2,2} = \text{range } (0.54-2.17)$, $R_{0,w,1,2} = \text{range } (0.36-1.44)$, $R_{0,w,2,1} = \text{range } (0.36-1.44)$. (Bottom panels) Vacc. trans. positive correlation: $R_{0,v,1,1} = 0.54$, $R_{0,v,2,2} = 0.18$, $R_{0,v,1,2} = 0.18$, $R_{0,v,2,1} = 0.18$, Vacc. trans. negative correlation: $R_{0,v,1,1} = 0.18$, $R_{0,v,2,2} = 0.54$, $R_{0,v,1,2} = 0.18$, $R_{0,v,2,1} = 0.18$, Pathogen trans.: $R_{0,w,1,1} = \text{range } (1.09-4.35)$, $R_{0,w,2,2} = \text{range } (0.36-1.45)$, $R_{0,w,1,2} = \text{range } (0.36-1.44)$, $R_{0,w,2,1} = \text{range } (0.36-1.44)$. Parameters conserved across panels: $\gamma = 0.02$, $d = 0.01$, $b_1 = 10$, $b_2 = 10$.

negatively correlated vaccine decreases with increasing heterogeneity (Fig. 4).

If the subgroup of the population that transmits the pathogen to a greater degree is preferentially targeted, the benefit of a transmissible vaccine increases with population heterogeneity, and the optimal vaccination strategy becomes more biased towards the subgroup that transmits the pathogen to a high degree (right side of Fig. 4). Similar to the prophylaxis result, if the optimal vaccination strategy can be achieved and both population subgroups maintain an R_0 greater than one, a negatively correlated transmissible vaccine is the most beneficial vaccine design. This result can be seen in Fig. 4 where the two vaccine designs switch in order of benefit. However, if the subgroup of the population that weakly transmits the pathogen is preferentially targeted, the benefit of a transmissible vaccine is greatly diminished across a wide range of heterogeneity in host transmission (Fig. 4). This occurs because when the pathogen is endemic, a high proportion of the high transmission subgroup is already infected with the pathogen, thus reducing vaccine transmission.

3.3. SNV invasion in deer mice

Many viruses in wildlife populations, including Sin Nombre virus (SNV) in deer mice, maintain relatively low population level R_0 values, typically estimated to be between one and two [18]. Even though these

low R_0 values suggest that disease control should be possible with relatively low vaccine coverage, the challenges of delivering a traditional vaccine to wildlife populations make meeting even these low thresholds a formidable challenge. To evaluate how a transmissible vaccine would perform in a situation where host access is limited, we consider SNV in deer mice, a virus in which transmission is mostly facilitated by males [19,20].

When parameterized with data on SNV in deer mice, our model indicates that if a non-transmissible vaccine is used, a strongly biased vaccination strategy may be required to prevent pathogen invasion in a population of deer mice when vaccination effort is constrained (Appendix: SNV Invasion in Deer Mice, Fig. 5)). However, biasing vaccination effort towards male deer mice may be nearly impossible. In contrast, a transmissible vaccine can achieve prophylaxis over a much broader range of direct vaccination strategies (blue curves in Fig. 5). In particular, a transmissible vaccine can prevent pathogen invasion, even when applied randomly to males and females, a much more realistic goal. We constrain the vaccination effort in this example to account for the inability to vaccinate most wildlife populations to a high degree. Although vaccination campaigns significantly differ based on the biological system of interest, we include reference to a rabies vaccination campaign to simply highlight the fact that a SNV vaccination campaign would be limited in some sense. Still, our results suggest a transmissible vaccination program (positive or negative correlation) could achieve

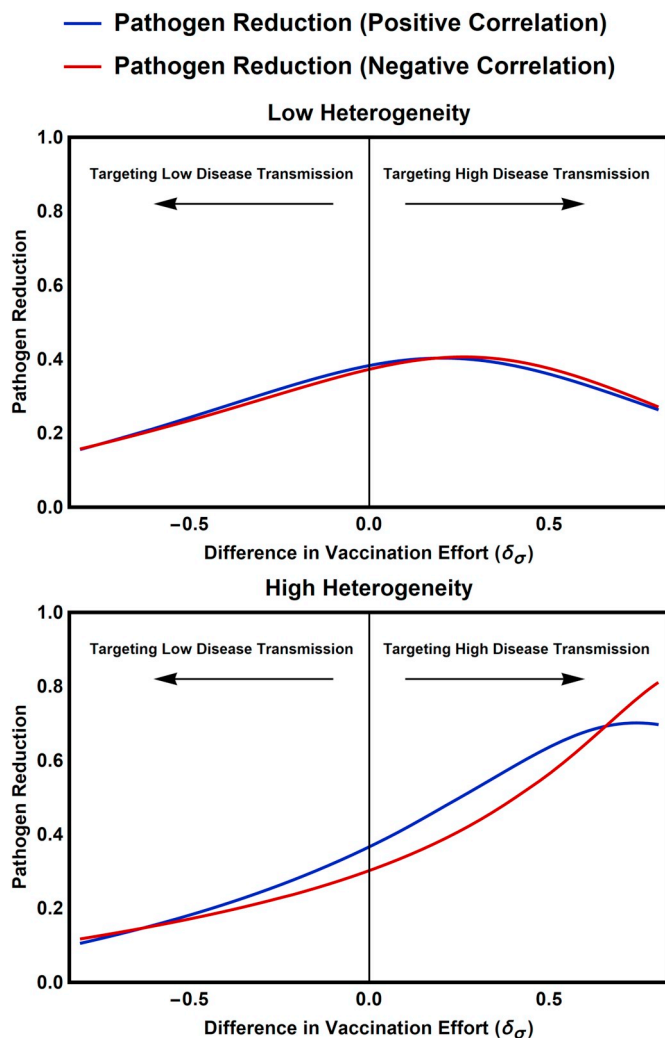


Fig. 4. The proportional reduction in pathogen incidence attributed to vaccine transmission for a vaccine experiencing negative and positive correlation with respect to heterogeneity in pathogen transmission. Left panel: Global $R_{0,w} = 3.70$, global $R_{0,v} = .88$. Right panel: Global $R_{0,w} = 4.19$, global $R_{0,v} = 1.00$. Note that although the average within subgroup transmission remains constant, increasing heterogeneity increases the R_0 of the infectious agents. Parameter values used in the figure: (Top panel) Vaccine transmission w/positive correlation: $R_{0,v,1,1} = 0.7$, $R_{0,v,2,2} = 0.5$ Vaccine transmission w/negative correlation: $R_{0,v,1,1} = 0.5$, $R_{0,v,2,2} = 0.7$ Pathogen transmission: $R_{0,w,1,1} = 2.94$, $R_{0,w,2,2} = 2.1$. (Bottom Panel) Vaccine transmission w/positive correlation: $R_{0,v,1,1} = 0.9$, $R_{0,v,2,2} = 0.3$ Vaccine transmission w/negative correlation: $R_{0,v,1,1} = 0.3$, $R_{0,v,2,2} = 0.9$ Pathogen transmission: $R_{0,w,1,1} = 3.78$, $R_{0,w,2,2} = 1.26$. Parameters conserved across panels: $\bar{\sigma} = 0.4$, $\gamma = 0.02$, $d = 0.01$, $b_1 = 10$, $b_2 = 10$, $R_{0,v,1,2} = 0.26$, $R_{0,v,2,1} = 0.26$, $R_{0,w,1,2} = 1.1$, $R_{0,w,2,1} = 1.1$.

population protection using a substantially reduced level of direct vaccination when compared to a traditional vaccine (Fig. 5). Our analyses demonstrate that a transmissible vaccine could facilitate control of SNV for scenarios where vaccine and pathogen transmission correlate positively or negatively; however, the benefits of vaccine transmission are maximized when the correlation is positive. This occurs because SNV experiences a low population level $R_{0,w}$, where the pathogen only circulates well in one of the population subgroups (here defined as males).

4. Discussion

Our study demonstrates that transmissible vaccines may provide a

useful tool for controlling zoonoses in heterogeneous wildlife populations. However, maximizing the potential benefit of a transmissible vaccine requires careful consideration of the structure of the target population, the transmission characteristics of the pathogen and vaccine, and the extent to which the vaccine can be preferentially administered to subgroups. For instance, if the target pathogen is characterized by self-sustained spread in only one subgroup of the population, a transmissible vaccine with transmission coefficients positively correlated with those of the pathogen is the best option. We have shown this to be the case for a population of deer mice, where the pathogen maintains an R_0 greater than one in only the males (see Appendix: SNV Invasion in Deer Mice). Since many pathogens in wildlife populations have relatively low R_0 values [18], this suggests that the optimal transmissible vaccine will generally be one designed to mirror the transmission patterns of the target pathogen. If, however, the subgroups of the target population maintain local R_0 values greater than one, there are scenarios where it would be best to design a transmissible vaccine with patterns of transmission opposite to those of the pathogen.

Including heterogeneity in host transmission in epidemiological models generally inflates the global R_0 of an infectious agent [15]. Therefore, intuition suggests that a transmissible vaccine would benefit from heterogeneity in host transmission because the vaccine would spread through high transmission pathways in the population, effectively vaccinating more susceptible individuals than in a population with homogeneous transmission. Indeed, this intuition holds for another transmissible therapy known as TIPs, where high transmission individuals are autonomously targeted in the population [13]. However, we have demonstrated that this result does not hold for a weakly transmissible vaccine targeting pathogens that are already present in the population. The reason for this stems from differences in the biology of the transmissible therapies. TIPs maintain the ability to autonomously target high transmission individuals because TIP transmission is facilitated by co-infection with the targeted pathogen. Conversely, a transmissible vaccine competes with the wild-type pathogen for susceptible hosts. Therefore, the realized boost in R_0 that a transmissible vaccine experiences from host heterogeneity is neutralized by a proportional boost in the pathogen R_0 .

Although our model yields insights into the performance of transmissible vaccines in heterogeneous populations, it could be extended in numerous ways. For instance, our model assumes that vaccination can target only susceptible individuals, whereas wildlife vaccination programs often rely on distributing vaccine laced baits that target only those individuals who actively forage. Additionally, our model assumes that recovery rates from vaccine and pathogen infection are equal. This may be a reasonable assumption for an attenuated transmissible vaccine, but may not hold for an engineered recombinant vector vaccine [17]. Generalizing our model to these alternative scenarios is an important focus for future work, particularly as parameter estimates become available for transmissible vaccines now under development [7,21].

Upon further development of transmissible vaccines, we will gain better insight into the manufacturing process, and the cost to produce such vaccines. If transmissible vaccines can be produced at a comparable cost to traditional vaccines, however, they will greatly reduce the cost of a wildlife vaccination campaigns. Our model analyses demonstrate this point by showing how vaccine transmission between individuals can greatly reduce the threshold vaccination rate required for prophylaxis or a desired level of pathogen reduction. Even if transmissible vaccines cost more than traditional vaccines, our models suggest they may still be more cost effective, although this will depend largely on the epidemiological details of the target pathogen and the transmission rate of the transmissible vaccine.

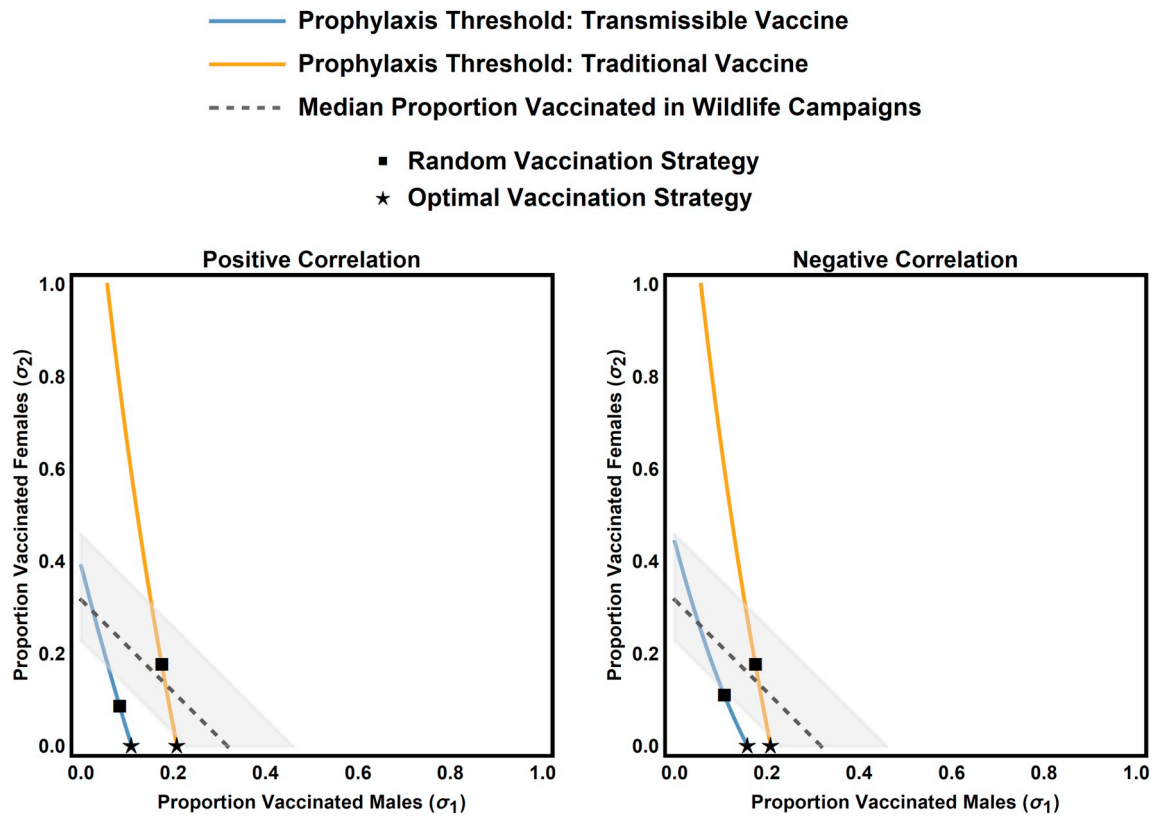


Fig. 5. Proportion of male/female deer mice that must be vaccinated for prophylaxis against Sin Nombre Virus. The pathogen maintains a global $R_{0,w} = 1.21$, and two possible vaccine designs maintaining a global $R_{0,v} = 0.61$. The gray region provides a reference for typical values of the proportion of individuals successfully vaccinated in a wildlife vaccination campaign (see Appendix: SNV Invasion in Deer Mice). Fractional reduction in vaccination effort provided by a transmissible vaccine (left to right): a.) Optimal strat. = 0.47, Random strat. = 0.52 b.) Optimal strat. = 0.24, Random strat. = 0.38. Parameters: a.) $R_{0,v,1,1} = 0.53$, $R_{0,v,2,2} = 0.18$, $R_{0,v,1,2} = 0.18$, $R_{0,v,2,1} = 0.18$, $R_{0,w,1,1} = 1.06$, $R_{0,w,2,2} = 0.36$, $R_{0,w,1,2} = 0.36$, $R_{0,w,2,1} = 0.36$ b.) $R_{0,v,1,1} = 0.18$, $R_{0,v,2,2} = 0.53$, $R_{0,v,1,2} = 0.18$, $R_{0,v,2,1} = 0.18$, $R_{0,w,1,1} = 1.06$, $R_{0,w,2,2} = 0.36$, $R_{0,w,1,2} = 0.36$, $R_{0,w,2,1} = 0.36$.

5. Conclusion

Although a transmissible vaccine does not receive a significant boost in performance due to host heterogeneity, our analyses indicate that they can still be an effective tool for reducing pathogen prevalence and preventing pathogen invasion in wildlife populations. Our models indicate that vaccine transmission significantly reduces the threshold of vaccination effort required to prevent pathogen spread in heterogeneous wildlife populations. When these thresholds cannot be met, vaccine transmission greatly reduces pathogen prevalence in a heterogeneous population. Together, our analyses provide support for the continued development of transmissible vaccines to control zoonoses in wildlife reservoirs.

Author contributions

T.J.V., A.J.B., C.H.R., and S.L.N. conceived of the study; T.J.V.

performed model analyses; T.J.V., A.J.B., C.H.R. and S.L.N. helped draft the manuscript. All authors gave final approval for publication.

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Declarations of interest

Declarations of interest: none.

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Appendix A

This section elaborates on the methods used to evaluate the benefit of a transmissible vaccine in a population with heterogeneity in transmission. First, we find the level of direct vaccination required to prevent pathogen invasion, and use the resulting expression to define a benefit of vaccine transmission. Next, we analyze the case where pathogen invasion cannot be prevented, and instead evaluate a transmissible vaccine's ability to reduce a pathogen's prevalence in the host population. Finally, we parameterize our model to Sin Nombre virus in Deer mice, a wildlife system that has been documented to experience heterogeneity in transmission, to assess the effectiveness of a transmissible vaccine in a real-world scenario. As described by Section 2 in the main text, we developed a system of differential equations to describe the population dynamics of a transmissible vaccine in a heterogeneous population:

$$\begin{aligned}
 \frac{dS_i}{dt} &= b_i(1 - \sigma_i) - dS_i - \sum_{j=1}^2 (\beta_{v,i,j}S_iV_j + \beta_{w,i,j}S_iW_j) \\
 \frac{dV_i}{dt} &= b_i\sigma_i - (\gamma + d)V_i + \sum_{j=1}^2 \beta_{v,i,j}S_iV_j \\
 \frac{dW_i}{dt} &= -(\gamma + d)W_i + \sum_{j=1}^2 \beta_{w,i,j}S_iW_j \\
 \frac{dR}{dt} &= -dR + \sum_{j=1}^2 (\gamma V_j + \gamma W_j)
 \end{aligned} \tag{1}$$

We first non-dimensionalize Eq. (1) to reduce the number of parameters. We scale each state variable by the steady state carrying capacity of the corresponding subgroup, $\frac{b_i}{d}$, so that $s_i = S_i / (\frac{b_i}{d})$, $v_i = V_i / (\frac{b_i}{d})$, and $w_i = W_i / (\frac{b_i}{d})$. We introduce non-dimensional basic reproduction numbers that describe the spread of the pathogen and vaccine between each pair of population subgroups; $R_{0,w,i,j} = \frac{\beta_{w,i,j}b_j}{d(d+\gamma)}$ describes the average number of secondary infections in subgroup i caused by an infected individual dropped into subgroup j . We also define a new non-dimensional parameter $\hat{d} = \frac{d}{d+\gamma}$ that gives the probability of death before recovery of an infected individual. Substituting these new parameters and state variables into Eq. (1) yields the non-dimensionalized system:

$$\begin{aligned}
 \frac{ds_i}{dt} &= \hat{d}(1 - s_i - \sigma_i) - \sum_{j=1}^2 R_{0,w,i,j}s_iw_j - \sum_{j=1}^2 R_{0,v,i,j}s_iv_j \\
 \frac{dw_i}{dt} &= -w_i + \sum_{j=1}^2 R_{0,w,i,j}s_iw_j \\
 \frac{dv_i}{dt} &= -v_i + \hat{d}\sigma_i + \sum_{j=1}^2 R_{0,v,i,j}s_iv_j
 \end{aligned} \tag{2}$$

A.1. Pathogen prophylaxis

Preemptively vaccinating wildlife populations prior to the introduction of a pathogen threat can prevent the pathogen's invasion into the population and therefore reduce the chance of spillover into human populations [7]. To assess the utility of a transmissible vaccine in preventing pathogen invasion into a wildlife population, we first identify the vaccination thresholds required to prevent pathogen invasion for both a traditional and transmissible vaccine. We identify two relevant vaccination strategies, and then measure the benefit provided by vaccine transmission under each strategy. The first strategy, random vaccination, describes a scenario where vaccines are distributed evenly between subgroups so that $\sigma_1 = \sigma_2 = \sigma$. The second vaccine distribution strategy, optimal vaccination, describes a scenario where the vaccine can be preferentially disseminated to the subgroups in a way that minimizes the total vaccine distribution rate $\hat{d}(\sigma_1 + \sigma_2)$ across all possible vaccination strategies along the prophylaxis threshold. For both vaccination strategies and for each parameter set, we define the benefit of vaccine transmission (B), as the proportional reduction in the total vaccine distribution rate that results from a transmissible vaccine:

$$B = \left(1 - \frac{\sigma_{TV}}{\sigma_{NTV}} \right) \tag{3}$$

here, σ_{TV} is the prophylaxis vaccination effort when using a transmissible vaccine, and σ_{NTV} is the prophylaxis vaccination effort when using a non-transmissible vaccine.

To derive vaccination thresholds that prevent pathogen invasion, we calculate the pathogen's global basic reproductive number $R_{0,w}$ using the Next Generation Matrix (NGM) method [22]. Briefly, the NGM is a matrix whose elements describe the number of new infections of each type that are produced by each type of infected individual. The $R_{0,w}$ is calculated as the spectral radius of the NGM. In Eq. (2), the infectious subsystem is

$$\begin{aligned}
 \frac{dw_1}{dt} &= -w_1 + R_{0,w,1,1}s_1w_1 + R_{0,w,1,2}s_1w_2 \\
 \frac{dw_2}{dt} &= -w_2 + R_{0,w,2,1}s_2w_1 + R_{0,w,2,2}s_2w_2.
 \end{aligned} \tag{4}$$

We linearize around the steady-state that describes the vaccinated host population in the absence of the pathogen. Defining the perturbation from steady state as $\tilde{w} = (\tilde{w}_1, \tilde{w}_2)$, the linearized subsystem can be written in matrix form,

$$\dot{\tilde{w}} = J\tilde{w} \tag{5}$$

where, J is the 2×2 Jacobian of the infectious subsystem (4) evaluated at the relevant pathogen-free equilibrium:

$$J = \begin{bmatrix} R_{0,w,1,1}s_1^* - 1 & R_{0,w,1,2}s_1^* \\ R_{0,w,2,1}s_2^* & R_{0,w,2,2}s_2^* - 1 \end{bmatrix}. \tag{6}$$

Next, we decompose the matrix components of J as the sum of two matrices, $J = T_w + \Sigma_w$. Here T_w contains terms from J that describe the production of new infected individuals within each subgroup:

$$T_w = \begin{bmatrix} s_1^*R_{0,w,1,1} & s_1^*R_{0,w,1,2} \\ s_2^*R_{0,w,2,1} & s_2^*R_{0,w,2,2} \end{bmatrix}. \tag{7}$$

Specifically, element (i,j) of T_w describes the rate at which new infected hosts in subgroup i arise due to pathogen-infected individuals in subgroup j . The matrix Σ_w describes the rates at which hosts leave each infectious state, due to either death or recovery:

$$\Sigma_w = \begin{bmatrix} -1 & 0 \\ 0 & -1 \end{bmatrix}. \tag{8}$$

From T_w and Σ_w , the NGM with large domain is calculated as

$$\begin{aligned}
K_L &= -\Sigma_w^{-1} \cdot T_w \\
&= \begin{bmatrix} S_1^* R_{0,w,1,1} & S_2^* R_{0,w,2,1} \\ S_1^* R_{0,w,1,2} & S_2^* R_{0,w,2,2} \end{bmatrix}
\end{aligned} \tag{9}$$

Element (i,j) of K_L gives the number of secondary infections of type i that are produced by an individual of infectious type j , throughout the course of infection. The pathogen R_0 is defined as the spectral radius of the NGM K_L :

$$R_{0,w} = \frac{1}{2} (\text{Tr}(K_L) + \sqrt{\text{Tr}(K_L)^2 - 4 \text{Det}(K_L)}), \tag{10}$$

where Tr and Det denote the trace and determinant, respectively. Eq. (10) gives the relationship between the number of susceptible individuals in each subgroup at the pathogen-free steady-state and the pathogen's ability to invade the population.

Prophylactic vaccination serves to reduce the steady state number of susceptible individuals s_1^* and s_2^* , and, if successful, reduces the pathogen's realized $R_{0,w}$ to a value less than one. To evaluate the pathogen's R_0 that results from a given direct vaccination effort, we numerically solve for the steady states of Eq. (2) with the pathogen absent (i.e. $w_1 = 0, w_2 = 0$). Specifically, we numerically integrate system (1) forward in time until the maximum magnitude of the differentials is less than 10^{-4} . Numerical solutions were found using the ParametricNDSolve and WhenEvent functions in Mathematica version 10.4.1.0, and the Mathematica code is available as a supplementary file.

With this method, we determine the minimal amount of direct vaccination effort, given by $\sigma_1 + \sigma_2$, that reduces the pathogen's $R_{0,w}$ to one for a non-transmissible vaccine. The benefit of vaccine transmission is measured as the fractional reduction in the amount of vaccination effort that is necessary to maintain the pathogen $R_{0,w}$ at one (Eq. (3)).

A.2. Endemic pathogen reduction

If it is impossible to vaccinate the population to an extent that precludes pathogen invasion, the pathogen will invade and persist in the population. In this case, the benefit of vaccine transmission can be assessed by the reduction in the pathogen's incidence that can be attributed to vaccine transmission. Naturally, the reduction due to vaccine transmission will depend on how the vaccine is distributed to the subgroups of the population. To clarify the effect of biasing direct vaccination effort between the two subgroups, we reparameterized the model in terms of the average fraction of newborns vaccinated, $\bar{\sigma} = \frac{1}{2}(\sigma_1 + \sigma_2)$, for the two subgroups of the population. Additionally, we define $\delta_\sigma = \sigma_1 - \sigma_2$, as the bias towards subgroup 1 of the vaccination strategy. For a fixed average vaccination level, we vary δ_σ to study how differentially targeting subgroups impacts the proportional reduction in pathogen incidence.

To calculate the reduction in pathogen incidence as a result of vaccine transmission, we numerically solve the system of differential Eq. (2) forward in time until steady state is reached, across a range of parameters that allow for pathogen persistence. We determine that the system has reached steady state once the maximum magnitude of the differentials is less than 10^{-4} . Next, we calculate the total number of pathogen-infected individuals in the aggregate population at steady-state that result when a non-transmissible vaccine is used, denoted w_0 . We then calculate the incidence that results when a transmissible vaccine is used, termed w_{iv} . From these quantities, we calculate the proportional reduction P in pathogen incidence, as a result of vaccine transmission:

$$P = \left(1 - \frac{w_{iv}}{w_0}\right). \tag{11}$$

A.3. SNV Invasion in Deer Mice

In this section, we parameterize our model to Sin Nombre virus (SNV), a type of Hantavirus that circulates in deer mice (*Peromyscus maniculatus*). When transmitted to human populations, SNV causes Hantavirus Pulmonary Syndrome (HPS), a deadly disease with a case fatality rate of about 40% [23,24]. Studies on SNV prevalence in deer mice show that the pathogen spreads between males and females at different rates, resulting in a higher prevalence among males than females [20]. It is hypothesized that this heterogeneity in prevalence is maintained by aggressive interactions between males that, in turn, facilitate pathogen transmission [19].

Due to the high mortality rate caused by SNV in human populations [24], non-transmissible vaccines that target SNV in deer mice have been developed and tested [25,26]; however, a widespread vaccination campaign has not yet been implemented. Here, we parameterize Eq. (2) to describe SNV transmission in an uninfected deer mouse population, and as before, quantify the benefit of using a transmissible vaccine to prevent the invasion of SNV. Here, the subgroups of our model allow us to track SNV infection among male (subgroup 1) and female (subgroup 2) deer mice. We use data on SNV prevalence in male and female deer mice, as reported in Adler, Clay, & Lehmer (2008), to parameterize a version of Eq. (2) that is specific to SNV when the vaccine is absent in the population. Because SNV infection is known to persist for the lifespan of deer mice [27], we set the recovery rate $\gamma = 0$, which, in the non-dimensional model is equivalent to setting $\hat{d} = 1$. The resulting equations describing the susceptible and infectious classes for each subgroup, s_i and w_i are:

$$\begin{aligned}
\frac{ds_1}{dt} &= 1 - s_1 - (R_{0,w,1,1} w_1 + R_{0,w,1,2} w_2) s_1 \\
\frac{ds_2}{dt} &= 1 - s_2 - (R_{0,w,2,1} w_1 + R_{0,w,2,2} w_2) s_2 \\
\frac{dw_1}{dt} &= (R_{0,w,1,1} s_1) w_1 + R_{0,w,1,2} s_1 w_2 - w_1 \\
\frac{dw_2}{dt} &= R_{0,w,2,1} s_2 w_1 + (R_{0,w,2,2} s_2) w_2 - w_2
\end{aligned} \tag{12}$$

When simulated to steady state, Eq. (12) predict the equilibrium prevalence of SNV in male and female deer mice as a function of the four non-dimensional parameters $R_{0,w,i,j}$. We use this relationship to find values of $R_{0,w,i,j}$ that produce similar prevalences of SNV in males and females reported in Adler, Clay, & Lehmer (2008). To further constrain the allowed values $R_{0,w,i,j}$, we assume that male-male interactions (interactions

between hosts of subgroup 1) are responsible for most of the SNV transmission in the population. As a consequence, $R_{0,w,1,1}$ is larger than $R_{0,w,1,2}$, $R_{0,w,2,1}$, and $R_{0,w,2,2}$. In addition, we assume that the rate of male-to-female, female-to-male, and female-to-female interactions are the same so that $R_{0,w,1,2} = R_{0,w,2,1} = R_{0,w,2,2}$. With these assumptions, we adjust the remaining two free parameters to match prevalence reported in Adler, Clay, & Lehmer (2008) yielding $R_{0,w,1,1} = 1.06$ and $R_{0,w,1,2} = R_{0,w,2,1} = R_{0,w,2,2} = 0.36$, resulting in predicted SNV prevalences of 0.19 (empirical: 0.19) in males, and 0.09 (empirical: 0.09) in females. To simplify the presentation of the terms $R_{0,w,i,j}$ we combine them into a matrix, $R_{0,w}$, defined as

$$R_{0,w} = \begin{pmatrix} 1.06 & 0.36 \\ 0.36 & 0.36 \end{pmatrix} \quad (13)$$

where entry (i,j) gives $R_{0,w,i,j}$.

The benefit of using a transmissible vaccine will clearly depend on the terms $R_{0,v,i,j}$. Because empirical research into transmissible vaccine designs is still in its infancy, it is not possible to use empirical data to parameterize the spread of the vaccine in the model. Instead, we assume that the average number of secondary infections per vaccine-infected host is half the average number of secondary infections per pathogen-infected host. In the supplementary Mathematica file, we show that this condition also implies that the global R_0 of the vaccine is half of the global R_0 of the pathogen. In addition to constraining the average amount of vaccine transmission in the population, we must also describe how the vaccine transmits between the various subgroups. We investigate two plausible vaccine behaviors, termed positive and negative correlation, that describe how the vaccine spreads relative to the biased spread of the pathogen. Values of the vaccine transmission matrix were selected to represent the most extreme scenarios of positive and negative correlation with the pathogen transmission matrix. The vaccine with positive correlation transmits the most within the subgroup that also spreads the pathogen best, so that

$$R_{0,v+} = \begin{pmatrix} 0.53 & 0.18 \\ 0.18 & 0.18 \end{pmatrix}. \quad (14)$$

Alternatively, the vaccine might be negatively correlated so that the pathogen spreads best in the subgroup with the least amount of within-group pathogen transmission, so that

$$R_{0,v-} = \begin{pmatrix} 0.18 & 0.18 \\ 0.18 & 0.53 \end{pmatrix}. \quad (15)$$

In our invasion analysis of SNV in a deer mouse population, we include a reference vaccination threshold of $(\sigma_1 + \sigma_2) = .317$, which is the median proportion of vaccinated individuals for rabies vaccination programs led by the USDA across multiple states, animal species, and years [28–32]. In addition to the median threshold, we include a shaded region that includes the 25th and 75th percentile of the vaccination data. We emphasize that, although vaccines targeting SNV in deer mice have been developed [26], a wide spread vaccination campaign has not been implemented. We understand that this data may not relate to vaccinating deer mice, and simply include this measure to show that wildlife vaccination campaigns are inherently limited in the fraction of individuals that can be vaccinated.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.onehlt.2019.100084>.

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