Vaccine 37 (2019) 1153–1159

Contents lists available at ScienceDirect

Vaccine

journal homepage: www.elsevier.com/locate/vaccine

Transmissible vaccines whose dissemination rates vary through time, with applications to wildlife

Mark W. Smithson [a], Andrew J. Basinki [b], Scott L. Nuismer [b,c], James J. Bull [d,e,f,*]

[a] School of Biological Sciences, Washington State University, Pullman, WA 99163, United States
[b] School of Mathematics, University of Idaho, Moscow, ID 83843, United States
[c] Department of Biological Sciences, University of Idaho, Moscow, ID 83843, United States
[d] Dept of Integrative Biology, University of Texas, Austin, TX 78712, United States
[e] Inst. Cellular and Molecular Biology, University of Texas, Austin, TX 78712, United States
[f] Center for Computational Biology and Bioinformatics, University of Texas, Austin, TX 78712, United States

ARTICLE INFO

Article history:
Received 10 March 2018
Received in revised form 27 December 2018
Accepted 9 January 2019
Available online 25 January 2019

Keywords:
Infectious vaccine
Gene therapy
Population dynamics

ABSTRACT

Transmission is a potential property of live viral vaccines that remains largely unexploited but may lie within the realm of many engineering designs. While likely unacceptable for vaccines of humans, transmission may be highly desirable for vaccines of wildlife, both to protect natural populations and also to limit zoonotic transmissions into humans. Defying intuition, transmission alone does not guarantee that a vaccine will perform well: the benefit of transmission over no transmission depends on and increases with the basic reproductive number of the vaccine, R_0. The R_0 of an infectious agent in a homogeneous population is typically considered to be a fixed number, but some evidence suggests that dissemination of transmissible vaccines may change through time. One obvious possibility is that transmission will be greater from hosts directly vaccinated than from hosts who acquire the vaccine passively, but other types of change might also accrue. Whenever transmission changes over time, the R_0 estimated from directly vaccinated hosts will not reflect the vaccine's long term impact. As there is no theory on the consequences of changing transmission rates for a vaccine, we derive conditions for a transmissible vaccine with varying transmission rates to protect a population from pathogen invasion. Being the first in the transmission chain, the R_0 from directly vaccinated hosts has a larger effect than those from later steps in the chain. This mathematical property reveals that a transmissible vaccine with low long term transmission may nonetheless realize a big impact if early transmission is high. Furthermore, there may be ways to artificially elevate early transmission, thereby achieving high herd immunity from transmission while ensuring that the vaccine will ultimately die out.

1. Introduction

Many viral vaccines consist of 'live' viruses that grow in the host with reduced capacity to cause disease. The growth is enough to trigger an immune response that protects against subsequent infection by the pathogen. Currently, live vaccines are delivered to each patient individually and directly. For some vaccines currently in use, however, there is a possibility of vaccine transmission from a vaccinated individual to a naive host. Transmission is so far an uncommon property of nearly all vaccines, but genetic engineering now enables the design of vaccines that might transmit well [1–3]. Vaccine transmission offers the benefit of increased vaccine coverage for a given level of direct vaccination, facilitating the attainment of population-wide herd immunity. If transmission is high enough, an entire population can be vaccinated with few direct vaccinations.

The concept of a transmissible vaccine is relatively new but parallels earlier proposals to suppress wildlife with engineered, immuncontraceptive viruses [4–7]. An immunocontraceptive virus infects a host and causes the host to build antibodies against specific reproductive proteins, thus sterilizing the host without otherwise harming it. By being transmissible (self-disseminating), a sterilizing virus might sustain itself with only occasional releases. The approaches of immunocontraceptive viruses and transmissible vaccines are united by use of engineered viruses that spread autonomously after being introduced, and in eliciting host immunity. The chief difference lies in their intended outcome: a reduction in the density of the host population, versus a reduction in the density of unvaccinated individuals in the host population.

* Corresponding author at: Dept of Integrative Biology, University of Texas, Austin, TX 78712, United States.
E-mail address: bull@austin.utexas.edu (J.J. Bull).

https://doi.org/10.1016/j.vaccine.2019.01.018
0264-410X/

Transmission means that the vaccine is delivered to some hosts passively through contacts mediated by normal social behavior. Such indirect vaccination is a possible concern with many human applications, but far less so in wildlife. Indeed, transmission of a wildlife vaccine opens the door for programs that might not otherwise be feasible, with transmission reaching individuals inaccessible for direct vaccination. Although wildlife vaccines were historically considered almost solely for the goal of immunocontraception, transmissible wildlife vaccines are gaining recognition as a possible intervention for human zoonoses [2]. Dog rabies, Ebola virus, and arenaviruses acquired from rodent reservoirs (e.g, Lassa fever) are just a few of the many zoonoses that might benefit from a transmissible wildlife vaccine [8–11].

The benefit conferred by a transmissible vaccine depends on how much it transmits, encapsulated in its basic reproduction number, R_0 (the average number of secondary infections caused by a single infection in a susceptible host population). Understandably, the few models that have included vaccine transmission assumed a constant R_0 [5–7,12,13]. Here, we relax that constraint (Fig. 1).

Vaccine transmission is a relatively new concept with few examples, so the possibility of transmission changing in time has scarcely been entertained. The oral polio vaccine (OPV) is perhaps the best documented case of vaccine transmission. Its transmission may stem from rapid vaccine evolution toward reduced attenuation, from which we would expect transmission to increase as it spreads. Other studies have reported or suggested transmission in the other direction, especially being greatest in those individuals that are directly vaccinated and lower from subsequent hosts. It is thus plausible that, for any vaccine that does transmit, the rate will vary across generations and that varying transmission might even be engineered deliberately. For example, a vaccine that transmits well in the short term but extinguishes itself in the long term might overcome many objections to its release. A first step is to identify the effect on disease suppression that is due to variation in vaccine transmission.

Here, we extend the existing theory of transmissible vaccines and immunocontraceptive vaccines [5–7,12,13] to explore vaccine transmission that changes with generation of infection. Our analysis is motivated by empirical studies showing vaccine transmission decreases with infection generation, but our model does not require changes in any particular direction. We first review those empirical studies and other reasons that suggest vaccine transmission may change over the course of transmissions. Then we develop a mathematical model to quantify how variable transmission modifies the estimated vaccination effort required to preemptively protect a pathogen-naive population. Lastly, we propose strategies that exploit varying transmission by manipulating directly vaccinated individuals.

2. Observations and arguments for changing transmission

2.1. Declining transmission of a rabbit vaccine

A naturally attenuated myxomavirus was engineered to express a capsid protein from rabbit hemorrhagic disease virus (RHDV). The resulting vaccine consisted of a fully competent and potentially transmissible myxomavirus with an additional antigenic cargo belonging to RHDV. The vaccine product was tested for its ability to immunize a caged rabbit population against both myxomavirus and RHDV. In three separate tests, directly vaccinated rabbits (DV) were housed with unvaccinated rabbits (UV-0). Two tests evaluated direct contact transmission, one evaluated flea-mediated transmission. The mode of direct vaccination was by inoculation in 2 of the studies, orally in the third. Transfer of the vaccine between rabbits was inferred by seroconversion of UV-0 rabbits, as well as challenge with either virus.

All three studies observed seroconversion of at least some unvaccinated (UV-0) rabbits: seroconversion occurred for approximately half of 24 UV-0 rabbits exposed to inoculated cage mates and for all 4 UV-0 rabbits whose cage mates were vaccinated orally. Seroconverted rabbits also survived challenge with lethal virus (either MV or RHDV). Two of the tests also evaluated second-generation transmission by co-housing the UV-0 unvaccinated rabbits, previously housed with directly vaccinated rabbits, with a new group of unvaccinated rabbits, termed UV-1. Only 2 of 24 UV-1 rabbits seroconverted, and both survived challenge. Thus, rabbits that were indirectly vaccinated by contact had lower transmission than directly vaccinated rabbits [1]. Vaccine transmission was also observed in a field trial, but the study was not set up to measure changes in transmission [14].

2.2. Declining transmission of a candidate virus for recombinant vector vaccines

Cytomegalovirus (CMV) is a herpesvirus that is common in mammals and holds promise as a vector for future recombinant vector vaccines (http://www.violinet.org/vaxvec/index.php). Despite being a widespread virus, individual strains of CMV are believed to be highly species specific, so that its use does not pose a threat of crossing species boundaries [15]. A mouse experiment conducted in semi-wild conditions tracked the spread of murine CMV (MCMV) in small groups of naive mice [16]. When MCMV was administered to approximately 25% of the population, over 80% of naive adults became infected. However, transmission to second and third generation offspring was significantly reduced. Though the mechanisms causing the observed reduction were not determined, this study nonetheless supports the existence of waning transmission.

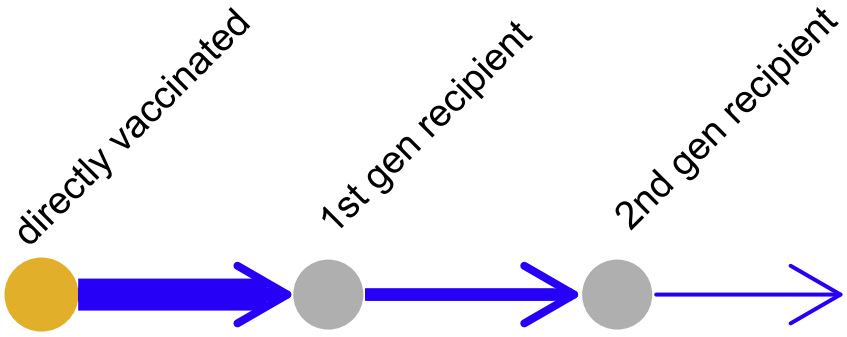

Fig. 1. Schematic of variable vaccine transmission in time. Hosts are represented by circles, transmission rates by blue arrows. Differing widths of arrows indicate different magnitudes of transmission with host 'generation number.' For illustration, directly vaccinated hosts (yellow circle) transmit the most; lower levels of vaccine transmission occur in the first host infected passively ('1st generation recipient'), still lower in the second host in the transmission chain (2nd generation recipient). Note that the model analyzed in the text addresses transmission changes in either direction, not just decreases.

2.3. Possible mechanisms for changing transmission

Dose and delivery. Perhaps the most obvious difference between directly and indirectly vaccinated hosts that may affect transmission lies in the dose and delivery of vaccine: direct vaccination can apply any dose that is necessary to generate an immune response, and the tissues of direct vaccination need not be those involved in vaccine transmission. An empirical study on the replication and transmission of an attenuated vaccine against infectious laryngotracheitis virus (ILT) in chickens found that higher vaccine doses were associated with increased protection and immunity [17]. In the study, flocks of chickens were inoculated with one of two doses of vaccine. The flock receiving the high dose was 100% immune for the first 5 weeks post-vaccination, and 50% immune at 31 weeks. In contrast, the low dose flock was 100% immune for the first 10 days but only 10% immune by week 10. Unvaccinated contacts were shown to seroconvert and be protected at moderate levels. The vaccine R_0 appears to have been considerably less than 1, as the ratio of directly vaccinated individuals to indirectly seroconverted individuals was less than 0.2. The effect of vaccine dose on transmission was not studied.

Evolution. Transmission might increase over time for some vaccines. Vaccine evolution is perhaps the most obvious reason for an increase, especially with attenuated designs. OPV is the best-documented example, in which the few attenuating mutations rapidly revert and the vaccine evolves back to a wild-type status [18]. We are unaware of studies specifically measuring changes in transmission rates across this evolution, but it is easily imagined that increased transmission would result from attenuation reversal. Recombinant vectored vaccines might also evolve to lose the antigenic cargo and thereby increase transmission rates [3], but that evolution would, in effect, actually decrease the rate at which effective vaccine is transmitted.

3. Methods

The central component of our study is a mathematical analysis. The model is of a standard type in epidemiology, an 'SIR' model using ordinary differential equations. It assumes an infinite population consisting of susceptible hosts, hosts infected with pathogen, hosts infected with vaccine, and recovered individuals (Fig. 2). The main differences from the standard, simple vaccine models are (i) individuals infected with vaccine can transmit the vaccine to susceptibles [as in 12], and (ii) the vaccine transmission rate depends on the number of hosts through which the vaccine has been transmitted since the directly vaccinated host (the 'host generation' number). To accommodate changing transmission rates with generation number, a separate category is needed for each generation of vaccine-infected hosts (Fig. 2).

Using a superior dot to indicate a derivative with respect to time,

$$\begin{aligned}
\dot{S} &= b(1-\sigma) - \beta_W SW - S\sum_{i=0}\beta_i I_i - dS \qquad (1)\\
\dot{W} &= \beta_W SW - \delta_W W - (d+x)W\\
\dot{I}_0 &= b\sigma - \delta_I I_0 - dI_0\\
\dot{I}_1 &= \beta_0 I_0 S - \delta_I I_1 - dI_1\\
\dot{I}_2 &= \beta_1 I_1 S - \delta_I I_2 - dI_2\\
&\vdots\\
\dot{Z} &= \delta_W W + \sum_{i=0}\delta_I I_i - dZ,
\end{aligned}$$

with notation in Table 1. $R_{0,W}$ is the basic reproductive number of the pathogen, and $R_{0,i}$ is the basic reproductive number of the vaccine in generation i,

$$R_{0,i} = \frac{\beta_i}{\delta_I + d}\left(\frac{b}{d}\right), \qquad (2)$$

where b/d is the equilibrium density of susceptible hosts in the absence of the pathogen and vaccine. This is the standard definition for basic reproductive number, but in our case, it applies to a specific generation number, i.

The analysis of this model consists of finding the equilibrium when the population lacks the pathogen, with the vaccine being introduced at a constant rate (σ). Then, with the pathogen introduced at low density (small W), the value of σ is found that

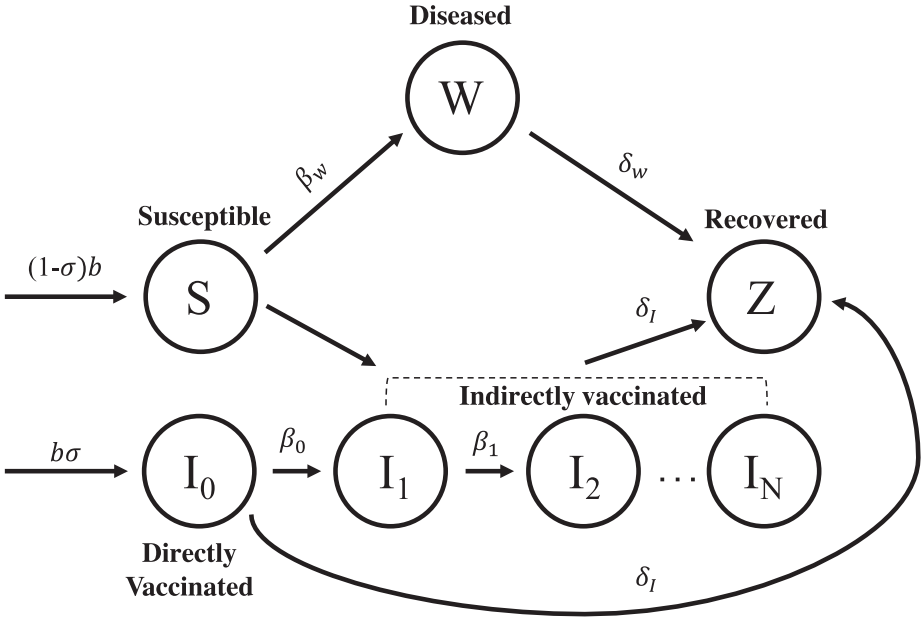

Fig. 2. Flow diagram of the model with susceptible (S), pathogen infected (W), directly vaccinated (I_0), indirectly vaccinated ($I_1 - I_N$), and recovered hosts (Z). The difference from standard SIR models for a transmissible vaccine is the inclusion of multiple classes of vaccine-infected hosts, each defined by its 'age' class and each with a possibly different transmission parameter (β_i). Death rate arrows are not shown.

Table 1
Model variables and parameters.

Notation	Description
Variables (time t)	
$S(t)$	density of susceptible hosts
$W(t)$	density of pathogen (wild-type) infected hosts
$I_0(t)$	density of manually vaccinated hosts
$I_i(t)$	density of hosts receiving vaccine by transmission ($i > 0$)
$Z(t)$	density of recovered hosts (lifetime immunity)
Parameters	
β	transmission rate (subscripted accordingly)
δ	rate of recovery (subscripted accordingly)
b	births added to population per time unit
σ	fraction of newborns manually vaccinated
d	death rate
x	increased death rate due to infection with pathogen

is minimally sufficient to prevent the pathogen from increasing (pathogen 'prophylaxis'). The threshold σ for blocking pathogen invasion can be written in terms of the vaccine and pathogen R_0 values, as given below.

4. Results

To understand the implications of vaccine transmission that varies in time, we assign unique vaccine transmission rates to each infection generation. The generation number is the number of hosts through which the ancestry of a vaccine genome can be traced, starting with the host receiving the vaccine directly. Generation number is specific to the individual vaccine genome being considered and is not synchronous across the vaccine population: at any point in time, two different vaccine genomes from the same vaccine introduction may have different generation numbers because they had different infection histories.

4.1. Visualizing the spread of an agent whose properties change with generation number

The spread of an infectious agent is similar to a population growth process, where the rate of growth is determined by the relative rates of births and deaths. For an infectious agent, a fundamental property of its growth process is encapsulated in the basic reproduction number, R_0. For any infectious agent (henceforth 'virus'), R_0 is the average number of new infections that are established over the lifetime of a single infection that occurs in a completely susceptible population. In the absence of interfering infections, the initial spread of the infectious agent is a geometric process, one infected individual giving rise to R_0 secondary infections, each of those themselves infecting R_0, and so on. Thus, there is a progression from 1 infection resulting from direct vaccination to R_0 secondary infections. This pattern continues with R_0^2, R_0^3, etc. infections until the decrease in density of susceptible individuals begins to block subsequent infections. This progression is not synchronous with generation number (e.g., the R_0^2 infections are not all happening at the same time). However, this progression captures the increase in infected individuals, and the contribution of each 'generation' of infection.

When the infection properties change with generation of the infection – first host, second host, etc., the progression is equally easy to calculate. The single infected individual in generation 0 gives rise to $R_{0,1}$ new infections, where the subscript $_1$ indicates the first generation. The number of second-generation infections is thus $R_{0,1}R_{0,2}$, with $R_{0,2}$ possibly being different than $R_{0,1}$. Assuming, as before, that the infectious agent is rare and the density of susceptible individuals is large, the accumulated number of current and past infections approximately obeys

$$1 + R_{0,1} + R_{0,1}R_{0,2} + R_{0,1}R_{0,2}R_{0,3} + \ldots. \tag{3}$$

The reproductive number with the biggest multiplicative impact in this sum is $R_{0,1}$, with $R_{0,2}$ next, and so on. Any $R_{0,i} = 0$ ends the progression. This progression is useful for intuition, but its utility for other purposes is limited. We thus turn to a formal model of transmission.

4.2. Blocking pathogen invasion when vaccine transmission varies with generation number

We use the model introduced in (1) to derive conditions for which a transmissible vaccine can prevent the spread of a pathogen in a pathogen-naive population, termed pathogen prophylaxis. We can express conditions necessary for pathogen prophylaxis in terms of the vaccine and pathogen basic reproduction numbers. Using notation from above, and as derived in the Appendix, the vaccine level sufficient to keep the pathogen from invading is

$$\sigma_{crit} > \left(\frac{1}{1 + \frac{R_{0,1}}{R_{0,W}} + \frac{R_{0,1}}{R_{0,W}}\frac{R_{0,2}}{R_{0,W}} + \frac{R_{0,1}}{R_{0,W}}\frac{R_{0,2}}{R_{0,W}}\frac{R_{0,3}}{R_{0,W}} + \ldots}\right)\left(1 - \frac{1}{R_{0,W}}\right) \tag{4}$$

The rightmost term in parentheses is the standard eradication threshold for a non-transmissible vaccine. The parenthetical term to its left is a reduction due to vaccine transmission. Its form is reminiscent of the expression in (3), except that each of the vaccine $R_{0,i}$ terms is discounted by the pathogen $R_{0,W}$. The series in the denominator converges if $R_{0,i}$ is zero for some particular vaccine-infected class, or, if $R_{0,i} > 0$ for all vaccine-infected classes, when the limit of $R_{0,i}$ is less than $R_{0,W}$: $\lim_{i\to\infty} R_{0,i} < R_{0,W}$. Although our proof (Appendix) is formally one of pathogen prophylaxis, we conjecture that result (4) is also the eradication condition. Indeed, if the $R_{0,i}$ are constant (with constant parameters) for all i, with $R_{0,i} < R_{0,W}$, this result equals the eradication condition [12]. Finally, if $\lim_{i\to\infty} R_{0,i} > R_{0,W}$, the spread of the vaccine eliminates the pathogen, without requiring any direct vaccination (σ_{crit} = 0). In this case, the vaccine is a superior competitor and eliminates with a single introduction.

An interpretation of this result is that, at the prophylaxis threshold, every vaccine transmission is the equivalent of an extra direct vaccination, discounted (or inflated) by how much (little) the pathogen would spread over the same number of generations. Discounting is understandable in that a direct vaccination occurs at birth, whereas transmissions are occurring at later times that allow greater pathogen spread. Less obvious is why the discounting is based on R_0 values, as pathogen and vaccine might spread at different rates (and R_0 is not a per-time measure). We conjecture that the scaling is generation-dependent but not time-dependent because the result applies at dynamic equilibrium, at which time drops out. Inequality (4) shows that, for variable $R_{0,i}$, the first generation of transmission will likely have the largest effect on σ_{crit}, as it multiplies each of the remaining reproductive numbers in subsequent generations.

From Eq. (4) the impact of early transmission can be profound, even if the transmission chains last only a few steps. Assuming that all transmission chains progress only 1 step beyond directly vaccinated hosts, an $R_{0,1}$ that equals that of the pathogen cuts the usual (non-transmissible) vaccination effort in half; if double the pathogen $R_{0,W}$, the vaccination effort is down to a third of that required for a non-transmissible vaccine. Fig. 3 compares the effect of generation-1 transmission alone ($R_{0,i}/R_{0,W}$) to constant transmission ($R_{0,V}/R_{0,W}$): generation-1 transmission that equals that of the

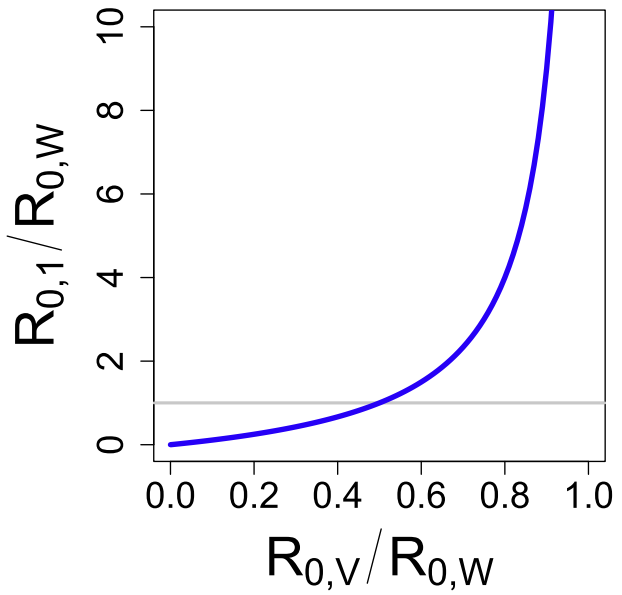

Fig. 3. From Eq. (4), the blue curve shows the level of vaccine transmission for the first generation only ($R_{0,1}/R_{0,W}$) required to have the same effect on pathogen suppression as fixed vaccine transmission at a constant rate over all generations ($R_{0,V}/R_{0,W}$). As $R_{0,V}/R_{0,W}$ approaches 1, the constant-rate vaccine comes ever closer to being able to suppress pathogen invasion without ongoing direct vaccination, hence ever greater values of generation-1 transmission alone are required to achieve the same effect. The horizontal gray line is at $R_{0,1}/R_{0,W} = 1$, at which vaccine transmission in generation 1 matches that of the pathogen; this level of generation-1 transmission has the same benefit as a fixed vaccine transmission at half the level of the pathogen.

pathogen has the same effect as constant transmission at half the pathogen level.

5. Discussion

Transmissible vaccines are still not mainstream, but the revolution in genome engineering poises them to become so [2,3]. Efforts over the last 2–3 decades to develop sterilizing vaccines in wildlife have provided a foundation for transmissible vaccine research. It is now evident that transmissible vaccines offer fundamentally new possibilities for controlling wildlife diseases, especially in blocking zoonotic invasions of humans (e.g., Ebola, Lassa fever, dog rabies), and even possibly for some human vaccines. At this stage, there is much to be discovered about how to maximize their impact while avoiding possible downsides, especially vaccine evolution.

In this study, we investigated the consequences of a transmissible vaccine that disseminates at different rates as it moves into the host population. Though empirical evidence is limited, several studies of transmissible vaccines suggest that transmission rates are higher from directly vaccinated individuals than from those acquiring the vaccine passively. We analyzed an SIR model that allows for any combination of changing transmission rates. Early transmission rates have a disproportionate effect on vaccine utility, so any later reductions in transmissions are somewhat mitigated. Indeed, vaccines whose early transmissions can be elevated but whose later transmission assures eventual extinction may help allay concerns about evolution and escape of a transmissible vaccine.

5.1. Manipulations to enhance early transmission

Understanding how temporally varying transmission impinges on eradication opens new possibilities for the management of vaccine design or delivery that are not options for vaccines with constant properties. The generation with the biggest impact is that of directly vaccinated individuals. That result suggests the possibility of manipulating or choosing directly vaccinated hosts to modify transmission – up or down. The fact that the directly vaccinated hosts will often be in hand enables many possible types of manipulations (Table 2). These modifications are likely to affect transmission in ways that do not carry over to hosts acquiring the vaccine by transmission. Implementation will likely be specific to the vaccine and possibly the host species. Some strategies are suitable only for use in non-humans, as they involve higher risk to those manually vaccinated.

When considering these manipulations, it should be appreciated that the model in (1) imposes direct vaccination on newborns. Many of the manipulations proposed below might well be applied to newborns, but many may also work on adults or only on adults. For various reasons, direct vaccination of adults may have a lesser impact than vaccination of newborns [21]. The result in (4) also raises the possibility of choosing the alternatives of maximizing the number of hosts directly vaccinated (σ in the formula) versus the impact of those hosts on spreading the infection ($R_{0,i}$ in the formula). These choices raise several possibilities for maximizing vaccine efficacy.

5.2. Alternative population structures

The assumption of mass action in the SIR model is mathematically convenient, but other epidemiological processes warrant consideration. Most obviously, contact rates may not be uniform. Asymmetry in contact rates among individuals provides a subtle but powerful benefit to a transmissible vaccine: the contacts of randomly chosen individuals tend to be skewed towards hosts with higher-than average contact rates [22–24]. This type of asymmetry means that a transmissible vaccine will be disproportionately transmitted to individuals that are most likely to spread a disease (i.e., superspreaders), and thus will have a greater impact in blocking viral infection than under mass action [see also 25]. This result assumes the vaccine is introduced before the pathogen, otherwise a significant fraction of superspreaders might already be

Table 2
Manipulations to enhance early transmission

Manipulation	Explanation
Vaccine dose	For individuals vaccinated directly, transmission may be manipulated by controlling the dose of vaccine or the tissue of delivery. A low dose can amplify into a high dose [e.g., 19], so any effect will need to be established empirically.
Host physiology	Hormones might be administered to alter behavior in ways favorable to vaccine spread. Immune suppressants, such as routinely given to animals in experiments, may allow the vaccine to avoid clearance longer and thus transmit longer and at an elevated level.
Choice of host	Hosts with particular immune defects may transmit longer than others; hosts with many contacts may transmit to more individuals; some age classes may have higher levels of susceptibility than others.
Choice of vector	Recombinant vector vaccines may be more easily chosen to be transmissible than are attenuated vaccines [3], but transmission is not the only relevant factor. The immune response may be weaker to vectored vaccines than to attenuated ones [20], and prevailing herd immunity to the vector may interfere [13]. Some vectors may experience little herd immunity, as proposed for CMV [2].

immune to, and hence unable to transmit, the vaccine. In the context of epidemiological networks, this process has been modeled as a process of vaccinating 'acquaintances' of randomly chosen individuals [23]. The qualitative result appears to generalize across several forms of contact asymmetry: a vaccine that transmits even one generation beyond those directly vaccinated will disproportionately hit superspreaders (highly connected nodes).

6. Conclusions

The R_0 of a transmissible vaccine is a measure of that vaccine's ability to spread beyond direct vaccinations. However, the R_0 for a transmissible vaccine may assume different values as it spreads beyond direct vaccinations, and the R_0 measured from individuals directly vaccinated may often overestimate the values further down transmission chains. The R_0 from directly vaccinated hosts has the largest impact of any R_0 over the chain of transmissions, and there are several possible means to inflate that stage of transmission and thereby augment the overall impact of vaccine transmission. Thus, a 'safe' strategy is suggested in the form of enhancing early transmission for a vaccine whose long term transmission is low enough to ensure its ultimate loss from the population.

Conflict of interest

The authors declared that there is no conflict of interest.

Acknowledgments

We thank Spencer Fox for insight about network models. Two anonymous reviewers helped us clarify the ms. Some figures were generated in R [26]. Supported by NIH GM 122079.

Appendix A

We offer a formal proof of the result in (4). Suppose a simple n-step vaccine model defined with 1 susceptible class and n + 1 infected classes that recover and die at rates δ and d respectively.

For the purposes of this derivation, the class of recovered individuals (Z in model (1)) is irrelevant. Pathogen-infected individuals (W) will be assumed rare and are also neglected for now.We begin by deriving the equilibrium state for a population consisting of just susceptible and vaccine-infected individuals. Equilibrium for susceptibles requires

$$0 = b(1-\sigma) - S\sum_{i=0}^{n}\beta_i I_i - dS \tag{A.1}$$

$$S = \frac{b(1-\sigma)}{d + \sum_{i=0}^{n}\beta_i I_i} \tag{A.2}$$

To find the steady-state incidence in the infected classes, set the left hand side (LHS) of equations $\dot{I_0}, \dot{I_1}, \dot{I_2}, \ldots, \dot{I_{i+1}}$ to 0. Recursively solving for the I_i yields

$$I_0 = \frac{b\sigma}{\delta + d} \tag{A.3}$$

$$I_1 = \frac{\beta_0 S I_0}{\delta + d} = \left(\beta_0 S \frac{b\sigma}{(\delta+d)^2}\right) \tag{A.4}$$

$$I_2 = \frac{\beta_1 S I_1}{\delta + d} = \left(\beta_1 S\left(\beta_0 S \frac{b\sigma}{(\delta+d)^3}\right)\right) = \frac{S^2 b\sigma}{(\delta+d)^3}\beta_0\beta_1 \tag{A.5}$$

$$I_i = \frac{S^i\, b\sigma}{(\delta+d)^{i+1}}\prod_{j=0}^{i-1}\beta_j \tag{A.6}$$

We now derive the value of σ that reduces the steady state incidence of susceptibles to the highest value compatible with eradication. Protection against pathogen invasion ('prophylaxis') requires that the number of susceptibles be so low that the pathogen is always in decline. This condition is given in Eq. (1) when $\dot{W}$ is negative: $S\beta_W - \delta_W - d - x < 0$. This expression is easily rearranged as $S < \frac{\delta_W + d + x}{\beta_W}$. As the equilibrium value of S in a purely susceptible population is $\frac{b}{d}$, the pathogen $R_{0,W}$ can be written as $(\frac{b}{d})\frac{\beta_W}{\delta_W + d + x}$. Thus the threshold value of S for prophylaxis is equivalent to $\frac{b}{dR_{0,W}}$. Using that value of S in the expression A.2:

$$\frac{b}{d}\frac{1}{R_{0,W}} = \frac{b(1-\sigma)}{\sum_{i=0}^{n}\beta_i I_i + d} = \frac{b(1-\sigma)}{\sum_{i=0}^{n}\frac{\beta_i\left(\frac{b}{d}\frac{1}{R_{0,W}}\right)^i b\sigma}{(\delta+d)^{i+1}}\prod_{j=0}^{i-1}\beta_j + d} \tag{A.7}$$

Solving for σ,

$$\frac{b}{d}\frac{1}{R_{0,W}}\left(\sum_{i=0}^{n}\frac{\beta_i\left(\frac{b}{d}\frac{1}{R_{0,W}}\right)^i b\sigma}{(\delta+d)^{i+1}}\prod_{j=0}^{i-1}\beta_j + d\right) = b(1-\sigma) \tag{A.8}$$

$$\frac{1}{R_{0,W}}\sum_{i=0}^{n}\frac{\beta_i\left(\frac{b}{d}\frac{1}{R_{0,W}}\right)^i b\sigma}{(\delta+d)^{i+1}}\prod_{j=0}^{i-1}\beta_j + d\frac{1}{R_{0,W}} = d - d\sigma \tag{A.9}$$

$$\sigma\left(\frac{1}{R_{0,W}}\sum_{i=0}^{n}\frac{\beta_i\left(\frac{b}{d}\frac{1}{R_{0,W}}\right)^i b}{(\delta+d)^{i+1}}\prod_{j=0}^{i-1}\beta_j + d\right) = d\left(1 - \frac{1}{R_{0,W}}\right) \tag{A.10}$$

$$\sigma = \left(1 - \frac{1}{R_{0,W}}\right)\frac{1}{\left(\frac{1}{R_{0,W}}\sum_{i=0}^{n}\beta_i\frac{\left(\frac{b}{dR_{0,W}}\right)^i}{(\delta+d)^{i+1}}\frac{b}{d}\prod_{j=0}^{i-1}\beta_j + 1\right)} \tag{A.11}$$

$$\sigma = \left(1 - \frac{1}{R_{0,W}}\right)\frac{1}{\left(\sum_{i=0}^{n}\beta_i\left(\frac{b}{d(\delta+d)}\frac{1}{R_{0,W}}\right)^{i+1}\prod_{j=0}^{i-1}\beta_j + 1\right)} \tag{A.12}$$

Inserting β_i into the β product notation term,

$$\sigma = \left(1 - \frac{1}{R_{0,W}}\right)\frac{1}{\left(\sum_{i=0}^{n}\left(\frac{b}{d(\delta+d)}\frac{1}{R_{0,W}}\right)^{i+1}\prod_{j=0}^{i}\beta_j + 1\right)}. \tag{A.13}$$

The term

$$\left(\frac{b}{d(\delta+d)}\frac{1}{R_{0,W}}\right)^{i+1}\prod_{j=0}^{i}\beta_j \tag{A.14}$$

may be rewritten as $\frac{\left(\prod_{j=0}^{i}R_j\right)}{R_{0,W}^{i+1}}$, yielding the simplified result

$$\sigma = \left(1 - \frac{1}{R_{0,W}}\right)\frac{1}{\left(\sum_{i=0}^{n}\left(\frac{\prod_{j=0}^{i}R_j}{R_{0,W}^{i+1}}\right) + 1\right)}. \tag{A.15}$$

Below, we verify the convergence criterion for the infinite sum

$$1 + \frac{R_{0,1}}{R_{0,W}} + \frac{R_{0,1}}{R_{0,W}}\frac{R_{0,2}}{R_{0,W}} + \frac{R_{0,1}}{R_{0,W}}\frac{R_{0,1}}{R_{0,W}}\frac{R_{0,3}}{R_{0,W}} + \ldots \tag{A.16}$$

By the ratio test of series convergence, a series $\sum_{i=1}^{\infty}a_i$ converges if the absolute value of the ratio of consecutive terms limits to a number less than 1:

$$\lim_{i\to\infty}\left|\frac{a_{i+1}}{a_i}\right| < 1, \tag{A.17}$$

and diverges if the limit is greater than 1. For the sequence at hand, the ratio of consecutive terms i and $i+1$ is always positive and equal to $\frac{R_{0,i}}{R_{0,W}}$. Assuming the limit $\lim_{i\to\infty} R_{0,i}$ exists, convergence requires

$$\lim_{i\to\infty}\frac{R_{0,i}}{R_{0,W}} < 1. \tag{A.18}$$

For fixed $R_{0,W}$, this implies

$$\lim_{i\to\infty} R_{0,i} < R_{0,W}. \tag{A.19}$$

is required for convergence. A similar argument shows the series diverges to infinity if $\lim_{i\to\infty} R_{0,i} > R_{0,W}$.

References

[1] Bárcena J, Morales M, Vázquez B, Boga JA, Parra F, Lucientes J, et al. Horizontal transmissible protection against myxomatosis and rabbit hemorrhagic disease by using a recombinant myxoma virus. J Virol 2000;74(3):1114–23.

[2] Murphy AA, Redwood AJ, Jarvis MA. Self-disseminating vaccines for emerging infectious diseases. Expert Rev Vaccines 2016;15(1):31–9. https://doi.org/10.1586/14760584.2016.1106942.

[3] Bull JJ, Smithson MW, Nuismer SL. Transmissible viral vaccines. Trends Microbiol 2018;26(1):6–15. https://doi.org/10.1016/j.tim.2017.09.007.

[4] Tyndale-Biscoe CH. Virus-vectored immunocontraception of feral mammals. Reprod Fertil Dev 1994;6(3):281–7.

[5] Barlow ND. Predicting the effect of a novel vertebrate biocontrol agent: a model for viral-vectored immunocontraception of New Zealand possums. J Appl Ecol 1994;31(3):454–62. https://doi.org/10.2307/2404442. , <http://www.jstor.org.ezproxy.lib.utexas.edu/stable/2404442>.

[6] Barlow ND. Modelling immunocontraception in disseminating systems. Reprod Fertil Dev 1997;9(1):51–60.

[7] Hood GM, Chesson P, Pech RP. Biological control using sterilizing viruses: host suppression and competition between viruses in non- spatial models. J Appl Entomol 2000;37:914–25.

[8] Fooks AR, Banyard AC, Horton DL, Johnson N, McElhinney LM, Jackson AC. Current status of rabies and prospects for elimination. Lancet 2014;384(9951):1389–99.

[9] Rupprecht C, Hanlon C, Slate D. Oral vaccination of wildlife against rabies: opportunities and challenges in prevention and control. Dev Biol 2004;119:173–84.

[10] Wang Y, Li J, Hu Y, Liang Q, Wei M, Zhu F. Ebola vaccines in clinical trial: the promising candidates. Human Vaccines Immunotherapeutics 2017;13(1):153–68.

[11] Martinez-Sobrido L, de la Torre JC. Novel strategies for development of hemorrhagic fever arenavirus live-attenuated vaccines. Exp Rev Vaccines 2016;15(9):1113–21.

[12] Nuismer SL, Althouse BM, May R, Bull JJ, Stromberg SP, Antia R. Eradicating infectious disease using weakly transmissible vaccines. Proc Biol Sci 1841;283. https://doi.org/10.1098/rspb.2016.1903.

[13] Basinski AJ, Varrelman TJ, Smithson MW, May RH, Remien CH, Nuismer SL. Evaluating the promise of recombinant transmissible vaccines. Vaccine 2018;36(5):675–82. https://doi.org/10.1016/j.vaccine.2017.12.037.

[14] Torres JM, Sánchez C, Ramrez MA, Morales M, Bárcena J, Ferrer J, et al. First field trial of a transmissible recombinant vaccine against myxomatosis and rabbit hemorrhagic disease. Vaccine 2001;19(31):4536–43.

[15] Kim KS, Carp RI. Growth of murine cytomegalovirus in various cell lines. J Virol 1971;7(6):720–5.

[16] Farroway LN, Gorman S, Lawson MA, Harvey NL, Jones DA, Shellam GR, et al. Transmission of two Australian strains of murine cytomegalovirus (MCMV) in enclosure populations of house mice (Mus domesticus). Epidemiol Infect 2005;133(4):701–10.

[17] Hilbink FW, Oei HL, van Roozelaar DJ. Virulence of five live vaccines against avian infectious laryngotracheitis and their immunogenicity and spread after eyedrop or spray application. Vet Q 1987;9(3):215–25. https://doi.org/10.1080/01652176.1987.9694103.

[18] Georgescu MM, Balanant J, Macadam A, Otelea D, Combiescu M, Combiescu AA, et al. Evolution of the sabin type 1 poliovirus in humans: characterization of strains isolated from patients with vaccine-associated paralytic poliomyelitis. J Virol 1997;71(10):7758–68.

[19] Monath TP, Levenbook I, Soike K, Zhang ZX, Ratterree M, Draper K, et al. Chimeric yellow fever virus 17d-Japanese encephalitis virus vaccine: dose-response effectiveness and extended safety testing in rhesus monkeys. J Virol 2000;74(4):1742–51.

[20] Lauring AS, Jones JO, Andino R. Rationalizing the development of live attenuated virus vaccines. Nature Biotechnol 2010;28(6):573–9. https://doi.org/10.1038/nbt.1635.

[21] Keeling MJ, Rohani P. Modeling infectious diseases in humans and animals. Princeton University Press; 2008.

[22] Newman MEJ. Networks: an introduction. Oxford, New York: Oxford University Press; 2010.

[23] Cohen R, Havlin S, Ben-Avraham D. Efficient immunization strategies for computer networks and populations. Phys Rev Lett 2003;91(24):247901. https://doi.org/10.1103/PhysRevLett.91.247901.

[24] Pastor-Satorras R, Castellano C, Van Mieghem P, Vespignani A. Epidemic processes in complex networks. Rev Mod Phys 2015;87(3):925–79. https://doi.org/10.1103/RevModPhys.87.925. , <https://link.aps.org/doi/10.1103/RevModPhys.87.925>.

[25] Metzger VT, Lloyd-Smith JO, Weinberger LS. Autonomous targeting of infectious superspreaders using engineered transmissible therapies. PLoS Comput Biol 2011;7(3):e1002015. https://doi.org/10.1371/journal.pcbi.1002015.

[26] R Core Team. R: a language and environment for statistical computing. Vienna, Austria: R Foundation for Statistical Computing; 2017. URL <https://www.R-project.org/>.