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Evaluating the promise of recombinant transmissible vaccines

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ABSTRACT

Transmissible vaccines have the potential to revolutionize infectious disease control by reducing the vaccination effort required to protect a population against a disease. Recent efforts to develop transmissible vaccines focus on recombinant transmissible vaccine designs (RTVs) because they pose reduced risk if intra-host evolution causes the vaccine to revert to its vector form. However, the shared antigenicity of the vaccine and vector may confer vaccine-immunity to hosts infected with the vector, thwarting the ability of the vaccine to spread through the population. We build a mathematical model to test whether a RTV can facilitate disease management in instances where reversion is likely to introduce the vector into the population or when the vector organism is already established in the host population, and the vector and vaccine share perfect cross-immunity. Our results show that a RTV can autonomously eradicate a pathogen, or protect a population from pathogen invasion, when cross-immunity between vaccine and vector is absent. If cross-immunity between vaccine and vector exists, however, our results show that a RTV can substantially reduce the vaccination effort necessary to control or eradicate a pathogen only when continuously augmented with direct manual vaccination. These results demonstrate that estimating the extent of cross-immunity between vector and vaccine is a critical step in RTV design, and that herpesvirus vectors showing facile reinfection and weak cross-immunity are promising.

1. Introduction

Vaccines have had a wide range of positive impacts on the health of human and animal populations. In many cases, however, the full potential of vaccination cannot be realized because it is difficult or impossible to vaccinate a substantial proportion of the host population. Particularly challenging scenarios for efficient vaccine delivery include human diseases in regions with poorly developed public health infrastructure and diseases of wild animal populations. An important consequence of the challenges associated with vaccinating large proportions of wild animal populations is that we may be missing opportunities to eliminate or reduce reservoir populations of diseases that occasionally spill over into human populations (e.g., Ebola, Rabies; [1–5]), or that provide the raw material for full scale host shifts into the human population (e.g., SARS; [6]). This problem is particularly pressing in light of evidence suggesting that the incidence of such host-shifts is increasing due to the greater prevalence of humans in regions with high levels of wildlife diversity [7]. One promising new technology for dealing with the challenges associated with these difficult-to-immunize animal populations is the development of transmissible vaccines.

In the most general sense, transmissible vaccines are vaccines that can spread from one individual to the next, with the benefit being that for every individual that is immunized directly, additional individuals are immunized indirectly. One way in which a transmissible vaccine can be developed is through the process of attenuation [8]. Although attenuation can be accomplished in many ways, the goal in all cases is the transformation of the original viral disease into a benign yet transmissible vaccine. This approach has been used to develop transmissible vaccines both unintentionally, as with the oral polio vaccine [8,9], and intentionally, as with myxoma virus in rabbits [10–12]. However, there are limitations and risks associated with transmissible vaccines produced through attenuation. For instance, because attenuated vaccines are built from the pathogen itself, the ability of the vaccine to

Abbreviations: RTV, recombinant transmissible vaccine.

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spread between hosts is bounded by the transmissibility of the pathogen. More worrisome is the possibility of reversion to wild type virulence, as has been observed in the oral polio vaccine [9,13,14]. For this reason, and the constraints imposed by the process of attenuation itself, transmissible vaccines developed through attenuation will generally be only weakly transmissible. Despite these limitations, recent theoretical work has demonstrated that weakly transmissible attenuated vaccines could be highly effective tools, particularly against infectious diseases with relatively low transmission rates [15].

An alternative approach to designing a transmissible vaccine relies on recombinant genetic engineering rather than traditional attenuation. Specifically, rather than weakening the pathogen itself through a process of attenuation, recombinant transmissible vaccines (RTVs), also called transmissible recombinant vectored vaccines [16], are developed by inserting one or more pathogen genes with antigenic activity into the genome of a benign but transmissible vector organism. Infection with the modified vector, now termed the vaccine, exposes the host immune system to pathogen antigens and prompts a pathogen-specific immune response (Fig. 1). This approach has been used to develop a transmissible vaccine against Sin Nombre Virus within deer mice [17], and is now being used to develop a transmissible vaccine against Ebola within mice and nonhuman primate models [18,19].

In principle, RTVs offer several advantages over vaccines produced by attenuation. For instance, evolutionary reversion in a RTV is likely to produce the benign vector organism rather than the virulent pathogen itself. Also, because the transmission rate of the vaccine is related to the transmission rate of the vector rather than the pathogen, there are fewer limitations on the vaccine transmission rate. However, because a RTV necessarily integrates components of both disease and vector, it may struggle to spread through a host population where substantial cross-immunity to either the disease or vector already exists [20,21]. This reduction in effectiveness is important in cases where the vector organism is already present in the population, or where vaccine-reversion produces free vector. For these reasons, it is currently unclear whether RTVs that generate cross-immunity can serve as effective tools in the battle against infectious disease.

The limitations imposed by cross-immunity have focused research efforts on vectors thought to largely circumvent existing host immunity [4]. Cytomegalovirus (CMV), for example, is a type of herpesvirus that can evade an existing immune response, in part by down-regulating the presentation of MHC antigens [22,23]. RTV's that use CMV as a backbone are seemingly capable of re-infecting hosts that have had previous exposure to the vaccine, and superinfecting hosts with previous exposure to the CMV vector from which the vaccine was built [17,24]. These studies suggest that under natural conditions, CMV-based vaccines may experience little or no cross-immunity with the vector, and therefore largely escape the detrimental consequences of competition with the vector.

For RTVs in general, levels of cross-immunity are likely to lie somewhere between the extremes of perfect host exclusion, in

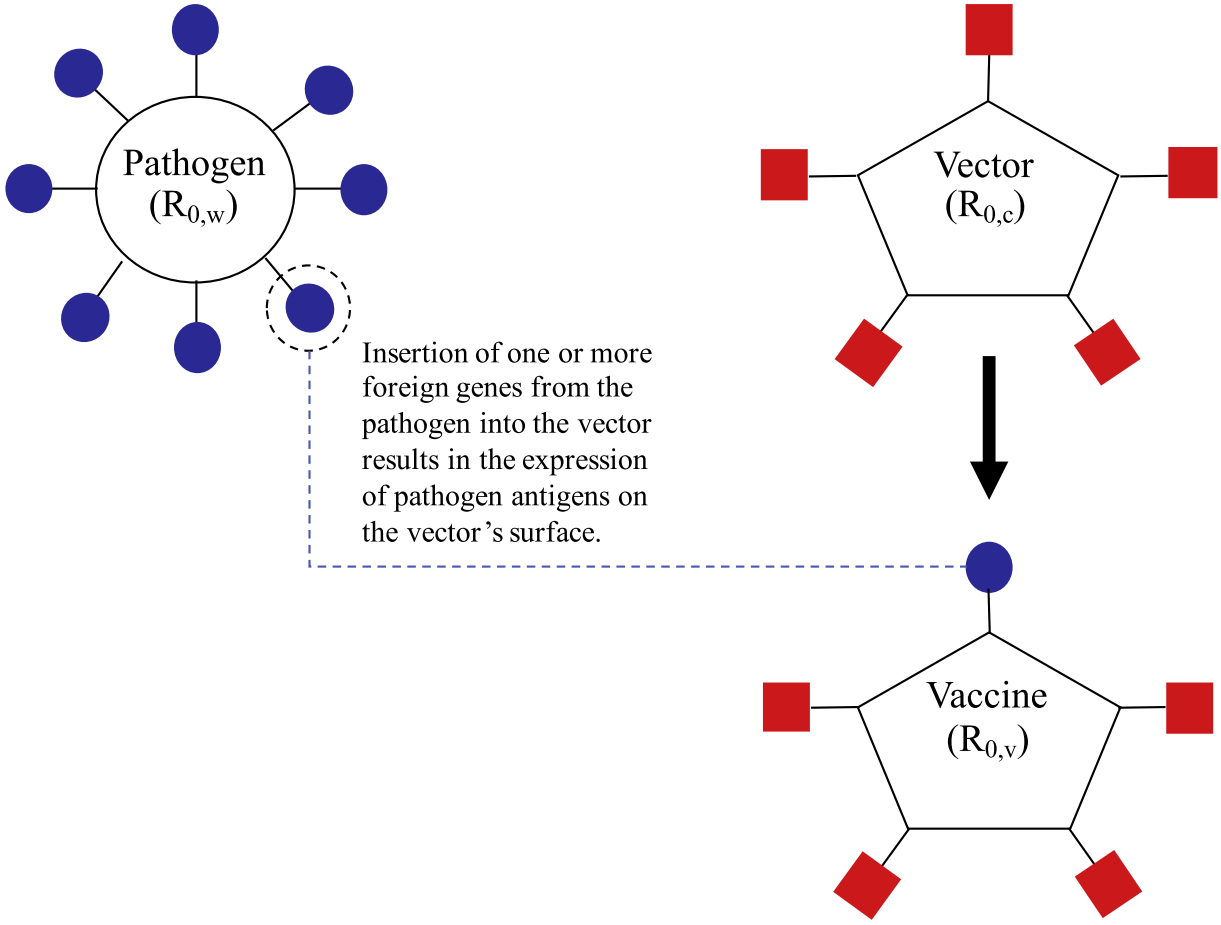

Fig. 1. Title: The design of a recombinant transmissible vaccine (RTV). **Description:** Pathogen genes are inserted into a benign vector organism, resulting in the expression of pathogen antigen(s) on the viral vector, now termed the vaccine. Infection with the vaccine exposes the host immune system to pathogen antigen(s), and prompts a pathogen-specific immune response. $R_{0,c}$, $R_{0,v}$, and $R_{0,w}$ represent the basic reproduction numbers of the vector, vaccine, and pathogen, respectively. Because the vaccine is produced by inserting non-beneficial foreign genes into the vector organism, the vaccine R_0 is likely bounded above by the vector's R_0 ($R_{0,v} < R_{0,c}$).

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