Behavioral incentives in a vaccination-dilemma setting with optional treatment

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Social dilemmas are situations wherein individuals choose between selfish interest and common good. One example of this is the vaccination dilemma, in which an individual who vaccinates at a cost protects not only himself but also others by helping maintain a common good called herd immunity. There is, however, a strong incentive to forgo vaccination, thus avoiding the associated cost, all the while enjoying the protection of herd immunity. To analyze behavioral incentives in a vaccination-dilemma setting in which an optional treatment is available to infected individuals, we combined epidemiological and game-theoretic methodologies by coupling a disease-spreading model with treatment and an evolutionary decision-making model. Extensive numerical simulations show that vaccine characteristics are more important in controlling the treatment adoption than the cost of treatment itself. The main effect of the latter is that expensive treatment incentivizes vaccination, which somewhat surprisingly comes at a little cost to society. More surprising is that the margin for a true synergy between vaccine and treatment in reducing the final epidemic size is very small. We furthermore find that society-centered decision making helps protect herd immunity relative to individual-centered decision making, but the latter may be better in establishing a novel vaccine. These results point to useful policy recommendations as well as to intriguing future research directions.

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I. INTRODUCTION

Vaccines are an effective means of combating infectious diseases that is largely responsible for worldwide successes against smallpox, polio, and tetanus. Even when they confer only transient immunity and/or their efficacy is far from perfect, as is in the case of influenza, vaccines produce a positive economic effect by keeping the society healthier [1]. Wide vaccination coverage, in particular, gives rise to herd immunity whereby the fraction of vaccinated individuals is high enough to offer a degree of protection even to those who have not been vaccinated [2]. Vaccination, however, comes at a cost that can be manifest, e.g., paying a doctor's bill for getting vaccinated, and/or latent, e.g., overcoming the fear of a vaccine's side effects [3] even when scientific evidence shows that such fears are unfounded [4–6]. To avoid this cost, some individuals resort to free riding in hope that others will vaccinate and protect them from the disease, yet such behavior ultimately undermines herd immunity and increases the chances of an epidemic outbreak. Once people get infected, they resort to *ex post* treatments such as the widespread use of Oseltamivir (Tamiflu) against influenza, which in itself is also costly in monetary terms and accompanied with potentially serious side effects [7]. Seeing herd immunity as a public good [8,9] opens the door to game theoretic analyses of behaviors in the face of infection risks [10–23], which is precisely our objective too, but with a twist that agents may not only get vaccinated at the onset of a seasonal epidemic, but also get treated if infected.

To this end, we constructed an SITR/V compartmental epidemic model to which, in addition to the usual susceptible (S), infectious (I), and removed (R) compartments [24,25], we added a compartment for agents under treatment (T) and agents who chose to vaccinate at the onset of the epidemic (V). Mathematical modeling of antiviral treatments heretofore has largely focused on the effectiveness of drugs in containing epidemics and the implications of drug-resistant viral strains for disease spreading [26–34]. Even models that incorporate antiviral treatments in conjunction with vaccination impose vaccination coverage exogenously [35–40], falling short of taking into consideration individual-level decision making. Coupling our SITR/V epidemics model with game-theoretic concepts allowed us to comprehensively analyze incentives that drive individual human behaviors when facing dilemma situations [41]. Specifically, agents in the model make *ex ante* decisions on whether to vaccinate or not at the onset of the epidemic. These decisions are based on the total cost incurred during the previous epidemic season, which generally is some combination of vaccination, infection, and treatment costs. Agents who fared well against a standard for comparison, which comprises either individual- or society-based risk assessment (abbreviated IB-RA or SB-RA, respectively), will tend to keep their current strategy, whereas agents who fared poorly will tend to switch [9,42]. Additionally, agents who

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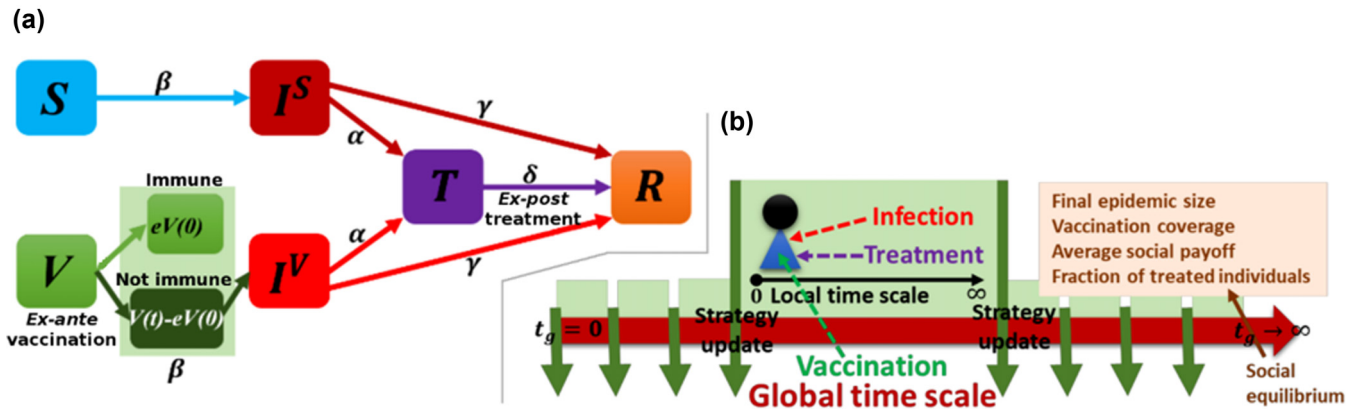

FIG. 1. *Schematic model diagram:* (a) In our SITR/V epidemic model, susceptible (S) individuals get infected at rate β, which applies even to a fraction of vaccinated individuals for whom vaccination failed to induce immunity. This fraction, as well as the fraction of vaccinated and immune individuals, is determined by vaccine efficacy e. Disease carriers are considered infectious (I), in which case they may receive an antiviral treatment with probability rate α, and then recover at rate δ or recover without treatment at rate $\gamma < \delta$. Once an individual is recovered, they are removed (R) from further consideration on the local timescale at which the epidemic progresses. (b) Aside from the disease progression on the local timescale, the evolutionary decision-making process takes place on a global time scale, t_g. Here an individual decides whether to vaccinate or not at the onset of an epidemic season based on how they fared in the previous epidemic season relative to others. Those agents who fared well are unlikely to change their strategy with respect to vaccination, and vice versa for agents who fared poorly.

become infectious during the current epidemic season may receive *ex post* treatment, but we assume that the decision is in the hands of a medical professional (i.e., healthcare establishment) rather than the agent themselves. The described setup [Fig. 1(a)] naturally leads to two separate timescales; *ex ante* decisions on vaccination (i.e., strategy updating) take place on a "global" or "evolutionary" timescale, whereas an epidemic season and *ex post* decisions on treatment unwind on a "local" timescale [Fig. 1(b)].

In what follows, we first describe our modeling approach in great detail. This is followed by an extensive model analysis using numerical simulations, including the most direct implications for maximizing vaccination coverage and minimizing epidemic size, while keeping the fraction of treated individuals and the average social cost at bay. We end by outlining more indirect implications and future research directions and with general concluding remarks.

II. MODEL FORMULATION

A. Epidemic model

Our SITR/V model (Fig. 1) most naturally fits seasonal, influenza-like diseases for which vaccination confers only temporary immunity. A season then unwinds on a local timescale, while the global timescale is interseasonal. With minor adjustments, however, it is possible to think of the local timescale as a timescale of a generation of agents who make vaccination decisions for a lifetime. The global timescale would then be intergenerational. From the perspective of mathematical epidemiology, the SITR/V model belongs to a class of compartmental epidemic models comprising, in this case, six compartments: $S(t)$ denotes susceptible nonvaccinated agents, $I^{\mathrm{S}}(t)$ denotes infectious nontreated agents who originally were susceptible, $V(t)$ denotes vaccinated agents irrespective of whether they subsequently acquired immunity of not, $I^{\mathrm{V}}(t)$ denotes infectious nontreated agents who originally were vaccinated, $T(t)$ denotes treated agents, and finally $R(t)$ denotes removed agents. The dynamics of these compartments [Fig. 1(a)] is given by

$$\dot{S} = -\beta S(t)[I^{\mathrm{S}}(t) + I^{\mathrm{V}}(t)], \tag{1}$$

$$\dot{V} = -\beta[V(t) - eV(0)][I^{\mathrm{S}}(t) + I^{\mathrm{V}}(t)], \tag{2}$$

$$\dot{I}^{\mathrm{S}} = \beta S(t)[I^{\mathrm{S}}(t) + I^{\mathrm{V}}(t)] - \alpha I^{\mathrm{S}}(t) - \gamma I^{\mathrm{S}}(t), \tag{3}$$

$$\dot{I}^{\mathrm{V}} = \beta[V(t) - eV(0)][I^{\mathrm{S}}(t) + I^{\mathrm{V}}(t)] - \alpha I^{\mathrm{V}}(t) - \gamma I^{\mathrm{V}}(t), \tag{4}$$

$$\dot{T} = \alpha I^{\mathrm{S}}(t) + \alpha I^{\mathrm{V}}(t) - \delta T(t), \tag{5}$$

$$\dot{R} = \gamma I^{\mathrm{S}}(t) + \gamma I^{\mathrm{V}}(t) + \delta T(t). \tag{6}$$

Here $\beta > 0$ is infection rate, $\alpha > 0$ is antiviral treatment probability rate, $\gamma > 0$ is recovery rate, $\delta > \gamma$ is accelerated recovery rate due to treatment, and $0 < e \leqslant 1$ is vaccine efficacy. We worked with a normalized population such that $S(t) + V(t) + I^{\mathrm{S}}(t) + I^{\mathrm{V}}(t) + T(t) + R(t) = 1$, also implying that each of the six state variables refers to a population fraction in a particular state. The initial condition is $S(0) = 1 - x$ and $V(0) = x$, where x is the fraction of vaccinators, which we set to 50% at the onset of the very first epidemic season but later determine using evolutionary considerations as described below.

B. Reproduction numbers

In a classic SIR model, the basic reproduction number R_0 is the average number of secondary infections caused by a single infectious agent in a completely susceptible population. It can be shown that $R_0 = \beta/\gamma$, and that if $R_0 > 1$ the infection spreads through the population, whereas in the opposite case,

the infection dies out in the long run. In our SITR/V model, however, instead of the whole population, only the fraction $S(0)+(1-e)V(0)$ is susceptible due to vaccination. Furthermore, the clearance rate of infectious individuals is not just γ, but $\gamma+\alpha$ due to the admission to treatment. It is therefore more appropriate to look at the control reproduction number R_c [43] defined as

$$R_c = \frac{\beta}{\gamma+\alpha}[S(0)+(1-e)V(0)]. \tag{7}$$

For this control reproduction number, it still holds that the infection spreads through the population if $R_c > 1$ but dies out otherwise.

C. Evolutionary game payoff structure

An agent's fate during the epidemic season determines their costs and ultimately the total payoff. Only forgoing vaccination and staying healthy is costless. Getting infected costs C_i, getting vaccinated costs $C_v < C_i$, and similarly getting treated costs $C_t < C_i$. We simplified considerations by setting $C_i = 1$ and then working with a relative cost of vaccination $C_V = C_v/C_i$ and a relative cost of treatment $C_T = C_t/C_i$.

To calculate the total payoff of an agent at the end of an epidemic season, i.e., when an equilibrium is reached on a local timescale, we reclassified agents into six classes. These are healthy vaccinated H_V°, healthy nonvaccinated H_V^n, infected vaccinated and treated $I_{VT}^{\circ\circ}$, infected vaccinated and nontreated $I_{VT}^{\circ n}$, infected nonvaccinated and treated $I_{VT}^{n\circ}$, and infected nonvaccinated and nontreated I_{VT}^{nn}. Each class can be linked to the results of the SITR/V model. To see how, we first note that when the SITR/V model reaches the equilibrium, i.e., $t\to\infty$, we have $S(\infty)+V(\infty)+R(\infty)=1$, while $I^S(\infty)=I^V(\infty)=T(\infty)=0$. By definition we further have that $H_V^\circ = V(\infty)$ and $H_V^n = S(\infty)$. Each of the remaining four classes, $I_{VT}^{\circ n}$, I_{VT}^{nn}, $I_{VT}^{\circ\circ}$, and $I_{VT}^{n\circ}$, can be thought of as a contribution to $R(\infty)$. We can separate these contributions using Eqs. (5) and (6), from which it follows that $R(\infty)=\gamma\int I^V(t)\,dt+\gamma\int I^S(t)\,dt+\delta\int T(t)\,dt$ and $\delta\int T(t)\,dt=\alpha\int I^V(t)\,dt+\alpha\int I^S(t)\,dt+T(\infty)$, where the integration is performed from $t=0$ to $t\to\infty$. Because at the equilibrium the epidemic season is finished and thus $T(\infty)=0$, we finally obtain $R(\infty)=\gamma\int I^V(t)\,dt+\gamma\int I^S(t)\,dt+\alpha\int I^V(t)\,dt+\alpha\int I^S(t)\,dt$ showing that $I_{VT}^{\circ n}=\gamma\int I^V(t)\,dt$, $I_{VT}^{nn}=\gamma\int I^S(t)\,dt$, $I_{VT}^{\circ\circ}=\alpha\int I^V(t)\,dt$, and $I_{VT}^{n\circ}=\alpha\int I^S(t)\,dt$.

Based on the payoff structure specification so far, an agent's total payoff is determined by their class membership as summarized in Table I. In addition, it is possible to calculate the average social payoff, $\langle\pi\rangle$, the expected payoff of a vaccinator, $\langle\pi_C\rangle$, and the expected payoff of a nonvaccinator, $\langle\pi_D\rangle$, as follows:

$$\langle\pi\rangle = -C_V H_V^\circ - (C_V+C_T+1)I_{VT}^{\circ\circ} - (C_V+1)I_{VT}^{\circ n} - (C_T+1)I_{VT}^{n\circ} - I_{VT}^{nn}, \tag{8}$$

$$\langle\pi_C\rangle = \frac{1}{x}\left[-C_V H_V^\circ - (C_V+C_T+1)I_{VT}^{\circ\circ} - (C_V+1)I_{VT}^{\circ n}\right], \tag{9}$$

$$\langle\pi_D\rangle = \frac{1}{1-x}\left[-(C_T+1)I_{VT}^{n\circ} - I_{VT}^{nn}\right]. \tag{10}$$

TABLE I. Agent classes and the corresponding costs depending on how agents of each class fared during an epidemic season.

Status	Healthy	Infected	Infected and treated
Vaccinated	H_V°	$I_{VT}^{\circ n}$	$I_{VT}^{\circ\circ}$
	$-C_V$	$-C_V-1$	$-(C_V+C_T)-1$
Nonvaccinated	H_V^n	I_{VT}^{nn}	$I_{VT}^{n\circ}$
	0	-1	$-C_T-1$

D. Strategy updating

At the onset of an epidemic season, after the previous epidemic cycle on the local timescale has unwound and reached an equilibrium, agents decide whether to vaccinate or not, thus updating their strategy. This update is based on imitating what works better than the agent's own strategy. The most widespread way of choosing whom to imitate is known as individual-based risk assessment (hereafter IB-RA), which consists of comparing one's own payoff, π_i, arising from strategy s_i, to that of a randomly selected neighbor, π_j, whose strategy is s_j, and then adopting this neighbor's strategy with transition probability $P(s_i \leftarrow s_j)$. Transition probabilities are generally functions of the payoff difference, $\pi_j-\pi_i$ (Table II), where among several available functional forms [41], we implemented the Fermi pairwise function, itself a member of a family of functions dubbed the smoothed best response [44]. A plausible alternative to individual-based risk assessment is society-based risk assessment (hereafter SB-RA), wherein agents compare their performance not to that of their randomly selected neighbor, π_j, but to the average performance of the whole class to which the neighbor belongs, $\langle\pi_j\rangle$ [12]. Herein there are two such classes, the class of vaccinators C (for cooperation) and the class of nonvaccinators D (for defection).

E. Evolutionary dynamics

The fraction of vaccinators, x, at the onset of an epidemic season, such that $S(0)=1-x$ and $V(0)=x$, is a dynamical variable on a global timescale. Although heretofore we often referred to agents and their actions, we expressed the evolutionary dynamics of variable x in terms of mean-field equations. This implies that the underlying spatial structure or agent connectivity is homogeneous enough to have little impact on the results [45]. Put alternatively, the difference between an agent's neighborhood and the whole population is insubstantial. When such an approximation holds, the mean-field approach often yields deep insights into the dynamics of complex systems, e.g., the existence of bifurcation points, bistability, and hysteresis [46–48]. An interested reader may find a direct comparison—in the context of vaccination—between multiagent simulations and mean-field approximations in Ref. [23].

The fraction of vaccinators, $x = H_V^\circ(x)+I_{VT}^{\circ\circ}(x)+I_{VT}^{\circ n}(x)$, increases whenever there is a net tendency among agents to imitate one of the vaccinator classes H_V°, $I_{VT}^{\circ n}$, and $I_{VT}^{\circ\circ}$.

TABLE II. List of all possible payoff differences for inserting into the Fermi rule in the case of individual-based risk assessment and society-based risk assessment.

Pairwise Fermi	Individual-based risk assessment (IB-RA) $P(s_i \leftarrow s_j) = \frac{1}{1+\exp[-\frac{\pi_j-\pi_i}{\kappa}]}$		Society-based risk assessment (SB-RA) $P(s_i \leftarrow s_j) = \frac{1}{1+\exp[-\frac{\langle\pi_j\rangle-\pi_i}{\kappa}]}$	
	$s_i \leftarrow s_j$	$\pi_j - \pi_i$	$s_i \leftarrow s_j$	$\langle\pi_j\rangle - \pi_i$
Payoff difference	$H_V^\circ \leftarrow H_V^n$	$0-(-C_V)$	$H_V^\circ \leftarrow D$	$\langle\pi_D\rangle-(-C_V)$
	$H_V^\circ \leftarrow I_{VT}^{n\circ}$	$(-C_T-1)-(-C_V)$	$I_{VT}^{\circ\circ} \leftarrow D$	$\langle\pi_D\rangle-[-(C_V+C_T+1)]$
	$H_V^\circ \leftarrow I_{VT}^{nn}$	$-1-(-C_V)$	$I_{VT}^{\circ n} \leftarrow D$	$\langle\pi_D\rangle-(-C_V-1)$
	$H_V^n \leftarrow H_V^\circ$	$-C_V-0$	$H_V^n \leftarrow C$	$\langle\pi_C\rangle-0$
	$H_V^n \leftarrow I_{VT}^{\circ\circ}$	$-(C_V+C_T+1)-0$	$I_{VT}^{n\circ} \leftarrow C$	$\langle\pi_C\rangle-(-C_T-1)$
	$H_V^n \leftarrow I_{VT}^{\circ n}$	$(-C_V-1)-0$	$I_{VT}^{nn} \leftarrow C$	$\langle\pi_C\rangle-(-1)$
	$I_{VT}^{n\circ} \leftarrow H_V^\circ$	$-C_V-(-C_T-1)$		
	$I_{VT}^{nn} \leftarrow H_V^\circ$	$-C_V-(-1)$		
	$I_{VT}^{\circ\circ} \leftarrow H_V^n$	$0-(-C_V-C_T-1)$		
	$I_{VT}^{\circ n} \leftarrow H_V^n$	$0-(-C_V-1)$		
	$I_{VT}^{\circ\circ} \leftarrow I_{VT}^{n\circ}$	$(-C_T-1)-(-C_V-C_T-1)$		
	$I_{VT}^{\circ\circ} \leftarrow I_{VT}^{nn}$	$-1-(-C_V-C_T-1)$		
	$I_{VT}^{\circ n} \leftarrow I_{VT}^{n\circ}$	$(-C_T-1)-(-C_V-1)$		
	$I_{VT}^{\circ n} \leftarrow I_{VT}^{nn}$	$-1-(-C_V-1)$		
	$I_{VT}^{n\circ} \leftarrow I_{VT}^{\circ\circ}$	$(-C_V-C_T-1)-(-C_T-1)$		
	$I_{VT}^{nn} \leftarrow I_{VT}^{\circ\circ}$	$(-C_V-C_T-1)-(-1)$		
	$I_{VT}^{n\circ} \leftarrow I_{VT}^{\circ n}$	$(-C_V-1)-(-C_T-1)$		
	$I_{VT}^{nn} \leftarrow I_{VT}^{\circ n}$	$(-C_V-1)-(-1)$		

Conversely, variable x decreases whenever agents predominantly imitate one of the nonvaccinator classes: H_V^n, $I_{VT}^{n\circ}$, and I_{VT}^{nn}. In the case of individual-based risk assessment (IB-RA), the total number of possibilities is 18 because a member of each of the three vaccinator classes can imitate any of the three nonvaccinator classes and vice versa. Accordingly, we have

$$\begin{aligned}\frac{dx}{dt} = {} & H_V^n(x)H_V^\circ(x)\big[\mathrm{P}\big(H_V^n \leftarrow H_V^\circ\big) - \mathrm{P}\big(H_V^\circ \leftarrow H_V^n\big)\big] \\ & + I_{VT}^{n\circ}(x)H_V^\circ(x)\big[\mathrm{P}\big(I_{VT}^{n\circ} \leftarrow H_V^\circ\big) - \mathrm{P}\big(H_V^\circ \leftarrow I_{VT}^{n\circ}\big)\big] \\ & + I_{VT}^{nn}(x)H_V^\circ(x)\big[\mathrm{P}\big(I_{VT}^{nn} \leftarrow H_V^\circ\big) - \mathrm{P}\big(H_V^\circ \leftarrow I_{VT}^{nn}\big)\big] \\ & + H_V^n(x)I_{VT}^{\circ\circ}(x)\big[\mathrm{P}\big(H_V^n \leftarrow I_{VT}^{\circ\circ}\big) - \mathrm{P}\big(I_{VT}^{\circ\circ} \leftarrow H_V^n\big)\big] \\ & + H_V^n(x)I_{VT}^{\circ n}(x)\big[\mathrm{P}\big(H_V^n \leftarrow I_{VT}^{\circ n}\big) - \mathrm{P}\big(H_V^n \leftarrow I_{VT}^{\circ n}\big)\big] \\ & + I_{VT}^{n\circ}(x)I_{VT}^{\circ\circ}(x)\big[\mathrm{P}\big(I_{VT}^{n\circ} \leftarrow I_{VT}^{\circ\circ}\big) - \mathrm{P}\big(I_{VT}^{\circ\circ} \leftarrow I_{VT}^{n\circ}\big)\big] \\ & + I_{VT}^{nn}(x)I_{VT}^{\circ\circ}(x)\big[\mathrm{P}\big(I_{VT}^{nn} \leftarrow I_{VT}^{\circ\circ}\big) - \mathrm{P}\big(I_{VT}^{\circ\circ} \leftarrow I_{VT}^{nn}\big)\big] \\ & + I_{VT}^{n\circ}(x)I_{VT}^{\circ n}(x)\big[\mathrm{P}\big(I_{VT}^{n\circ} \leftarrow I_{VT}^{\circ n}\big) - \mathrm{P}\big(I_{VT}^{\circ n} \leftarrow I_{VT}^{n\circ}\big)\big] \\ & + I_{VT}^{nn}(x)I_{VT}^{\circ n}(x)\big[\mathrm{P}\big(I_{VT}^{nn} \leftarrow I_{VT}^{\circ n}\big) - \mathrm{P}\big(I_{VT}^{\circ n} \leftarrow I_{VT}^{nn}\big)\big], \end{aligned} \tag{11}$$

where the notation CLASS(x) explicitly specifies that the fraction of agents belonging to a certain class depends on x, whereas products of the form $\mathrm{CLASS}_1(x)\cdot\mathrm{CLASS}_2(x)$ are probabilities that any two individual members of the two classes get in contact for imitation to be possible.

In the case of society-based risk assessment (SB-RA), any vaccinator (resp., nonvaccinator) compares their performance to the average performance of nonvaccinators (resp., vaccinators) as a whole. This leaves us with only six possibilities as follows:

$$\begin{aligned}\frac{dx}{dt} = {} & -H_V^\circ(x)\mathrm{D}(x)\mathrm{P}\big(H_V^\circ \leftarrow \mathrm{D}\big) - I_{VT}^{\circ\circ}(x)\mathrm{D}(x)\mathrm{P}\big(I_{VT}^{\circ\circ} \leftarrow \mathrm{D}\big) \\ & - I_{VT}^{\circ n}(x)\mathrm{D}(x)\mathrm{P}\big(I_{VT}^{\circ n} \leftarrow \mathrm{D}\big) + H_V^n(x)\mathrm{C}(x)\mathrm{P}\big(H_V^n \leftarrow \mathrm{C}\big) \\ & + I_{VT}^{n\circ}(x)\mathrm{C}(x)\mathrm{P}\big(I_{VT}^{n\circ} \leftarrow \mathrm{C}\big) + I_{VT}^{nn}(x)\mathrm{C}(x)\mathrm{P}\big(I_{VT}^{nn} \leftarrow \mathrm{C}\big), \end{aligned} \tag{12}$$

where $\mathrm{C}(x) = x$ is the fraction of all vaccinators and $\mathrm{D}(x) = 1 - x$ is the fraction of all nonvaccinators. The notation C and D stand for cooperators and defectors, respectively.

F. The utility of treatment

Initially, we introduced the antiviral treatment probability rate, α, and the accelerated recovery rate due to treatment, δ, as independent parameters. If, however, δ were much larger than the natural recovery rate, γ, the preference for treatment should also be much higher than if δ were only marginally higher than γ. Put more explicitly, δ^{-1} is the average number of days to recovery under treatment as opposed to γ^{-1} which is the average number of days to unaided (i.e., natural) recovery. If $\gamma^{-1} - \delta^{-1} \gg 0$, then the utility of treatment is very high, and treatment should be a highly sought-after option. Parameter α should therefore be a function of difference $\gamma^{-1} - \delta^{-1}$. The exact form of this functional dependence is unknown, but as with payoff differences, decision making under a utility difference is often captured using the smoothed

best response. In our case, this is the Fermi pairwise rule:

$$\alpha = \frac{\omega}{1 + \exp\left[-\frac{\gamma^{-1} - \delta^{-1}}{\kappa}\right]}, \tag{13}$$

where ω is the maximum antiviral treatment probability rate achieved when treatment dramatically speeds up recovery. Of note is that in the limit $\kappa \to 0$, Eq. (13) turns into a threshold rule, with $\alpha = \omega$ if $\gamma^{-1} > \delta^{-1}$ and $\alpha = 0$ otherwise. Values $\kappa > 0$ smooth the threshold rule into a sigmoidal function recognizable as the smoothed best response, which allows selecting an inferior (in terms of payoff or utility) option with nonzero probability. Parameter κ is therefore often called the strength of irrational selection. We used value $\kappa = 0.1$ in all simulations.

III. RESULTS

Here we numerically explore the SITR/V model, first in isolation and then coupled to evolutionary dynamics equations. Quantities of interest include vaccination coverage, treatment adoption in terms of the fraction of treated agents during an epidemic season, final epidemic size (abbreviated FES), and average social payoff as a measure of policy burden to society. Aside from already mentioned $\kappa = 0.1$, parameters have the following default values unless specified otherwise: $\beta = 2.5/3$, $\alpha = 0.1$, $\gamma = 1/3$ $(R_0 = \beta/\gamma = 2.5)$, $\delta = 0.5$, and where applicable $\omega = 0.1$.

A. SITR/V dynamics

Setting $\alpha = \delta = 0$ and assuming $x = e = 0.5$ collapses the SITR/V model into a traditional SIR/V model whose outputs serve as a benchmark [Fig. 2(a)]. Compared to this benchmark, reintroducing the option of treatment with $\alpha = \delta = 0.1$ considerably reduces the peak fraction of infectious agents while slightly lengthening the duration of the epidemic [Fig. 2(a)]. Increasing the recovery rate under treatment from $\delta = 0.1$ to $\delta = 0.6$ has no bearing on the dynamics of infectious agents [Fig. 2(a)], but it does decrease the peak fraction of treated agents (not shown), which is important in practice not to overwhelm healthcare institutions. Of note is that considering situations $\delta < \gamma$, despite the greatly diminished utility of a treatment that prolongs recovery, makes sense in that the peak fraction of infectious agents still gets reduced simply by virtue of diverting some of them to treatment. Doubling the treatment probability rate to $\alpha = 0.2$ suppresses the peak fraction of infectious agents approximately 4.5-fold [Fig. 2(a)], suggesting that eventually there may be no epidemic at all. This indeed transpires at $\alpha = 0.3$ when $R_c \approx 0.99 < 1$ (not shown). When the utility of treatment as prescribed by Eq. (13) is added to the mix, we see [Fig. 2(b)] that sufficiently prolonged recovery (i.e., $\delta \ll \gamma$) leads to ignoring the treatment option (i.e., $\alpha = 0$), unaffected recovery (i.e., $\delta \approx \gamma$) leads to treatment adoption at half the maximum probability rate (i.e., $\alpha = \omega/2$), and sufficiently accelerated recovery (i.e., $\delta \gg \gamma$) leads to the maximum treatment adoption (i.e., $\alpha = \omega$). Expectedly, the larger the treatment probability rate is, the lower the control reproduction number and ultimately the final epidemic size [Fig. 2(c)]. This holds for any given vaccination coverage, but the full synergistic effect of vaccination and treatment occurs when the control reproduction number is pushed below unity, in which case the epidemic is avoided altogether [Fig. 2(c)]. Akin to a larger treatment probability rate, an increasing vaccine efficacy also lowers the control reproduction number, and thus the final epidemic size, with an obvious difference that these positive effects are highly dependent on the vaccination coverage [Fig. 2(d)]. Finally, the need for treatment diminishes with an increasing vaccination coverage and may even be completely eliminated if the population attains herd immunity [Fig. 2(e)]. The latter, however, is possible only if vaccine efficacy is sufficiently high [Fig. 2(e)].

B. Interplay between vaccination and treatment costs

The primary benefit of coupling epidemiological and game theoretic methodologies is the ability to analyze incentives for various human behaviors in a dilemma situation. Here the dilemma is whether to vaccinate or not, and how the availability of the treatment option sways the popular opinion. Interestingly, we find that the cost of treatment has a relatively small effect on vaccination coverage, which is primarily controlled by the cost of vaccine itself, as well as the vaccine efficacy (Fig. 3). When efficacy is low, the population responds in a binary manner whereby everyone vaccinates if vaccine is cheap, and no one vaccinates if vaccine is expensive, and this irrespective of the treatment cost (Fig. 3). The population-level response to vaccination cost becomes much more gradual as efficacy increases, with the influence of the cost of treatment being most pronounced at intermediate vaccine prices and efficacies (Fig. 3). This influence is such that a more expensive treatment creates an incentive to act cautiously and vaccinate more in place of testing one's own luck by abstaining, and then resorting to treatment if struck by the disease (Fig. 3).

Looking beyond vaccination coverage reveals that treatment is secondary to vaccination in the sense that the vaccination cost, rather than the treatment cost, largely controls the adoption of treatment (Fig. 4). Simply put, the most expensive vaccines are avoided irrespective of efficacy, and eventually the fraction of infected agents who receive treatment during the epidemic season is maximized (Fig. 4). For more reasonable cost-efficacy combinations, however, cheap and expensive treatments alike start giving way to vaccination (Fig. 4). A direct consequence of all this is that the primary determinants of the final epidemic size (FES) are vaccine characteristics. Specifically, the avoidance of expensive vaccines leads to the maximum FES that is kept in check only by the treatment adoption (Fig. 5). The situation improves as vaccines become cheaper, with efficacy being the primary determinant of how cheap is cheap enough (Fig. 5). The dependence of FES on the cost of treatment is mostly weak. The burden to society in terms of the average social payoff is even less dependent on the treatment cost, with this dependence being more pronounced when vaccines are expensive and almost nonexistent when vaccines are cheap (Fig. 6). An interesting consequence is that when expensive treatment incentivizes vaccination, it does so at a relatively little cost to society.

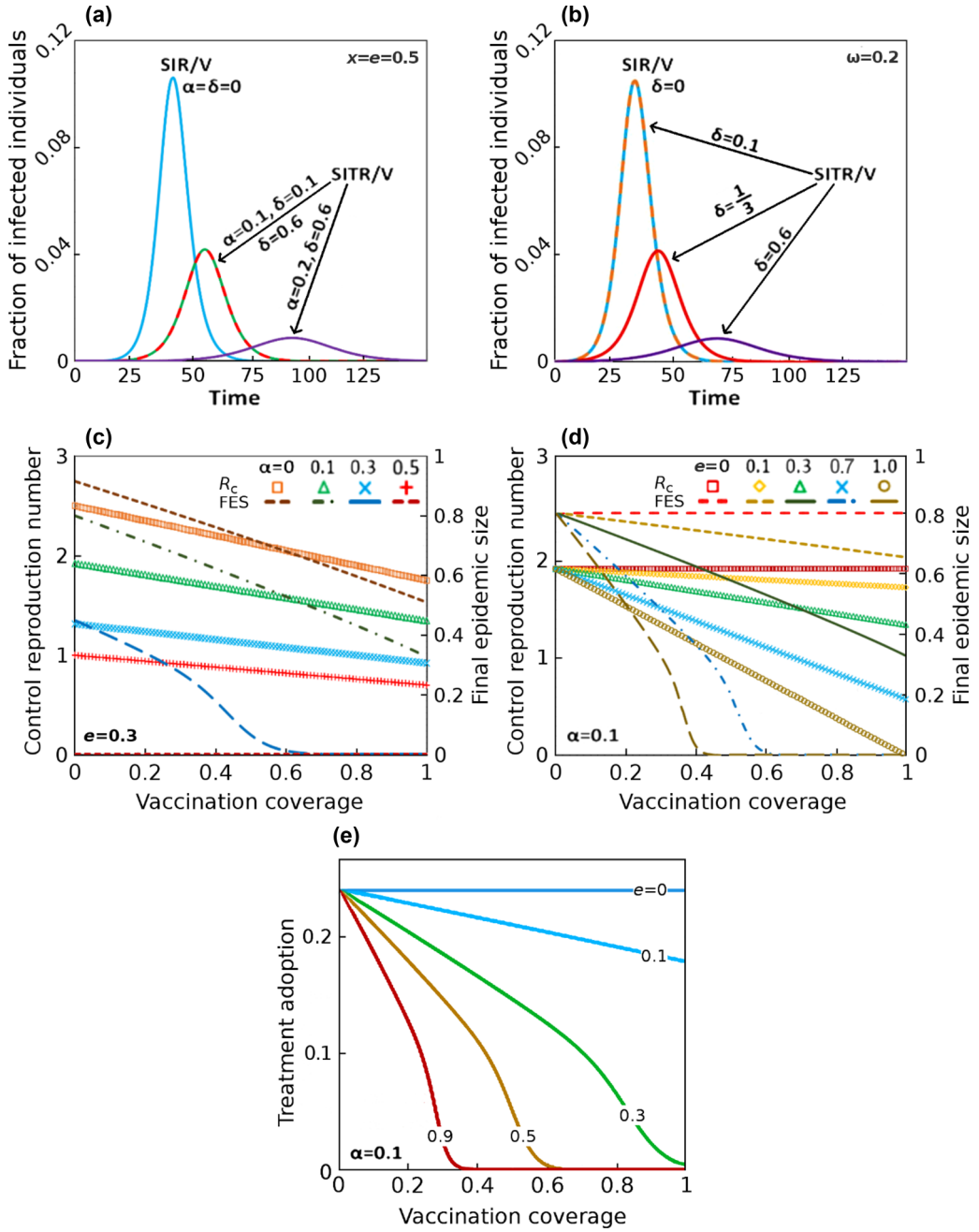

FIG. 2. *SITR/V dynamics:* (a) and (b) Progression of an epidemic season without and with Eq. (13) implemented, respectively. (c) and (d) Control reproduction number and final epidemic size as functions of the vaccination coverage for various treatment probability rates and vaccine efficacies, respectively. (e) Treatment adoption as a function of vaccination coverage for various vaccine efficacies. Parameter values are $\beta = 2.5/3$ and $\gamma = 1/3$, with other values specified in the plots. See the accompanying description in the text for details.

C. Individual- versus society-centered decision making

Judging from phase diagrams in Figs. 3–6, a general impression is that the society-based risk assessment (SB-RA) is advantageous over the individual-based risk assessment (IB-RA), but the truth is more complicated. Looking closely into this issue, we find that when vaccines are cheap, the SB-RA indeed supports a wider vaccination coverage, and thus also a smaller final epidemic size (Fig. 7). However, as vaccines get more expensive, and especially if their efficacy is high as well, it is the IB-RA that supports a wider vaccination coverage and thus also a smaller final epidemic size (Fig. 7). The reason for this is that the SB-RA subdues contrarian decisions relative to the IB-RA. For example, in a population dominated by vaccinators, implying cheaper vaccines, a lone nonvaccinator is less likely to get infected and may fare above average by refusing to vaccinate, thus creating a strong incentive for imitating this behavior under the IB-RA and ultimately causing a lower vaccination coverage than under the SB-RA. In a population dominated by nonvaccinators, it is a lone vaccinator who is likely to fare above average, thus reversing

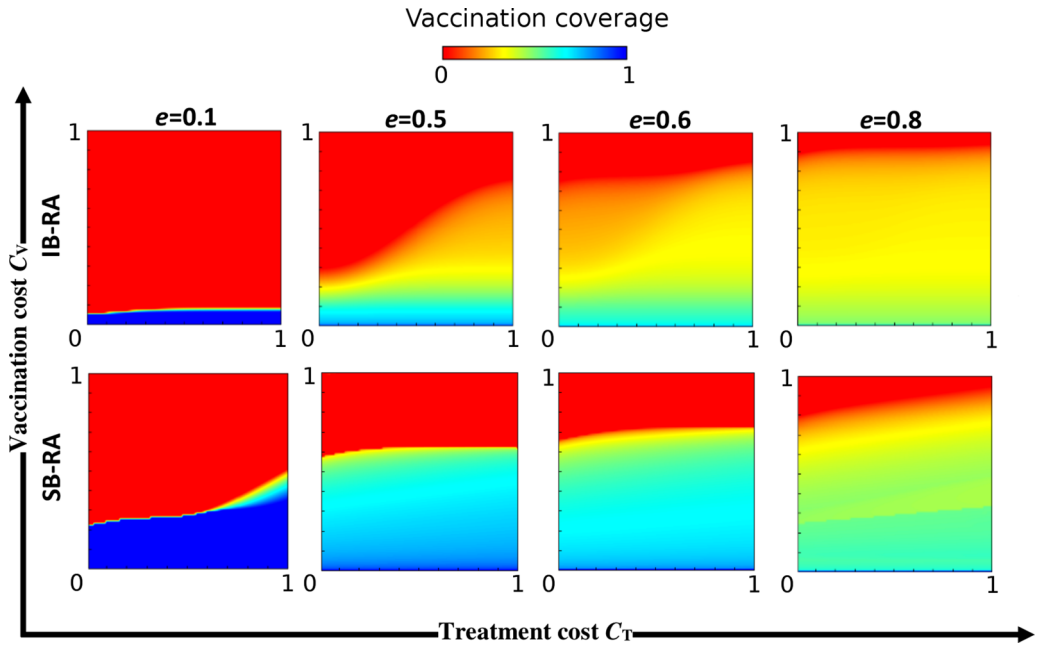

FIG. 3. *Vaccination coverage is primarily controlled by vaccine cost and efficacy:* The vaccination coverage as a function of relative vaccination cost C_V and relative treatment cost C_T. The most expensive vaccines are rejected even if very efficacious. Interestingly, cheaper vaccines may achieve less coverage with an increasing efficacy, but this is because they better suppress outbreaks. Also interesting is that a costlier treatment increases the vaccination coverage when vaccine is rightly priced and sufficiently efficacious. The individual-based risk assessment (IB-RA; top row) generally leads to a somewhat lower vaccination coverage compared to the society-based risk assessment (SB-RA; bottom row). Parameters used are $\beta = 2.5/3$, $\alpha = 0.1$, $\gamma = 1/3$, and $\delta = 0.5$, while efficacy improves from $e = 0.1$ (leftmost column) to $e = 0.8$ (rightmost column).

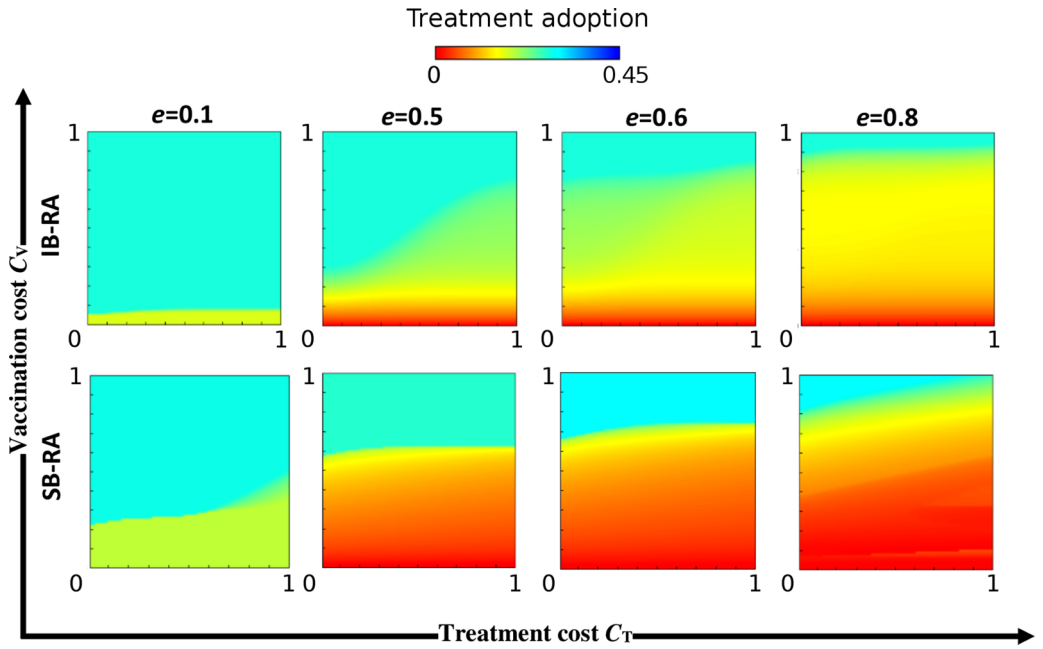

FIG. 4. *Treatment is secondary to vaccination:* The treatment adoption as a function of relative vaccination cost C_V and relative treatment cost C_T. In the limit of expensive vaccine, 30% of infected individuals eventually get treated irrespective of the cost of treatment. As vaccine becomes affordable, however, which implies the right combination of cost and efficacy, treatment is abandoned in favor of vaccination. These plots are therefore a mirror image of the plots in Fig. 3, and the individual-based risk assessment (IB-RA; top row) generally leads to a somewhat higher treatment adoption compared to the society-based risk assessment (SB-RA; bottom row). Color bar is synchronized with Fig. 9. Parameters used are $\beta = 2.5/3$, $\alpha = 0.1$, $\gamma = 1/3$, and $\delta = 0.5$, while efficacy improves from $e = 0.1$ (leftmost column) to $e = 0.8$ (rightmost column).

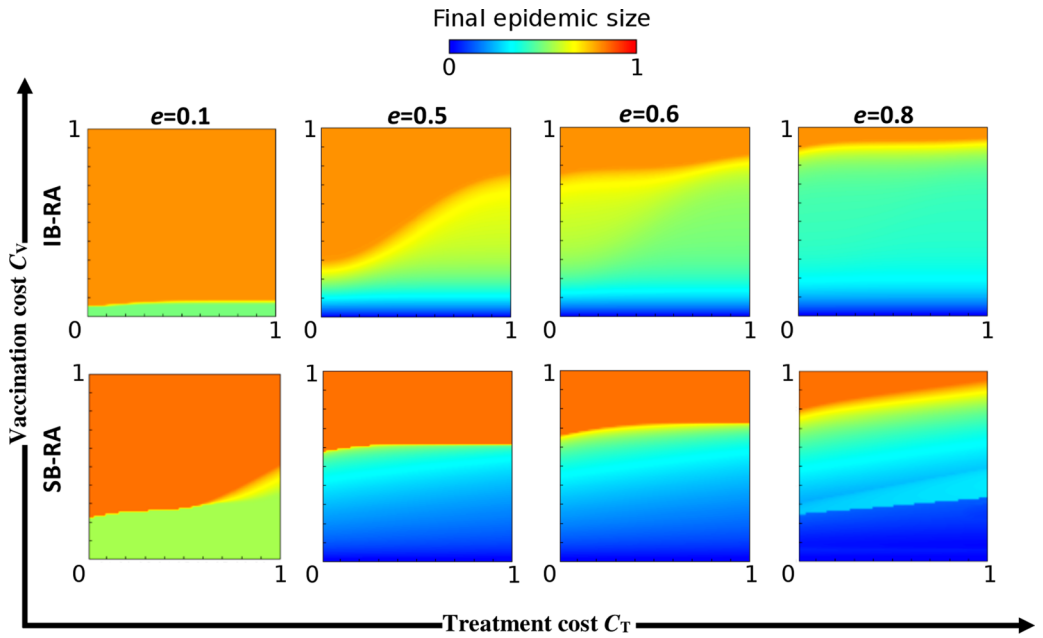

FIG. 5. *Outbreak size mirrors the vaccination coverage:* Put alternatively, the final epidemic size is largely controlled by the coverage, and thus vaccine cost and efficacy. Shown is the final epidemic size as a function of relative vaccination cost C_V and relative treatment cost C_T. A costlier treatment suppresses outbreaks by turning agents proactive instead of reactive, but this works only if vaccine is rightly priced and sufficiently efficacious. The individual-based risk assessment (IB-RA; top row) generally leads to somewhat poorer outcomes compared to the society-based risk assessment (SB-RA; bottom row). Parameters used are $\beta = 2.5/3$, $\alpha = 0.1$, $\gamma = 1/3$, and $\delta = 0.5$, while efficacy improves from $e = 0.1$ (leftmost column) to $e = 0.8$ (rightmost column).

the outcome. The described distinction between IB-RA and SB-RA, as discussed later, has important implications for the popularity of the present-day antivaccination movements.

D. Interplay between vaccine and treatment characteristics

Aside from costs, it is worthwhile emphasizing how other parameters conspire to control outbreaks. Increasing the treat-

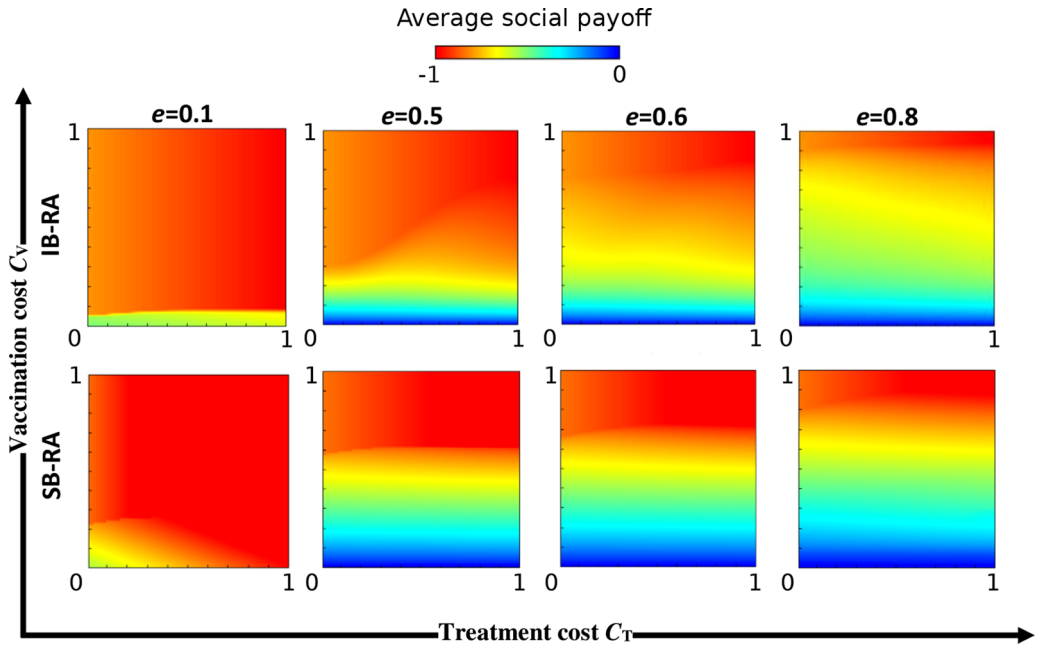

FIG. 6. *Burden to society is weakly sensitive to the treatment cost:* Shown is the average social payoff as a function of relative vaccination cost C_V and relative treatment cost C_T. Plots reveal a relatively small decrease in the average social payoff even in the limit of expensive treatment. The individual-based risk assessment (IB-RA; top row) is generally somewhat more burdensome than the society-based risk assessment (SB-RA; bottom row). Parameters used are $\beta = 2.5/3$, $\alpha = 0.1$, $\gamma = 1/3$, and $\delta = 0.5$, while efficacy improves from $e = 0.1$ (leftmost column) to $e = 0.8$ (rightmost column).

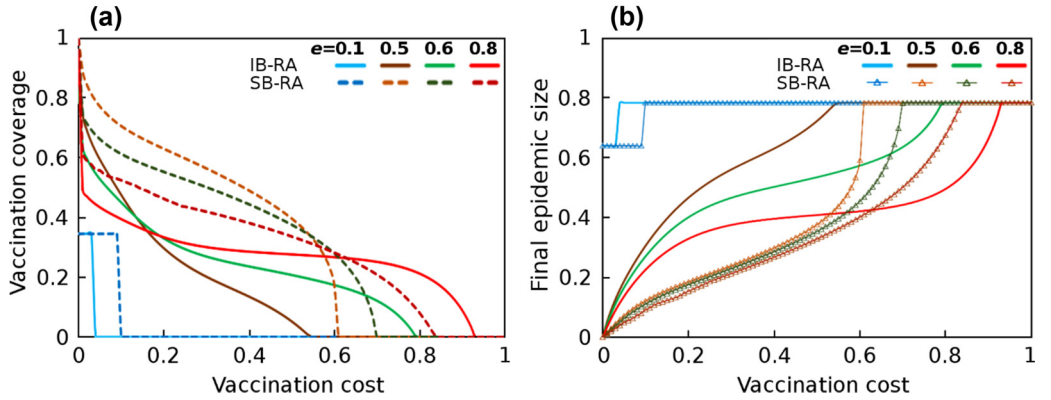

FIG. 7. *Society-based risk assessment resists contrarian decisions:* When vaccines are cheap and there are many vaccinators, a lone nonvaccinator is less likely to get infected and may fare above average by taking a contrarian stance. In such circumstances, the individual-based risk assessment (IB-RA) provides a local signal to the surrounding vaccinators to imitate the successful nonvaccinator, with the overall result being less vaccination coverage and a larger final epidemic size than with the society-based risk assessment (SB-RA). Reverse reasoning holds when vaccines are expensive and there are many nonvaccinators, in which case a lone vaccinator is more likely to avoid infection and thus fare above average by taking the contrarian stance. The overall result is then a wider vaccination coverage and a smaller final infection size with IB-RA than SB-RA. (a) and (b) The vaccination coverage and the final epidemic size, respectively, under IB-RA and SB-RA as a function of relative vaccination cost C_V for a range of vaccine efficacies e. Parameters used are $\beta = 2.5/3$, $\alpha = 0.1$, $\gamma = 1/3$, and $C_T = 0.5$.

ment probability rate, α, at first leads to a higher treatment adoption, but as treatment becomes more widely administered and the epidemic is better controlled, further increasing parameter α only decreases the treatment adoption until the epidemic is fully eradicated (Fig. 8). Interestingly, the results are insensitive to vaccine efficacy if efficacy is too low. Here the precise meaning of "too low" depends on the vaccination cost (Fig. 8). If moreover the utility of the drug is taken into

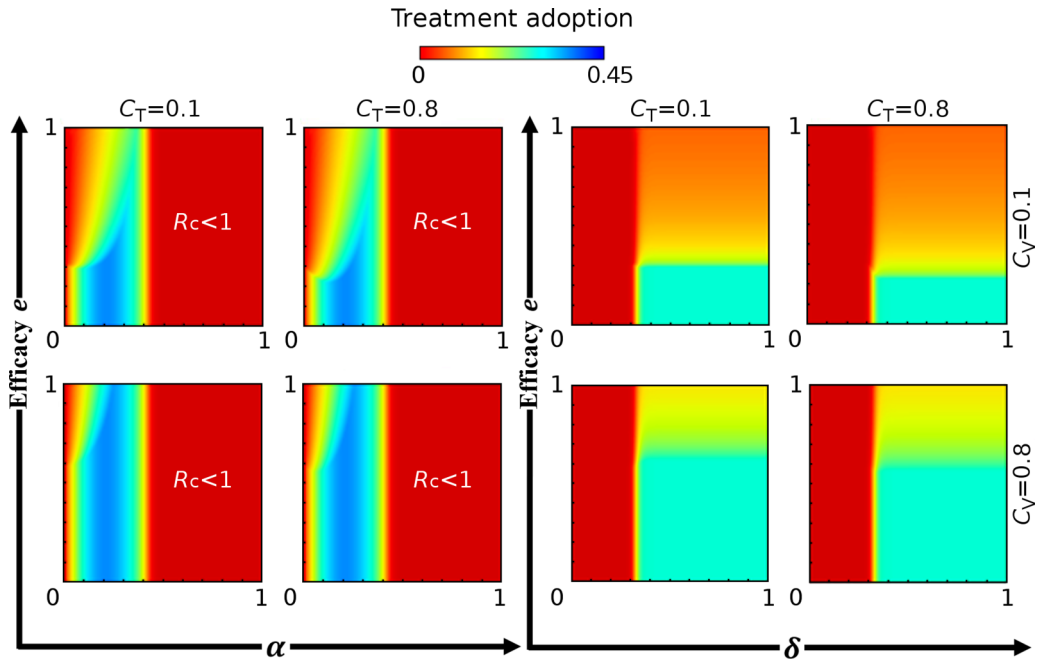

FIG. 8. *How vaccine and treatment characteristics control the treatment adoption:* When Eq. (13) is not implemented (i.e., α is independent of δ; left panels), increasing treatment probability rate α first leads to a wider treatment adoption, but as the epidemic gets more effectively suppressed, the treatment adoption begins to decrease. At sufficiently high values of parameter α ($\alpha > 0.4$), the control reproduction number falls below unity and the epidemic is eradicated. Interestingly, the results are almost independent of the cost of treatment, yet vaccine characteristics matter. When efficacy is low, parameter α alone controls the treatment adoption, but with high enough efficacy, fewer treatments are necessary. How much "high enough" is depends on the vaccination cost. When Eq. (13) is implemented (i.e., α is related to δ; right panels), treatments that prolong recovery are ignored, whereas treatments that shorten recovery are adopted equally irrespective of their cost. Instead, more important are the vaccine efficacy and the vaccination cost. Parameters used are $\beta = 2.5/3$ and $\gamma = 1/3$; $\delta = 0.5$ in the left panels and $\omega = 0.1$ in the right panels.

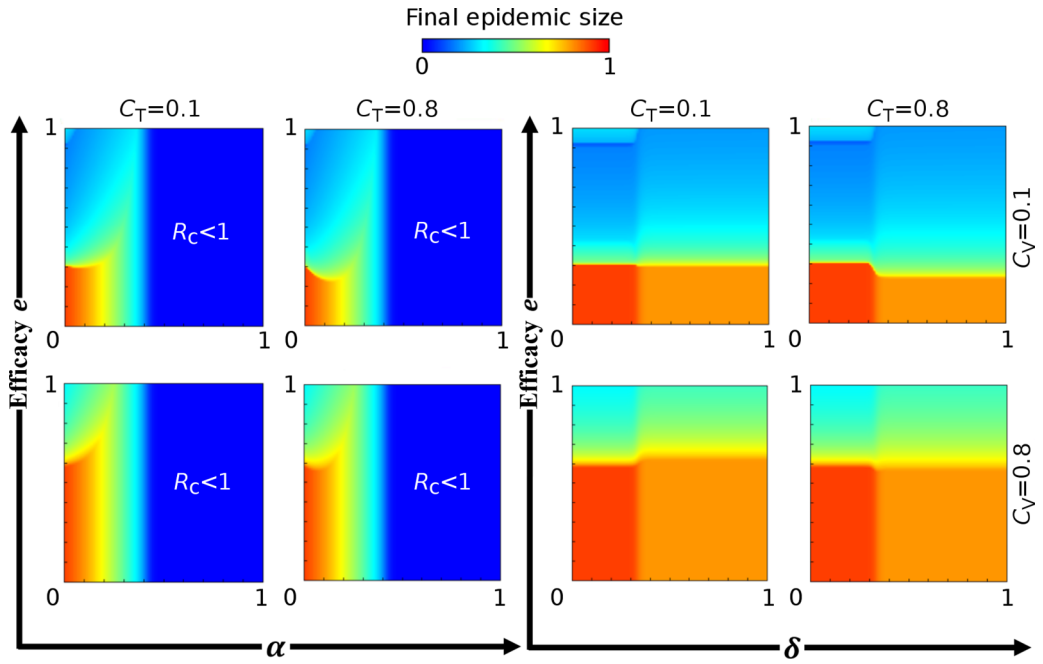

FIG. 9. *How vaccine and treatment characteristics control the final epidemic size:* When Eq. (13) is not implemented (i.e., α is independent of δ; left panels), increasing treatment probability α eventually leads to the eradication of the disease ($\alpha > 0.4$). Vaccines with overly low efficacy have no bearing on the final epidemic size (FES), but what "overly low" means is decided by the vaccination cost. Interestingly, directing more agents to treatment interferes with the ability of a highly efficacious vaccine to control the epidemic, thus actually causing FES to increase alongside parameter α until treatment is administered often enough to overwhelm the disease. When Eq. (13) is implemented (i.e., α is related to δ; right panels), treatments that prolong recovery are ignored, as are vaccines with overly low efficacy, allowing the disease to spread freely. Again, what "overly low" means is decided by the vaccination cost. Treatments that shorten recovery are indeed adopted, but they reduce FES only when the vaccine efficacy is low and end up increasing FES when efficacy is high. Parameters used are $\beta = 2.5/3$ and $\gamma = 1/3$, while $\delta = 0.5$ in the left panels and $\omega = 0.1$ in the right panels.

account as prescribed by Eq. (13), treatment that prolongs recovery ($\delta \ll \gamma$) gets ignored, whereas treatment that shortens recovery ($\delta \gg \gamma$) is adopted as much as this is allowed by the vaccine efficacy and the vaccination cost (Fig. 8).

Effects of vaccine and treatment characteristics on the final epidemic size (FES) only partly mirror the described effects on the treatment adoption and in fact reveal further complexities. Expectedly, increasing the treatment probability rate, α, gradually reduces FES and even eradicates the disease when treatment is administered widely enough (Fig. 9). As with the treatment adoption, overly low vaccine efficacy is inconsequential, but what constitutes "overly low" is decided

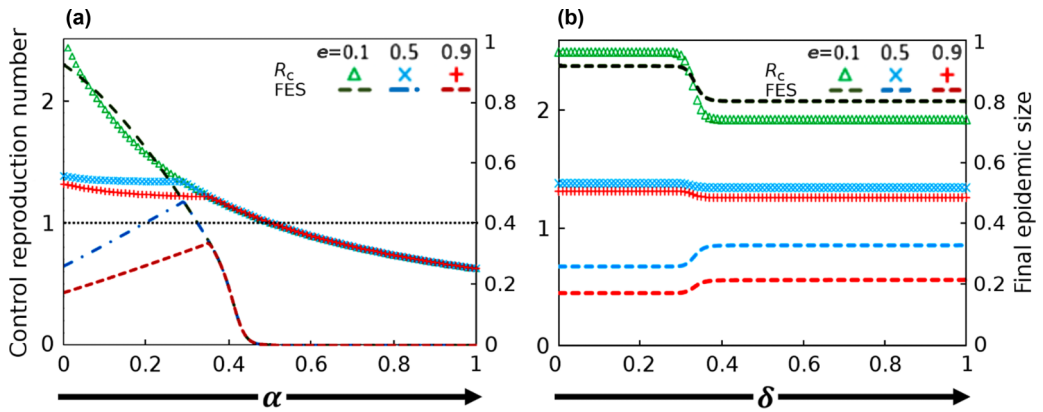

FIG. 10. *Treatment interferes with vaccine's control of the final epidemic size:* (a) When Eq. (13) is not implemented (i.e., α is independent of δ), treatment helps to lower the control reproduction number (R_c). In terms of the final epidemic size (FES), however, when the treatment probability rate is moderate, a reduced disease prevalence prompts some vaccinators to forgo vaccination, thus actually increasing FES in comparison to no-treatment setting. (b) The same mechanism is at work even when Eq. (13) is implemented (i.e., α is related to δ). Here the treatment adoption helps to reduce FES only in the case of a low-efficacy vaccine. If vaccine is efficacious enough, introducing treatment at moderate probability rates worsens the disease prevalence. Parameters used are $\beta = 2.5/3$ and $\gamma = 1/3$, while the relative costs of vaccine and treatment are $C_V = C_T = 0.1$, respectively.

by the vaccination cost (Fig. 9). With a highly efficacious vaccine available, we would expect a FES-reducing synergy between vaccine and treatment. It turns out, however, that the margin for such a synergy is very small, and in most instances, treatment ends up interfering with vaccine's ability to control FES (Fig. 9). Similar is seen when the utility of the drug is accounted for via Eq. (13). Treatment that shortens recovery indeed helps to decrease FES, but only when vaccine efficacy is low. When the opposite is true, FES actually increases (Fig. 9). This interference of treatment with vaccine is more clearly illustrated in Fig. 10. The mechanism in play here is that treatment acts to reduce FES initially, but as the evolutionary time progresses, restricted seasonal spreading of the disease prompts some agents to stop vaccinating. The end result is that FES is larger than it would have been without the treatment option.

IV. DISCUSSION AND CONCLUSIONS

Herein we proposed a coupling of epidemiological and game-theoretic methodologies to study behavioral incentives in the face of a vaccination dilemma when treatment is available as an *ex post* fallback option. We largely focused on a situation in which the treatment probability rate is moderate, meaning that the availability of treatment considerably reduces the final epidemic size but is insufficient to fully eliminate the epidemic. Put more technically, the control reproduction number is considerably lower than the basic reproduction number but still above unity. This situation is, in fact, the most interesting from an epidemiological perspective because excessive use of drugs hastens the evolution of resistance, and furthermore there may be technological limitations to drug availability even when the price of the drug is not an issue. In this context, we found that treatment indeed takes a back seat compared to vaccination because the cost of the latter, in conjunction with efficacy, primarily determines the vaccination coverage and the treatment adoption. The final epidemic size is consequently also much more sensitive to the vaccination cost and efficacy than the treatment cost. The most important effect of the treatment cost is that expensive treatment creates an incentive for resorting to vaccination, especially when the vaccine cost-efficacy combination is right. Because the consequent increase in burden to society is small, in situations when both quality vaccines and treatments exist, it makes sense to incentivize vaccination with higher treatment prices, especially if doing so can prolong the evolution of resistance to drugs. This is further justified by the narrow margin for truly synergistic effects of vaccine and treatment in suppressing the final epidemic size.

Present-day society is facing an emergence of mistrust towards vaccines, often centered around influential public figures who express skeptical sentiments against vaccination [49–51]. It is interesting in this context that the individual-based risk assessment (IB-RA) is more prone to succumbing to such contrarian views than the society-based risk assessment (SB-RA). Namely, when the vaccine coverage is high, individuals who refuse vaccination are protected by others and thus fare very well by getting the protection for free. Seeing no downside for nonvaccinators, the IB-RA quickly leads to imitating this behavior. The SB-RA, however, implies a modicum of "collective memory," whereby the harm that may befall nonvaccinators is more difficult to ignore. The question, therefore, is how to reinforce this collective memory enough to guide health-related decisions that may save lives. Game-theoretic experiments have already shown ways to promote cooperation in generic social-dilemma situations [52–55], and while similar work is in progress in the context of the vaccination dilemma [56–58], there seems to be a lack of understanding of decision making in dilemmas that evoke strong emotions, as is the case with vaccine skepticism.

There is much space for future work in relation to the vaccination dilemma. Aside from the mentioned potential for experimental studies, theory can be advanced too. For example, we introduced the option of antiviral treatment as if the decision to opt for treatment was predominantly in the hands of medical professionals. This, of course, is not entirely true, and a full consideration should be given to a double dilemma that analyzes individual incentives whether to vaccinate or not and whether to proceed with treatment or not. Coevolution of multiple traits has already proven as a powerful promoter of cooperation [59–62]. We are yet to see the same in the context of the vaccination dilemma.

ACKNOWLEDGMENTS

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