Vaccination and the evolution of seasonal influenza

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Abstract

Although vaccines against seasonal influenza are designed to protect against currently circulating strains, they may also affect the emergence of antigenically divergent strains and thereby change the rate of antigenic evolution. Such evolutionary effects could change the benefits that vaccines confer to vaccinated individuals and to the host population (i.e., the private and social benefits of vaccination). To investigate the potential evolutionary impacts of vaccination, we simulated the dynamics of an influenza A/H3N2-like pathogen in a host population receiving annual vaccines. On average, increasing vaccination rates decreased the cumulative amount of antigenic evolution of the viral population and the incidence of disease. Vaccination at a 5% random annual vaccination rate, implying a 48% cumulative vaccine coverage after 20 years, decreased cumulative evolution by 56% and incidence by 76%. These effects were mediated by the breadth of immunity conferred by the vaccine. To understand how the evolutionary effects of vaccination might affect its private and social benefits over multiple seasons, we fit linear panel models to simulated longitudinal infection and vaccination histories. Including the evolutionary effects of vaccination lowered the private benefits by 14% but increased the social benefits by 30% (at a 5% annual vaccination rate) compared to when evolutionary effects were ignored. Thus, in the long term, vaccines' private benefits may be lower and social benefits may be higher than predicted by current measurements of vaccine impact, which do not capture long-term evolutionary effects. These results suggest that conventional seasonal vaccines against influenza, if protective against transmission, could greatly reduce the burden of disease by slowing antigenic evolution. Additionally, these evolutionary effects could compound collective action problems, increasing the importance of social policies to encourage vaccination.

1 Introduction

As seasonal influenza evolves from year to year, antigenic differences between previously and currently circulating strains contribute to low vaccine efficacy [1–4] and high incidence of influenza

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illness [2, 5]. The influenza A/H3N2 subtype evolves faster than influenza A/H1N1 and B [6], and the vaccine is least effective against A/H3N2 on average compared to other circulating subtypes [7]. While vaccines regularly undergo reformulation to accommodate antigenic evolution, it is also theoretically possible for vaccines to affect antigenic evolution [8]. Traditional estimates of the public health benefits of influenza vaccines tend to focus on the benefits of vaccination in the current season and assume viral evolution is unchanged by the vaccine [9–12]. Accounting for the potential evolutionary impact of vaccines, however, may alter assessments of their long-term value.

In theory, seasonal influenza vaccines might be able to slow antigenic evolution [13–15]. Universal vaccines, which confer immunity against all antigenic variants, are predicted to slow antigenic evolution by uniformly decreasing the fitness of all strains [15]. Conventional vaccines against seasonal influenza, which protect against some strains more than others and thereby confer narrower immunity, might have similar effects. First, by reducing the prevalence of infection, they reduce viral population size and thus the probability that antigenic escape mutants will arise. Second, although vaccination increases the growth rate of antigenically distant mutants relative to less distant mutants (which can lead to strain replacement in other pathogens [16–26]), it also increases the amount of immunity in the population. This increased immunity reduces the growth rate or invasion fitness of escape mutants, slowing the rate of strain replacement (SI 1.1, Eq. S19, Fig. S1). Finally, smaller viral population sizes increase the rate at which different strains go stochastically extinct, weakening selection for more antigenically diverged strains. However, vaccination might *accelerate* antigenic evolution if the vaccine is ineffective against some strains that compete with vaccine-targeted strains, leading to strain replacement or vaccine escape [27, 28].

Vaccination's potential evolutionary effects may change the private and social benefits of vaccination. Vaccination confers a private benefit to vaccinated individuals by directly reducing their risk of infection: the vaccine reduces the within-season rate of clinical laboratory-confirmed influenza infections in healthy adult recipients by 41% (95% CI 36-47%) [29]. Vaccination also confers a social benefit to the host population by reducing the burden of disease, although these effects are infrequently measured. Vaccinating children reduces the risk of influenza infection in unvaccinated household contacts by 30-40% [30, 31], in the local community by up to 5-82% [32], and in a metropolitan county by up to 59% [33]. The valuation of private and social benefits changes according to how much vaccination decreases the burden of disease. If vaccines slow antigenic evolution and thereby further decrease incidence, then the social benefit increases. However, the private benefit may fall as the lower infection risk reduces vaccines' marginal protective benefit. As the private benefit falls, additional incentives might be necessary to compensate for less frequent voluntary vaccination [34,35]. A reduction in antigenic evolution from vaccination could also reduce the need to update vaccines as frequently.

Empirical estimates of the benefits of vaccination have so far been unable to measure the potential long-term evolutionary effects of vaccination. Most studies estimating the value of vaccination occur in temperate populations such as North America, Europe, and Oceania, which have high vaccine coverage but do not consistently contribute to influenza's long-term evolution [7, 36–39]. By contrast, source populations that contribute more to influenza's evolution (e.g., China and India) have almost zero vaccination [36–38], and few studies of vaccination occur there [40].

We consider here the consequences of an idealized vaccination strategy, where vaccination occurs in populations that shape influenza's long-term evolution. To assess the potential effects of vaccines on antigenic evolution, we simulated the evolutionary and epidemiological dynamics of an influenza-like pathogen. We evaluated how different rates of vaccination may slow antigenic evolution and in turn decrease the total burden of disease. We then quantified how the evolutionary effects change the relative magnitude of the private and social benefits of vaccination in the short and long term.

2 Results

2.1 Modeling approach and choice of parameters

We adapted a model to simulate the transmission and evolution of an influenza-like pathogen over 20 years in a well-mixed population (Methods) [41]. Individuals infected with a strain of the virus can transmit their infection to susceptible individuals upon contact. The risk of infection given contact depends on the antigenic identities (phenotypes) of previous infections and the challenging strain. After recovering from infection, individuals acquire immunity against the infecting strain, whose antigenic phenotype is represented by a point in two-dimensional Euclidean space (Fig. 1A). Geometrically distributed mutations displace strains in this space (Table S1, Fig. 1D). This space is analogous to the main components after multidimensional scaling of pairwise measurements of cross-reactivity in hemagglutination inhibition (HI) assays, where one antigenic unit of distance represents a twofold dilution of antiserum [6,42]. Each antigenic unit difference in distance between strains increases susceptibility by 7% (Fig. 1C) [1, 41, 43].

The model reproduces characteristic epidemiological and evolutionary patterns of the A/H3N2 subtype in the absence of vaccination (Fig. 1A,B). Unvaccinated populations are best for model validation because they contribute most to the evolution of seasonal influenza in reality [36, 38]. We chose transmission and mutation parameters (Table S1) such that simulated epidemiological and evolutionary patterns most resembled qualitative patterns observed for H3N2 [44]. H3N2 has remained endemic in the human population since its emergence in 1968 and also has low standing genetic and antigenic diversity. Due to the stochastic nature of the simulations, the viral population goes extinct 18% of the time and becomes too diverse 29% of the time across replicate simulations. A viral population is considered too diverse when the time separating two co-circulating lineages (time to most recent common ancestor, or TMRCA) exceeds 10 years, since recent H3N2 HA lineages have coexisted for no more than 7 years. The remaining 53% of simulations that show qualitatively influenza-like dynamics reproduce epidemiological and evolutionary statistics of H3N2. The viral population has low genealogical diversity with an average TMRCA across replicates of 3.80 years (SD = 0.52), comparable to empirical estimates of 3.84 years [38]. The path of evolution in antigenic space is mostly constrained to one dimension (Fig. 1A), characteristic of H3N2's antigenic evolution [6,42]. Antigenic evolution occurs at an average rate of 1.09 antigenic units per year (SD = 0.14), comparable to an observed rate of 1.01 antigenic units per year [6]. The mean annual incidence is 9.0% (SD = 1.0%). Annual incidence across all types of seasonal influenza ranges from 9-15% [45]. To confirm the accuracy of the model's transmission dynamics, we compared model outputs against analytic expectations without evolution (since analytic solutions for a model with evolution are intractable) (Figs. S2, S3, S4, and S5).

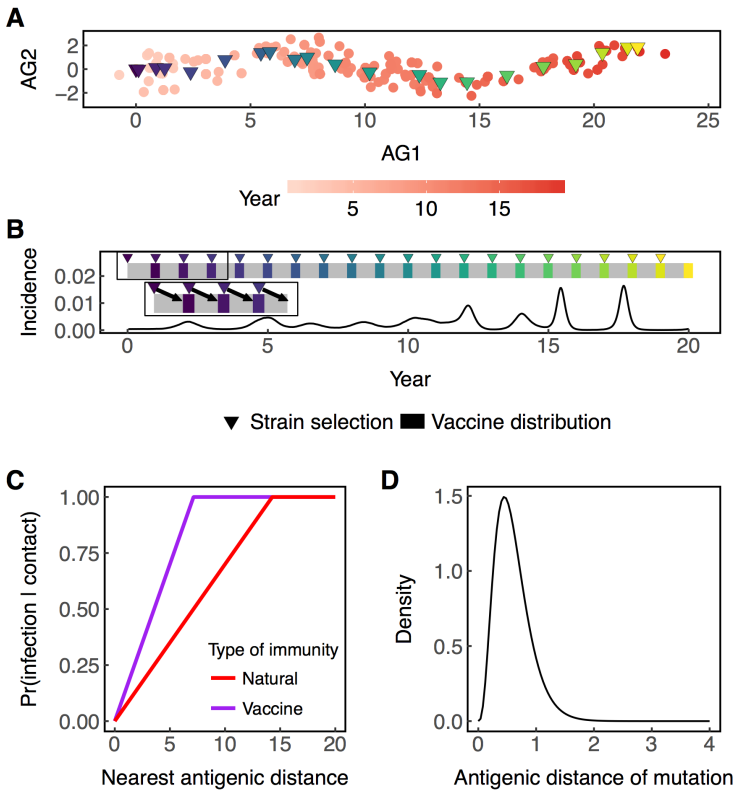

Figure 1: Properties of the model. (A) Antigenic phenotypes are represented as points in two-dimensional space (AG1 is antigenic dimension 1 and AG2 is antigenic dimension 2). Over time, new strains appear as old strains can no longer transmit to immune hosts. Viral evolution is mostly linear in antigenic space. The amount of evolution is calculated as the distance between the founding strain and the average phenotype of strains circulating at the end of the simulation. Vaccine strains (triangles) are chosen at the beginning of each year by averaging the antigenic phenotype of all circulating strains. Strains are colored according time. (B) Incidence per 10 days is shown. Cumulative incidence (not shown) is calculated as the sum of cases over the duration of the simulation. Vaccines are distributed beginning 300 days after strain selection for 120 days. Strain selection for the following year occurs during the distribution of the current vaccine (inset). (C) Upon contact, the risk of infection increases linearly with the distance between the infecting strain and the strain in the host's infection or vaccination history that minimizes the risk of infection (Eq. 3) (D) The sizes of antigenic mutations are chosen from a gamma distribution with mean and standard deviation δ_{mean} and δ_{sd}. The radial directions (not pictured) of mutations are chosen from a random uniform distribution. In this example, vaccines confer half the breadth of immunity as natural immunity ($b = 0.5$).

To assess the potential effects of vaccination on antigenic evolution and disease burden, we introduced vaccination to the host population. At the beginning of each year, a vaccine strain is selected with the average antigenic phenotype of circulating strains. In the United States, the seasonal influenza vaccine is typically distributed from September through February. Distribution usually peaks in October or November, 8-9 months after strain selection [46]. In the model, the vaccine is distributed 300 days after strain selection and for a period of 120 days. During distribution, individuals are randomly vaccinated at a constant daily rate (Eq. 2). Since individuals are

randomly vaccinated each year, the fraction of vaccinated individuals over time. At a 5% annual vaccination rate, approximately 4.9% of individuals in the population are vaccinated every year (due to sampling with replacement in the model) and 48.4% of the population has been vaccinated at least once by the twentieth year (Fig. S6A). At this rate, vaccination effectively renders 26.0% of individuals immune when vaccination is in equilibrium with antigenic evolution (Fig. S6B). We also tested the effects of the breadth of cross-immunity conferred by vaccination. The vaccine's breadth b is defined as the ratio of the vaccine-induced immunity to that of infection-induced (or "natural") immunity (Fig. 1). Vaccines with $b = 1$ have breadth identical to natural immunity, whereas vaccines with $b < 1$ ($b > 1$) have respectively smaller (larger) breadth compared to natural immunity.

We initially used two metrics to quantify the effects of vaccination on the evolution and epidemiology of the virus. First, because antigenic phenotypes evolve roughly linearly in two dimensions [6, 41, 42], we measured the cumulative amount of antigenic evolution by calculating the antigenic distance between the founding strain's antigenic phenotype and the average antigenic phenotype of strains circulating at the end of the simulation (Fig. 1). Second, we measured the burden of disease by calculating the cumulative incidence, or the total number of cases over the duration of the simulation divided by the population size (Fig. 1). In calculating the amount of antigenic evolution and incidence, we included simulations where the viral population remained endemic or went extinct. However, we excluded simulations where the viral population became too diverse (TMRCA $>$ 10 years) because our measure of cumulative antigenic evolution is inadequate for branching viral populations.

Because vaccination may qualitatively alter evolutionary patterns of H3N2, we used an additional metric to asses evolutionary effects, namely the probability that viral populations would become too diverse (TMRCA $>$ 10 years) under different vaccination regimes. Viral populations that are too diverse have the potential to cause high morbidity because hosts are unlikely to have immunity against many antigenic variants. Influenza subtypes H1N1 and B evolve antigenically slower than H3N2 but have greater genetic diversity at any time [6,38,47,48] Thus, we also examine whether vaccination, by affecting antigenic evolution, could also impact diversification.

To estimate the contribution of evolution to vaccination's epidemiological impact, we compared simulations in which vaccination could affect antigenic evolution to simulations where it could not. We generated the latter by first running simulations without vaccination and recording strain phenotypes and relative abundances at every time step to use as a reference. Then, in each time step of the simulations with vaccination, we replaced all infections with randomly selected contemporaneous strains from an unvaccinated reference simulation, matching the reference frequencies. In this way, temporal changes in strain frequencies were unaffected by vaccination.

2.2 Vaccination reduces the average amount of antigenic evolution and disease burden

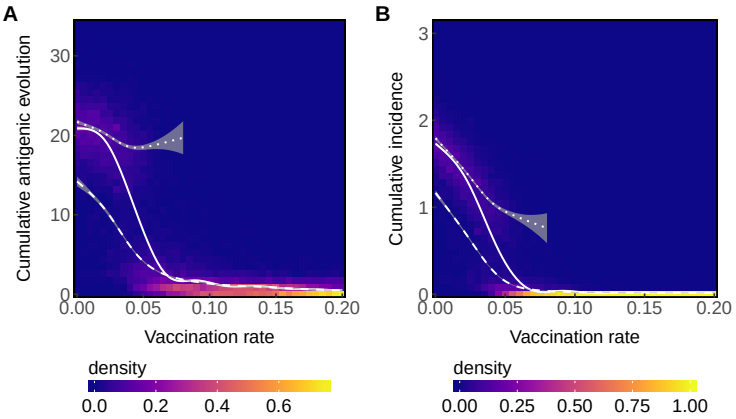

Figure 2: High vaccination rates decrease the average amount of (A) cumulative antigenic evolution and (B) cumulative incidence. The solid white lines show LOESS curves fit to cumulative antigenic evolution and incidence across all simulations. The dotted white lines show fits for simulations where the viral population survived until the end of the simulation. The dashed white lines show fits for simulations where the viral population went extinct. Shaded areas show 95% confidence intervals. Densities reflect 500 total simulations for each vaccination rate with excessively diverse simulations (TMRCA $>$ 10 years) excluded, leaving $\sim 300 - 400$ simulations.

Vaccination reduces the average amount of antigenic evolution (Spearman's $\rho = -0.75$, $p < 0.001$) and incidence (Spearman's $\rho = -0.86$, $p < 0.001$, Fig. 2) when the breadth of vaccine-induced immunity is the same as that of infection. Without vaccination, the viral population evolves on average 21.5 (SD = 3.3) antigenic units and causes an average of 1.8 (SD = 0.2) cases per person over the 20-year simulation. By reducing susceptibility in the host population, vaccination decreases the number of cases and the average size of surviving mutations, thus slowing the rate of antigenic evolution. In turn, slower antigenic evolution further reduces the force of infection, often driving the virus extinct. Once extinct, the viral population can no longer evolve or cause new infections. Above a 10% annual vaccination rate, implying a 28% cumulative vaccination rate over 4 years, extinction occurs rapidly, typically within 2.3 years (SD = 0.6, Fig. S7). Eliminating the time interval between strain selection and vaccine distribution reduces the amount of antigenic evolution (Wilcoxon rank-sum test, $p < 0.001$) and incidence (Wilcoxon rank-sum test, $p < 0.001$) even more (Fig. S8).

Increasing the vaccination rate also decreases the probability that the viral population becomes too diverse (TMRCA $>$ 10 years on average, Fig. S9). Thus, vaccination is unlikely to increase morbidity from diversifying viral populations.

We next examined how much these reductions could be attributed solely to the "ecological" effects of vaccination—the reduction in prevalence and increased extinction risk from enhanced herd immunity—versus the combined ecological and evolutionary impacts. Relative to the case where the evolutionary effects of vaccination are blocked, vaccination with evolutionary effects decreases both the rate of antigenic evolution and the burden of disease (Wilcoxon rank-sum test, $p < 0.001$), (Fig. 3). Also relative to the same baseline, eradication is achieved at a lower vaccination rate. At an 8.5% annual vaccination rate ($\sim$ 20% cumulative vaccine coverage within 5 years), vaccination eradicates

the virus 100% of the time (within 3.3 years on average) when vaccines can affect evolution but only does so 68% of the time (within 5.6 years on average) when vaccines cannot affect evolution.

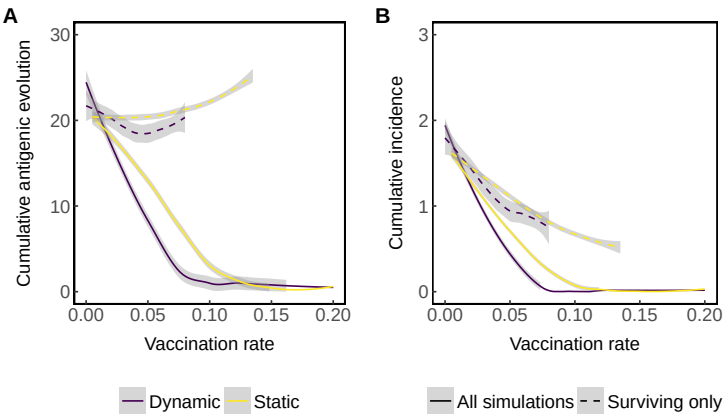

Figure 3: Vaccination further decreases incidence when vaccines can affect antigenic evolution compared to when they cannot. Purple lines represent simulations where vaccination can affect antigenic evolution. Yellow lines represent simulations where vaccination cannot affect antigenic evolution. The solid lines show LOESS fits to cumulative (A) antigenic evolution and (B) incidence across all simulations. The dotted lines show LOESS fits for simulations where the viral population does not go extinct. Shaded areas show 95% confidence intervals. Lines reflect 500 total simulations for each vaccination rate and evolutionary condition with excessively diverse simulations (TMRCA > 10 years) excluded, leaving $\sim 300 - 400$ simulations.

The breadth of vaccine-induced immunity and the delay between vaccine strain selection and distribution change the impact of vaccination. With narrower vaccines, higher vaccination rates are needed to achieve the same average reductions in cumulative antigenic evolution and incidence using broader vaccines (Fig. S10). Regardless of breadth, distributing vaccines immediately after strain selection helps vaccines achieve the same average reductions in evolution and incidence at lower vaccination rates (Fig. S12).

2.3 Vaccine-driven excessive evolution is rare

We developed a test to determine whether vaccination causes excess evolution. We defined excess evolution as more than 21 antigenic units (the average amount of evolution without vaccination) over the duration of the simulation, or when the TMRCA exceeded 10 years. We counted the number of "excessively evolved" simulations for each vaccination rate and breadth. If vaccination does not affect the rate of evolution, the frequency of excessively evolved simulations should be the same as in vaccine-free case (Fig. S14). In contrast, if vaccination increases the rate of evolution, the frequency of excessively evolved simulations should be greater than without vaccination.

Although viral populations that survive are associated with more evolution (Figs. 2, 3, S10), this apparent excess evolution is generally not caused by vaccination. Instead, these viral populations evolved just as much in the absence of vaccination, and only survive vaccination because they evolved unusually quickly. In these cases, more vaccination does not increase the rate of antigenic evolution, but instead drives slowly evolving viral populations extinct while occasionally allowing persistence of quickly evolving populations (Fig. S14). Thus, apparent increases in the amount of antigenic evolution among survivors generally reflect selection among simulations (not among

viruses within a simulation) for fast-evolving populations, and these populations would appear at the same rate without vaccination.

We found that vaccine-driven excess evolution was only possible at low-intermediate immune breadth ($b = 0.2$ or 0.3) and at low vaccination rates (Fig. S13). Even when we detected statistically significant excess evolution, these outcomes were only 10% more common with vaccination relative to without. Based on this analysis, we conclude that vaccine-driven excessive evolution is rare for the influenza-like parameters considered.

2.4 Ignoring the evolutionary effects of vaccination overestimates the private benefit and underestimates the social benefit of vaccination

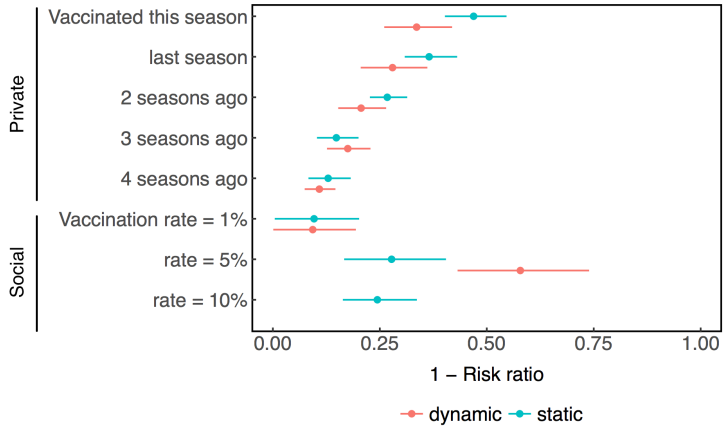

Figure 4: Comparison of the private and social benefits of vaccination when vaccination can or cannot affect antigenic evolution. Risk ratios are calculating using coefficients from a linear panel model fitted to the last 17 years of simulated hosts' infection and vaccination histories. Mean estimates and 95% confidence intervals are shown. Red lines represent simulations where vaccination can affect antigenic evolution (dynamic). Blue lines represent simulations where vaccination cannot affect antigenic evolution (static). The relative risk for a population with a 10% annual vaccination rate could not be calculated because all simulations were driven extinct within the first 3 years.

To quantify the private and social benefits of vaccination, we collected panel data consisting of individual hosts' vaccination and infection histories from simulations where vaccination could affect antigenic evolution and simulations where vaccination could not affect antigenic evolution. We then fit linear panel models to these data (Eq. 4). We measured the private benefit of vaccination as vaccine efficacy, or one minus the risk of infection having been vaccinated relative to the risk of infection having not been vaccinated (Eq. 5). To measure the social benefit, we used an analogous risk ratio. The social benefit is one minus the risk of infection in a population vaccinated at a given rate relative to the risk of infection in an unvaccinated population (Eq. 6). The social benefit reflects a reduction in the force of infection due to vaccination.

The social benefit of vaccination rises when vaccines can slow antigenic evolution compared to when evolutionary effects are omitted. The average risk of infection over the course of a season without vaccination is ∼10% (Table S3). When 5% of the host population is vaccinated annually, the average host is 60.5% less likely to become infected compared to a host in an unvaccinated population (Fig. 4, Table S3). However, when vaccination cannot affect antigenic evolution, the

average host is only 27.7% less likely to become infected (Fig. 4, Table S3) at the same vaccination rate relative to a host in an unvaccinated population. The social benefits accounting for evolution at 10% vaccination rate could not be calculated because the virus was always eradicated quickly.

Since the evolutionary effects of vaccination further reduce the overall risk of infection in the population, individuals personally benefit less from getting vaccinated when vaccines affect antigenic evolution than when vaccines do not. The reduction in the private benefit due to evolutionary effects is a natural consequence of lower incidence: when the overall risk of infection is low, the marginal benefit of vaccination is lower than when incidence is high (Eq. 5). Individuals receiving the current vaccine are 36.0% less likely to become infected in the same season compared to unvaccinated individuals when vaccines can affect evolution (Fig. 4, Table S3). However, when vaccines cannot affect antigenic evolution, vaccinated individuals are 49.5% less likely to become infected (Fig. 4, Table S3). We observed similar patterns when the breadth of vaccine-induced immunity was half that of natural immunity (Table S4).

By slowing antigenic evolution, vaccination prolongs its own effectiveness. When vaccination cannot affect antigenic evolution, the private benefit decreases by 9.0% per passing year compared to only 5.6% per passing year when vaccines can affect evolution (Fig. 4, Table S3). Thus, evolutionary effects cause the private benefits of vaccination to decay slower with time. Consequently, ignoring the evolutionary effects of vaccines also undervalues the long-term private benefits relative to the short-term private benefits.

3 Discussion

We found that vaccination against seasonal influenza could hypothetically slow antigenic evolution and thereby reduce the disease burden beyond its immediate impact on transmission. Indeed, annual vaccination rates as low as 10%, which imply a 28% cumulative vaccine coverage after 4 years, can reliably eradicate the virus in simulation. This is a previously unrecognized potential benefit of widespread vaccination. At a 5% annual vaccination rate (16% cumulative coverage after 4 years), evolution increases the social benefits of vaccination by 30.4%, which in turn decreases the private benefits by 13.5% compared to when evolutionary effects are omitted. Thus, while the evolutionary effects of vaccination yield a large social benefit by reducing incidence, they reduce the private benefit to vaccinated individuals.

Though our simulations suggest that a 10% annual vaccination rate could eradicate influenza, this prediction may not appear realistic since up to 8% of the global population is vaccinated each year [36]. However, vaccination is almost exclusively concentrated in seasonal populations rather than in the populations that contribute most to influenza's evolution [36–38]. For instance, from the 2008-2009 season to the 2014-2015 season, seasonal vaccine coverage averaged 43.4% in the United States and 13.5% across European countries, but was <1% in China and India [36, 49]. Moreover, the same people tend to get vaccinated repeatedly, which lessens the accumulation of vaccine-induced immunity in the population over time. In the United States, up to 68.4% of vaccine recipients get vaccinated every year [50, 51]. Consecutive vaccinations may also reduce vaccine effectiveness by interacting with prior immune responses, although these effects are not well understood [52–55]. Thus, the effective amount of vaccine-induced immunity in a population is potentially lower than vaccine coverage estimates would suggest, implying higher vaccination rates might be necessary for eradication.

The seasonal influenza vaccine is unlikely to cause excessive evolution, assuming that the breadth of vaccine-induced immunity is similar to that of natural immunity. In simulations, vaccine-driven accelerated antigenic evolution only occurs when the breadth of vaccine-induced immunity is nar-

rower than that of natural infection and then only at low vaccination rates. The relative breadths of vaccine-induced and and natural immunity are unclear. One difference is that although natural infection elicits antibodies that bind both the hemagglutinin and the neuraminidase (NA) antigens, inactivated vaccines may induce fewer antibodies to NA [56], suggesting that the breadth of vaccine-induced immunity could be narrower than that of natural immunity. Host immune history also affects the generation of immune responses [57–61], and by extension the breadths of vaccine-induced and natural immunity, in ways that are largely unexplored.

Although our simulations show vaccines typically slow evolution (and drive extinction) in a single, closed population (i.e., a global population), other models predict faster evolution or higher incidence under particular assumptions. Vaccination accelerates antigenic evolution when stochastic extinctions in small viral populations are ignored [27]. In contrast, stochastic extinctions in our agent based model weaken selection in small viral populations. Vaccines can also accelerate antigenic evolution locally when antigenically diverged strains can immigrate re-seed seasonal epidemics [28]. Our model simulates a closed global population where immigration is not a source of novel strains and extinct viral populations cannot be re-seeded. Finally, assuming that new strains do not appear by mutation, vaccination targeting a single strain potentially increases incidence when two competing strains co-circulate [62]. In our model, strains emerge dynamically by mutation, so the novel strains are less likely to appear when prevalence is low.

Improved understanding of the fine-scale evolutionary and immunological dynamics might shift predictions. For instance, the rate of vaccine-driven evolution is sensitive to transmission rates and the distribution of mutation sizes. We chose transmission and mutation parameters such that the simulated epidemiological and evolutionary dynamics match those of H3N2 [41, 44]. However, in this model, increasing the mutation rate, skewing the distribution of mutation sizes toward large mutations, or increasing the transmission rate increases the rate of antigenic evolution and the tendency for viral populations to diversify [41,44]. Such changes would also increase the probability that viral populations survive to evolve further or diversify especially under small amounts of vaccination (or vaccines with narrow breadth). Our model assumes that an individual's immune responses against multiple infections or vaccinations are independent, but immunity from prior infection or vaccination affects subsequent immune responses [63]. Consistent with this hypothesis, there is evidence that vaccination history [52–54] and recipient age (potentially a proxy for infection history) [64] affect vaccine efficacy.

Our results suggest that conventional seasonal influenza vaccines, already have the potential to slow antigenic evolution and eradicate seasonal influenza. In theory, universal vaccines that immunize against all strains necessarily slow antigenic evolution by not discriminating between antigenic variants [15]. Increasing seasonal vaccine coverage, especially in populations that contribute substantially to influenza's evolution, would help realize similar evolutionary benefits. However, as vaccination further reduces disease burden, people may require more incentives to get vaccinated [34, 35, 65].

4 Methods

4.1 Model overview

We adapted an individual-based model of influenza's epidemiological and evolutionary dynamics [41] to include vaccination. In each time step of a tau-leaping algorithm, individuals can be born, can die, can become infected after contacting other hosts, can recover from infection, or can be vaccinated. Transmission occurs by mass action, with the force of infection given by

$$\lambda(t) = \beta \frac{I(t)}{N}, \tag{1}$$

where I is the number of infected hosts. For computational efficiency, individuals cannot be co-infected.

Antigenic phenotypes are represented as points in 2-dimensional Euclidean space, analogous to antigenic maps produced using pairwise measurements of serum cross-reactivity [6, 42]. One antigenic unit corresponds to a two-fold antiserum dilution in a hemagglutination inhibition (HI) assay. At the beginning of the simulation, a single founding strain is introduced at the endemic equilibrium in the host population. When hosts recover from infection, they acquire lifelong immunity to the infecting strain. Upon contact with an infected host, the probability that the susceptible host becomes infected is proportional to the distance d_{n} between the infecting strain and the nearest strain in the susceptible host's infection history, with one unit of antigenic distance conferring a 7% absolute increase in risk (Eq. 3) [1, 41, 43].

Each infection mutates to a new antigenic phenotype at a rate μ mutations per day. The mutation's radial direction is drawn from a uniform distribution, and the size (distance) is drawn from a gamma distribution with mean δ_{mean} and standard deviation δ_{sd}.

Vaccination occurs at rate r, breadth b (relative to natural immunity), and lag θ (relative to the timing of strain selection). The vaccine strain is selected on the first day of each year. By default, the vaccine is distributed for 120 days. During the period of vaccine distribution, individuals are randomly vaccinated at a constant daily rate according to the specified annual vaccination rate.

$$r_{\mathrm{day}} = r_{\mathrm{annual}} \times \frac{1 \text{ year}}{365 \text{ days}} \tag{2}$$

By default, the breadth of vaccine-induced and natural immunity are equal. Thus, a host's probability of infection upon contact is given by

$$\mathrm{Risk} = P(\mathrm{infection}|\mathrm{contact}) = \min\{1, cd_{\mathrm{n}}, \frac{cd_{\mathrm{v}}}{b}\} \tag{3}$$

where d_{n} is the distance between the infecting strain and the nearest strain in the host's infection history, and d_{v} is the distance between the infecting strain and the nearest strain in the host's vaccination history (if the host is vaccinated) and $c = 0.07$ is a constant for converting antigenic distance to a risk of infection [1, 41, 43].

4.2 Simulation of vaccine-independent evolution

We created a simulation where vaccination could not affect antigenic evolution, the "static" simulation. We first ran 500 simulations of the model without vaccination. For each simulation, we recorded the circulating strains and their relative abundances at each time step to use as reference viral populations. The evolution of these reference viral populations is unaffected by vaccination since they were obtained from simulations without vaccination.

To run the static simulation where vaccination could not affect antigenic evolution, we first randomly selected one of the reference viral populations. In each time step of the static simulation, the composition of the viral population was replaced with that of the reference viral population at the matched time step, scaled for prevalence. In this way, vaccination could still alter the overall viral abundance, but the rate of antigenic evolution was already previously set by the dynamics of the simulation without vaccination. Thus, vaccination was separated from the evolutionary process.

4.3 Estimating the private and social benefits of vaccination

To generate panel data, we ran simulations at four annual vaccination rates r (0%, 1%, 5%, and 10%) and recorded individual hosts' dates of infection and vaccination. We randomly sampled 0.005% of individuals from the host population at the end of the simulation for analysis. We fit a linear panel model (equation 4) to the simulated longitudinal vaccination data from multiple simulations j. Observations are at host i level in each time period τ (see Table S2 for hypothetical example). The dependent variable indicator variable $I_{ij\tau} = 1$ if a host is infected in the current season τ, and 0 otherwise. The indicator $V_{ij\tau} = 1$ if a host is vaccinated in the current season. Analogously lags $V_{ij\tau-k}$ measure vaccination in period $\tau - k$. If the annual vaccination rate in the host population is, e.g., 5%, then $r_{5ij} = 1$. The regression is estimated as a linear probability model (with random effects) in order to simplify interpretation of reported coefficients. Standard errors are clustered at the simulation-level to account for correlation in outcomes across hosts in a simulation. The equation estimated is as follows.

$$\begin{aligned} I_{ij\tau} = \beta_0 + \beta_1 V_{ij\tau} + \beta_2 V_{ij\tau-1} + ... + \beta_5 V_{ij\tau-4} + \\ \beta_6 r_{1ij} + \beta_7 r_{5ij} + \beta_8 r_{10ij} + \epsilon_i + u_{j\tau} \end{aligned} \tag{4}$$

The fitted coefficients estimate the change in probability of infection given an individual's vaccination status (direct effects) and the host population's vaccination rate (indirect effects). For example, the coefficient β_1 estimates the absolute change in the probability of becoming infected in the current season for a host who has also been vaccinated in the current season. Likewise, $\beta_2, \beta_3, \beta_4,$ and β_5 estimate the respective changes in the risk of becoming infected in the current season given vaccination one, two, three, and four seasons ago. Collectively, $\beta_1, \cdots, \beta_5$ represent the direct benefits of vaccination. More formally, $\sum_{k=1}^{5} \beta_k$ is the impulse response to vaccination over 5 years and measures the total direct protective benefit of vaccination over time.

The coefficients β_6, β_7, and β_8 estimate the change in an individual's risk of infection in the current season when the population vaccination rate is 1%, 5%, or 10%, respectively. Thus, β_6, β_7, and β_8 represent the indirect benefits of vaccination under different vaccination policies.

To estimate the private benefit (equivalent to vaccine efficacy), the absolute reduction in risk can be expressed in terms of a relative risk.

$$\text{Private} = \left[1 - \frac{P(I = 1|V = 1)}{P(I = 1|V = 0)}\right] \times 100\% \tag{5}$$

To estimate the social benefit (or a social vaccine efficacy) for a specific vaccination rate R, we calculate an analogous relative risk:

$$\text{Social} = \left[1 - \frac{P(I = 1|r = R)}{P(I = 1|r = 0)}\right] \times 100\% \tag{6}$$

5 Data and code availability

The source code of the model can be found at `https://github.com/cobeylab/antigen-vaccine`. All data and code used to generate the results in this manuscript are available at `https://github.com/cobeylab/vaccine-manuscript`.

6 Competing interests

We have no conflicts of interests to declare.

7 Author contributions

AM and SC conceived the study. FW performed the analysis and wrote the first draft of the paper. All of the authors contributed to and approved the final version.

8 Acknowledgements

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1 Supplementary Information

1.1 Vaccination and the invasion fitness of mutants

We use invasion analysis to understand how vaccination affects the invasion fitness of antigenically diverged strains by effectively reducing susceptibility. We develop an expression for the fitness of an invading mutant strain to explain how the antigenic selection gradient with vaccination.

Here, S, I, and R represent the fraction of susceptible, infected, and recovered individuals. The birth rate ν and the death rate are equal, so the population size is constant. All individuals are born into the susceptible class. Transmission occurs at rate β, and recovery occurs at rate γ. We vaccinate some fraction p of newborns. In practice, this approximates vaccination of young children, who are primarily responsible for influenza transmission. Vaccinated individuals move into the recovered class.

$$\frac{dS}{dt} = \nu(1-p) - \beta SI - \nu S \tag{S1}$$

$$\frac{dI}{dt} = \beta SI - \gamma I - \nu I \tag{S2}$$

$$\frac{dR}{dt} = \gamma I - \nu R + \nu p \tag{S3}$$

The endemic equilibrium of S_{eq}, I_{eq}, and R_{eq} is

$$S_{\text{eq}} = \frac{\gamma + \nu}{\beta} \equiv \frac{1}{R_0} \tag{S4}$$

$$I_{\text{eq}} = \frac{\nu(R_0(1-p)-1)}{\beta} \tag{S5}$$

$$R_{\text{eq}} = 1 - \frac{1}{R_0} - \frac{\nu(R_0(1-p)-1)}{\beta} \tag{S6}$$

where R_0, the basic reproductive number, is the number of secondary infections from a single infected individual in a totally susceptible population.

The disease-free equilibrium (when $p > 1 - \frac{1}{R_0}$) is

$$S_{[I\,=\,0]} = 1 - p \tag{S7}$$

$$I_{[I\,=\,0]} = 0 \tag{S8}$$

$$R_{[I\,=\,0]} = p \tag{S9}$$

We introduce a single invading mutant $I' = \frac{1}{N}$. To find the growth rate of the mutant, we develop an expression for the amount of immunity against the mutant strain. The single mutant has an antigenic phenotype d antigenic units away from the resident. The conversion factor between antigenic units and infection risk is notated by c. Thus, the susceptibility to the mutant is given by $\min\{cd, 1\}$, and immunity to the mutant is $\max\{1 - cd, 0\}$. For convenience, we assume $cd \leq 1$.

We can decompose R_{eq} into immunity conferred by recovery natural infection R_{n} and immunity conferred by vaccination R_{v}:

$$R_{\mathrm{n}} = 1 - \frac{1}{R_0} - \frac{\nu(R_0 - 1)}{\beta} \tag{S10}$$

$$R_{\mathrm{v}} = \frac{\nu R_0 p}{\beta} \tag{S11}$$

$$R_{\mathrm{eq}} = R_{\mathrm{n}} + R_{\mathrm{v}} \tag{S12}$$

The fraction of the population immune to the invading strain from previous infection is denoted R'. Assuming that vaccines confer a breadth of immunity relative to natural immunity b,

$$R' = (1 - cd)R_{\mathrm{n}} + (1 - \frac{cd}{b})R_{\mathrm{v}} \tag{S13}$$

Note that when the mutant and resident are identical ($d = 0$), the immunity to the invading strain is identical to the immunity against $R' = R_{\mathrm{eq}}$. Allowing for coinfection, the fraction susceptible to the invading strain is

$$S' = 1 - R' - \frac{1}{N} \tag{S14}$$

$$= 1 - R' \tag{S15}$$

for large N. When the vaccination rate exceeds $1 - \frac{1}{R_0}$, the resident is eradicated and S' and R' are calculated using the disease-free equilibrium.

The invasion fitness s of the mutant relative to the endemic strain is the difference between the per-capita growth rates. Note that since the resident is in equilibrium, $dI/dt = 0$.

$$s = \frac{1}{I'}\frac{dI'}{dt} - \frac{1}{I}\frac{dI}{dt} = [\beta S' - (\gamma + \nu)] - 0 \tag{S16}$$

$$= \beta S' - (\gamma + \nu) \tag{S17}$$

The value of s increases with greater distance between the mutant and resident, but decreases as more hosts become vaccinated (Fig. S1A). The expected s can be used to determine the effect of vaccine coverage on the expected invasion fitness of the mutant $\frac{\partial \mathbf{E}(s)}{\partial p}$. $\mathbf{E}(s)$ is a function of the expected distance of a mutant $\mathbf{E}(d)$. In our model, we assume gamma distributed mutation sizes with a mean δ_{mean} of 0.3 antigenic units and standard deviation δ_{sd} of 0.6 antigenic units (Fig. S1C).

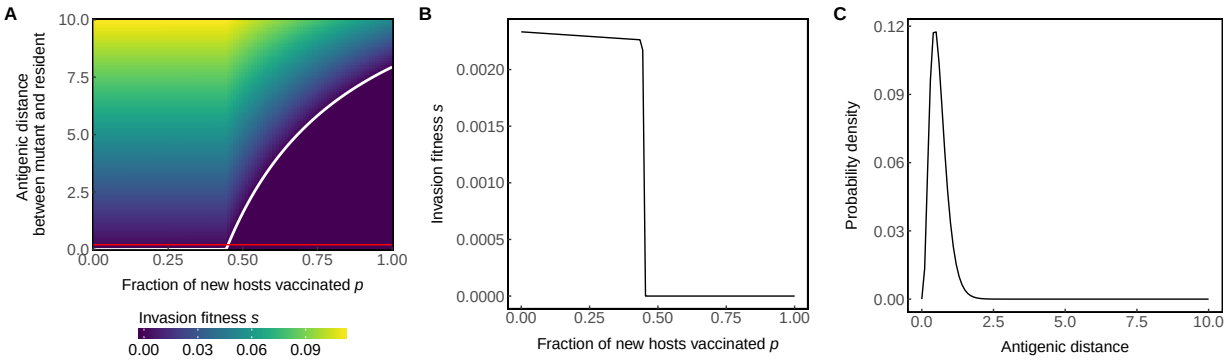

Figure S1: (A) High vaccination rates decrease the invasion fitness of mutant strains. For a given vaccination rate, the invasion fitness of a mutant increases with antigenic distance. However, the invasion fitness of a mutant at a given distance decreases as vaccine coverage increases. An example profile of invasion fitnesses is shown for $d = 0.2$ (the red line) in (B). Above the invasion threshold for the resident ($\rho > 1 - 1/R_0$), the mutant must be increasingly more distant to invade. The white curve shows the invasion threshold, where the invasion fitness for the mutant strain is zero. Mutants above the above the curve can invade, while mutants below the curve cannot. (C) Density of gamma distributed mutations with a $\delta_{\text{mean}} = 0.3$ and $\delta_{\text{sd}} = 0.6$.

We decompose $\frac{\partial \mathbf{E}(s)}{\partial p}$ to understand how vaccines affect susceptibility and resistance to change the invasion fitness of the mutant.

$$\frac{\partial \mathbf{E}(s)}{\partial p} = \left(\frac{\partial \mathbf{E}(s)}{\partial S'}\right)\left(\frac{\partial S'}{\partial R'}\right)\left(\frac{\partial R'}{\partial R_{\text{v}}}\right)\left(\frac{\partial R_{\text{v}}}{\partial p}\right) \tag{S18}$$

$$= (\beta)(-1)(1 - \frac{c\mathbf{E}(d)}{b})(\frac{\nu R_0}{\beta}) \tag{S19}$$

Since $1 - \frac{c\mathbf{E}(d)}{b} \geq 0$ (i.e. one cannot be more than 100% immune to infection), vaccination must decrease the expected invasion fitness of the mutant $\frac{\partial \mathbf{E}(s)}{\partial p} \leq 0$, slowing evolution. This decrease is attributed to vaccination reducing susceptibility to the mutant by increasing immunity ($\frac{\partial S'}{\partial R'} \leq 0$ and $\frac{\partial R'}{\partial p} > 0$) against any mutant. Larger breadth of vaccine-induced immunity (b) also decreases the expected invasion fitness.

1.2 Model validation without antigenic evolution

In the main text, we show general agreement between our simulations and observations of influenza's epidemiology and evolution using our parameterization. We further validate the epidemiological processes of our agent-based model by removing evolution and comparing output against analytic solutions to a model using deterministic ordinary differential equations. A simple analytic solution to a model with antigenic evolution is intractable.

Classical SIR models include vaccination of newborns only. In a newborn-only vaccination model, the threshold eradication rate $p_t = 1 - 1/R_0 \equiv \frac{\gamma+\nu}{\beta}$. Here, we derive an eradication threshold vaccination rate for a model where all hosts are vaccinated at the same rate.

$$\frac{dS}{dt} = \nu - \nu S - \beta SI - pS \tag{S20}$$
$$\frac{dI}{dt} = \beta SI - \gamma I - \nu I - pI \tag{S21}$$
$$\frac{dR}{dt} = \gamma I - \nu R - pR \tag{S22}$$
$$\frac{dV}{dt} = p - \nu V - pV \tag{S23}$$

At equilibrium:

$$\frac{dI}{dt} = 0 = \beta S^* I^* - \gamma I^* - \nu I^* - pI^* \tag{S24}$$
$$S^* = \frac{\gamma + \nu + p}{\beta} \equiv \frac{1}{R_0} \tag{S25}$$

We find agreement between the simulated equilibrium fraction susceptible and the theoretical S^* for a range of influenza-like values of R_0 (1.2-3.0) S2.

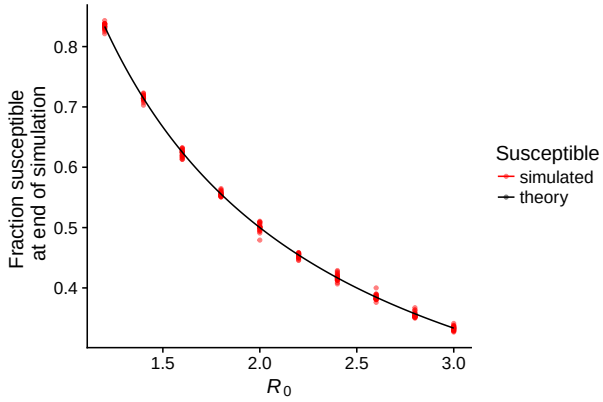

Figure S2: Simulated susceptible fraction at the end of 20 years without vaccination. The theoretical equilibrium fraction susceptible is given by $S^* = \frac{1}{R_0}$

We derive a general expression for the eradication threshold first by calculating I^*:

$$\frac{dS}{dt} = 0 = \nu - \nu S^* - \beta S^* I^* - pS^* \tag{S26}$$
$$0 = \nu - S^*(\nu + \beta I^* + p) \tag{S27}$$
$$\nu \frac{\beta}{\gamma + \nu + p} = \nu + p + \beta I^* \tag{S28}$$
$$\nu \frac{\beta}{\gamma + \nu + p} - \nu - p = \beta I^* \tag{S29}$$
$$I^* = \frac{\nu}{\beta}(R_v - 1) - \frac{p}{\beta} \tag{S30}$$

The condition for the existence of a disease-free equilibrium is $I^* > 0$. We derive an eradication threshold p_t for which $I^* = 0$:

$$I^* = \frac{\nu}{\beta}(R_v - 1) - \frac{p_t}{\beta} = 0 \tag{S31}$$

$$\frac{\nu}{\beta}(R_v - 1) - \frac{p_t}{\beta} = 0 \tag{S32}$$

$$\nu(R_v - 1) = p_t \tag{S33}$$

$$\frac{\nu\beta}{\nu + \gamma + p} - \nu = p \tag{S34}$$

$$\nu\beta - \nu(\nu + \gamma + p) = p^2 + (\gamma + \nu)p \tag{S35}$$

$$\nu\beta - \nu(\nu + \gamma) = p^2 + (\gamma + 2\nu)p \tag{S36}$$

$$0 = p^2 + (\gamma + 2\nu)p - \nu\beta + \nu(\nu + \gamma) \tag{S37}$$

Since $p \geq 0$, we take the nonnegative root.

$$p = \frac{-(\gamma + 2\nu)}{2} + \frac{\sqrt{(\gamma + 2\nu)^2 - 4(\nu(\nu + \gamma) - \nu\beta)}}{2} \tag{S38}$$

$$= \frac{-(\gamma + 2\nu)}{2} + \frac{\sqrt{\gamma^2 + 4\nu\gamma + 4\nu^2 - 4\nu^2 - 4\nu\gamma + 4\nu\beta)}}{2} \tag{S39}$$

$$= \frac{-(\gamma + 2\nu)}{2} + \frac{\sqrt{\gamma^2 + 4\nu\beta}}{2} \tag{S40}$$

Again, we find agreement between the simulated and theoretical eradication threshold vaccination rates over a range of influenza-like values of R_0 (Figs. S3, S4). Because we initialize the simulations at the endemic equilibrium *without* vaccination, some damped oscillation is to be expected, which may cause eradication at slightly lower vaccination rates than expected by theory (Fig. S5). For instance, at $R_0 = 1.8$, theory predicts eradication at $p = 0.0267$ day^{-1}, while simulation achieves extinction in 20/20 simulations within 20 years at $p = 0.024$ (Fig. S5).

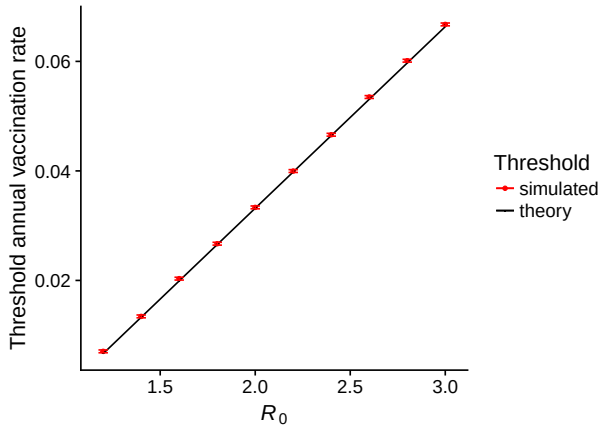

Figure S3: With vaccination, the simulated eradication thresholds agree with analytic predictions. The simulated threshold is the minimum vaccination rate where 40/40 simulations go extinct within 20 years. Error bars show the sampling resolution (Fig. S4). Simulations were initialized at the analytically derived equilibrium S, I, and R with vaccination (equation S40).

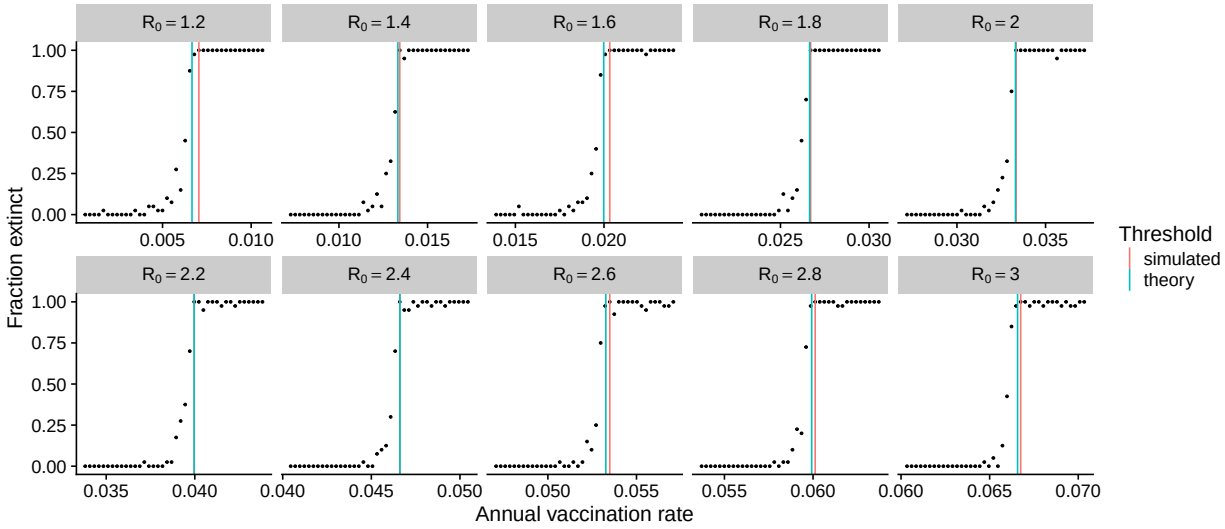

Figure S4: Estimation of simulated eradication thresholds without evolution, starting at the equilibrium S, I, and R with vaccination. To generate response curves, we ran 40 replicate simulations for each combination of R_0 and vaccination rate and calculated the fraction of extinct simulations. The simulated eradication threshold is the minimum vaccination rate that causes 40/40 simulations to go extinct within 20 years. When the analytic equilibrium I was nonnegative, we initialized the simulation with a single infection.

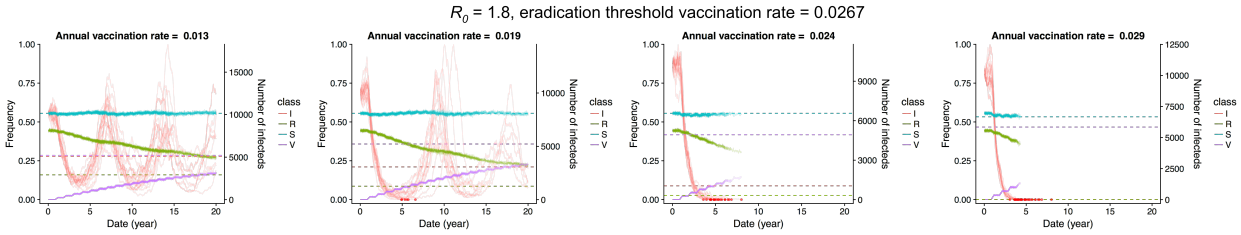

Figure S5: Simulated timeseries without evolution, starting at the endemic equilibrium *without* vaccination (i.e., $S_0 = 1/R_0 \equiv \frac{\gamma+\mu+p}{\beta}$, as in the manuscript, but in contrast to Appendix Figures 2 and 3). Because the population starts away from the vaccinated equilibrium, the system experiences damped oscillations, which increase the probability of stochastic extinction. Thus, we observe extinction even when the vaccination rate is slightly below the expected eradication threshold. Vaccination remains pulsed in 9-month periods, as in the model. Frequencies of susceptible (S), infected (I), recovered (R), and vaccinated (V) individuals are shown for 20 replicate simulations. The left y-axis shows the frequencies of S (blue), R (green), and V (purple). The right y-axis shows the number of infections (red). The dashed lines shows the expected equilibrium frequencies for each class.

2 Supplementary tables and figures

Table S1: Parameters

Parameter	Value	Reference
Intrinsic reproductive number (R_0)	1.8	[66, 67]
Duration of infection $1/\gamma$	5 days	[68]
Population size N	50 million	(see text)
Birth/death (turnover) rate ν	$1/30$ year^{-1}	[69]
Mutation rate μ	10^{-4} day^{-1}	(see text)
Mean mutation step size δ_{mean}	0.6 antigenic units	(see text)
SD mutation step size δ_{sd}	0.3 antigenic units	(see text)
Infection risk conversion c	0.07	[1, 41, 43]
Duration of simulation	20 years	
Annual vaccination rate r	0.0-0.2 year^{-1}	
Breadth of vaccine-induced immunity b	100%	
Temporal lag between vaccine strain selection and distribution θ	300 days	

Table S2: Sample panel data

Identifier			Data								Interpretation
τ	i	j	$I_{ij\tau}$	$V_{ij\tau-1}$	$V_{ij\tau-2}$	$V_{ij\tau-3}$	$V_{ij\tau-4}$	r_{1ij}	r_{5ij}	r_{10ij}	
1	1	1	1	0	1	0	0	0	1	0	The host was infected this season (1) and only vaccinated 2 seasons ago. The population vaccination rate is 5%
1	2	1	0	1	0	0	1	0	1	0	Host not infected this season (1). Host vaccinated this season and 4 seasons ago. Population vaccination rate is 5%
...											
10	1	2	1	0	0	0	1	0	0	1	Host infected this season (10). Host vaccinated 4 seasons ago. Population vaccination rate is 10%

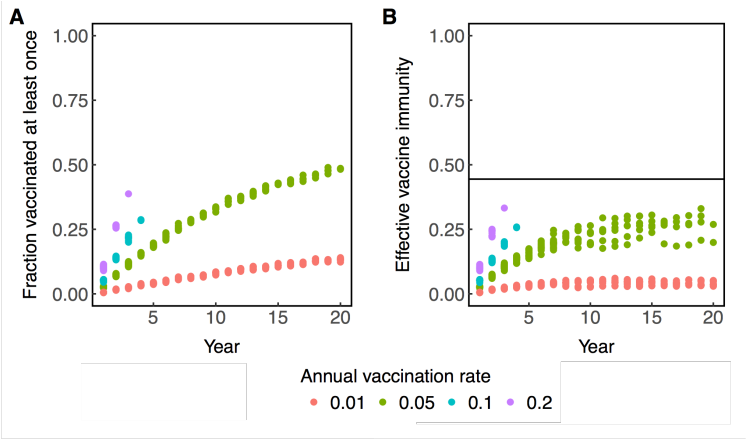

Figure S6: (A) Vaccine coverage and (B) effective vaccine-induced immunity over time calculated from simulations. (A) The fraction of individuals who have been vaccinated at least once accumulated over time and saturates at 50%. (B) The effective amount of vaccine-induced immunity in the population is calculated using the mean antigenic distance between circulating strains and the vaccinated hosts' vaccine strains. At any given time, the effective vaccine immunity is $\frac{1}{N}\sum_i^{Np} \min\{0, 1 - cd_{xv_i}\}$, where N is the host population size, p is the fraction of vaccinated, v_i is the vaccine strain received by individual i, x is the average circulating strain, d is the antigenic distance between the strains, and c is a constant that converts between antigenic distance and risk. The horizontal line indicates the theoretical eradication threshold in an antigenically homogenous population $1 - 1/R_0$.

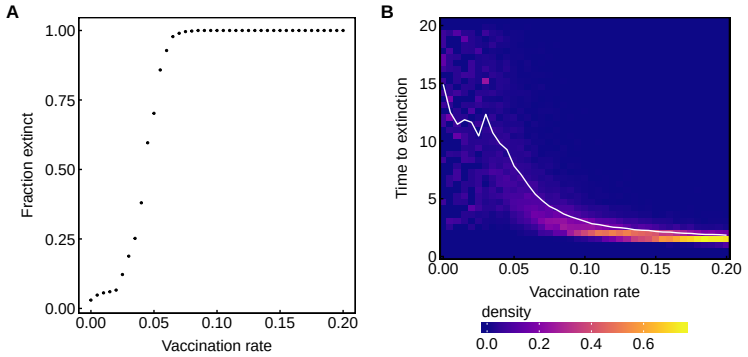

Figure S7: High vaccination rates increase the probability of extinction and shorten the average time to extinction. (A) Points show the fraction of simulations where the viral population went extinct before 20 years. (B) Density of times to extinction. The solid white line shows the average time to extinction across these simulations. Lines reflect 500 total simulations for each vaccination rate with excessively diverse simulations (TMRCA $>$ 10 years) excluded, leaving $\sim 300 - 400$ simulations.

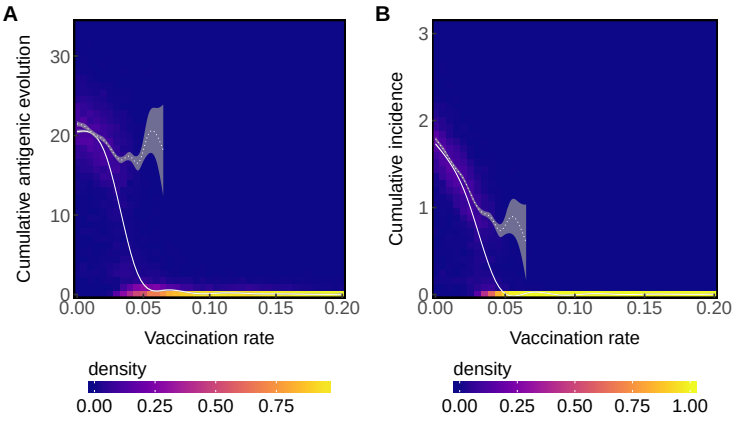

Figure S8: With no temporal lag between vaccine strain selection and distribution, increasing the vaccination rate quickly decreases the average amount of (A) cumulative antigenic evolution (A) and (B) incidence. The solid white line shows a LOESS fit to cumulative antigenic evolution and incidence across all simulations. The dotted white line shows a LOESS fit to cumulative antigenic evolution and incidence for simulations where the viral population did not go extinct. Shaded areas show 95% confidence intervals.

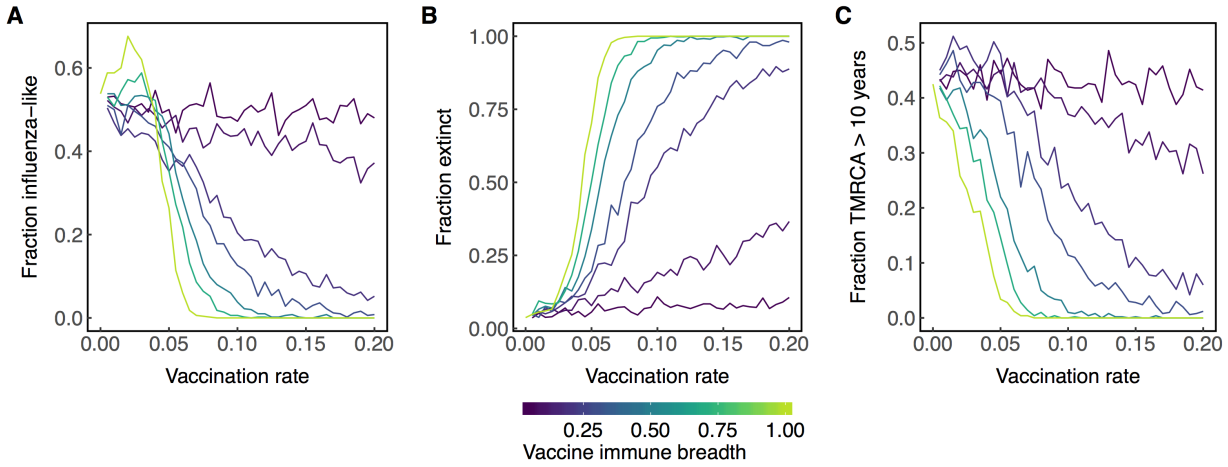

Figure S9: Increasing the vaccination rate increases the probability that the viral population will go extinct (B) and decreases the probability of exhibiting influenza-like dynamics (A) or excessive diversification (TMRCA $>$ 10 years) (C). Lines are colored according to the breadth of the vaccine. Data are collected from 500 replicate simulations per unique combination of vaccination rate and vaccine immune breadth with excessively diverse simulations (TMRCA $>$ 10 years) excluded, leaving $\sim 300 - 400$ simulations per parameter combination.

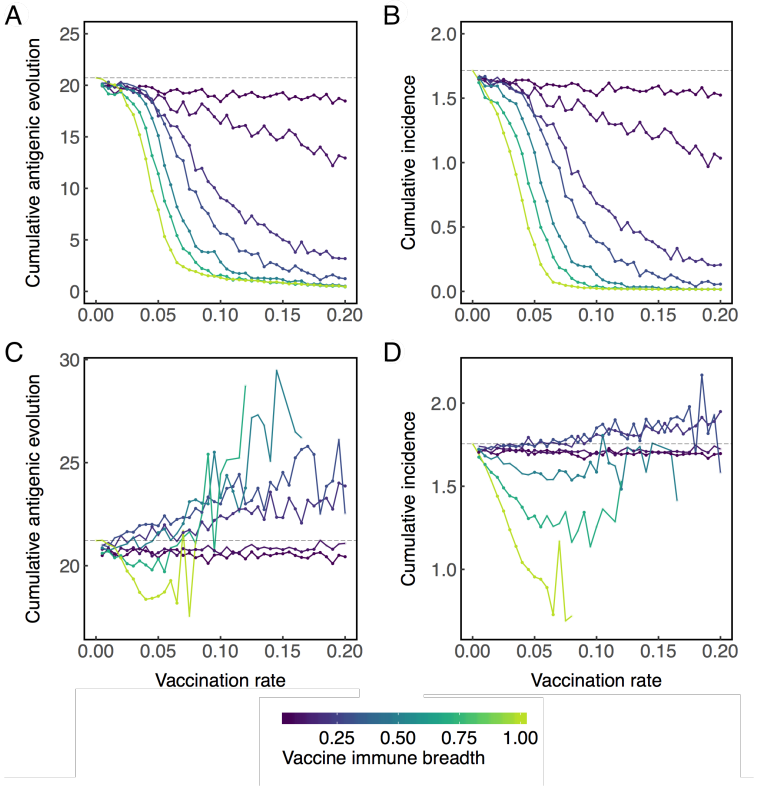

Figure S10: Across all simulations (A&B), vaccination decreases the average (A) cumulative antigenic evolution and (B) incidence regardless of breadth. In the subset of simulations where the viral population does not go extinct (C&D), vaccines with narrow breadth are associated with greater average antigenic evolution (C) and incidence (D), but these increases are not necessarily caused by vaccination (see Fig. S13. Lines are colored according to the breadth of vaccine-induced immunity. The grey dashed lines indicate the average amount of antigenic evolution (A,C) or incidence (B,D) without vaccination. Points indicate significant decrease (below the dashed line) or increase (above the dashed line) compared to no vaccination according to a Wilcoxon rank-sum test ($p < 0.05$) performed on at least 5 replicate simulations. Complete data are shown in Figures S11 and S14 Data are collected from 500 replicate simulations per unique combination of vaccination rate and vaccine immune breadth with excessively diverse simulations (TMRCA > 10 years) excluded, leaving $\sim 300 - 400$ simulations per parameter combination.

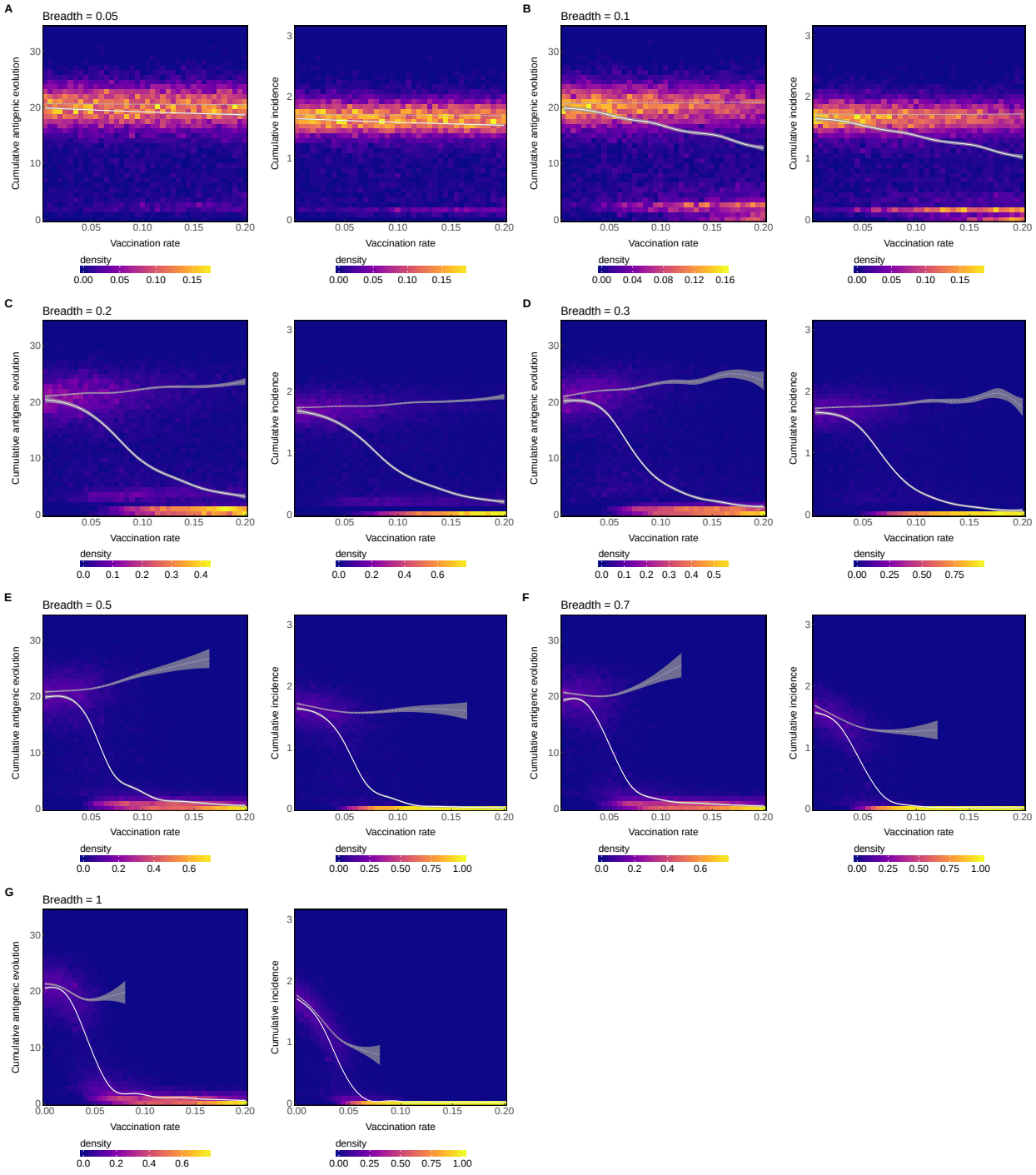

Figure S11: Density plots of complete simulation data corresponding to Figure S10. The solid white lines show a LOESS fit to cumulative antigenic evolution or incidence across all simulations. The dotted white lines show a LOESS fit to cumulative antigenic evolution or incidence for simulations where the viral population did not go extinct. Shaded areas show 95% confidence intervals Data are collected from 500 replicate simulations per unique combination of vaccination rate and vaccine immune breadth with excessively diverse simulations (TMRCA $>$ 10 years) excluded, leaving $\sim 300 - 400$ simulations per parameter combination.

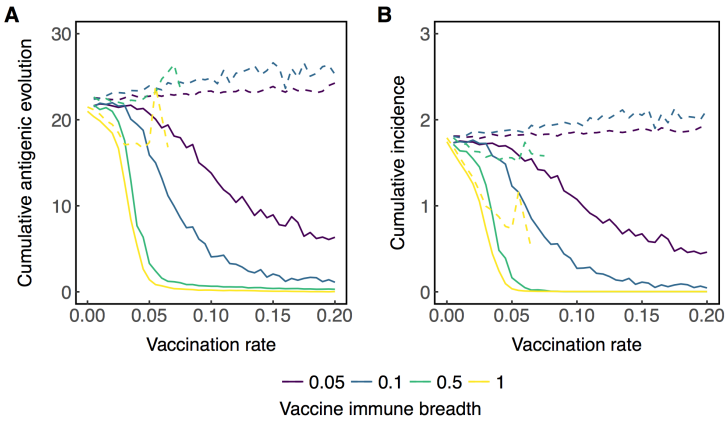

Figure S12: With no temporal lag between vaccine strain selection and distribution, lower vaccination rates are needed to achieve the same reductions in (A) cumulative antigenic evolution and (B) cumulative incidence compared to when vaccines are distributed 300 days after strain selection (Fig. S10). The solid lines show averages across all simulations, while dotted lines show averages over simulations where the viral population did not go extinct. Lines are colored according to the breadth of vaccine-induced immunity. Data are collected from 500 replicate simulations per unique combination of vaccination rate and vaccine immune breadth with excessively diverse simulations (TMRCA $>$ 10 years) excluded, leaving $\sim 300 - 400$ simulations per parameter combination.

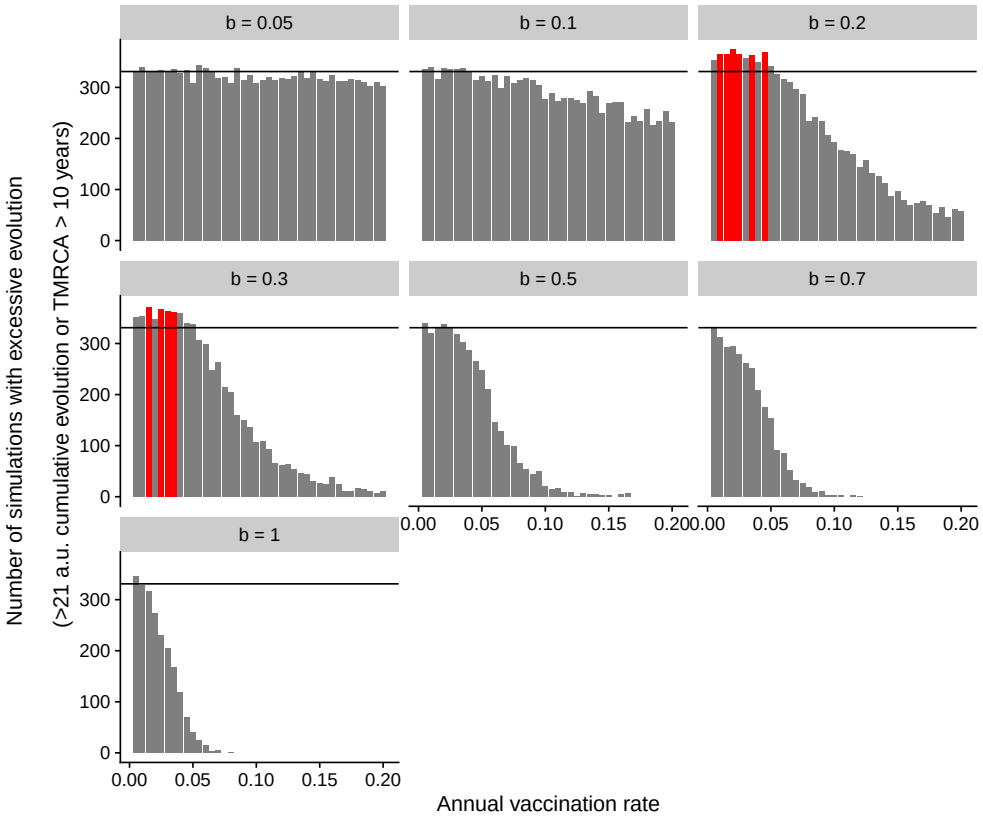

Figure S13: Vaccination almost always reduces the rate of antigenic evolution. The subplots show the number of simulations (out of 1000 replicates for each unique combination of parameters) that demonstrate excessive evolution for each vaccination rate and breadth b. Here, excessive evolution is defined by either more than 21 antigenic units of cumulative evolution or a TMRCA > 10 years. Black lines show the number of simulations that evolve excessively without vaccination (the null expectation if vaccines do not drive faster evolution). Red bars show significantly more counts of excessive evolution compared to unvaccinated simulations ($p < 0.05$, Pearson's χ^2 test).

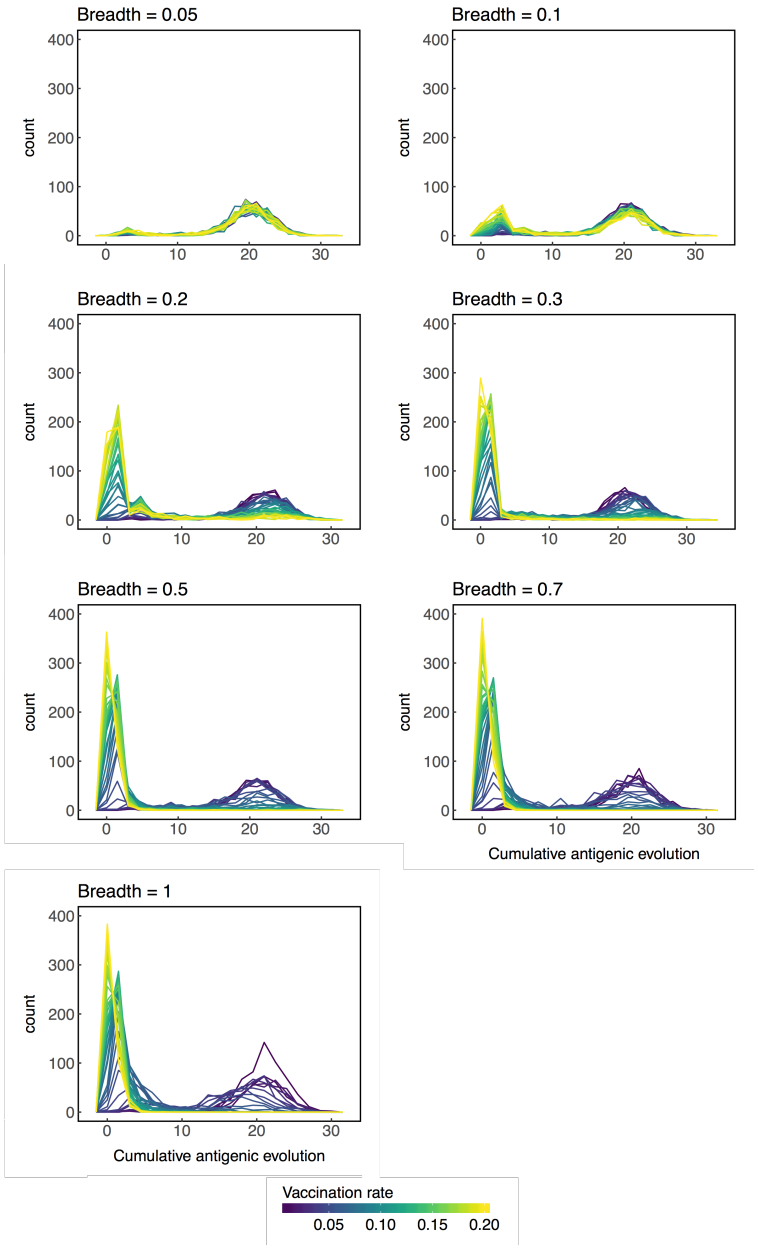

Figure S14: The distributions of cumulative antigenic evolution are profiles along each vaccination rate shown in figure S11. Data are collected from 500 replicate simulations per unique combination of vaccination rate and vaccine immune breadth with excessively diverse simulations (TMRCA $>$ 10 years) excluded, leaving $\sim 300 - 400$ simulations per parameter combination.

Table S3: Private and social benefits of vaccination. In the static model, vaccination cannot affect antigenic evolution. In the dynamic model, vaccination can affect antigenic evolution. Statistics are computed using a linear panel model on longitudinal panel data of simulated hosts' infection and vaccination histories. Robust standard errors shown in brackets are clustered by simulation.

	Probability of infection in the current season (τ)	
	Static ($\times 10^{-2}$)	Dynamic ($\times 10^{-2}$)
Constant	9.91***	9.94***
	[0.35]	[0.23]
Vaccinated in current season (τ)	-4.65***	-3.34***
	[0.20]	[0.32]
Vaccinated 1 season ago (τ-1)	-3.62***	-2.78***
	[0.18]	[0.33]
Vaccinated 2 seasons ago (τ-2)	-2.65***	-2.05***
	[0.13]	[0.24]
Vaccinated 3 seasons ago (τ-3)	-1.47***	-1.74***
	[0.19]	[0.22]
Vaccinated 3 seasons ago (τ-4)	-1.28***	-1.08***
	[0.20]	[0.16]
Vaccination rate = 1%	-0.95**	-0.93**
	[0.46]	[0.47]
Vaccination rate = 5%	-2.75***	-5.75***
	[0.50]	[0.65]
Vaccination rate = 10%	-2.42***	
	[0.35]	
Observations	1,627,500	987,500
Number of hosts	140,000	87,500
Vaccine efficacy (%)	**46.95**	**33.58**
Vaccine efficacy (%, social $r = 1\%$)	**9.28**	**9.36**
Vaccine efficacy (%, social $r = 5\%$)	**27.4**	**57.8**
Vaccine efficacy (%, social $r = 10\%$)	**24.1**	–

Table S4: Private and social benefits of vaccination for a vaccine that provides half the immune breadth of natural immunity ($b = 0.5$). In the static model, vaccination cannot affect antigenic evolution. In the dynamic model, vaccination can affect antigenic evolution. Statistics are computed using a linear panel model on longitudinal panel data of simulated hosts' infection and vaccination histories. Robust standard errors shown in brackets are clustered by simulation.

	Probability of infection in the current season (τ)	
	Static ($\times 10^{-2}$)	Dynamic ($\times 10^{-2}$)
Constant	9.63***	9.84***
	[0.25]	[0.44]
Vaccinated this season (τ)	-3.48***	-3.22***
	[0.19]	[0.22]
Vaccinated 1 seasons ago (τ-1)	-2.00***	-1.72***
	[0.16]	[0.22]
Vaccinated 2 seasons ago (τ-2)	-0.88***	-0.82***
	[0.14]	[0.19]
Vaccinated 3 seasons ago (τ-3)	-0.08	0.26
	[0.15]	[0.19]
Vaccinated 4 seasons ago (τ-4)	0.19	0.27
	[0.19]	[0.20]
Vaccination rate = 1%	0.68	-0.20
	[0.44]	[0.53]
Vaccination rate = 5%	-1.50***	-0.34
	[0.41]	[0.50]
Vaccination rate = 10%	-0.91	-4.85***
	[0.88]	[1.11]
Observations	1,727,500	927,500
Number of hosts	155,000	82,500
Vaccine efficacy (%, private)	**36.10**	**32.68**
Vaccine efficacy (%, social $r = 1\%$)	**-9.24**	**2.03**
Vaccine efficacy (%, social $r = 5\%$)	**1.34**	**3.05**
Vaccine efficacy (%, social $r = 10\%$)	**7.27**	**49.3**