Vaccination and the evolution of seasonal influenza

Frank T. Wen*[a,1], Anup Malani[b,c], and Sarah Cobey[a]

[a]Department of Ecology and Evolution, University of Chicago, 1101 E. 57th St., Chicago, IL 60637

[b]The University of Chicago Law School, 1111 E. 60th St., Chicago, IL 60637

[c]The University of Chicago Pritzker School of Medicine, 924 E. 57th St., Chicago, IL 60637

July 12, 2017

1 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 the host population (i.e. private and social benefits). To investigate vaccinations potential evolutionary impacts, we simulated the dynamics of an influenza-like pathogen in an annually vaccinated host population. On average, vaccination decreased the cumulative amount of antigenic evolution of the viral population and the incidence of disease. Vaccination at a 5% random annual vaccination rate (48% cumulative vaccine coverage after 20 years) decreased cumulative evolution by 56% and incidence by 76%. 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 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 greater than predicted by current measurements of vaccine impact, which do not capture long-term evolutionary effects. These results suggest that conventional vaccines against seasonal influenza could greatly reduce the burden of disease by slowing antigenic evolution like universal vaccines. Furthermore, vaccination's evolutionary effects compound a collective action problem, highlighting the importance on social policies concerning vaccination.

2 Introduction

As 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 illness [2, 5]. While vaccines regularly undergo reformulation to address this mismatch, vaccines may also affect antigenic evolution. 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 [6–9]. Accounting for the evolutionary impact of vaccines, however, may alter assessments of their long-term value.

In theory, seasonal influenza vaccines could slow antigenic evolution [10–13]. Universal vaccines, which confer immunity against all antigenic variants, slow antigenic evolution by uniformly decreasing the fitness of all strains [12]. Conventional vaccines against seasonal influenza, which confer narrower immunity, might also slow antigenic evolution. 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

*frankwen@uchicago.edu

the growth rate of antigenically distant mutants relative to less distant mutants (which can lead to strain replacement in other pathogens [14–20]), 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. S2). Finally, smaller viral population sizes increase the rate at which different strains go stochastically extinct, weakening selection for more antigenically diverged strains.

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 inactivated vaccine reduces the within-season rate of influenza infections in healthy adult recipients by up to 75% [21–25]. 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% [26,27], in the local community by up to 5-82% [28], and in a metropolitan county by up to 59% [29]. 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 decrease incidence, then the social benefit increases. However, the private benefit may fall as increased herd immunity reduces vaccines' marginal protective benefit. As the private benefit falls, additional incentives might be necessary to compensate for less frequent voluntary vaccination [30,31]. 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. Vaccination mostly occurs in temperate populations such as North America, Europe, and Oceania, which do not consistently contribute to the long-term evolution of influenza viruses [32–34]. Yet this is where most studies estimating the value of vaccination take place [21,22]. By contrast, source populations that contribute more to influenza's evolution (e.g., China and India) have almost zero vaccination [32–34], and few studies of vaccination occur there [35].

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.

3 Results

3.1 Modeling approach and choice of parameters

We simulated the transmission and evolution of an influenza A H3N2-like pathogen over 20 years in a well-mixed population [36]. 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 [37,38]. Each antigenic unit difference in distance between strains increases susceptibility by 7% (Fig. 1C) [1,36,39].

The model reproduces characteristic epidemiological and evolutionary patterns of H3N2 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 [32,34]. We first chose transmission and mutation parameters (Table S1) such that simulated epidemiological and evolutionary patterns were most likely to reflect qualitative patterns observed for H3N2 [40]. H3N2 has remained endemic in the human population since its emergence in 1968 and also has low standing 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 lineages of H3N2 have coexisted for no more than 5 years [34]. The remaining 53% of simulations that show qualitatively influenza-like dynamics reproduce ecological 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 [34]. The path of evolution in antigenic space is mostly constrained to one dimension (Fig. 1A), characteristic of H3N2's antigenic evolution [37, 38]. Antigenic evolution occurs at an average rate of 1.09 antigenic units per year (SD = 0.14), comparable to observed an observed rate of 1.01 antigenic units per year [38]. The mean annual incidence is 9.0% (SD = 1.0%). Reported annual incidence across all types of seasonal influenza ranges from 9-15% [41].

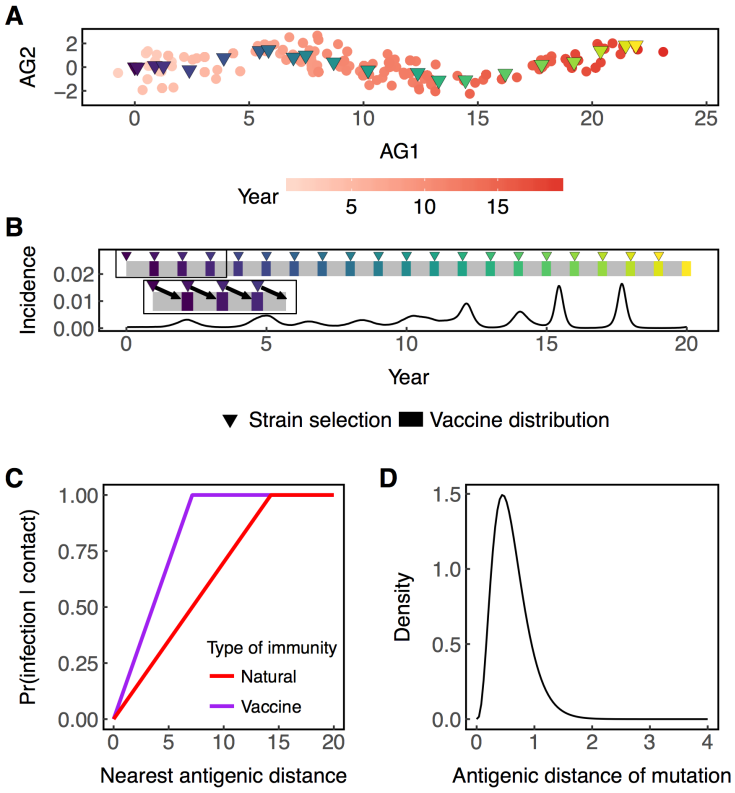

Figure 1: Properties of the model. (A) Antigenic phenotypes are represented as points in two-dimensional space (AG1 is antigenic dimension 1 and AG2 is antigenic dimension 2). Over time, new strains appear as old strains can no longer transmit to immune hosts. Viral evolution is mostly linear in antigenic 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. Note that strain selection for the following year occurs during the distribution of the current vaccine (inset). (C) 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. (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 (Eqs. 2, 4) In this example, vaccines confer half the breadth of immunity as natural immunity ($b = 50\%$).

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, 9-10 months after strain selection [42]. 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

according to the annual vaccination rate (Eq. 3). Since individuals are randomly vaccinated each year, the fraction of vaccinated individuals accumulates over time. At a 5% annual vaccination rate, approximately 4.9% of individuals in the population are vaccinated every year and 48.4% of the population has been vaccinated at least once by the twentieth year (Fig. S1A). For the same rate, vaccination effectively renders 26.0% of individuals immune when vaccination is in equilibrium with antigenic evolution (Fig. S1B). 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 $\times 100\%$ (Fig. 1). Vaccines with $b = 100\%$ have breadth identical to natural immunity, whereas vaccines with $b < 100\%$ ($b > 100\%$) 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 [36–38], 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, and 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 also measured both 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 (and in the case of B, antigenic) diversity at any time [34, 38, 43, 44] Thus, we chose to examine whether vaccination, by affecting antigenic evolution, could also impact diversification.

To estimate how much of vaccination's epidemiological impact was due to evolutionary effects, we compared simulations in which vaccination could affect antigenic evolution to simulations where it could not. We generated the latter by first running a set of 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 contemporary strains from an unvaccinated reference simulation at the same frequencies. In this way, we obtained simulations in which the temporal changes in strain frequencies were unaffected by vaccination.

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

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 slows 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, extinction occurs rapidly, typically within 2.3 years (SD = 0.6, Fig. S3). Compared to vaccines distributed 300 days after strain selection, vaccines distributed immediately after strain selection further reduce antigenic evolution (Wilcoxon rank-sum test, $p < 0.001$) and incidence (Wilcoxon rank-sum test, $p < 0.001$) (Fig. S4).

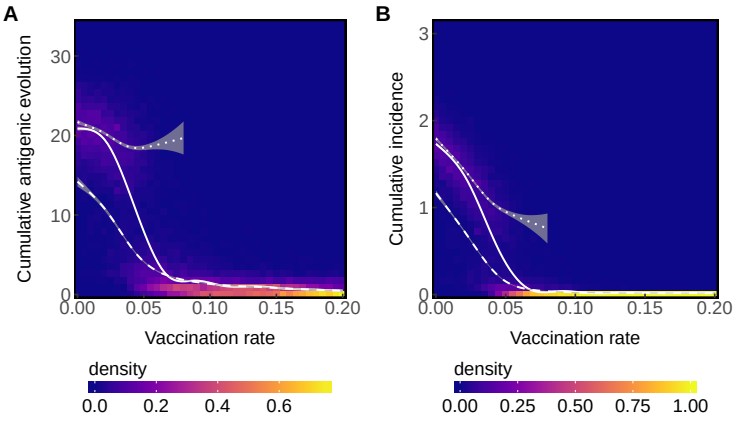

Figure 2: High vaccination rates decrease the average amount of (A) cumulative antigenic evolution and (B) cumulative incidence. The solid white lines show LOESSs fit to cumulative antigenic evolution and incidence across all simulations. The dotted white lines show fits for simulations where the viral 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.

Increasing the vaccination rate also decreases the probability that the viral population becomes too diverse (TMRCA $>$ 10 years, Fig. S5). Thus, vaccination is unlikely to increase morbidity from diversifying viral populations.

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 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.

Although high vaccination rates appear to increase the amount of antigenic evolution in surviving populations, they do so by reduce the probability that less evolved strains survive.

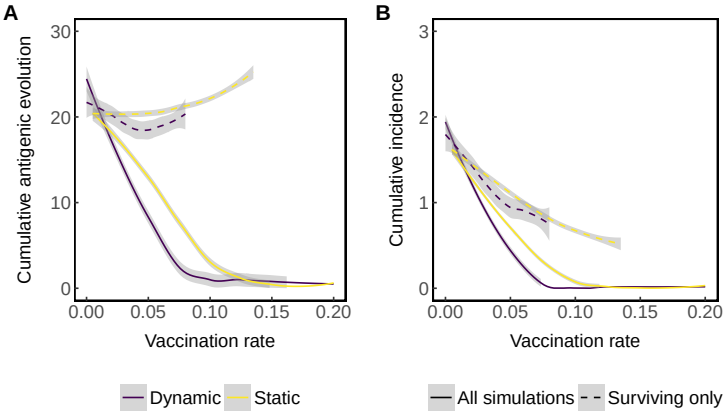

Figure 3: Vaccination further decreases incidence when vaccines can affect antigenic evolution compared to when they cannot. Purple lines represent simulations where vaccination can affect antigenic evolution. Yellow lines represent simulations where vaccination cannot affect antigenic evolution. The 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.

3.3 Narrow breadth of vaccine-induced immunity is associated with more antigenic evolution and disease burden

More vaccination always reduces the average amount of antigenic evolution and incidence across all simulations, regardless of breadth (Fig. 4A,B), mainly because vaccination drives strains extinct. However, contingent on the unlikely survival of the viral population, vaccines with narrow breadth ($b < 100\%$) are associated with more evolved viral populations that can occasionally cause more disease than without vaccination (Fig. 4C,D). In these cases, more vaccination does not directly increase the rate of antigenic evolution, but instead drives slow-evolving viral populations extinct while occasionally allowing persistence of fast-evolving populations (Fig. S7). Thus, any apparent increase in the amount of antigenic evolution among survivors reflects "selection" for fast-evolving populations that would also appear in the absence of vaccination.

Compared to vaccines with 100% breadth, vaccines with narrower breadth are associated with survival of more evolved viral populations. For example, under vaccines with a 30% breadth and a 15% annual vaccination rate, to survive for 20 years, viral populations must evolve 15.6% more relative to no vaccination (Wilcoxon rank-sum test, $p < 0.001$) (Fig. 4C). Under vaccines with moderate to large breadth ($b = 50\%$ or 70%), surviving viral populations are further evolved (Fig. 4C) but the average amount of cumulative evolution is less compared to vaccines with narrow breadth ($b = 20\%$ or 30%) (Fig. 4A). This is because only the furthest evolved viral populations can survive vaccination at large breadth, while less evolved viral populations can still survive vaccination at narrow breadth. At extremely narrow breadth ($b = 5\%$ or 10%), even slow-evolving viral populations survive, so vaccination decreases antigenic evolution on average among all viral populations and among surviving viral populations. Together, these results suggest that fast-evolving viral populations are more likely to survive under vaccination using vaccines with narrow breadth.

Even though surviving viral populations are more evolved under vaccines with greater breadth, they do not always lower incidence. For example, above a 5% annual vaccination rate using vaccines with a 50% breadth, surviving viral populations evolve 4.5% more (Wilcoxon rank-sum test, $p < 0.001$) than without vaccination but still cause 10% fewer cases (Wilcoxon rank-sum test, $p < 0.001$). In these situations, the viral population's survival requires more evolution, but strong herd immunity limits prevalence. In the limit of 100% breadth, viral populations would theoretically have to be extremely antigenically evolved to survive, but strong herd immunity makes survival extremely unlikely. Thus, although more antigenic evolution usually correlates with more disease (Spearman's $\rho = 0.92, p < 0.001$), vaccines with large breadth can instill strong herd immunity to reduce infections.

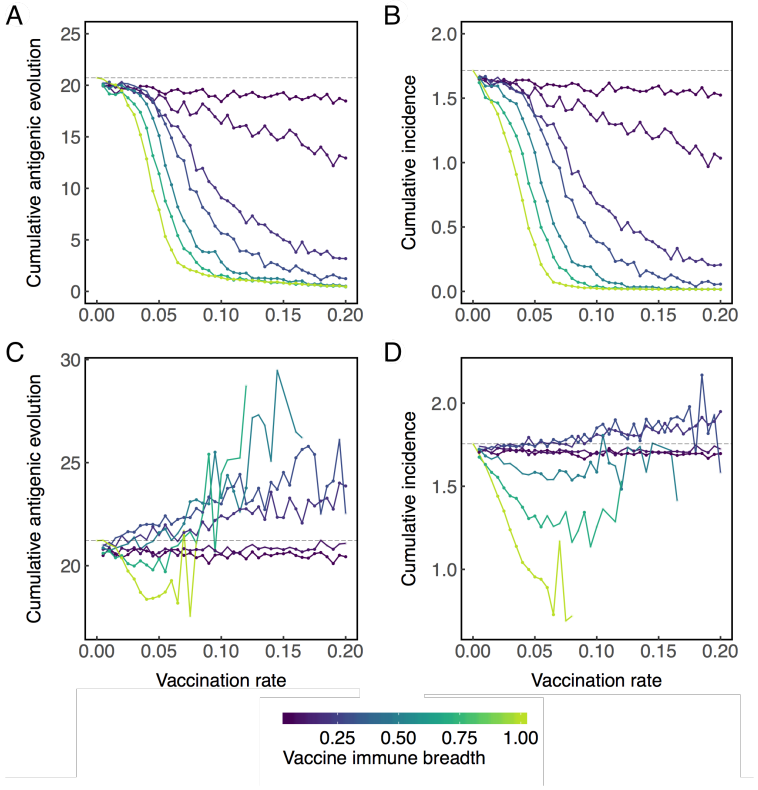

Figure 4: Across all simulations (A&B), vaccination decreases the average (A) cumulative antigenic evolution and (B) incidence regardless of breadth. In the subset of simulations where the viral population does not go extinct (C&D), vaccines with narrow breadth increase the average antigenic evolution (C) and incidence (D). 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 S6 and S7.

The apparent increases in cumulative antigenic evolution among surviving populations are not driven by vaccination–but instead reflect "selection" for fast-evolving viral populations. At any breadth, the relative likelihood of viral populations being more antigenically evolved is indistinguishable (for viral populations that evolve more than 15 antigenic units) over different vaccination rates (Fig. S7). Since the underlying distributions do not change, vaccination does not directly accelerate antigenic evolution. Instead, increased evolution at high vaccination rates in surviving viral populations reflects eradication of slow-evolving viral populations. When considering the extinct and surviving populations together, vaccination always decreases the average amount of evolution on average.

Viral populations are more likely to diversify antigenically when immune breadth is small (Fig. S5). However, regardless of breadth, more vaccination always decreases the probability of excess diversification compared to no vaccination (Fig. S5). Thus, it is unlikely that vaccines of any breadth would contribute to excess morbidity relative to no vaccination.

As the delay between the selection of strains and vaccine distribution falls, selection for increased antigenic evolution is only possible with vaccines with very narrow breadth. When vaccines are distributed immediately after strain selection, vaccines with a 5% or 10% breadth increase the amount of antigenic evolution (Spearman's $\rho = 0.15$, $p < 0.001$) and incidence (Spearman's $\rho = 0.14$, $p < 0.001$) when the viral population survives (Fig. S8). As above, the amount of evolution and disease, averaged across all simulations, decreases with vaccination regardless of breadth.

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

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. 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. 6). To measure the social benefit, we used an analogous risk ratio. The social benefit is one minus the risk of infection in a vaccinated population relative to the risk of infection in an unvaccinated population (Eq. 7). The social benefit reflects a reduction in the force of infection due to vaccination.

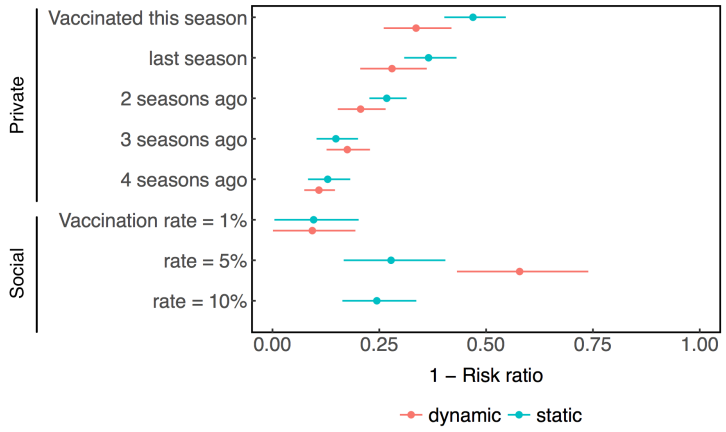

Figure 5: Comparison of the private and social benefits of vaccination when vaccination can or cannot affect antigenic evolution. Risk ratios are calculating using coefficients from a linear panel model fitted to the last 17 years of simulated hosts' infection and vaccination histories. Mean estimates and 95% confidence intervals are shown. Red lines represent simulations where vaccination can affect antigenic evolution. Blue lines represent simulations where vaccination cannot affect antigenic evolution. 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.

The social benefit of vaccination rises when vaccines can affect 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 S2). 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. 5, Table S2). However, when vaccination cannot affect antigenic evolution, the average host is only 27.7% less likely to become infected (Fig. 5, Table S2) at the same vaccination rate. 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, vaccinated individuals benefit less than when vaccines do not affect antigenic evolution. The reduction in the private benefit due to evolutionary effects is a natural consequence of reduced incidence: when the overall risk of infection is low, the marginal benefit of vaccination is lower than when incidence is high (Eq. 6). 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. 5, Table S2). However, when vaccines cannot affect antigenic evolution, vaccinated individuals are 49.5% less likely to become infected (Fig. 5, Table S2). We observed similar patterns when the breadth of vaccine-induced immunity was half that of natural immunity (Table S3).

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. 5, Table S2). 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.

4 Discussion

We found that vaccination against seasonal influenza can slow antigenic evolution and thereby reduce the disease burden beyond its immediate impact on transmission. In simulation, annual vaccination rates as low as 10%, which imply a 28% cumulative vaccine coverage after 4 years, can reliably eradicate the virus. The probability of survival is higher when using vaccines that confer narrow breadth, which allows fast-evolving populations to survive, but even here vaccination usually decreases antigenic evolution. At a 5% annual vaccination rate (33% cumulative coverage after 10 years), evolution increases the social benefits of vaccination by 30.4% and 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 is sufficient to eradicate influenza, this prediction may not appear realistic since up to 8% of the global population already receives the seasonal influenza vaccine each year [32]. However, vaccination is almost exclusively concentrated in seasonal populations rather than in the populations that contribute most to influenza's evolution [32–34]. During the 2012-2013 season, 47% of the United States and 23% of the United Kingdom populations were vaccinated [32]. By contrast, less than 1% of individuals in China and India were vaccinated over the same time period [32,45], and these populations have contributed substantially to the evolution of seasonal influenza [34]. Moreover, vaccination is concentrated among individuals who consistently vaccinate annually, 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 [46, 47]. Consecutive vaccination may also reduce vaccine effectiveness potentially due to interaction with prior immune responses, although the mechanisms underlying these effects are not well understood [23, 48, 49]. Thus, the effective amount of vaccine-induced immunity in a population is potentially lower than vaccine coverage estimates would suggest. Reducing the rate of repeat vaccination while maintaining high vaccination rates might partially overcome the effects of prior vaccines and allow vaccine-induced immunity to accumulate in the population. In our model, vaccines are distributed randomly in a single population. At a 5% vaccination rate, vaccination effectively makes $\sim$26.0% of the population immune to the circulating strain at the end of the simulation (Fig. S1B).

Current estimates of vaccines' effects likely do not capture evolutionary effects. As previously mentioned, because most vaccination occurs in populations that do not consistently contribute to influenza's long-term evolution, current vaccines are unlikely to have enduring effects on influenza's evolution to begin with [32–34]. Additionally, vaccine efficacy and effectiveness studies are conducted in small populations typically over individual seasons [21, 22]. To measure evolutionary effects, vaccine studies would have to take place over several seasons in a population that contributes to influenza's long-term evolution.

By affecting regional antigenic evolution, vaccination has the potential to change influenza's phylogeography. Presently, tropical and subtropical Asia contribute disproportionately to the evolution of H3N2 [33,34,50–52], which may be due to higher regional transmission [40]. High vaccine coverage in seasonal populations may compound the propensity for Asia to produce antigenically advanced strains that contribute to influenza's long-term evolution. Vaccination in Asia might have a disproportionately large impact on influenza's global circulation by reducing its production of antigenically advanced strains.

Our results suggest that the seasonal influenza vaccine is unlikely to accelerate antigenic evolution or cause excess diversification. In simulations, more evolved viral populations can only survive when the breadth of vaccine-induced immunity is much narrower than that of natural infection, and even in these cases, survival is rare. However, vaccination and infection stimulate similarly broad collective antibody responses (measured by serum HI) [53], suggesting that the breadths of vaccine-induced and natural immunity are similar.

While our simulations show vaccines typically slow evolution (and drive extinction) in a single, closed population (i.e., a global population), other studies predict faster evolution when antigenically diverged strains are guaranteed to emerge and survive. When stochastic loss of strains is ignored, vaccination below the threshold for invasion always increases the amount of antigenic evolution over the course of an epidemic [54]. Similarly, vaccines also accelerate evolution in the long-term when antigenically diverged strains are

re-introduced after extinction to cause new epidemics [55]. Such theoretical scenarios are possible on a local scale, where external host populations can produce diverged strains. In a metapopulation, frequent immigration may facilitate local vaccine-driven selection for diverged strains, but we would still expect slower rates of antigenic evolution globally when vaccinating in source populations. In contrast to these scenarios, our model simulates a closed global population with stochastic extinctions, which allows vaccination to slow evolution.

Different distributions of mutation sizes (i.e. fitness effects) and transmission rates may change how vaccination affects antigenic evolution. We selected mutational and transmission parameters such that the simulated epidemiological and evolutionary dynamics match those of H3N2 [36, 40]. 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 [36, 40]. 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 [56]. Consistent with this hypothesis, there is evidence that vaccination history [23, 48, 49] and recipient age (potentially a proxy for infection history) [57] affect vaccine efficacy. Models that include more realistic features of immunity might demonstrate how interactions between existing immunity and novel responses affect the impact of vaccination on influenza's evolution.

Although the evolutionary benefits of influenza vaccination may reduce the burden of disease, the public health benefits may be counterbalanced by weaker personal incentives for vaccination. Vaccination's evolutionary benefits greatly reduce incidence, which incurs a large social benefit. However, lower overall risk of infection reduces the private benefit to vaccinated individuals. Since individuals are less likely to get vaccinated if they perceive a low risk of influenza infection [30] or a low vaccine effectiveness [31], the evolutionary benefits of vaccination potentially exacerbate an existing collective action problem [58]. This tradeoff emphasizes the significance of information campaigns, subsidies, or regulations concerning societal vaccination.

Our results suggest that conventional seasonal influenza vaccines already have the potential to slow antigenic evolution and eradicate seasonal influenza. Universal vaccines that immunize against all strains necessarily slow antigenic evolution by not discriminating between antigenic variants [12]. However, despite the fact that conventional vaccines create selective gradients among antigenic variants, our results suggest that conventional vaccines still reduce evolution and drive extinction. Increasing vaccine coverage, especially in populations that contribute substantially to influenza's evolution, would help realize the evolutionary benefits of vaccination in the long term. However, as vaccination further reduces the burden of disease, individuals may require additional incentives to get vaccinated.

5 Materials and Methods

5.1 Model overview

We adapted an individual-based model of influenza's epidemiological and evolutionary dynamics [36] to include vaccination. The state of the simulation is updated using a tau-leaping algorithm. In each time step, 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 coinfected.

Antigenic phenotypes are represented as points in 2-dimensional Euclidean space, analogous to antigenic maps produced using pairwise measurements of serum cross-reactivity [37,38]. One antigenic unit corresponds to a two-fold dilution in antiserum 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. When a susceptible host contacts 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. The probability of infection upon contact is given by

$$\text{Risk} = P(\text{infection}|\text{contact}) = \min\{1, cd_{\mathrm{n}}\}, \tag{2}$$

where $c = 0.07$ is a constant for converting antigenic distance to a risk of infection [1, 36, 39].

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.

$$r_{\mathrm{day}} = r_{\mathrm{annual}} \times \frac{1 \text{ year}}{365 \text{ days}} \tag{3}$$

By default, the breadth of vaccine-induced and natural immunity are equal. For a vaccinated individual, the probability of infection upon contact is given by

$$\text{Risk} = P(\text{infection}|\text{contact}) = \min\{1, cd_{\mathrm{n}}, \frac{cd_{\mathrm{v}}}{b}\} \tag{4}$$

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.

5.2 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.

5.3 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 in the host population at the end of the simulation for analysis. We defined each season τ as starting when vaccine distribution for year τ begins and ending before vaccine distribution for the year $\tau+1$. In a simulation j, host i is considered infected ($I = 1$) in season τ if infected in this time interval and vaccinated ($V = 1$) in season τ if vaccinated in the same interval. We excluded hosts sampled during the vaccine period because they could have been infected before vaccination, which would bias our estimates of vaccine efficacy.

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

The coefficient β_1 estimates the absolute reduction in the risk of becoming infected in the current season from having been vaccinated in the current season. Coefficients $\beta_2, \ldots, \beta_5$ estimate the reduction in the risk of infection in the current season from having been vaccinated in prior seasons. Collectively, $\beta_1, \ldots, \beta_5$ measure the private benefits of vaccination.

The coefficients β_6, β_7, and β_8 measure the social benefits of vaccination at 1%, 5%, and 10% annual vaccination rates, respectively. More specifically, they estimate the absolute reduction in the risk of infection for any host in the population given the annual vaccination rate.

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

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

To estimate the social benefit for a specific vaccination rate R, we calculate an analogous relative risk:

$$\text{Social} = \left[1 - \frac{P(I = 1|r = R)}{P(I = 1|r = 0)}\right] \times 100\% \tag{7}$$

6 Data accessibility

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`.

7 Competing interests

We have no conflicts of interests to declare.

8 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.

9 Acknowledgements

This work was completed in part with resources provided by the University of Chicago Research Computing Center. FW and SC were supported by NIH grant DP2AI117921. FW was also supported by NIH grant T32GM007281. We thank Ed Baskerville for programming guidance and Mercedes Pascual for insightful comments.

References

[1] Gupta V, Earl DJ, Deem MW. Quantifying influenza vaccine efficacy and antigenic distance. Vaccine. 2006 May;24(18):3881–3888.

[2] Bridges CB, Thompson WW, Meltzer MI, Reeve GR, Talamonti WJ, Cox NJ, et al. Effectiveness and cost-benefit of influenza vaccination of healthy working adults: A randomized controlled trial. JAMA. 2000 Oct;284(13):1655–1663.

[3] Belongia EA, Kieke BA, Donahue JG, Greenlee RT, Balish A, Foust A, et al. Effectiveness of inactivated influenza vaccines varied substantially with antigenic match from the 2004-2005 season to the 2006-2007 season. The Journal of Infectious Diseases. 2009 Jan;199(2):159–167.

[4] Zimmerman RK, Nowalk MP, Chung J, Jackson ML, Jackson LA, Petrie JG, et al. 2014–2015 Influenza Vaccine Effectiveness in the United States by Vaccine Type. Clinical Infectious Diseases. 2016 Dec;63(12):1564–1573.

[5] Carrat F, Flahault A. Influenza vaccine: The challenge of antigenic drift. Vaccine. 2007 Sep;25(39-40):6852–6862.

[6] Bansal S, Pourbohloul B, Meyers LA. A comparative analysis of influenza vaccination programs. PLoS Medicine. 2006 Oct;3(10):e387–10.

[7] Weycker D, Edelsberg J, Halloran ME, Longini IM, Nizam A, Ciuryla V, et al. Population-wide benefits of routine vaccination of children against influenza. Vaccine. 2005 Jan;23(10):1284–1293.

[8] Medlock J, Galvani AP. Optimizing influenza vaccine distribution. Science. 2009 Sep;325(5948):1705–1708.

[9] Shim E, Galvani AP. Distinguishing vaccine efficacy and effectiveness. Vaccine. 2012 Oct;30(47):6700–6705.

[10] Gog JR, Grenfell BT. Dynamics and selection of many-strain pathogens. Proceedings of the National Academy of Sciences. 2002 Dec;99(26):17209–17214.

[11] Kucharski A, Gog JR. Influenza emergence in the face of evolutionary constraints. Proceedings of the Royal Society B. 2012 Feb;279(1729):645–652.

[12] Arinaminpathy N, Ratmann O, Koelle K, Epstein SL, Price GE, Viboud C, et al. Impact of cross-protective vaccines on epidemiological and evolutionary dynamics of influenza. Proceedings of the National Academy of Sciences of the United States of America. 2012 Feb;109(8):3173–3177.

[13] Lin J, Andreasen V, Casagrandi R, A Levin S. Traveling waves in a model of influenza A drift. Journal of theoretical biology. 2003 Jun;222(4):437–445.

[14] Carman WF, Zanetti AR, Karayiannis P, Waters J, Manzillo G, Tanzi E, et al. Vaccine-induced escape mutant of hepatitis B virus. The Lancet. 1990 Aug;336(8711):325–329.

[15] Lipsitch M. Vaccination against colonizing bacteria with multiple serotypes. Proceedings of the National Academy of Sciences. 1997 Jun;94(12):6571–6576.

[16] Pai R, Moore MR, Pilishvili T, Gertz RE, Whitney CG, Beall B, et al. Postvaccine genetic structure of Streptococcus pneumoniae serotype 19A from children in the United States. The Journal of Infectious Diseases. 2005 Dec;192(11):1988–1995.

[17] Lee CW, Senne DA, Suarez DL. Effect of Vaccine Use in the Evolution of Mexican Lineage H5N2 Avian Influenza Virus. Journal of Virology. 2004 Jul;78(15):8372–8381.

[18] Elomaa A, Advani A, Donnelly D, Antila M, Mertsola J, Hallander H, et al. Strain Variation among Bordetella pertussis Isolates in Finland, Where the Whole-Cell Pertussis Vaccine Has Been Used for 50 Years. Journal of Clinical Microbiology. 2005 Aug;43(8):3681–3687.

[19] Martcheva M, Bolker BM, Holt RD. Vaccine-induced pathogen strain replacement: what are the mechanisms? Journal of the Royal Society, Interface. 2008 Jan;5(18):3–13.

[20] Adam HJ, Richardson SE, Jamieson FB, Rawte P, Low DE, Fisman DN. Changing epidemiology of invasive Haemophilus influenzae in Ontario, Canada: Evidence for herd effects and strain replacement due to Hib vaccination. Vaccine. 2010 May;28(24):4073–4078.

[21] Osterholm MT, Kelley NS, Sommer A, Belongia EA. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. The Lancet Infectious diseases. 2012 Jan;12(1):36–44.

[22] Belongia EA, Simpson MD, King JP, Sundaram ME, Kelley NS, Osterholm MT, et al. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. The Lancet Infectious diseases. 2016 Aug;16(8):942–951.

[23] Ohmit SE, Thompson MG, Petrie JG, Thaker SN, Jackson ML, Belongia EA, et al. Influenza Vaccine Effectiveness in the 2011-2012 Season: Protection Against Each Circulating Virus and the Effect of Prior Vaccination on Estimates. Clinical Infectious Diseases. 2014 Jan;58(3):319–327.

[24] Skowronski DM, Janjua NZ, De Serres G, Sabaiduc S, Eshaghi A, Dickinson JA, et al. Low 2012–13 Influenza Vaccine Effectiveness Associated with Mutation in the Egg-Adapted H3N2 Vaccine Strain Not Antigenic Drift in Circulating Viruses. PLoS ONE. 2014 Mar;9(3):e92153–15.

[25] Petrie JG, Ohmit SE, Cheng CK, Martin ET, Malosh RE, Lauring AS, et al. Influenza Vaccine Effectiveness Against Antigenically Drifted Influenza Higher Than Expected in Hospitalized Adults: 2014-2015. Clinical infectious diseases : an official publication of the Infectious Diseases Society of America. 2016 Oct;63(8):1017–1025.

[26] Hurwitz ES, Haber M, Chang A, Shope T, Teo S, Ginsberg M, et al. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. JAMA. 2000 Oct;284(13):1677–1682.

[27] Principi N, Esposito S, Marchisio P, Gasparini R, Crovari P. Socioeconomic impact of influenza on healthy children and their families. The Pediatric Infectious Disease Journal. 2003 Oct;22(10 Suppl):S207–10.

[28] Loeb M, Russell ML, Moss L, Fonseca K, Fox J, Earn DJD, et al. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. JAMA. 2010 Mar;303(10):943–950.

[29] Pebody RG, Green HK, Andrews N. Uptake and impact of vaccinating school age children against influenza during a season with circulation of drifted influenza A and B strains, England, 2014/15. .... 2015;.

[30] Brewer NT, Chapman GB, Gibbons FX, Gerrard M, McCaul KD, Weinstein ND. Meta-analysis of the relationship between risk perception and health behavior: The example of vaccination. Health Psychology. 2007;26(2):136–145.

[31] Chapman GB, Coups EJ. Predictors of influenza vaccine acceptance among healthy adults. Preventive medicine. 1999 Oct;29(4):249–262.

[32] Palache A, Oriol-Mathieu V, Fino M, Xydia-Charmanta M, Influenza Vaccine Supply task force (IFPMA IVS). Seasonal influenza vaccine dose distribution in 195 countries (2004-2013): Little progress in estimated global vaccination coverage. Vaccine. 2015 Oct;33(42):5598–5605.

[33] Bedford T, Cobey S, Beerli P, Pascual M. Global migration dynamics underlie evolution and persistence of human influenza A (H3N2). PLoS Pathogens. 2010 May;6(5):e1000918.

[34] Bedford T, Riley S, Barr IG, Broor S, Chadha M, Cox NJ, et al. Global circulation patterns of seasonal influenza viruses vary with antigenic drift. Nature. 2015 Jul;523(7559):217–220.

[35] Tam JS, Capeding MRZ, Lum LCS, Chotpitayasunondh T, Jiang Z, Huang LM, et al. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. The Pediatric Infectious Disease Journal. 2007 Jul;26(7):619–628.

[36] Bedford T, Rambaut A, Pascual M. Canalization of the evolutionary trajectory of the human influenza virus. BMC Biology. 2012;10(1):38.

[37] Smith DJ, Lapedes AS, de Jong JC, Bestebroer TM, Rimmelzwaan GF, Osterhaus ADME, et al. Mapping the antigenic and genetic evolution of influenza virus. Science. 2004 Jul;305(5682):371–376.

[38] Bedford T, Suchard MA, Lemey P, Dudas G, Gregory V, Hay AJ, et al. Integrating influenza antigenic dynamics with molecular evolution. eLife. 2014;3:e01914.

[39] Park AW, Daly JM, Lewis NS, Smith DJ, Wood JLN, Grenfell BT. Quantifying the impact of immune escape on transmission dynamics of influenza. Science. 2009 Oct;326(5953):726–728.

[40] Wen F, Bedford T, Cobey S. Explaining the geographical origins of seasonal influenza A (H3N2). Proceedings of the Royal Society B. 2016 Sep;283(1838):20161312–9.

[41] Influenza Fact Sheet; 2014.

[42] FluVaxView; 2015.

[43] Chen R, Holmes EC. The evolutionary dynamics of human influenza B virus. Journal of Molecular Evolution. 2008 Jun;66(6):655–663.

[44] Cox NJ, Bender CA. The molecular epidemiology of influenza viruses. Seminars in Virology. 1995;.

[45] Palache A, Oriol-Mathieu V, Abelin A, Music T. Seasonal influenza vaccine dose distribution in 157 countries (2004–2011). Vaccine. 2014 Nov;32(48):6369–6376.

[46] Flood EM, Rousculp MD, Ryan KJ, Beusterien KM, Divino VM, Toback SL, et al. Parents' decision-making regarding vaccinating their children against influenza: A web-based survey. Clinical therapeutics. 2010 Aug;32(8):1448–1467.

[47] Uscher-Pines L, Mulcahy A, Maurer J, Harris K. The relationship between influenza vaccination habits and location of vaccination. PLoS ONE. 2014;9(12):e114863.

[48] McLean HQ, Thompson MG, Sundaram ME, Meece JK, McClure DL, Friedrich TC, et al. Impact of Repeated Vaccination on Vaccine Effectiveness Against Influenza A(H3N2) and B During 8 Seasons. Clinical Infectious Diseases. 2014 Oct;59(10):1375–1385.

[49] Skowronski DM, Chambers C, De Serres G, Sabaiduc S, Winter AL, Dickinson JA, et al. Serial vaccination and the antigenic distance hypothesis: effects on influenza vaccine effectiveness during A(H3N2) epidemics in Canada, 2010-11 to 2014-15. Journal of Infectious Diseases. 2017 Feb;.

[50] Rambaut A, Pybus OG, Nelson MI, Viboud C, Taubenberger JK, Holmes EC. The genomic and epidemiological dynamics of human influenza A virus. Nature. 2008 May;453(7195):615–619.

[51] Russell CA, Jones TC, Barr IG, Cox NJ, Garten RJ, Gregory V, et al. The Global Circulation of Seasonal Influenza A (H3N2) Viruses. Science (New York, NY). 2008 Apr;320(5874):340–346.

[52] Bahl J, Nelson MI, Chan KH, Chen R, Vijaykrishna D, Halpin RA, et al. Temporally structured metapopulation dynamics and persistence of influenza A H3N2 virus in humans. Proceedings of the National Academy of Sciences of the United States of America. 2011 Nov;108(48):19359–19364.

[53] Fonville JM, Wilks SH, James SL, Fox A, Ventresca M, Aban M, et al. Antibody landscapes after influenza virus infection or vaccination. Science. 2014 Nov;346(6212):996–1000.

[54] Boni MF, Gog JR, Andreasen V, Feldman MW. Epidemic dynamics and antigenic evolution in a single season of influenza A. Proceedings of the Royal Society B. 2006 Jun;273(1592):1307–1316.

[55] Subramanian R, Graham AL, Grenfell BT, Arinaminpathy N. Universal or Specific? A Modeling-Based Comparison of Broad-Spectrum Influenza Vaccines against Conventional, Strain-Matched Vaccines. PLoS Computational Biology. 2016 Dec;12(12):e1005204–17.

[56] Smith DJ, Forrest S, Ackley DH, Perelson AS. Variable efficacy of repeated annual influenza vaccination. Proceedings of the National Academy of Sciences. 1999 Nov;96(24):14001–14006.

[57] McLean HQ, Thompson MG, Sundaram ME, Kieke BA, Gaglani M, Murthy K, et al. Influenza vaccine effectiveness in the United States during 2012-2013: variable protection by age and virus type. Journal of Infectious Diseases. 2015 May;211(10):1529–1540.

[58] Galvani AP, Reluga TC, Chapman GB. Long-standing influenza vaccination policy is in accord with individual self-interest but not with the utilitarian optimum. Proceedings of the National Academy of Sciences. 2007 Mar;104(13):5692–5697.

[59] Jackson C, Vynnycky E, Mangtani P. Estimates of the transmissibility of the 1968 (Hong Kong) influenza pandemic: evidence of increased transmissibility between successive waves. American Journal of Epidemiology. 2010 Feb;171(4):465–478.

[60] Biggerstaff M, Cauchemez S, Reed C, Gambhir M, Finelli L. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC Infectious Diseases. 2014 Sep;14(1):1–20.

[61] Carrat F, Vergu E, Ferguson NM, Lemaitre M, Cauchemez S, Leach S, et al. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. American Journal of Epidemiology. 2008 Apr;167(7):775–785.

[62] World Population Prospects: The 2012 Revision. New York; 2013.

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}:

$$R_{\text{n}} = 1 - \frac{1}{R_0} - \frac{\nu(R_0-1)}{\beta} \tag{S10}$$
$$R_{\text{v}} = \frac{\nu R_0 p}{\beta} \tag{S11}$$
$$R_{\text{eq}} = R_{\text{n}} + R_{\text{v}} \tag{S12}$$

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. S2A). 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. S2C).

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.

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

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

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.

2 Supplementary tables and figures

Table S1: Parameters

Parameter	Value	Reference
Intrinsic reproductive number (R_0)	1.8	[59, 60]
Duration of infection $1/\gamma$	5 days	[61]
Population size N	50 million	(see text)
Birth/death (turnover) rate ν	$1/30$ year^{-1}	[62]
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, 36, 39]
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	

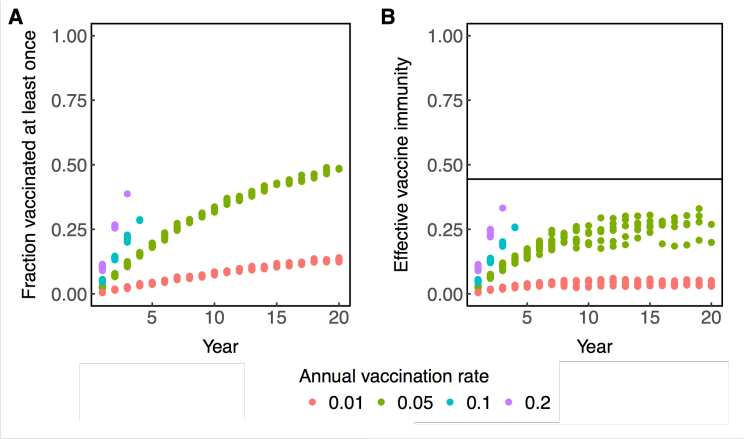

Figure S1: (A) Vaccine coverage and (B) effective vaccine-induced immunity over time calculated from simulations. (A) The fraction of individuals who have been vaccinated at least once accumulated over time and saturates at 50%. (B) The effective amount of vaccine-induced immunity in the population is 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 $1 - 1/R_0$.

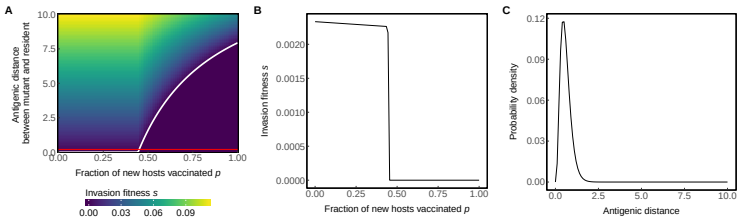

Figure S2: (A) High vaccination rates decrease the invasion fitness of mutant strains. For a given vaccination rate, the invasion fitness of a mutant increases with antigenic distance. However, the invasion fitness of a mutant at a given distance decreases as vaccine coverage increases. An example profile 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 $\delta_{\text{sd}} = 0.6$.

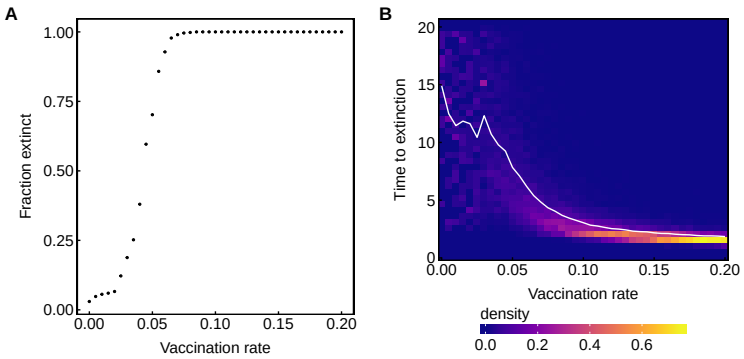

Figure S3: High vaccination rates increase the probability of extinction and shorten the average time to extinction. (A) Points show the fraction of simulations where the viral population went extinct before 20 years. (B) Density of times to extinction. The solid white line shows the average time to extinction across these simulations.

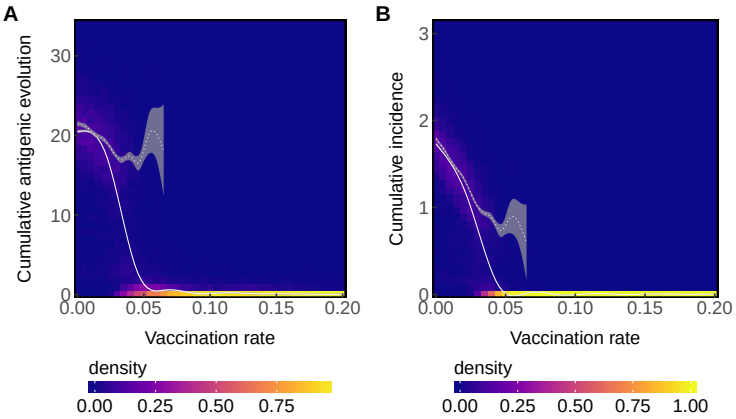

Figure S4: With no temporal lag between vaccine strain selection and distribution, increasing the vaccination rate quickly decreases the average amount of (A) cumulative antigenic evolution (A) and (B) incidence. The solid white line shows a LOESS fit to cumulative antigenic evolution and incidence across 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.

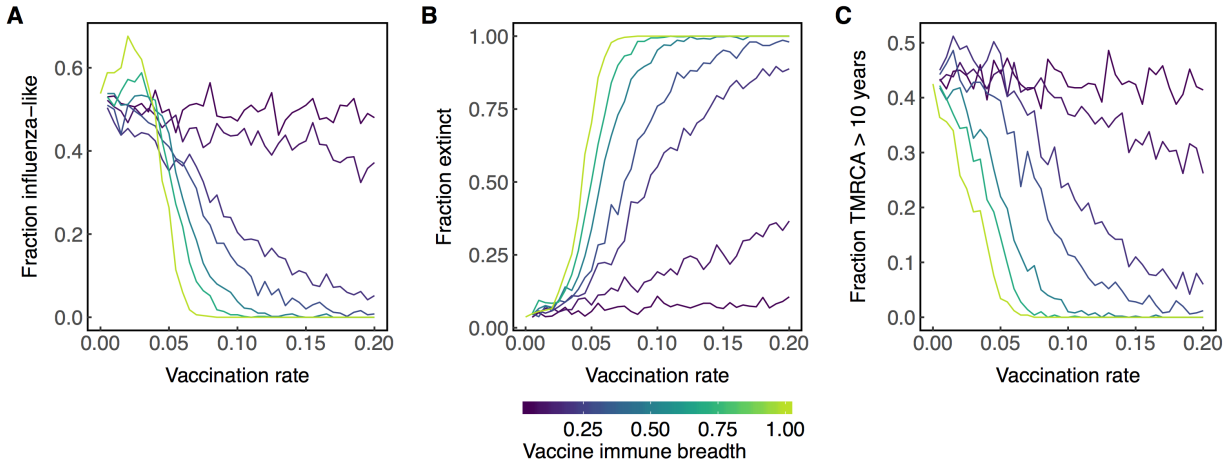

Figure S5: Increasing the vaccination rate increases the probability that the viral population will go extinct (B) and decreases the probability of exhibiting influenza-like dynamics (A) or excessive diversification (TMRCA $>$ 10 years) (C). Lines are colored according to the breadth of the vaccine. Data are collected from 500 replicate simulations per unique combination of vaccination rate and vaccine immune breadth

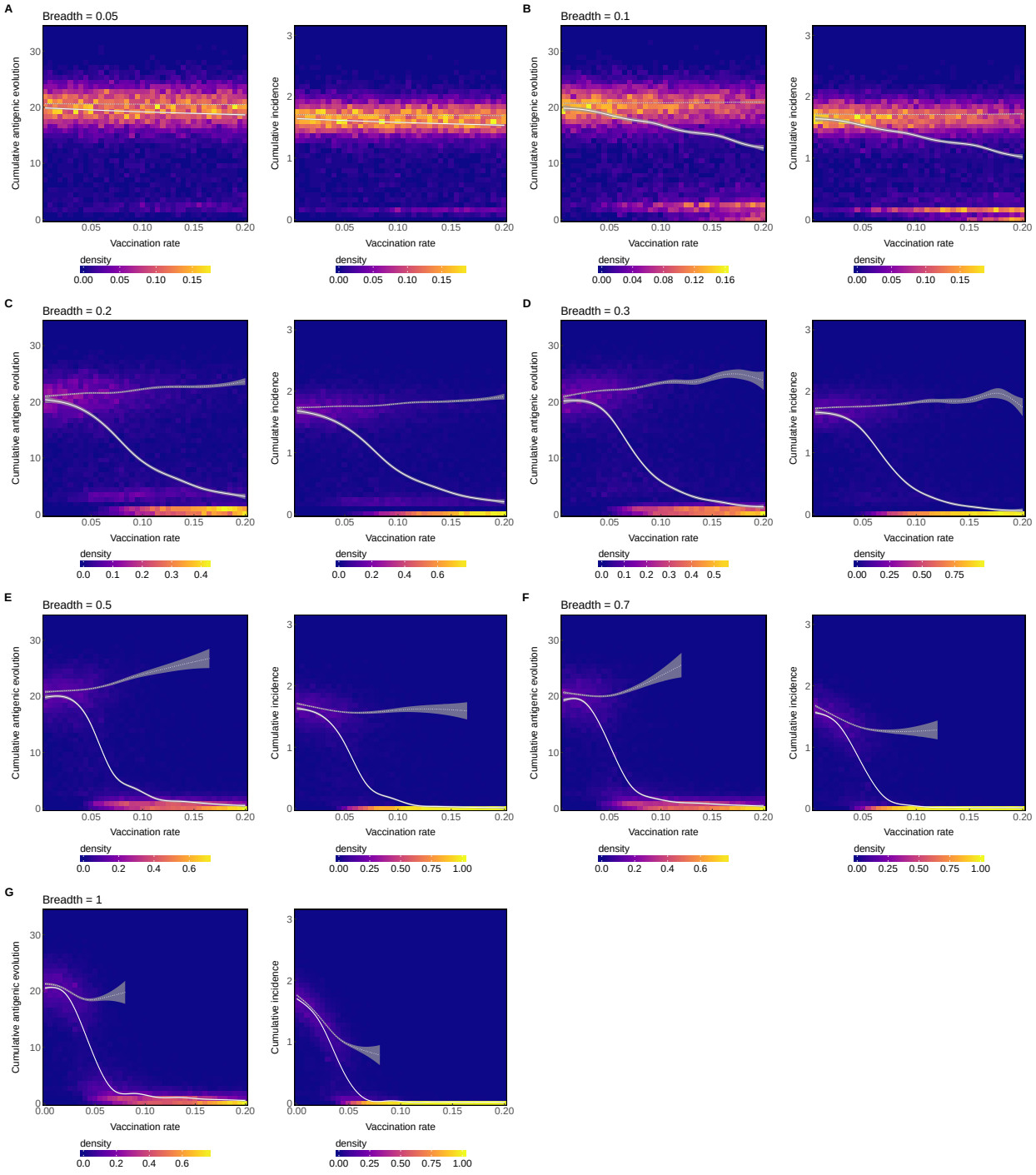

Figure S6: Density plots of complete simulation data corresponding to Figure 4. The solid white lines show a LOESS fit to cumulative antigenic evolution or incidence across all simulations. The dotted white lines show a LOESS fit to cumulative antigenic evolution or incidence for simulations where the viral population did not go extinct. Shaded areas show 95% confidence intervals.

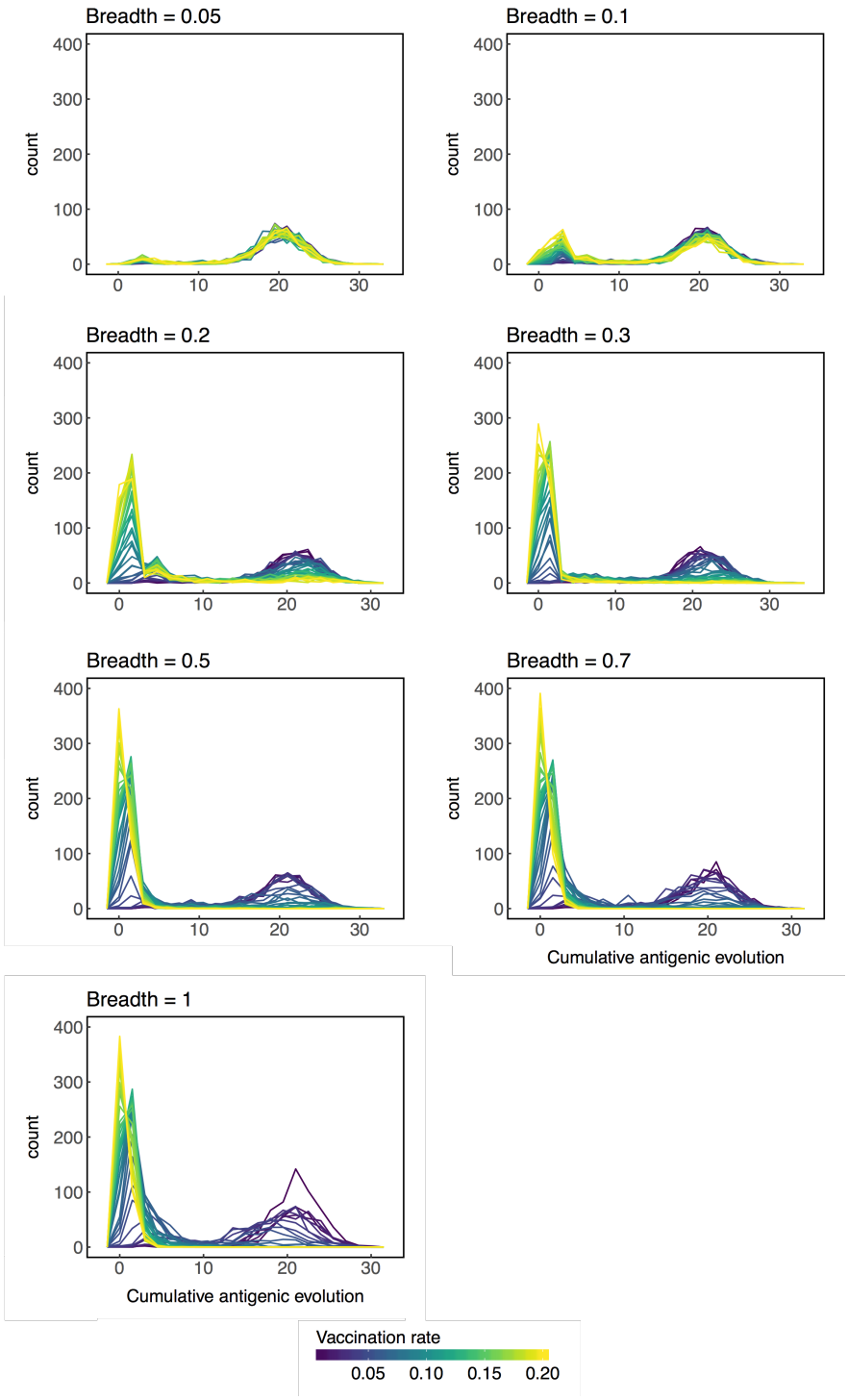

Figure S7: The distributions of cumulative antigenic evolution are profiles along each vaccination rate shown in figure S6. For a given breadth, the upper distributions (above 12 units of antigenic evolution) are indistinguishable by the Wilcoxon rank sum test, indicating that more vaccination does not directly increase the amount of antigenic evolution. More vaccination selects for fast-evolving viral populations without changing the underlying distribution of cumulative antigenic evolution.

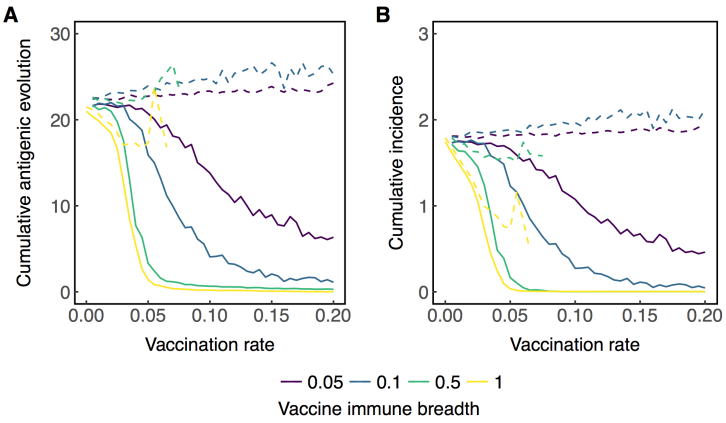

Figure S8: With no temporal lag between vaccine strain selection and distribution, only vaccines with extremely narrow breadth (5% and 10% of natural immunity) permit more frequent survival, and can cause increased (B) antigenic evolution and (C) incidence. The solid lines show averages across all simulations, 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.

Table S2: 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**

Table S3: Private and social benefits of vaccination for a vaccine that provides half the immune breadth of natural immunity ($b = 50\%$). 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 (%)	**36.10**	**32.68**