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Effects of behavioral response and vaccination policy on epidemic spreading - an approach based on evolutionary-game dynamics

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How effective are governmental incentives to achieve widespread vaccination coverage so as to prevent epidemic outbreak? The answer largely depends on the complex interplay among the type of incentive, individual behavioral responses, and the intrinsic epidemic dynamics. By incorporating evolutionary games into epidemic dynamics, we investigate the effects of two types of incentives strategies: partial-subsidy policy in which certain fraction of the cost of vaccination is offset, and free-subsidy policy in which donees are randomly selected and vaccinated at no cost. Through mean-field analysis and computations, we find that, under the partial-subsidy policy, the vaccination coverage depends monotonically on the sensitivity of individuals to payoff difference, but the dependence is non-monotonous for the free-subsidy policy. Due to the role models of the donees for relatively irrational individuals and the unchanged strategies of the donees for rational individuals, the free-subsidy policy can in general lead to higher vaccination coverage. Our findings indicate that any disease-control policy should be exercised with extreme care: its success depends on the complex interplay among the intrinsic mathematical rules of epidemic spreading, governmental policies, and behavioral responses of individuals.

Vaccination is one of the most effective tools for reducing morbidity and mortality associated with infectious diseases. In spite of the fact that voluntary vaccination may be infeasible to prevent pandemics¹, global vaccination programs for measles, pertussis, and polio have reduced the prevalence of these diseases dramatically over the last decades^{2,3}. However, vaccination represents a long-standing social dilemma for public health administration, because voluntary vaccination often cannot result in sufficiently strong herd immunity for disease eradication⁴ but compulsory vaccination may result in infringement of civil rights. In general, vaccination protects not only those who are vaccinated but also their neighbors. As a result, many others in the community can also be benefited, including those who have less incentive to be vaccinated. This scenario naturally leads to the “free-riding” problem commonly observed in public goods studies⁵. However, in voluntary vaccination, an individual’s decision-making with respect to vaccination may depend on many factors such as the perceived risk of infection, cost of infection, cost of vaccination, and the reactions of other vaccinated individuals. Generally, it has been demonstrated that a voluntary vaccination policy without incentives can hardly be effective to eradicate vaccine-preventable diseases^{6–17}. A possible resolution of the social dilemma with respect to vaccination is for the government or health organizations to implement some incentive programs, e.g., subsidy and insurance policies. In this regard, many quantitative studies addressed the effects of the incentive programs on disease eradication, and some optimal strategies were proposed^{18–20}.

There has been a great deal of recent interest in understanding the effects of incentives through mathematical modeling and computations. One general finding is that external incentives may alter the vaccination decisions of the broader public, thereby reducing the effectiveness of such programs or even making them detrimental. For example, by constructing an individual-level adaptive decision-making model based on the minority game theory, Vardavas *et al.*¹⁴ found that severe epidemics cannot be prevented unless vaccination programs offer



incentives. While incentive policies such as offering several years of free vaccines to individuals who pay for one year of vaccination can substantially reduce the frequency of severe epidemics, incentive programs that provide free vaccination to families could increase the frequency of severe epidemics²¹. In Ref. 22, Wells *et al.* showed that the effects of the so-called immunization strategies to vaccinate superspreader can be weakened or counteracted when other individuals make vaccination decisions about influenza based on the self-interested principle. In Ref. 23, authors assumed that farmers make decisions on whether or not to vaccinate their own herd based on self-interested rules such as the *payoff maximization rule*^{10,24} and showed that voluntary vaccination cannot eradicate disease among herd. Two incentive programs were then considered, namely subsidizing vaccination and compensating losses. It was found that the former can lead to a marked suppression of the disease, but cannot completely eradicate it. On the contrary, the compensating losses strategy has little impacts on the reduction of diseases. Recently, the effects of two types of subsidy policies, free- and partial-subsidy policies, were studied²⁵ based on the self-interested rule. The finding is that, due to the “herd immunity” effect, the free-subsidy policy on promoting the vaccination coverage is not as effective as the partial-subsidy policy.

This work is motivated by the intuition that human behavioral responses, naturally, would have some significant impact on the complex dynamical interplay among epidemic spreading, vaccination, and incentives. When facing the outbreak of an epidemic, it is often difficult or even impossible for individuals to act with perfect information to assess their chances of becoming infected. In this case, individuals may adopt new strategies through learning. The imitation (learning) rule has been fully studied in evolutionary game theory^{26–28}, and also been incorporated in many vaccination decision-making models, with the general finding that the rule can yield results different from those based on the self-interested principle^{3,6,12}.

In this paper, we investigate how the imitation rule affects two previously studied subsidy policies: (1) the partial-subsidy policy, where a certain proportion of subsidy is distributed to all vaccinated individuals and (2) the free-subsidy scenario in which, given the limited amount of subsidy, a certain number of individuals are randomly vaccinated without any personal cost. We focus on a flu-like vaccination and develop an epidemiological game-theoretic model by integrating a classical epidemic-spreading process and the subsidy policy into a simple agent-based model. Our analysis and computations indicate that the cost of vaccination and strength selection in the imitation rule play a vital role in the effectiveness of the subsidy policies. More specifically, for small cost of vaccination, the vaccination coverages for the two policies increase with the selection strength β characterizing the rational/cautious behaviors in the imitation rule. On the contrary, for large cost of vaccination, increasing the value of β gives rise to different results for the two subsidy policies: for the partial policy, the vaccination coverage increases with β when the proportion of subsidy is small and the opposite case occurs when the proportion of subsidy is considerable. For the free-subsidy policy, the vaccination coverage is non-monotonically dependent on the value of β . Owing to the role models of donees, the vaccination coverage for the free-subsidy case is generally higher than that of the partial-subsidy case. These results provide insights into the role of subsidy policies associated with vaccination in preventing large-scale epidemic outbreak.

Results

Model description and analysis are described in Methods. The parameter β in Eq. (1) is the strength of selection ($0 < \beta < \infty$), which characterizes the sensitivity of individuals in response to payoff differences, where a larger value of β means the individuals are more rational (less random) with respect to making decisions about vac-

ination. We first present results with homogeneous small-world networks (HSWN)^{29,30}, where we study the effects of different values of β on the two subsidy policies, as shown in Figs. 1 and 2 for $c = 0.5$ and $c = 0.9$ (we have checked the smaller values of c and found that the phenomenon persists. For example, the case of $c = 0.2$ is given in Fig. S1.), respectively, where c is the cost of vaccination [Eq. (1)]. We observe distinct effects on the vaccination coverage (V) and the epidemic size (R) for different costs of vaccination.

For small vaccination cost ($c = 0.5$, Fig. 1), as β is increased, the vaccination coverages (V) for the partial- and free-subsidy policies decrease monotonically and then reach a constant, leading to an increase in the epidemic size. For small values of β , the blind imitation behaviors of individuals in combination with small vaccination cost give rise to a relatively high level of vaccination coverage, resulting in a quite low level of the epidemic size. When β becomes larger, individuals are more sensitive to the payoff difference. In this case, on average those taking risk can get higher payoff than those taking vaccination since the epidemic size is small. As a result, more individuals tend to imitate the strategy of free riders. Eventually, the vaccination coverage is reduced, leading to an increase in the epidemic size. If the vaccination coverage keeps decreasing, then the epidemic size would increase continuously, generating greater risk for the non-vaccinators. Driven by rational thinking, certain individuals would choose to be vaccinated, leading to a turn-around in the number of vaccinated individuals. The two competing factors, namely higher payoff and risk, eventually make the vaccination coverage to converge to a stable level for large values of β . The stable, equilibrium value of the vaccination coverage can be theoretically predicted based on the mean-field approximation [Eq. (18) and Eq. (20) in Methods]. The insets of Fig. 1 give the differences in the vaccination coverage and epidemic size between the partial- and free-subsidy policies, $V_P - V_F$ and $R_P - R_F$, respectively, obtained from direct numerical simulation and theory. We observe reasonable agreement between numerics and theory.

Results for relatively large vaccination cost ($c = 0.9$) are more complicated than those for $c = 0.5$, as shown in Fig. 2. In particular, for the partial-subsidy policy, the vaccination coverage increases with β when the subsidy is not substantial [e.g., $\delta = 0.1$ in Fig. 2(a1) and $\delta = 0.4$ in Fig. 2(a2)], where δ is the fraction of total vaccination cost contributed by subsidy. For small values of β , individuals are not quite rational, so they are not willing to take vaccination due to the high cost, generating a relatively low level of vaccination coverage and, consequently, larger epidemic size. For sufficiently large values of β , individuals become more rational and are able to reason that the benefits of taking vaccination can significantly outweigh its cost. In this case, many nodes (including some hub nodes) choose to be vaccinated. The vaccination coverage reaches a stable level for very large values of β . However, for larger values of δ , the vaccination coverage decreases with β , as shown in Fig. 2(a3) for $\delta = 0.7$. Note that a large value of δ means small cost of vaccination ($c(1 - \delta) = 0.27$), so the behaviors are similar to those for $c = 0.5$.

For the free-subsidy policy, the vaccination coverage depends upon the value of β in a non-monotonic fashion. For small values of β , due to the existence of donees (vaccinated without personal cost), there is probability that certain individuals imitate these donees' strategy even though the vaccination cost is large. As these individuals become more rational (larger value of β), they tend to switch their vaccination strategy due to the large cost, leading to a sharp decline in the vaccination coverage and a rapid increase in the epidemic size correspondingly. As the vaccination coverage is increased, the risk of infection is reduced, and eventually the coverage is maintained at a fixed level for large values of β . The insets in Fig. 2 show the values of $V_P - V_F$ and of $R_P - R_F$ from numerical simulation and theory with reasonable agreement.

From Figs. 1 and 2, we can observe an interesting phenomenon. Specifically, the vaccination coverage for the free-subsidy case is

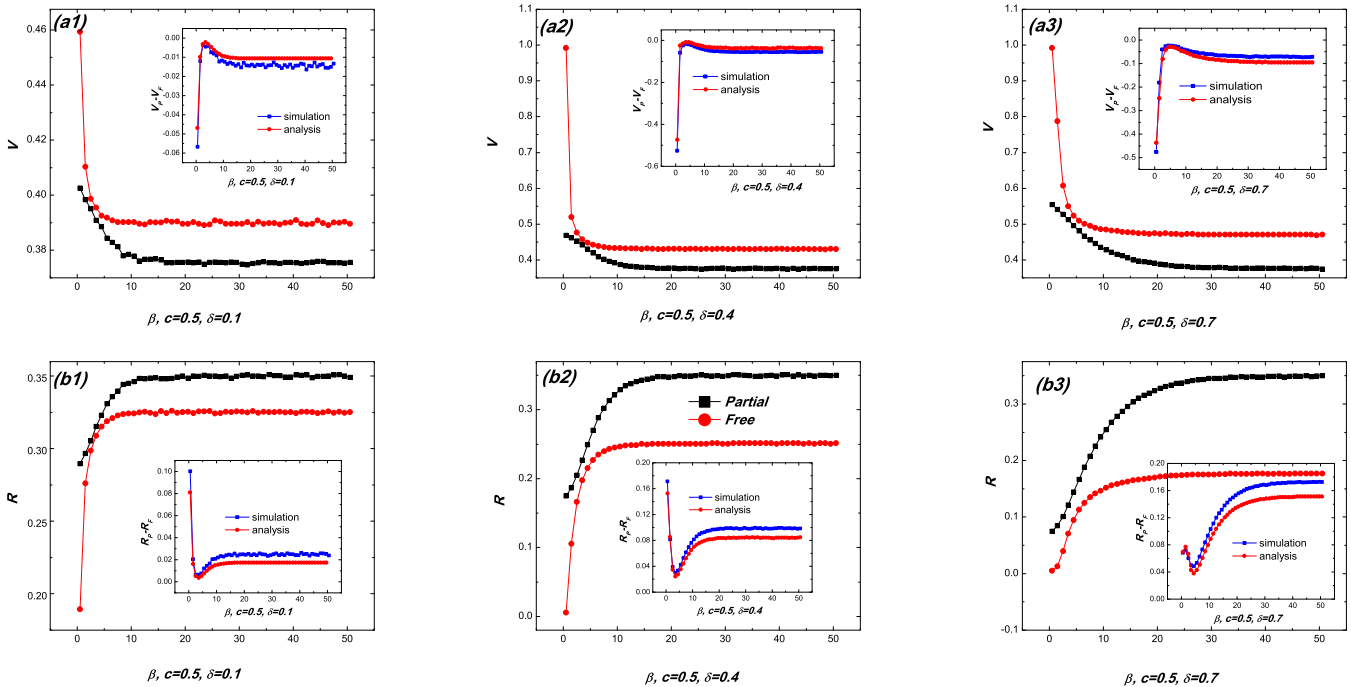


Figure 1 | Quantitative characterization of impacts of the selection strength β on epidemic spreading for partial- and free-subsidy policies for small vaccination cost. For homogeneous small-world networks (HSWN) and cost of vaccination $c = 0.5$, vaccination coverage (V , top panels) and epidemic size (R , bottom panels) for the two subsidy policies for $\delta = 0.1, 0.4$ and 0.7 (corresponding to the left, central, and right panels, respectively). Insets in the top panels show the difference in the vaccination coverage, $V_P - V_F$, between the partial- and free-subsidy policies. Insets in the bottom panels display the difference in epidemic size, $R_P - R_F$, between the two subsidy policies. Blue squares in the insets are simulation results, and the red circles are the theoretical predictions based on the mean-field method (see analysis in Methods). Other parameters are: network size $N = 1000$, transmission rate $\lambda = 0.072$, and average degree $\bar{k} = 10$.

larger than that for the partial-subsidy case in most cases, indicating that the former policy is more effective at controlling epidemic outbreaks. Qualitatively, this phenomenon can be understood, as follows. In the small β regime, although a blind imitation behavior exists in

both cases, the donees in the free-subsidy case never switch their strategies, leading to a larger probability for them to allure their neighbors into taking vaccination. This can be verified more explicitly by comparing the average fractions of imitated vaccinators

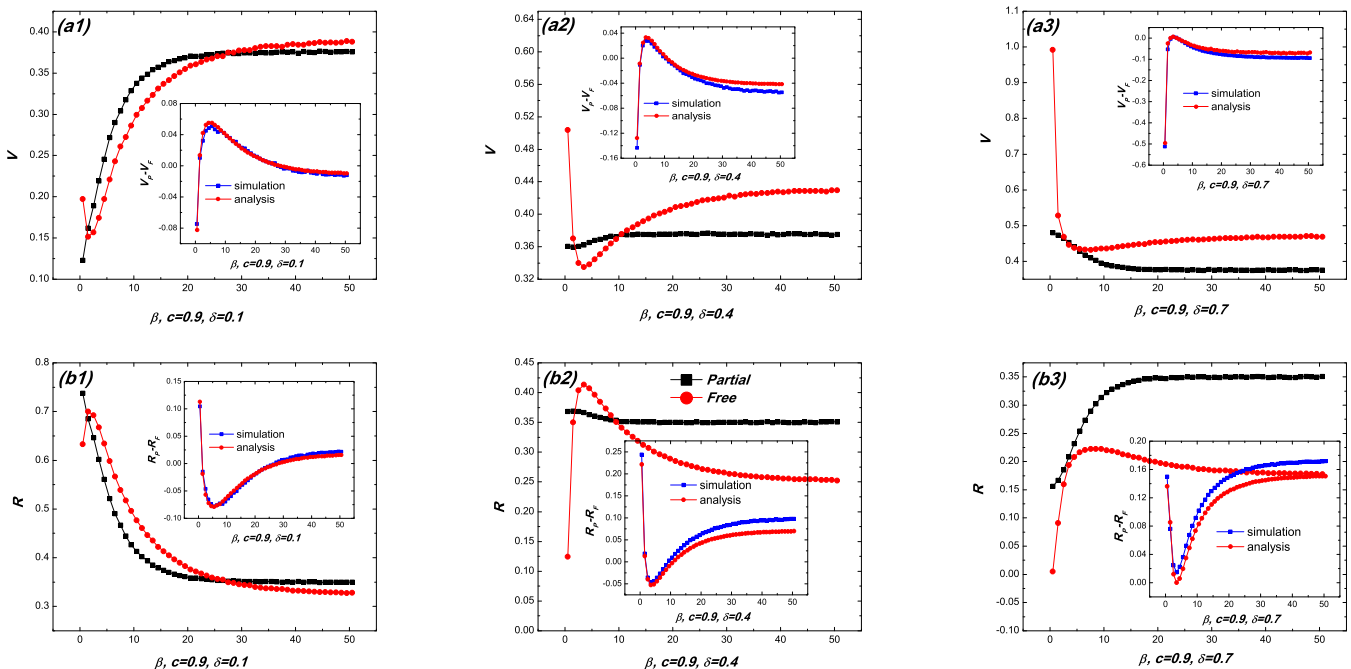


Figure 2 | Impacts of the selection strength β on partial- and free-subsidy policies for large vaccination cost. For HSWN and $c = 0.9$, vaccination coverage V (top panels) and epidemic size R (bottom panels) for the two subsidy policies for different values of δ ($\delta = 0.1, 0.4$ and 0.7 , corresponding to left, central, and right panels, respectively). Other parameters are the same as for Fig. 1.

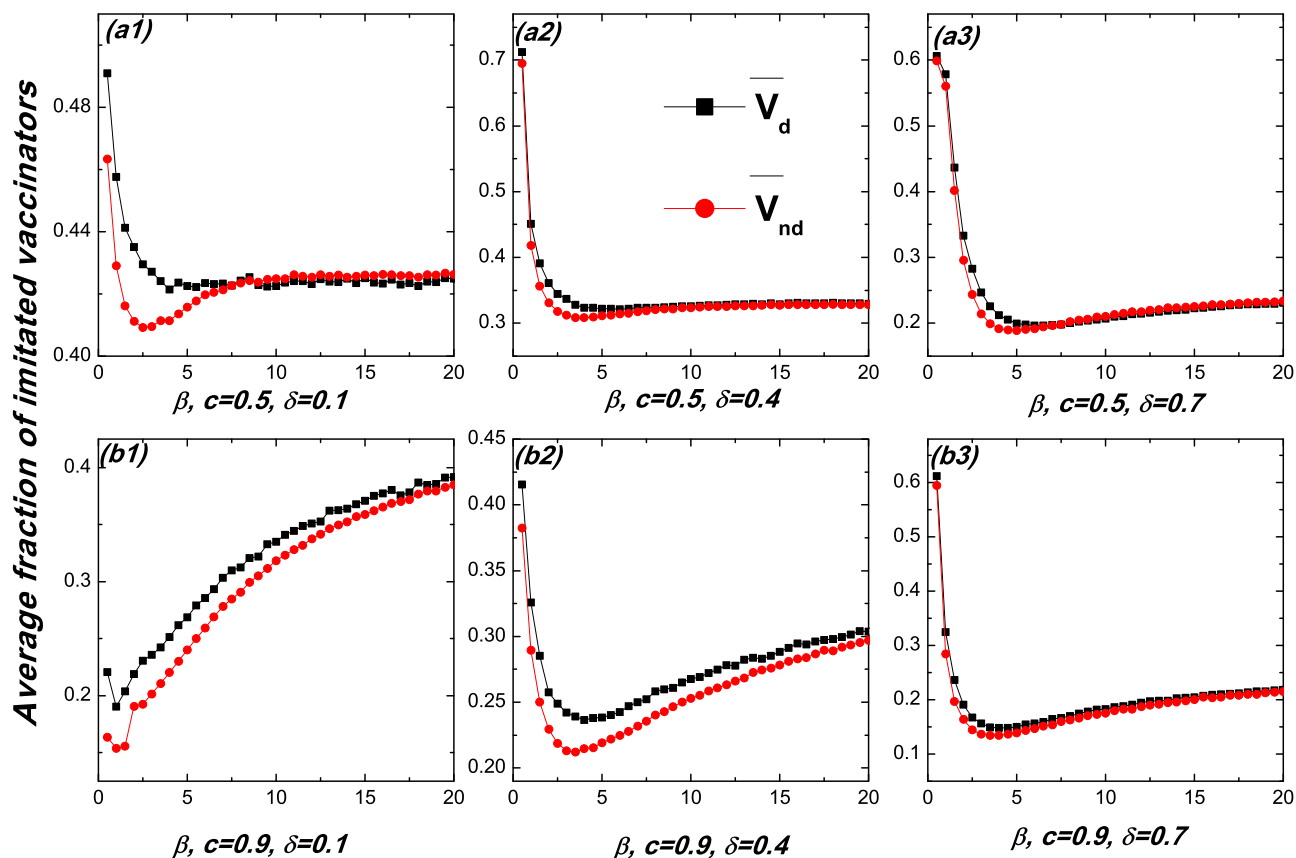


Figure 3 | The role of donees in epidemic dynamics under free-subsidy policy. Average fractions of imitated vaccinators among neighbors of donees (\bar{V}_d) and among non-subsidized vaccinators (\bar{V}_{nd}) for $c = 0.5$ (top panels) and $c = 0.9$ (bottom panels). Other parameters are the same as for Fig. 1.

(excluding donees) among donees' and non-subsidized vaccinators' neighbors, denoted by \bar{V}_d and \bar{V}_{nd} , respectively, for the free-subsidy case, as shown in Fig. 3. We observe that, for different values of c , the value of \bar{V}_d is no less than that of \bar{V}_{nd} , suggesting that the donees act as the "role models" and are more appealing than other vaccinators in attracting their neighbors to take vaccination. To gain further insights, we show in Fig. 4 snapshots of the states of individuals in a square lattice with periodic boundary conditions for the two policies for $c = 0.5$, $\beta = 1.0$ and $\delta = 0.4$, where the vaccination coverage (green) in the partial-subsidy case is lower than the free-subsidy case, leading to larger epidemic size (yellow) in the former case. As speculated, for the free-subsidy case [Fig. 4(b)], the freely vaccinated donees (red) are randomly distributed in the square lattice and they have many surrounding imitated vaccinators, forming *vaccination clusters*, and leading to relatively large vaccination coverage as compared with the partial-subsidy case [Fig. 4(a)].

For intermediate values of β , individuals possess some degree of rationality, so their imitation behaviors are affected by the value of c to certain extent. For example, for $c = 0.5$ (top panels of Fig. 1), as β is increased, while there is a sharp decrease in the vaccination coverage for the free-subsidy case, the coverage is still larger than that for the partial-subsidy case due to the relatively small value of c . However, for $c = 0.9$ (top panels of Fig. 2), the behaviors are different. Especially, when the values of δ are not too large [Figs. 2(a1–a2)], the vaccination coverage for the free-subsidy case is lower than that for the partial-subsidy case. There are two reasons for this. First, the fraction of donees in the population is small, as shown in Fig. 5(a) (red and black lines with $\delta = 0.1$ and $\delta = 0.4$, respectively). Second, large cost discourages other individuals from getting vaccinated. For example, from Fig. 5(b), it can be seen that the fractions of the imitated vaccinators are about 0.1 for $\delta = 0.1$ and 0.17 for $\delta = 0.4$

for $\beta \approx 3.0$. For large values of δ , the fraction of donees in the population is large, as shown in Fig. 5(a) (blue line). In this case, the vaccination coverage for the free-subsidy case is still larger than that for the partial-subsidy case even though the fraction of imitated vaccinators is very small [blue line in Fig. 5(b)]. These results heuristically explain why, under the free-subsidy policy, the vaccination coverages for $\delta = 0.1$ [Fig. 2(a1)] and $\delta = 0.4$ [Fig. 2(a2)] are smaller than that under the partial-subsidy policy but this phenomenon does not occur for $\delta = 0.7$ [Fig. 2(a3)].

In the large β regime (e.g., $\beta \geq 40$ in Figs. 1 and 2), the vaccination coverage for the free-subsidy case is again larger than that for the partial case, regardless of the values of δ and c . In this regime, individuals are *extremely* sensitive to the payoff difference. From Eq. (1), the probabilities for an individual to switch from a vaccinator to a

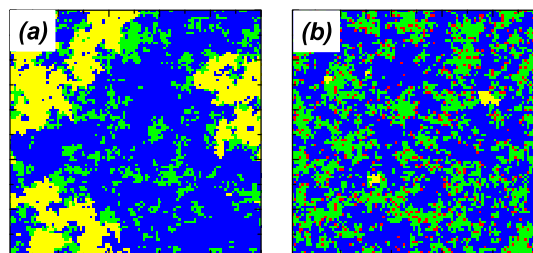


Figure 4 | Typical snapshots of stationary state configuration in a square lattice. Panels (a) and (b) are for partial- and free-subsidy policies, respectively. Other parameters: network size $N = 100 \times 100$, $c = 0.5$, $\beta = 1.0$ and $\delta = 0.4$. Blue, green, yellow, and red points represent free-riders (not vaccinated and healthy), imitated vaccinators, infected individuals, and freely vaccinated donees, respectively.

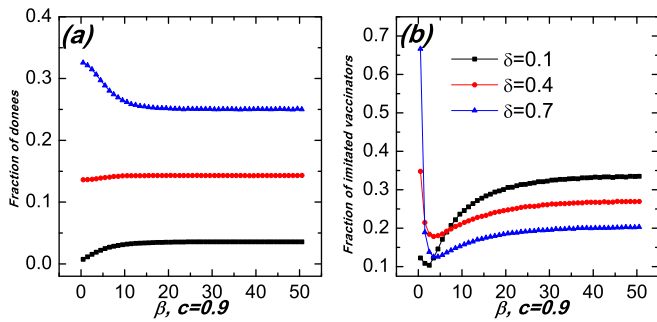


Figure 5 | Fractions of imitated vaccinators and donees under free-subsidy policy. For $c = 0.9$, fractions of donees (a) and imitated vaccinators (b) versus β for different values of δ . Other parameters are the same as for Fig. 1.

free rider and from being infected to a vaccinator are unity, and the other probabilities in the equation are zero insofar as $0 < c < 1$. As a result, the vaccination coverages for the two subsidy cases are not dependent upon the value of c any more. Consequently, the coverage for the partial-subsidy case no longer changes with the value of δ either, because of the condition $0 < c(1 - \delta) < 1$. (Numerical support for this can be found in Figs. 1 and 2, where the vaccination coverage for the partial-subsidy case is about 0.37.) Under the free-subsidy policy, if there are no donees in the population (i.e., $p = 0$), the vaccination coverage should be approximately the same as that for the partial-subsidy case. Furthermore, for the free-subsidy case, since some donees never switch their strategies and thus are capable of attracting some of their neighbors to take vaccination, a higher level of vaccination coverage would arise. This reasoning can also be verified theoretically (see Methods).

For even larger values of β , the equilibrium solution \bar{x} in Eqs. (18) and \hat{x} in Eq. (20) can be obtained by using Eqs. (12) [or Eq. (17)] and (19). In particular, Eq. (18) shows that the vaccination coverage for the partial-subsidy case is not dependent upon the value of c or δ . That is, when individuals become completely rational, the partial-subsidy policy has little effect on the epidemic dynamics. Nevertheless, for the free-subsidy case, Eq. (20) stipulates that the vaccination coverage is larger and in fact increases with the fraction of donees, p , where $p \equiv \delta \cdot V_p$, with V_p being the vaccination coverage for the partial-subsidy case. This gives theoretical support for the observation that the donees under free-subsidy policy can enhance the level of vaccination when individuals are completely rational. Figure 6 shows the simulation results for $\beta = 50$, together with the theoretical prediction from Eqs. (18) and (20). It can be seen that the vaccination coverage for the partial-subsidy case is nearly constant but the coverage for the free-subsidy case increases with the value of δ .

Figures 7 and 8 show the results from mean-field theory (Methods) for a systematic comparison of the effects on epidemic dynamics of the two distinct subsidy policies. In particular, Fig. 7 compares the effects of the two subsidy policies with respect to variations in the parameter plane (β - δ) for $c = 0.5$ and $c = 0.9$. From Fig. 7(a1), one can observe that, for $c = 0.5$, the vaccination coverage for the partial-subsidy policy is no larger than that for the free-subsidy case, rendering inefficient control of outbreak of epidemics using the partial-subsidy policy [Fig. 7(b1)]. For $c = 0.9$, the vaccination coverage for the partial-subsidy case can exceed that for the free-subsidy case but only for the small δ regime, as shown in Figs. 7(a2) and 7(b2). In Fig. 8, the comparison is carried out in the β - c parameter plane for $\delta = 0.1$ and $\delta = 0.7$, where it can be seen that the vaccination coverage for the partial-subsidy case can exceed that for the free-subsidy case only for c close to unity. However, the difference diminishes when δ becomes large, as shown in Fig. 8(b). Taken together, these results suggest that the free-subsidy policy can in

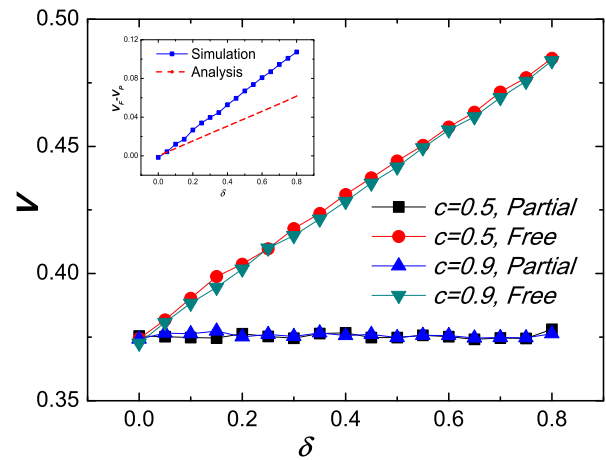


Figure 6 | Stable vaccination coverages under free- and partial-subsidy policy for very large value of β . For $\beta = 50$, numerically obtained difference in the vaccination coverages between the two cases, $V_F - V_P$, and the corresponding theoretical prediction from Eqs. (16)–(18). Other parameters are the same as for Fig. 1.

general control epidemic outbreak more effectively than the partial-subsidy policy, except for large values of c and intermediate values of β .

Real complex networked systems often possess certain degree of skewness in their degree distributions, typically represented by some scale-free topology. We thus implement our model of human-behavior based epidemic dynamics on the Barabási-Albert (BA) scale-free³¹ networks to assess the generality of the phenomena uncovered for regular and homogeneous networks. Figures 9 and 10 illustrate the effects of selection strength β under the two subsidy policies for $c = 0.5$ and $c = 0.9$ ($c = 0.2$ is given in Fig. S2.), respectively. (Results from the configuration network³² are also given in Figs. S3–S5.) We observe essentially similar results to those for HSWN networks (Fig. 1 and Fig. 2). Theoretical results under the two subsidy policies based on Eqs. (3)–(9) are given in the insets of Figs. 9 and 10. We observe a reasonable agreement between theory and numerics.

Discussion

The spontaneous behavioral responses of individuals to epidemic spreading have a significant impact on its dynamics. In the past decade, there was a great deal of interest in the development of mathematical models attempting to close the epidemic spreading \rightarrow behavioral changes \rightarrow epidemic-spreading feed-back loop^{33–44}. In the real world, various subsidy policies are often devised to encourage the individuals to actively participate in disease-prevention programs. However, governmental incentive programs can alter the behavioral responses of individuals, reducing the effectiveness of these programs and even leading to detrimental consequences. Studies of epidemic models should then take into account the interplay among spreading dynamics, individual behaviors, and public policies to yield insights into the complex dynamical process with useful and predictive results.

We propose a vaccination-decision model based on evolutionary game theory to assess the effectiveness of two realistic subsidy policies, the free- and partial-subsidy policies, in a quantitative manner. In particular, using a physically reasonable parameter, the selection strength, we uncover the complex and distinct roles played by the two policies in controlling epidemic spreading. When the partial-subsidy policy is imposed, for small cost of vaccination, individuals' being more rational can lead to smaller vaccination coverage. For high vaccination cost, as the individuals become more rational the vaccination coverage tends to increase. Under the free-subsidy policy, at small vaccination cost the eventual extent of vaccination exhibits

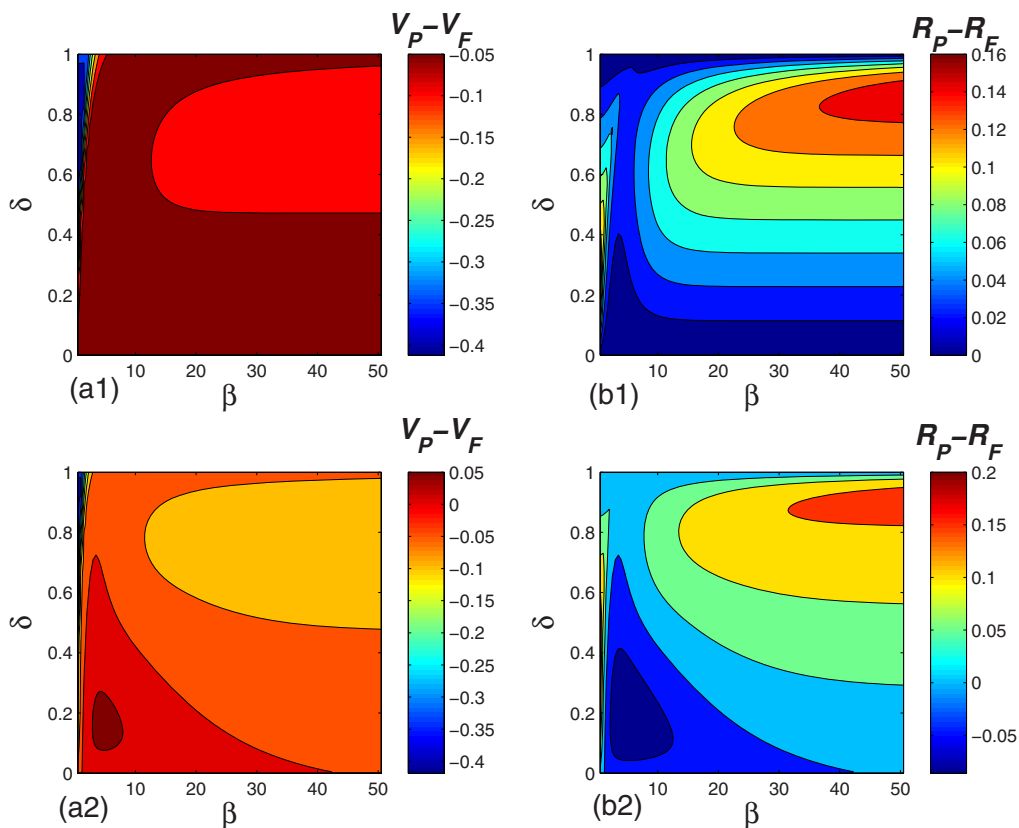


Figure 7 | Comparison between the effects of free- and partial-subsidy policies in the parameter plane (β, δ). Left and right panels: differences in the vaccination coverage and epidemic size, $V_P - V_F$ and $R_P - R_F$, respectively, in the β - δ plane for $c = 0.5$ (a1-b1) and $c = 0.9$ (a2-b2). Other parameters are the same as those in Fig. 1.

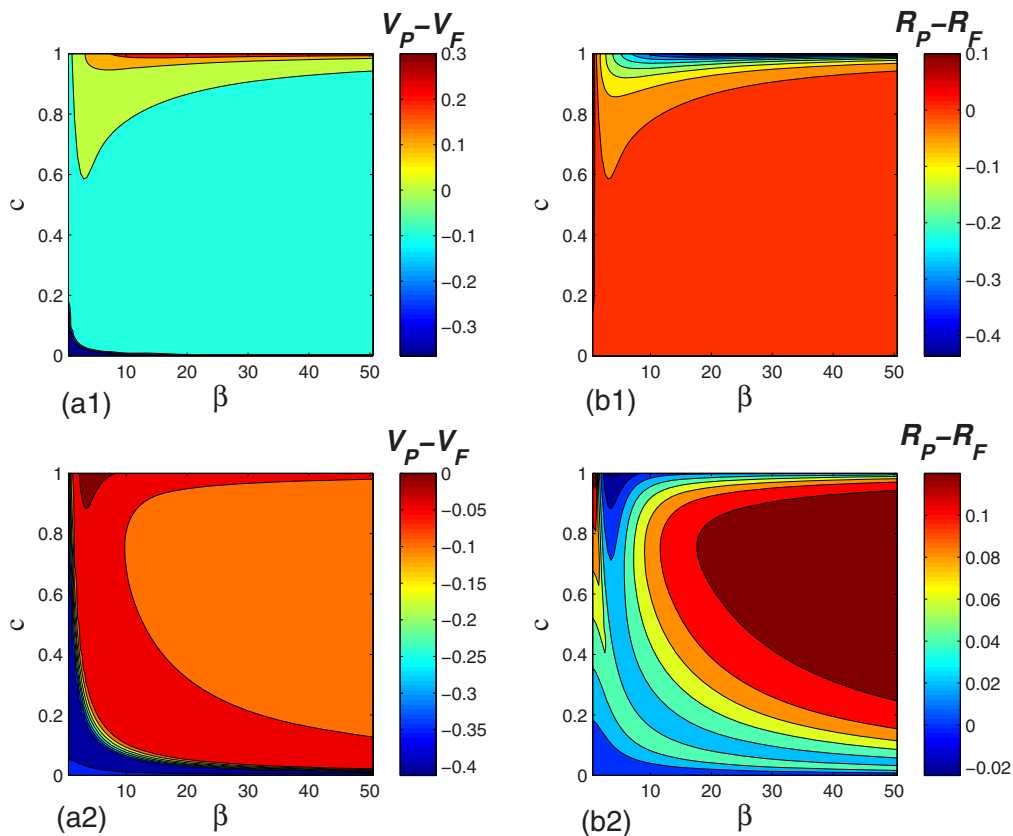


Figure 8 | Comparison between the effects of free- and partial-subsidy policies in the parameter plane (β, c). Left and right panels: differences in the vaccination coverage and epidemic size, $V_P - V_F$ and $R_P - R_F$, respectively, in the β - c plane for $\delta = 0.1$ (a1-b1) and $\delta = 0.7$ (a2-b2). Other parameters are the same as for Fig. 1.

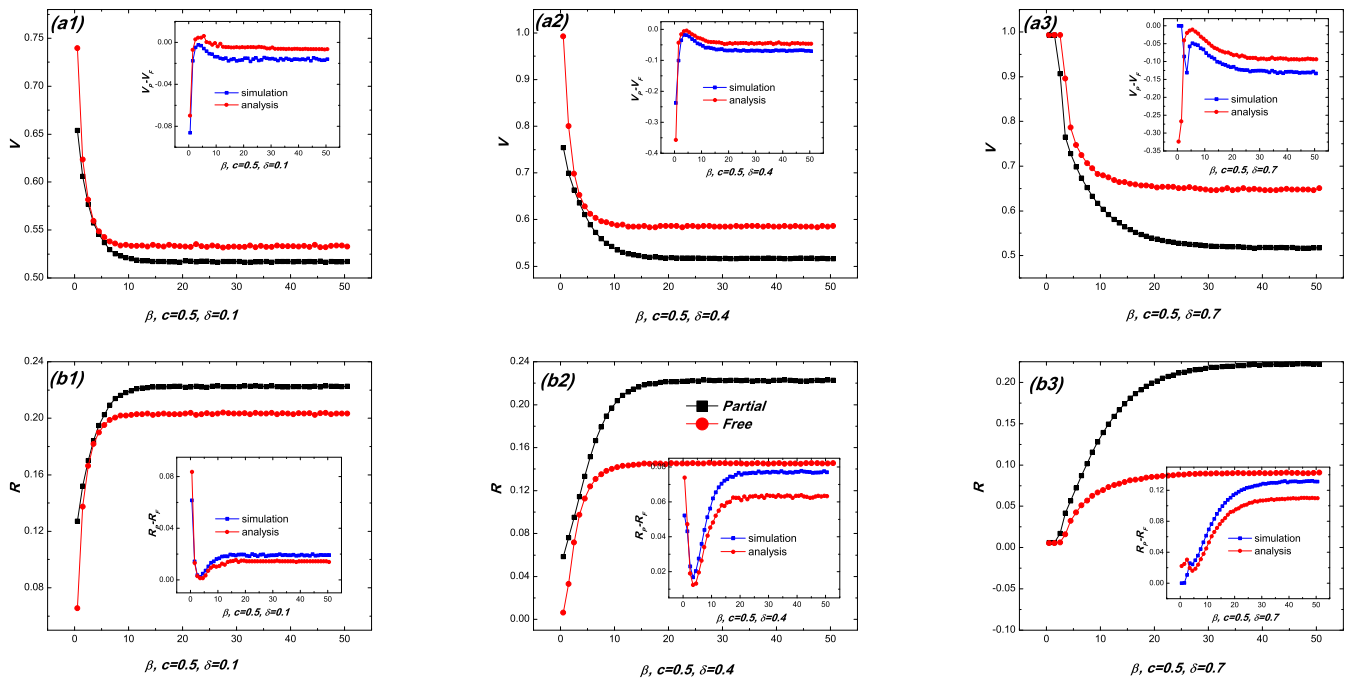


Figure 9 | Impacts of the selection strength β on epidemic dynamics for scale-free networks for small vaccination cost. Vaccination coverage V (top panels) and epidemic size R (bottom panels) under the two subsidy policies for scale-free networks for $c = 0.5$ and $\delta = 0.1, 0.4$ and 0.7 (corresponding to the left, central, and right panels, respectively). Insets in top and bottom panels show the difference in the vaccination coverage, $V_P - V_F$ and the difference in the final epidemic size, $R_P - R_F$, respectively, between the two subsidy policies, where the blue squares and red circles are simulation results and mean-field based theoretical prediction (Methods), respectively. Other parameters are: $N = 1000$, $\lambda = 0.18$, and average degree $\langle k \rangle = 6$.

similar behavior with respect to variations in the individual rationality to that under the partial-subsidy policy. However, for high vaccination cost, a complex chain of relationships emerges. Specifically, for a population with relatively less rational individuals, high vaccination coverage can arise. Having a more rational population of individuals can result in a sharp decline in the vaccination

coverage. For a population of extremely rational individuals, vaccination can be substantially favored again. This counterintuitive phenomenon, namely, under the free-subsidy policy relatively high vaccination coverages can occur in a population of either very irrational or very rational individuals, can be explained by focusing on a natural type of behavioral responses observed commonly in human

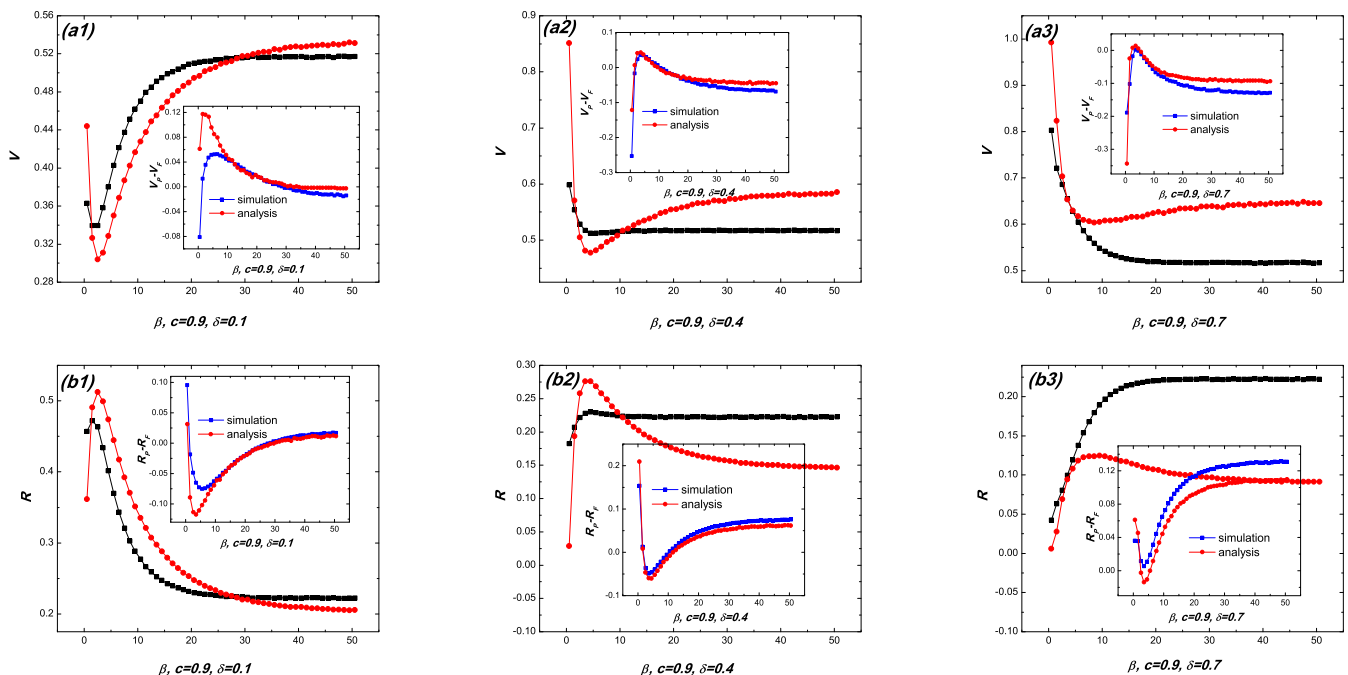


Figure 10 | Impacts of the selection strength β on epidemic dynamics under the partial- and free-subsidy policies for scale-free networks for large vaccination cost. Vaccination coverage V (top panels) and epidemic size R (bottom panels) for the two subsidy policies for $c = 0.9$ and $\delta = 0.1, 0.4$ and 0.7 (corresponding to left, central, and right panels, respectively). Other parameters are the same as those for Fig. 9.



societies: imitation. For irrational individuals, blind imitation behaviors promote the role models of the donees under the free-subsidy policy, leading to a higher vaccination coverage. For very rational individuals, the existence of the donees leads to a higher stable equilibrium in the vaccination coverage under the free-subsidy than under the partial-subsidy policy. All these results have been established by theoretical analysis and extensive computation for both homogeneous and heterogeneous complex networks, with good agreement between the respective results. Taken together, a free-subsidy strategy to control disease can be more effective than a partial-subsidy strategy, but the opposite holds if the level of rationality in the society is neither too low nor too high.

Our efforts may help push one step forward the field of quantitative analysis and mathematical modeling of epidemic spreading and disease control, an problem of paramount importance and broad interest in the modern time where rapid epidemic spreading on a global scale represents one of the most dangerous threats to the human race. Our findings reveal that counterintuitive phenomena can arise due to the complex interplay among epidemic dynamics, human behaviors, and governmental policies. Especially, the making and execution of any disease-control policy should be exercised with extreme caution: its success depends not only on a number of relevant factors but, more importantly, on their dynamical interplay. Our work provides considerable insights into the possible consequences of such interplay, calling for further efforts in this interdisciplinary field.

Methods

Model. Taking into account periodic outbreaks of flu-like diseases and the limited effectiveness of vaccines, we study models with two dynamical ingredients: seasonal updating and pre-emptive vaccination, in which individuals decide whether or not to get vaccinated before each epidemic season. Based on a previously studied model^{6,45}, we integrate the two dynamical ingredients by generating an iterative system of a two-stage process. Firstly, individuals make decisions during a yearly vaccination campaign - the vaccination stage. A vaccinated individual pays a cost C_V that depends on issues such as the time needed to get vaccinated (e.g., via public health services) and potential side effects^{46–48}. For simplicity, we assume that the vaccine provides full protection against the infection in the next epidemic season. The second stage is the epidemic season, during which each susceptible and non-vaccinated individual has certain probability to become infected sometime during the season. In this stage, the epidemic strain infects an initial number I_0 of individuals, and the disease spreads according to susceptible-infected-resistant/vaccinated (SIR) dynamics, with daily transmission rate λ and recovery rate μ . The epidemic continues until there are no more newly infected individuals. An individual who gets infected during the epidemic season pays a cost C_I . Without loss of generality, we rescale the payoff by defining the relative cost of vaccination as $c = C_V/C_I$. Generally, the vaccination cost should be smaller than the cost of infection so that $0 < c < 1$; otherwise, there is no incentive to be vaccinated. Those individuals who are neither vaccinated nor infected pay no cost, so they are the free riders.

Once the epidemic ends, individuals update their vaccination decisions for the next season by imitating the strategy of neighbors who have gained higher payoff. A commonly used updating strategy in evolutionary-game theory is one given by the Fermi rule. By this rule, an individual, say i , updates his/her vaccination strategy by randomly choosing one of the immediate neighbors, say j , compares their costs (or payoff), and adopts the strategy of j with the following probability as determined by the payoff difference⁴⁹:

$$W(s_i \leftarrow s_j) = \frac{1}{1 + \exp[-\beta(P_j - P_i)]}, \quad (1)$$

where $s_j = 1$ or 0 denotes the vaccination choice for individual i : either vaccinated or not, and P_i is the current payoff of individual i at season t . Without any subsidy, according to the costs of vaccination and infection, we have

$$P_i = \begin{cases} -c, & \text{vaccination;} \\ -1, & \text{infected;} \\ 0, & \text{free-rider,} \end{cases} \quad (2)$$

where β is a parameter characterizing the rationality of the individuals. In particular, irrational and very rational individuals correspond to $\beta \ll 1$ and $\beta \gg 1$, respectively.

We implement the above epidemiological/game-theoretic model on HSWNs, constructed by random link rewiring from a regular network such that the degree of each node remains unchanged. In particular, a pair of edges, $A - B$ and $C - D$, are randomly selected. They are then rewired to generate new link pairs $A - D$ and $B - C$. Multiple edges connecting the same pair of nodes are prohibited. The process

continues for PE steps, where E is the number of edges in the network and P characterizes the randomness of the network. For $P > 1$ the network topology is essentially random³⁰. (To be concrete, we set $P = 5.0$.) We also use the BA scale-free networks³¹. In our simulations, the initial state is composed of equal fractions of vaccinated and non-vaccinated individuals, who are randomly distributed throughout the entire population. The number of initially infected individuals is $I_0 = 5$. We calibrate the value of disease transmission probability to ensure that the infection risk in an non-vaccinated population is equal across all possible contact configuration. The transmission rate is chosen to be $\lambda = 0.072$ per day per person for HSWN with average degree 10, and $\lambda = 0.18$ per day per person for BA scale-free network with average degree 6. The value of μ is chosen to be $\mu = 0.25$ per day for all contact pairs to ensure that the final infection size is about $0.9^{6,25}$. We carry our 100 independent statistical realizations and, for each realization, the simulation is run for 3000 iterations, where the last 1000 iterations are used to calculate the statistical quantities about the epidemic.

Steps are also taken to ensure fair comparison between the two types of subsidy policies. In particular, for partial-subsidy policy, each vaccinated individual has his/her vaccination cost reduced by the relative amount δ , so the actual cost paid by the individual is $c(1 - \delta)$. The total amount of subsidy is $c\delta \sum_{t=1}^T N_V(t)$, where T is the total number of iterations and $N_V(t)$ is the total number of vaccinated individuals at season t . Under the free-subsidy policy, the total amount of subsidy is equally allocated to each vaccination stage, so the number of freely vaccinated donees at each stage is $c\delta \sum_{t=1}^T N_V(t) / (Tc) = \delta \sum_{t=1}^T N_V(t) / T$. Since, in this case, the number of donees at each vaccination stage is unchanged, we do not choose donees randomly at the following vaccination stages. That is, if one individual is selected as a donee for the initial season $t = 1$, then the individual will be a donee for subsequent seasons.

Analysis of epidemic dynamics in networks. For a complex network with degree distribution $P(k)$, we let $S_k(t)$, $I_k(t)$, $R_k(t)$ be the densities of susceptible, infected and recovery nodes of degree k at time t , respectively, where $S_k(t) + I_k(t) + R_k(t) \equiv 1$. Under the mean-field approximation, the time evolutions of the densities are given by the following set of coupled differential equations⁵⁰:

$$\begin{aligned} \frac{dS_k(t)}{dt} &= -\lambda k S_k(t) \Theta(t), \\ \frac{dI_k(t)}{dt} &= \lambda k S_k(t) \Theta(t) - \mu I_k(t), \\ \frac{dR_k(t)}{dt} &= \mu I_k(t), \end{aligned} \quad (3)$$

where the factor $\Theta(t) = \sum_k P(k|k) I_k(t)$ represents the probability that any given link points to an infected node. In absence of any degree correlations, $\Theta(t)$ is given by⁵¹

$$\Theta(t) = \sum_k k P(k) I_k(t) / \langle k \rangle.$$

Let x_k be the density of vaccinated nodes with degree k before the epidemic season. We have

$$\begin{aligned} \frac{dI_k(t)}{dt} &= \lambda k (1 - x_k - I_k(t) - R_k(t)) \Theta(t) - \mu I_k(t), \\ \frac{dR_k(t)}{dt} &= \mu I_k(t), \end{aligned} \quad (4)$$

After each epidemic season, one can obtain the degree-dependent fraction of epidemic size $R_k(\infty)$.

Without any subsidy policy, the payoff of each individual after each SIR epidemic season is given by Eq. (2). Specifically, for a vaccinated individual (V), the payoff is $P_V = -c$. For an non-vaccinated and healthy individual (H), we have $P_H = 0$. For an non-vaccinated and infected individual (I), the payoff is $P_I = -1$. Individuals are allowed to switch their vaccination strategies with probability given by Eq. (1).

Under the partial-subsidy policy, a vaccinated individual's payoff is modified as $P_{SV} = (1 - \delta)c$, where SV stands for subsidized vaccinators. In this case, whenever an SV changes to H or I state, the variable x_k is decreased according to

$$\begin{aligned} x_k^- &= \frac{x_k}{\langle k \rangle} \sum_k k P(k) R_k(\infty) W_{SV \rightarrow I} \\ &+ \frac{x_k}{\langle k \rangle} \sum_k k P(k) (1 - R_k(\infty) - x_k) W_{SV \rightarrow H}, \end{aligned} \quad (5)$$

where the first and second terms on the right-hand side of Eq. (5) denote the transitions from vaccinators to infected individuals and from vaccinators to free-riders, respectively. In the opposite case where an individual in H or I state is changed to being an SV individual, x_k is increased according to

$$\begin{aligned} x_k^+ &= \frac{R_k(\infty)}{\langle k \rangle} \sum_k k P(k) x_k W_{I \rightarrow SV} \\ &+ \frac{(1 - R_k(\infty) - x_k)}{\langle k \rangle} \sum_k k P(k) x_k W_{H \rightarrow SV}. \end{aligned} \quad (6)$$



Combining Eqs. (5) and (6), we can write the time evolution of the vaccination coverage x_k as

$$\frac{dx_k(\tau)}{d\tau} = x_k^+ - x_k^- \quad (7)$$

Here, to avoid confusion, we use t to specify the epidemic season and τ as the time variable for epidemic seasons. The equilibrium vaccination coverage and the final epidemic size can be calculated by numerically solving Eqs. (4) and (7) iteratively.

On average, the total amount of subsidy at each vaccination stage is $Nxc\delta$ for the partial-subsidy case with $x = \sum_k P(k)x_k$, so the fraction of freely vaccinated donees under the free-subsidy policy is $p = Nxc\delta/(Nc) = x\delta$. Similar to Eq. (5), the reduction in x_k^- , with freely vaccinated donees included, can be written as:

$$x_k^- = \frac{x_k - p}{\binom{k}{k}} \left\{ \sum_k kP(k)R_k(\infty)W_{V \rightarrow I} + \sum_k kP(k)(1 - R_k(\infty) - x_k)W_{V \rightarrow H} \right\}, \quad (8)$$

where $x_k - p$ is the fraction of the individuals with degree k that can change their vaccination strategy. Meanwhile, it is not necessary to replace p by p_k since the donees are randomly selected. The gain of x_k^+ for the free-subsidy case is given by

$$x_k^+ = \frac{R_k(\infty)}{\binom{k}{k}} \sum_k kP(k)x_k W_{I \rightarrow V} + \frac{(1 - R_k(\infty) - x_k)}{\binom{k}{k}} \sum_k kP(k)x_k W_{H \rightarrow V}. \quad (9)$$

For HSWNs under the partial-subsidy policy, $R_k(\infty)$ and x_k in Eqs. (5) and (6) can be replaced by $R(\infty)$ and x , respectively. By using Eq. (13) below [$R(\infty) = (1 - x)f(x)$], we can simplify Eqs. (5) and (6) as

$$x^- = x(1 - x)[f(x)W_{SV \rightarrow I} + (1 - f(x))W_{SV \rightarrow H}], \quad (10)$$

and

$$x^+ = x(1 - x)[f(x)W_{I \rightarrow SV} + (1 - f(x))W_{H \rightarrow SV}]. \quad (11)$$

After some straightforward algebra, we have

$$\begin{aligned} \frac{dx(\tau)}{d\tau} &= x(1 - x) \left\{ [1 - f(x)] \tanh \left[\frac{\beta}{2}(P_{SV} - P_H) \right] + f(x) \tanh \left[\frac{\beta}{2}(P_{SV} - P_I) \right] \right\} \\ &= x(1 - x) \left\{ [1 - f(x)] \tanh \left[\frac{\beta}{2}(-c(1 - \delta)) \right] + f(x) \tanh \left[\frac{\beta}{2}(-c(1 - \delta) + 1) \right] \right\}, \end{aligned} \quad (12)$$

where $f(x)$ is the probability that a susceptible individual finally gets infected in a population with vaccine coverage x , which is given by

$$f(x) = \frac{R(\infty)}{1 - x}. \quad (13)$$

The final epidemic size, $R(\infty)$, can then be determined by

$$\begin{aligned} \frac{dI(t)}{dt} &= \lambda \bar{k}(1 - x - I(t) - R(t))I(t) - \mu I(t), \\ \frac{dR(t)}{dt} &= \mu I(t), \end{aligned} \quad (14)$$

with \bar{k} being the degree of each node. Using a similar method of analysis for well-mixed network^{4,6}, we obtain the following self-consistent equation from Eq. (14):

$$R(\infty) = (1 - x) \left[1 - e^{-R_0 R(\infty)} \right], \quad (15)$$

where $R_0 = \bar{k}\lambda/\mu$ is the basic reproduction ratio of the epidemic. Combining Eqs. (13) and (15), we have

$$x = 1 + \frac{\ln(1 - f(x))}{R_0 f(x)}. \quad (16)$$

Setting the right-hand side of Eq. (12) to be 0, we get

$$f(x) = \frac{\tanh\left(\frac{-\beta}{2}c(1 - \delta)\right)}{\tanh\left(\frac{-\beta}{2}c(1 - \delta)\right) - \tanh\left(-\frac{\beta}{2}(c(1 - \delta) - 1)\right)}. \quad (17)$$

Substituting Eq. (17) into Eq. (16), we can obtain the steady vaccination coverage.

For large values of β , most values of c lie in the interval $1/\beta < (1 - \delta)c < 1 - 1/\beta$ since $1/\beta \rightarrow 0$. In this case, we have

$$f(x) = 1/2 \left[\tanh\left(\frac{-\beta}{2}c(1 - \delta)\right) \rightarrow -1 \text{ and } \tanh\left(-\frac{\beta}{2}(c(1 - \delta) - 1)\right) \rightarrow 1 \right].$$

Then, by substituting $f(x) = 1/2$ into Eq. (16) we have the following equilibrium solution under the partial-subsidy policy:

$$\bar{x} = 1 - \frac{2 \ln 2}{R_0}. \quad (18)$$

For HSWNs under the free-subsidy policy, by simplifying Eqs. (8) and (9) and writing them as Eq. (12), we have

$$\begin{aligned} \frac{dx(\tau)}{d\tau} &= x(1 - x)[(1 - f(x))W_{H \rightarrow V} + f(x)W_{I \rightarrow V}] \\ &\quad - (x - p)(1 - x)[(1 - f(x))W_{V \rightarrow H} + f(x)W_{V \rightarrow I}]. \end{aligned} \quad (19)$$

We can obtain the formula of $f(x)$ by letting the right-hand side of Eq. (19) be 0, and then substituting it into Eq. (16).

The steady-state vaccination coverage for the free-subsidy case can be numerically solved too. Especially, for large values of β , and c satisfying $1/\beta < c < 1 - 1/\beta$, the switch probabilities in Eq. (19) can be approximated as: $W_{H \rightarrow V} = 0$, $W_{I \rightarrow V} = 1$, $W_{V \rightarrow H} = 1$ and $W_{V \rightarrow I} = 0$, so we have $f(x) = (x - p)/(2x - p)$. Substituting it into Eq. (16), we obtain the following self-consistent equation for the equilibrium value \hat{x} for the free-subsidy case as

$$\hat{x} = 1 + \frac{(2\hat{x} - p) \ln \frac{\hat{x}}{2\hat{x} - p}}{R_0(\hat{x} - p)}. \quad (20)$$

- Stöhr, K. & Esveld, M. Will vaccines be available for the next influenza pandemic? *Science* **306**, 2195–2196 (2004).
- Reluga, T. C., Bauch, C. T. & Galvani, A. P. Evolving public perceptions and stability in vaccine uptake. *Math. Biosci.* **204**, 185–198 (2006).
- Mbah, M. L. N. *et al.* The impact of imitation on vaccination behavior in social contact networks. *PLoS Comput. Biol.* **8**, e1002469 (2012).
- Wu, B., Fu, F. & Wang, L. Imperfect vaccine aggravates the long-standing dilemma of voluntary vaccination. *PLoS One* **6**, e20577 (2011).
- Santos, F. C., Santos, M. D. & Pacheco, J. M. Social diversity promotes the emergence of cooperation in public goods games. *Nature* **454**, 213–216 (2008).
- Fu, F., Rosenbloom, D. I., Wang, L. & Nowak, M. A. Imitation dynamics of vaccination behaviour on social networks. *P. Roy. Soc. B-Biol. Sci.* **278**, 42–49 (2011).
- Liu, X.-T., Wu, Z.-X. & Zhang, L. Impact of committed individuals on vaccination behavior. *Phys. Rev. E* **86**, 051132 (2012).
- Zhang, H., Zhang, J., Zhou, C., Small, M. & Wang, B. Hub nodes inhibit the outbreak of epidemic under voluntary vaccination. *New. J. Phys.* **12**, 023015 (2010).
- Zhang, H., Zhang, J., Li, P., Small, M. & Wang, B. Risk estimation of infectious diseases determines the effectiveness of the control strategy. *Physica D* **240**, 943–948 (2011).
- Bauch, C. T., Galvani, A. P. & Earn, D. J. Group interest versus self-interest in smallpox vaccination policy. *Proc. Natl. Acad. Sci. USA.* **100**, 10564 (2003).
- Bauch, C. T. & Earn, D. J. Vaccination and the theory of games. *Proc. Natl. Acad. Sci. USA.* **101**, 13391–13394 (2004).
- Bauch, C. T. Imitation dynamics predict vaccinating behaviour. *P. Roy. Soc. B-Biol. Sci.* **272**, 1669–1675 (2005).
- Galvani, A. P., Reluga, T. C. & Chapman, G. B. Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum. *Proc. Natl. Acad. Sci. USA.* **104**, 5692–5697 (2007).
- Vardavas, R., Breban, R. & Blower, S. Can influenza epidemics be prevented by voluntary vaccination? *PLoS Comput. Biol.* **3**, e85 (2007).
- Reluga, T. C. & Galvani, A. P. A general approach for population games with application to vaccination. *Math. Biosci.* **230**, 67–78 (2011).
- Cornforth, D. M. *et al.* Erratic flu vaccination emerges from short-sighted behavior in contact networks. *PLoS Comput. Biol.* **7**, e1001062 (2011).
- Sahneh, F. D., Chowdhury, F. N. & Scoglio, C. M. On the existence of a threshold for preventive behavioral responses to suppress epidemic spreading. *Sci. Rep.* **2**, 632 (2012).
- Ball, F. G. & Lyne, O. D. Optimal vaccination policies for stochastic epidemics among a population of households. *Math. Biosci.* **177**, 333–354 (2002).
- Francis, P. J. Optimal tax/subsidy combinations for the flu season. *J. Econ. Dyn. Control* **28**, 2037–2054 (2004).
- Lin, F., Muthuraman, K. & Lawley, M. An optimal control theory approach to non-pharmaceutical interventions. *BMC Infect. Dis.* **10**, 32 (2010).
- Bhattacharyya, S. & Bauch, C. Mathematical models of the interplay between individual vaccinating decisions and disease dynamics: a need for closer integration of models and data. *Hum. Vacc. Immunother.* **8**, 842–844 (2012).
- Wells, C. R., Klein, E. Y. & Bauch, C. T. Policy resistance undermines superspreader vaccination strategies for influenza. *PLoS Comput. Biol.* **9**, e1002945 (2013).
- Rat-Aspert, O. & Fourichon, C. Modelling collective effectiveness of voluntary vaccination with and without incentives. *Prev. Vet. Med.* **93**, 265–275 (2010).
- Perlis, A. & Bauch, C. T. Social contact networks and disease eradication under voluntary vaccination. *PLoS Comput. Biol.* **5**, e1000280 (2009).



25. Zhang, H.-F. *et al.* Impacts of subsidy policies on vaccination decisions in contact networks. *Phys. Rev. E* **88**, 012813 (2013).
26. Wang, Z., Kokubo, S., Tanimoto, J., Fukuda, E. & Shigaki, K. Insight into the so-called spatial reciprocity. *Phys. Rev. E* **88**, 042145 (2013).
27. Wang, Z., Wang, L., Yin, Z.-Y. & Xia, C.-Y. Inferring reputation promotes the evolution of cooperation in spatial social dilemma games. *PLoS One* **7**, e40218 (2012).
28. Jin, Q., Wang, L., Xia, C.-Y. & Wang, Z. Spontaneous symmetry breaking in interdependent networked game. *Sci. Rep.* **4**, 4095 (2014).
29. Ren, J., Wang, W.-X. & Qi, F. Randomness enhances cooperation: a resonance-type phenomenon in evolutionary games. *Phys. Rev. E* **75**, 045101 (2007).
30. Lü, L., Chen, D.-B. & Zhou, T. The small world yields the most effective information spreading. *New. J. Phys.* **13**, 123005 (2011).
31. Barabási, A.-L. & Albert, R. Emergence of scaling in random networks. *Science* **286**, 509–512 (1999).
32. Newman, M. E., Strogatz, S. H. & Watts, D. J. Random graphs with arbitrary degree distributions and their applications. *Phys. Rev. E* **64**, 026118 (2001).
33. Wu, Q., Fu, X., Small, M. & Xu, X.-J. The impact of awareness on epidemic spreading in networks. *Chaos* **22**, 013101 (2012).
34. Gross, T., D'Lima, C. J. D. & Blasius, B. Epidemic dynamics on an adaptive network. *Phys. Rev. Lett.* **96**, 208701 (2006).
35. Funk, S., Salathé, M. & Jansen, V. A. Modelling the influence of human behaviour on the spread of infectious diseases: a review. *J. R. Soc. Interface* **7**, 1247–1256 (2010).
36. Funk, S., Gilad, E., Watkins, C. & Jansen, V. A. The spread of awareness and its impact on epidemic outbreaks. *Proc. Natl. Acad. Sci. USA*. **106**, 6872–6877 (2009).
37. Poletti, P., Ajelli, M. & Merler, S. The effect of risk perception on the 2009 h1n1 pandemic influenza dynamics. *PLoS One* **6**, e16460 (2011).
38. Perra, N., Balcan, D., Gonçalves, B. & Vespignani, A. Towards a characterization of behavior-disease models. *PLoS One* **6**, e23084 (2011).
39. Wang, L., Zhang, Y., Huang, T. & Li, X. Estimating the value of containment strategies in delaying the arrival time of an influenza pandemic: A case study of travel restriction and patient isolation. *Phys. Rev. E* **86**, 032901 (2012).
40. Meloni, S. *et al.* Modeling human mobility responses to the large-scale spreading of infectious diseases. *Sci. Rep.* **1**, 62 (2011).
41. Wang, B., Cao, L., Suzuki, H. & Aihara, K. Safety-information-driven human mobility patterns with metapopulation epidemic dynamics. *Sci. Rep.* **2**, 887 (2012).
42. Yang, H., Tang, M. & Zhang, H.-F. Efficient community-based control strategies in adaptive networks. *New. J. Phys.* **14**, 123017 (2012).
43. Granell, C., Gomez, S. & Arenas, A. Dynamical interplay between awareness and epidemic spreading in multiplex networks. *Phys. Rev. Lett.* **111**, 128701 (2013).
44. Wang, L., Wang, Z., Zhang, Y. & Li, X. How human location-specific contact patterns impact spatial transmission between populations? *Sci. Rep.* **3**, 1468 (2013).
45. Zhang, H.-F., Yang, Z., Wu, Z.-X., Wang, B.-H. & Zhou, T. Braess's paradox in epidemic game: Better condition results in less payoff. *Sci. Rep.* **3**, 3292 (2013).
46. Cardillo, A., Reyes-Suárez, C., Naranjo, F. & Gómez-Gardeñes, J. Evolutionary vaccination dilemma in complex networks. *Phys. Rev. E* **88**, 032803 (2013).
47. Xia, S. & Liu, J. A computational approach to characterizing the impact of social influence on individuals vaccination decision making. *PLoS One* **8**, e60373 (2013).
48. Wu, Z.-X. & Zhang, H.-F. Peer pressure is a double-edged sword in vaccination dynamics. *Europhys. Lett.* **104**, 10002 (2013).
49. Szabó, G. & Tóke, C. Evolutionary prisoner's dilemma game on a square lattice. *Phys. Rev. E* **58**, 69 (1998).
50. Moreno, Y., Pastor-Satorras, R. & Vespignani, A. Epidemic outbreaks in complex heterogeneous networks. *Eur. Phys. J. B* **26**, 521–529 (2002).
51. Xia, C.-Y., Wang, Z., Sanz, J., Meloni, S. & Moreno, Y. Effects of delayed recovery and nonuniform transmission on the spreading of diseases in complex networks. *Physica A* **392**, 1577–1585 (2013).

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Author contributions

H.F.Z., Z.X.W., M.T. and Y.C.L. designed research. H.F.Z. and M.T. performed numerical computations. H.F.Z. and Z.X.W. conducted theoretical analysis. H.F.Z. and Y.C.L. wrote the manuscript.

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