The Potential Beneficial Effects of Vaccination on Antigenically Evolving Pathogens

Frank T. Wen,[1,*] Anup Malani,[1,2] and Sarah Cobey[1]

1. Department of Ecology and Evolution, University of Chicago, Chicago, Illinois 60637; 2. University of Chicago Law School, Chicago, Illinois 60637; and University of Chicago Pritzker School of Medicine, Chicago, Illinois 60637

Submitted September 7, 2020; Accepted August 26, 2021; Electronically published January 3, 2022

Online enhancements: supplemental PDF.

ABSTRACT: Although vaccines against antigenically evolving pathogens such as seasonal influenza ; and are designed to protect against circulating strains by affecting the emergence and transmission of antigenically divergent strains, they might in theory also be able to change the rate of antigenic evolution. Vaccination might slow antigenic evolution by increasing immunity, reducing the overall prevalence or population size of the pathogen. This reduction could decrease the supply and growth rates of mutants and might thereby slow adaptation. But vaccination might accelerate antigenic evolution by increasing the transmission advantage of more antigenically diverged strains relative to less diverged strains (i.e., by positive selection). Such evolutionary effects could affect vaccination's direct benefits to individuals and indirect benefits to the host population (i.e., the private and social benefits). To investigate these potential impacts, we simulated vaccination against a continuously circulating influenza-like pathogen in a simple population. On average, more vaccination decreased the incidence of infection. Notably, this decrease was driven partly by a vaccine-induced decline in the rate of antigenic evolution. To understand how the evolutionary effects of vaccines might affect their social and private benefits, we fitted linear panel models to simulated data. By slowing evolution, vaccination increased the social benefit and decreased the private benefit. Thus, vaccination's potential social and private benefits may differ from current theory, which omits evolutionary effects. These results suggest that conventional vaccines against influenza and other antigenically evolving pathogens, if protective against transmission and given to the appropriate populations, could further reduce disease burden by slowing antigenic evolution.

Keywords: cross-protective vaccines, risk prediction, vaccine incentives.

Introduction

By strengthening host immunity, vaccination imposes selective pressures on pathogens. Pathogen strains that are less susceptible to vaccine-induced immunity can grow faster within hosts and be transmitted more easily between hosts than strains that cannot. This evolution can take the form of increased virulence, well established in theory (Levin and Pimentel 1981; Anderson and May 1982; Frank 1996; Gandon et al. 2001; Day and Proulx 2004; Alizon and van Baalen 2005) and demonstrated in the increasing virulence of Marek's disease virus to vaccination of poultry (Witter 1997; Atkins et al. 2013; Read et al. 2015). Pathogens can also evade vaccine-induced immunity by altering the targets of the adaptive memory responses. A simple form of vaccine-induced antigenic evolution has been shown repeatedly in humans after rollouts of pneumococcal conjugate vaccines, which led to the replacement of target serotypes (included in the vaccines) by nontarget serotypes (Hanage et al. 2010; Pilishvili et al. 2010; Weinberger et al. 2011; Feikin et al. 2013; Waight et al. 2015; Ladhani et al. 2018). In this case, previously circulating nontarget serotypes rose in prevalence as their competitors were suppressed by serotype-specific vaccine-induced responses. In contrast, other pathogens, including many RNA viruses, regularly evolve new antigenic variants that are selected by immunity from natural infection. This pattern of antigenic evolution driven by rapid mutation and immune-driven positive selection is exemplified by seasonal influenza viruses. Effective vaccines against such antigenically evolving pathogens have enormous potential to reduce disease burden, but the value of vaccines could be substantially increased or decreased after accounting for their evolutionary impacts in ways that are difficult to predict.

In theory, vaccines might slow or accelerate the antigenic evolution of antigenically evolving pathogens (Kimura 1979; Ohta 1992; Otto and Whitlock 1997; Gog and Grenfell 2002; Boni et al. 2006; Desai and Fisher 2007; Arinaminpathy et al. 2012; Good et al. 2012; Kucharski and Gog

* Corresponding author; email: frankwen@uchicago.edu.

ORCIDs: Wen, https://orcid.org/0000-0002-9262-1722; Malani, https://orcid.org/0000-0002-2594-5778; Cobey, https://orcid.org/0000-0001-5298-8979.

2012; Subramanian et al. 2016). When vaccines retain some effectiveness against antigenic variants, they can reduce the overall prevalence of infection. By reducing the prevalence of infection, vaccination reduces viral population size and opportunities for antigenic escape mutants to arise. Reduced transmission rates can lower the invasion fitness of escape mutants (supplemental PDF, sec. 1.1; eq. [S19]; fig. S1; figs. S1–S19 are available online) and their fixation probability (Otto and Whitlock 1997), and thereby the rate of antigenic evolution. Theory and experiment further show that when multiple asexual populations with multiple beneficial mutations compete and evolve, the rate of adaptation declines with total population size (Desai and Fisher 2007; Good et al. 2012). Finally, in very small populations, stochastic extinction dominates selection through genetic drift (Kimura 1979; Ohta 1992). Some of these mechanisms underlie predictions that a hypothetical universal influenza vaccine, assumed to protect equally well against all circulating strains, should reduce the rate of antigenic evolution (Arinaminpathy et al. 2012). However, conventional influenza vaccines might accelerate antigenic evolution if the vaccine is ineffective against mutant strains that compete with vaccine-targeted strains, leading to strain replacement or vaccine escape (Boni et al. 2006; Subramanian et al. 2016).

Evolutionary effects could change the individual-level and population-level benefits of vaccination, which we refer to as the private and social benefits, respectively. Vaccination confers a private benefit to vaccinated individuals by directly reducing their risk of infection; on average, the seasonal influenza vaccine reduces the within-season rate of clinical laboratory-confirmed influenza infections in healthy adult recipients by 41% (95% confidence interval [CI]: 36%–47%; Demicheli et al. 2018). Vaccination also confers a social benefit to the host population by reducing the burden of disease, although these effects are rarely measured. In the United States, vaccinating children has reduced the risk of symptomatic and clinical influenza infection in unvaccinated household contacts by 30%–40% (Hurwitz et al. 2000; Principi et al. 2003), in the local community by up to 5%–82% (Loeb et al. 2010), and in a metropolitan county by up to 59% (Pebody et al. 2015). In Japan, vaccinating children reduced mortality in the elderly by 17%–51% (Charu et al. 2011). The valuation of private and social benefits changes according to how much vaccination decreases the burden of disease. Increases in vaccination coverage have positive private and social benefits until the level required for herd immunity, at which point the disease risk (in a closed population) becomes zero, and there is no further benefit to vaccination (Geoffard and Philipson 1997). If vaccines slow antigenic evolution and thereby further decrease incidence, then their social benefit increases relative to the evolution-free case. However, as the social benefit decreases the risk of infection for the unvaccinated, their private benefit may fall commensurately. This decline in the private benefit may be attenuated if slower antigenic evolution improves the antigenic match between the vaccine and circulating strains. In contrast, if vaccines accelerate antigenic evolution and increase incidence, then their social benefit decreases and their private benefit increases relative to the evolution-free case.

Empirical estimates of the benefits of influenza vaccination have so far been unable to measure such potential evolutionary effects, partly because most vaccination occurs in seasonal populations where influenza regularly becomes extinct locally. Most studies estimating the value of influenza vaccination occur in temperate populations in North America, Europe, and Oceania (Osterholm et al. 2012; Belongia et al. 2016). Although these regions have relatively high vaccination coverage (up to ~40%; Palache et al. 2015; Wen et al. 2018), seasonal extinctions prevent these populations from consistently contributing to influenza's long-term antigenic evolution (Bedford et al. 2010, 2015). Consequently, vaccination in these regions is unlikely to have lasting global effects. By contrast, few studies (Tam et al. 2007) have been done in so-called source populations that contribute more to influenza's evolution (e.g., China and India; Bedford et al. 2010, 2015). These populations have <1% vaccination coverage (Palache et al. 2015). Thus, although the global supply of influenza vaccines can cover up to ~8% of the global population (Palache et al. 2015, 2017), the spatial distribution of current vaccination coverage implies that vaccination is unlikely to have lasting global effects.

To investigate how vaccination might affect a pathogen's rate of antigenic evolution, we consider the consequences of a hypothetical scenario in which vaccination occurs in a closed population where an influenza-like pathogen circulates continuously. Unlike previous approaches, the model allows open-ended antigenic evolution in a large population and can thus incorporate dynamics missing from models that assume only a few strains. Although motivated by influenza, the results are conceptually generalizable to other antigenically evolving pathogens with similar life histories. We first evaluated how different amounts of vaccination can slow antigenic evolution and in turn decrease the total burden of disease. We then quantified how the evolutionary effects change the private and social benefits of vaccination relative to when evolutionary effects are ignored.

Methods

Modeling Approach

To understand how vaccination on a global scale could affect the long-term antigenic evolution of an antigenically

evolving pathogen, we adapted an agent-based model to simulate the transmission and evolution of an influenza-like pathogen over 20 years in a closed, well-mixed population (Bedford et al. 2012). This simple model allows us to isolate the effects of vaccination on antigenic evolution as we vary vaccination coverage, breadth, and other factors. We chose to formulate and parameterize the model to reproduce the ecological and evolutionary dynamics of the seasonal influenza A/H3N2 subtype because H3N2 has circulated continuously in humans since 1968 and exemplifies a successful antigenically evolving pathogen. We do not aim to explicitly model all ecological and evolutionary processes (such as metapopulation structure, seasonality, temporal variation in population size, and age-assortative mixing) and instead seek to derive general principles for how vaccination affects pathogen evolution.

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 coinfected.

Antigenic phenotypes are represented as points in two-dimensional Euclidean space (fig. 1*A*). This space is analogous to the main components after multidimensional scaling of pairwise measurements of cross-reactivity in hemagglutination inhibition (HI) assays, used to measure antigenic difference between influenza viruses (Smith et al. 2004; Bedford et al. 2014). In HI assays, one antigenic unit of distance represents a twofold dilution of antiserum. 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. In reality, immunity to infecting strains of influenza appears to last on the order of decades, if not longer (Kung et al. 1978; Nakajima et al. 1978; Rozo and Gronvall 2015). Thus, the assumption of lifelong immunity to the infecting strains is appropriate over a 20-year simulation. On 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]; Gupta et al. 2006; Park et al. 2009; Bedford et al. 2012). Consequently, although immunity to the infecting strain is lifelong, immunity to circulating strains in general decays over time as new antigenic variants emerge and spread.

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} (fig. 1*D*; table S1; tables S1–S3 are available online).

Model Validation and Choice of Parameters

We find agreement between the model's epidemiological dynamics when comparing against analytic expectations without evolution, which indicates that the transmission dynamics behave as expected (supplemental PDF, sec. 1.2; figs. S2–S5). With evolution and without vaccination, the model reproduces characteristic epidemiological and evolutionary patterns of the seasonal A/H3N2 subtype (fig. 1*A*, 1*B*). We investigated the credibility of the model without vaccination because the evolution of H3N2 appears driven by populations with negligible vaccination rates; the dominant source populations have nearly 0% vaccine coverage (Bedford et al. 2014; Palache et al. 2015, 2017). We chose transmission and mutation parameters (table S1) such that simulated epidemiological and evolutionary patterns most resembled qualitative patterns and quantitative metrics observed for H3N2 (table 1; Wen et al. 2016). H3N2 has remained endemic in the human population since its emergence in 1968 and also has low standing genetic and antigenic diversity. Because of the stochastic nature of the simulations, the viral population becomes 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 cocirculating lineages (time to most recent common ancestor [TMRCA]) exceeds 10 years (Bedford et al. 2012; Wen et al. 2016), since recent H3N2 HA lineages have coexisted for no more than 8 years. The remaining 53% of simulations show qualitatively influenza-like dynamics that reproduce key epidemiological and evolutionary statistics of H3N2 (table 1).

That 47% of simulations are not H3N2-like does not necessarily imply that the model is inaccurate. The H3N2 lineage circulating since 1968 represents only a single instance of that subtype's global evolution; future evolutionary patterns may diverge from historical trends. For example, two lineages of influenza B emerged approximately 30 years ago and have cocirculated since, demonstrating an instance of high diversity in influenza. The unusually high diversity of H3N2 lineages that cocirculated before the COVID-19 pandemic (Hadfield et al. 2018) suggests that it might be capable of similar dynamics, which were not foreshadowed by the prior few decades of observation. However, for this model we use a conservative definition of H3N2-like evolution based on historical

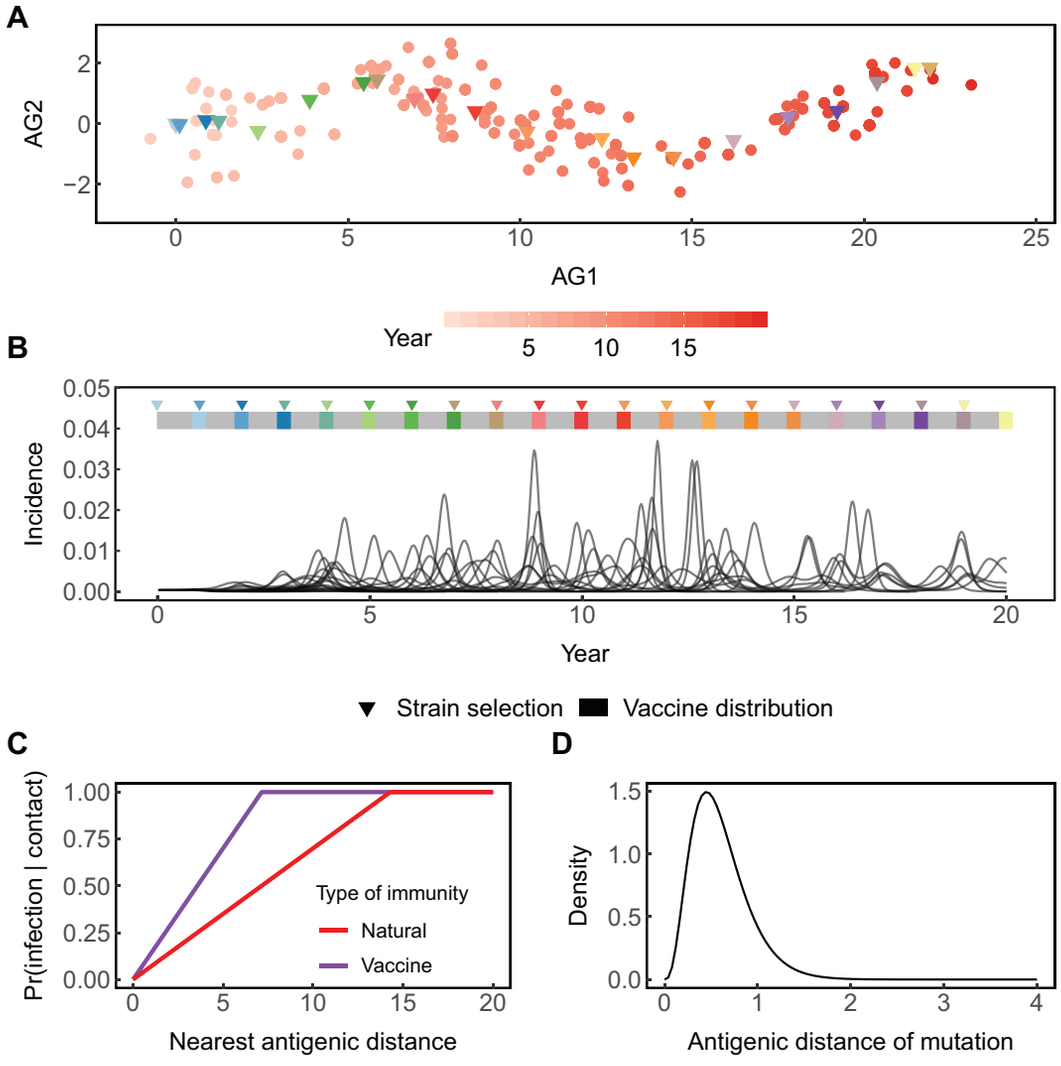


Figure 1: Properties of the model. *A*, Antigenic phenotypes are represented as red points in two-dimensional space (AG1 is antigenic dimension 1, and AG2 is antigenic dimension 2). The shading of the points corresponds to the time when the strains appear. Over time, new strains appear because old strains 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. *B*, Incidence per 10 days for 20 replicate simulations. Cumulative incidence (not shown) is calculated as the sum of cases over the duration of the simulation. Although the depicted model output is without vaccination, a hypothetical vaccine distribution schedule is shown by the bars and triangles. Strain selection occurs on the first day of each year. The vaccine is then distributed beginning 300 days after strain selection for 120 days. The triangles indicate the time points of vaccine strain selection, and the matching colored bars indicate the corresponding window of vaccine distribution for the selected vaccine strain. *C*, On 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]). In this example, for illustrative purposes vaccines confer half the breadth of natural immunity ($b = 0.5$). However, by default we simulate vaccines that have the same breadth as natural immunity ($b = 1.0$). *D*, The sizes of antigenic mutations are chosen from a gamma distribution. The radial directions (not pictured) of mutations are chosen from a random uniform distribution.

observations (Bedford et al. 2012; Wen et al. 2016). Extinctions are also not unexpected in a closed population. A more realistic metapopulation structure might provide some buffer against extinctions (Fox et al. 2017) but would not change the effects of vaccination, assuming that vaccination is distributed evenly in space.

While we parameterize the model to maximize the probability of observing H3N2-like evolutionary behavior

Table 1: Agreement between simulated and empirically measured epidemiological and evolutionary metrics of H3N2

Metric	Simulated value (SD)	Empirical estimate
TMRCA (years)	3.80 (.52)	3.84 (Bedford et al. 2015)
Antigenic evolutionary rate (antigenic units/year)	1.09 (.14)	1.01 (Bedford et al. 2014)
Annual incidence per person (%)	9.0 (1.0)	9–15 (WHO 2014)
Time between infections (years, 1/annual incidence)	11.1 (1.3)	5–11 (Axelsen et al. 2014; Du et al. 2017; Ranjeva et al. 2019)

Note: Simulated values are averages over 20 replicate simulations. TMRCA = time to most recent common ancestor.

without vaccination, we recognize that vaccination has the potential to drive the viral population into non-H3N2-like evolutionary regimes. We examine all simulations in different parts of the analysis, described in the "Model Output" and "Results" sections.

Modeling Vaccination

To assess the potential effects of vaccination on antigenic evolution and disease burden, we introduced vaccination to the host population. Vaccination occurs at an annual vaccination coverage r (i.e., the fraction of the population that is vaccinated each year), 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. The antigenic phenotype of the vaccine strain is the average (in two-dimensional antigenic space) of contemporaneous circulating strains. In reality, strains are considered for inclusion in the vaccine if they are considered likely to spread (e.g., those that circulate at high frequency or those that are highly antigenically diverged; CDC 2015). By default, the vaccine is distributed for 120 days. This schedule approximates influenza vaccine distribution in the United States, which usually runs from September through February and peaks in October or November, 8–9 months after strain selection (CDC 2015). During the period of vaccine distribution, individuals are randomly vaccinated at a constant daily Poisson rate according to the specified annual vaccination coverage (eq. [2]). Improvements to vaccine production (e.g., using messenger RNA vaccines) may shorten the delay between strain selection and vaccine deployment in the future (Newland et al. 2021):

$$r_{\text{day}} = \frac{r_{\text{annual}}}{\text{duration of vaccine distribution in days}}. \quad (2)$$

Vaccination is implemented to reflect individuals' tendency to follow the same pattern of vaccination from year to year. Observational studies in Canada and the United States show that 65%–88% of vaccine recipients in a given season were also vaccinated in the previous season (McLean et al. 2014; Arevalo et al. 2020; Kwong et al. 2020; Lindley et al. 2020), and 24%–40% of adults have never received an influenza vaccine (McLean et al. 2014; Uscher-Pines et al. 2014; Arevalo et al. 2020). Accordingly, in our model vaccinated hosts have an 80% chance of also being vaccinated in the next season, and 33% of hosts are never vaccinated. Under this vaccination strategy, the annual vaccination coverage remains constant, but the fraction of hosts who have been vaccinated at least once increases over time (fig. S19). The details of the implementation are described in section 2.1 of the supplemental PDF.

We also tested the effects of the breadth of 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 with natural immunity. Thus, a host's probability of infection on contact is given by

$$\text{risk} = P(\text{infection}|\text{contact}) = \min\left\{1, cd_{\text{n}}, \frac{cd_{\text{v}}}{b}\right\}, \quad (3)$$

where d_{n} is the distance between the infecting strain and the nearest strain in the host's infection history, 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, derived from vaccination studies (Gupta et al. 2006; Park et al. 2009; Bedford et al. 2012). By default, the breadth of vaccine-induced and natural immunity are equal ($b = 1$).

Model Output

We quantified vaccination's effects on viral evolution and epidemiology using four metrics: cumulative antigenic distance evolved, cumulative incidence, the probability of excessive diversity, and the probability of extinction. While

the model is parameterized to maximize the frequency of influenza-like evolution, we still analyze non-influenza-like behaviors (extinction and diversification) as possible outcomes of vaccination that have yet to be observed in reality because of low global vaccination coverage. First, because influenza evolves roughly linearly in two antigenic dimensions (Smith et al. 2004; Bedford et al. 2012, 2014), 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). We estimated cumulative antigenic evolution only in simulations that were not too diverse (TMRCA $<$ 10 years), since this metric is inadequate for viral populations with deep branching. 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). Third, we calculated the probability that viral populations would become too diverse (TMRCA $>$10 years), since vaccination may qualitatively alter evolutionary patterns. Viral populations that are too diverse can cause high incidence because hosts are unlikely to have immunity against distant antigenic variants. Fourth, we calculated the probability of extinction by calculating the fraction of simulations that became extinct out of 500 replicates.

Measuring Evolutionary Effects of Vaccination

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 (fig. S9). To generate the latter, we created a simulation where vaccination could not affect antigenic evolution, the "static" simulation (fig. S9). We first ran 500 simulations of the model without vaccination to be used as a reference. 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 had already been set by the dynamics of the simulation without vaccination (fig. S10). Thus, vaccination was separated from the evolutionary process.

Estimating the Private and Social Benefits of Vaccination

A linear panel regression model was fitted to simulated panel data to identify the private and social benefits of vaccines over 20 years. The social benefit is also known as the "indirect effect" and the private benefit is also known as the "direct effect," as defined in Halloran et al. (1991).

To generate panel data, we ran simulations at six annual vaccination coverages r (0%, 1%, 5%, 10%, 20%, and 30%) and recorded individual hosts' dates of infection and vaccination. We ran 20 replicates for each unique combination of rate and breadth and randomly sampled 2,500 individuals (0.005% of the entire host population) at the end of each simulation for analysis, yielding up to 2 million observations for each fitting. If a simulation was terminated early because the virus became extinct before 20 years, additional data points were filled in according to the initial vaccination rate and assuming no new infections. We fitted a linear panel model (eq. [4]) to the simulated longitudinal vaccination data from multiple simulations j. Observations are at host i level in each season τ (for a hypothetical example, see table S2). The dependent indicator variable $I_{ij\tau}$ equals 1 if a host is infected at any point in the current season τ and 0 otherwise. The indicator $V_{ij\tau}$ equals 1 if a host is vaccinated in the current season. Analogously, lags $V_{ij\tau-k}$ measure vaccination in period $\tau - k$ and are included to measure the benefits of vaccination that persist from previous seasons. The vaccination rate indicators R_{rij} equal 1 if the annual vaccination in the host population is equal to r% (e.g., when the rate is 5%, then $R_{5ij} = 1$). The regression is estimated as a linear panel 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 estimated equation is

$$\begin{aligned} I_{ij\tau} = {} & \beta_0 + \beta_1 R_{1ij} + \beta_2 R_{5ij} + \beta_3 R_{10ij} + \beta_4 R_{20ij} + \beta_5 R_{30ij} \\ & + \beta_6 R_{1ij} V_{ij\tau} + \beta_7 R_{1ij} V_{ij\tau-1} + \beta_8 R_{1ij} V_{ij\tau-2} \\ & + \beta_9 R_{1ij} V_{ij\tau-3} + \beta_{10} R_{1ij} V_{ij\tau-4} \\ & + \beta_{11} R_{5ij} V_{ij\tau} + \cdots + \beta_{15} R_{5ij} V_{ij\tau-4} \\ & + \beta_{16} R_{10ij} V_{ij\tau} + \cdots + \beta_{20} R_{10ij} V_{ij\tau-4} \\ & + \beta_{21} R_{20ij} V_{ij\tau} + \cdots + \beta_{25} R_{20ij} V_{ij\tau-4} \\ & + \beta_{26} R_{30ij} V_{ij\tau} + \cdots + \beta_{30} R_{30ij} V_{ij\tau-4} \\ & + \epsilon_i + u_{j\tau}. \end{aligned} \tag{4}$$

The fitted coefficients estimate the absolute change in the probability of infection given the host population's vaccination coverage and an individual's vaccination status. We converted these absolute risks to odds ratios in keeping with standard reporting of influenza vaccine effectiveness. For example, $((\beta_1 + \beta_0)/(1 - (\beta_1 + \beta_0)))/(\beta_0/(1 - \beta_0))$

gives the odds ratio of infection for an unvaccinated individual's risk of infection in the current season when the population vaccination coverage is 1% relative to the odds of infection in an unvaccinated population. The same formula applied to β_x for $x \in \{1, 2, 3, 4, 5\}$ represents the social or indirect benefits of vaccination under different vaccination policies.

The model is interacted (β_6 to β_{30}) to estimate the private benefit for each vaccination coverage. Thus, $((\beta_6 + \beta_0)/(1 - (\beta_6 + \beta_0)))/(\beta_0/(1 - \beta_0))$ gives the ratio of the odds of becoming infected in the current season for a host who has been vaccinated in the current season and is in a population with an annual vaccination coverage of 1% relative to the odds of infection for a host who is in a population with a 1% vaccination coverage but has not been vaccinated in 5 years. Likewise, $((\beta_7 + \beta_0)/(1 - (\beta_7 + \beta_0)))/(\beta_0/(1 - \beta_0))$ estimates the ratio of odds of becoming infected in the current season given vaccination one season ago and living under a 1% vaccination coverage policy relative to an unvaccinated host also living under a 1% vaccination coverage policy. More formally, $\sum_{k=6}^{10}\beta_k$ is the impulse response to vaccination over 5 years and measures the total individual-level protective benefit of vaccination over time when the vaccination coverage is 1%. The same reasoning applies to the terms associated with the other four vaccination coverages.

We also estimate the benefits of vaccination directly from incidence to validate the regression model. To estimate the social benefit (the indirect effect in Halloran et al. 1991) for a specific vaccination coverage r, we calculate the ratio of the odds of infection for an unvaccinated host in a vaccinated population relative to the odds of infection in an unvaccinated population. For $x \in \{1, 2, 3, 4, 5\}$,

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

$$= [1 - \exp(\beta_x)] \times 100\%. \tag{6}$$

To estimate the private benefit, we calculate an analogous odds ratio relative to the odds of infection for an unvaccinated host in the same vaccinated population. For $y \in \{6, \ldots, 30\}$,

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

$$= [1 - \exp(\beta_y)] \times 100\%. \tag{8}$$

Results

Vaccination Reduces the Average Amount of Antigenic Evolution and Disease Burden

For an influenza-like pathogen, vaccination reduces the average amount of antigenic evolution (Spearman's $\rho = -0.81$, $P < .001$) and incidence (Spearman's $\rho = -0.92$, $P < .001$; fig. 2) when the breadth of immunity from vaccination is the same as that of infection. Without vaccination, the viral population evolves on average 20.7 (SD = 3.1) antigenic units and causes an average of 1.7 (SD = 0.2) cases per person over the 20-year simulation. By reducing susceptibility in the host population and the supply of beneficial mutations, vaccination decreases the number of cases and the average size of surviving mutations, thus weakening selection for antigenic novelty and increasing the strength of drift. In turn, slower antigenic evolution further reduces transmission, often driving the virus extinct. Once extinct, the viral population can no longer evolve or cause new infections. Above 20% vaccination coverage, extinction typically occurs within 4.1 years (SD = 1.8; fig. S6).

Eliminating the delay between strain selection and vaccine distribution reduces the amount of antigenic evolution (Wilcoxon rank-sum test, $P < .001$) and incidence (Wilcoxon rank-sum test, $P < .001$) even more (fig. S7). For example, with a 300-day delay between vaccine strain selection and distribution at 15% vaccination coverage, the virus evolves a cumulative 9.3 (SD = 5.9) antigenic units and causes an average of 0.45 (SD = 0.31) cases per person over the 20-year simulation. With zero delay at the same vaccination coverage, the virus evolves a cumulative 3.6 (SD = 3.4) antigenic units and causes an average of 0.10 (SD = 0.12) cases per person over the 20-year simulation.

Increasing vaccination coverage also decreases the probability that the viral population becomes too diverse (fig. S8). Without vaccination, 46.5% of simulations becomes too diverse, whereas 34.5% and 9.0% become too diverse at a 10% and 20% annual vaccination coverage, respectively. Thus, the reduction in the rate of antigenic evolution caused by vaccination includes reductions in diversifying selection.

We next examined how much the reductions in incidence could be attributed solely to the "ecological" effects of vaccination—the reduction in prevalence and increased extinction risk from accumulating herd immunity—versus the combined ecological and evolutionary impacts. We accomplish this by comparing the outputs from simulations where vaccination can affect antigenic evolution to simulations where vaccination cannot antigenic evolution ("Methods," fig. S9). Relative to the case where the evolutionary effects are blocked, vaccination decreases cumulative antigenic evolution and incidence (fig. 3). The

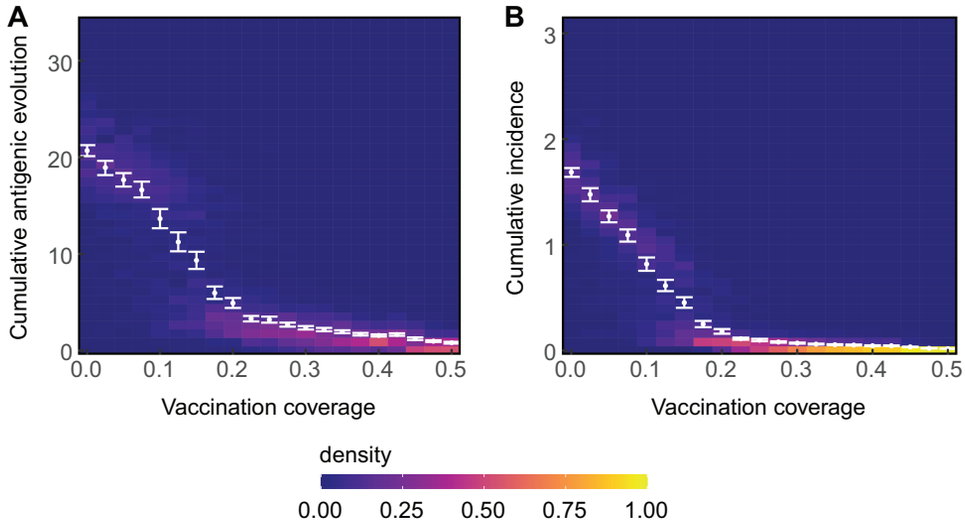


Figure 2: High vaccination coverage decreases the average amount of cumulative antigenic evolution (*A*) and cumulative incidence (*B*). Points show mean cumulative antigenic evolution or incidence for each level of coverage. Error bars show 95% nonparametric bootstrapped confidence intervals of the means. Densities are calculated for each coverage level, such that the sum of densities for each level equals 1. Data are collected across 200 total simulations for each rate with excessively diverse simulations (time to most recent common ancestor of >10 years) excluded, leaving ~150–180 simulations per rate.

maximum absolute evolutionary effect occurs at a 17.5% annual vaccination coverage, where the virus evolves 6.0 (95% CI = 5.3–6.7) antigenic units and causes 0.25 (95% CI = 0.22–0.28) cumulative cases per person with evolutionary effects, compared with 11.9 (95% CI = 10.9–12.9) antigenic units and 0.57 (95% CI = 0.52–0.62) cumulative cases per person years without. At all vaccination coverages, the virus never evolves more with vaccination

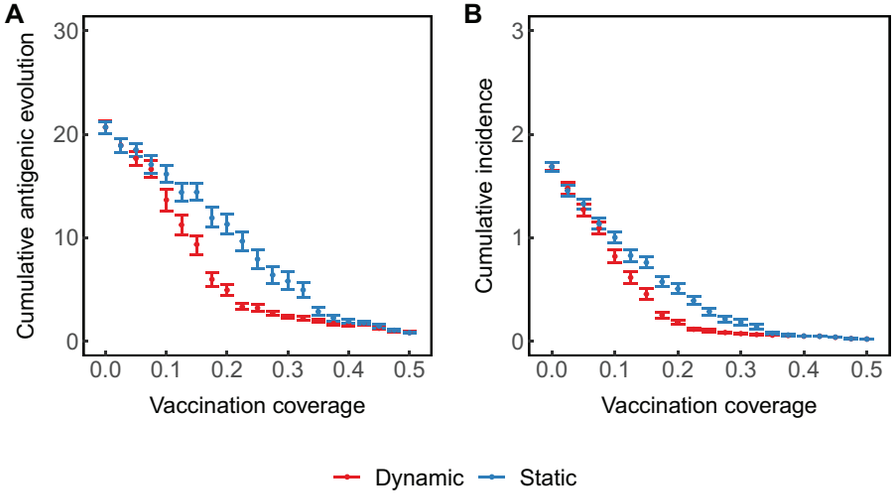


Figure 3: The evolutionary effects of vaccination further decrease incidence and antigenic evolution. Red points represent simulations where vaccination can affect antigenic evolution. Blue points represent simulations where vaccination cannot affect antigenic evolution. Points show the mean cumulative antigenic evolution (*A*; antigenic units) and incidence (*B*; infections per person over 20 years) across all simulations where vaccination does (red) or does not (blue) affect antigenic evolution for each vaccination coverage. Error bars show 95% nonparametric bootstrapped confidence intervals of the means. Data are collected from 200 total simulations for each vaccination coverage and evolutionary condition with excessively diverse simulations excluded, leaving ~150–180 simulations per rate.

than without. Thus, the strength of positive selection is not enough to overcome the factors that slow adaptive evolution relative to the zero vaccination case.

Eradication is achieved at lower vaccination coverage when vaccination can affect antigenic evolution compared with when it cannot. For example, at 36.25% coverage, vaccination eradicates the virus 100% of the time (within 7.4 years on average) when vaccines can affect antigenic evolution but does so only 68% of the time (within 8.7 years on average) when vaccines cannot affect antigenic evolution (fig. S6). This shows that vaccination slows evolution not only through extinction but also by directly slowing the rate of adaptation while the virus circulates.

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 coverage is needed to achieve the same average reductions in cumulative antigenic evolution and incidence using broader vaccines (fig. S11). Regardless of breadth, distributing vaccines immediately after strain selection (i.e., distributing more antigenically matched vaccines) helps vaccines achieve the same average reductions in evolution and incidence at lower vaccination coverage (fig. S13).

Vaccine-Driven Excessive Evolution Is Rare

We examined the frequencies of simulations with "excessive evolution" in a multivariate analysis to determine whether vaccination might ever accelerate antigenic evolution through directional or diversifying selection. For this test, we defined excessive 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 replicate simulations for each vaccination coverage and breadth. If vaccination increases the rate of evolution, the frequency of excessively evolved simulations should be greater than that in the vaccine-free case (fig. S15).

We found that vaccine-driven excessive evolution occurs only at low to intermediate immune breadth (b = 0.1, 0.2, or 0.3) and at low vaccination coverage (fig. S14). Among the parameters we tested, the most frequent cases of vaccine-driven excessive evolution occur at 7.5% vaccination coverage with 0.2 breadth, with 73.6% (95% CI = 69.5%–77.4%) of simulations showing excessive evolution (compared with 67.7% [95% CI = 66.0%–69.4%] without vaccination). In other words, even when we detect more frequent excessive evolution, these outcomes are at most ~9% more common with vaccination relative to without.

When the breadth of immunity from vaccination and infection are similar (b = 1), instances of excessive evolution are no more common with vaccination than without (fig. S15). For any vaccination coverage, however, the viral populations that survive tend to be more evolved antigenically than the ones that become extinct (fig. S11). This does not mean that vaccination accelerates antigenic evolution. Apparent increases in the amount of antigenic evolution among surviving viral populations generally reflect selection among simulations (not among viruses within a simulation) for fast-evolving populations, which appear at the same rate without vaccination.

Ignoring the Evolutionary Effects of Vaccination Incorrectly Estimates the Private and Social Benefits of Vaccination

We next quantified the private and social benefits of vaccination to understand how ignoring evolutionary effects might bias measurements of the epidemiological effects 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 it could not affect antigenic evolution and then fitted linear panel models to these data ("Estimating the Private and Social Benefits of Vaccination," eq. [4]). We define the social benefit as 1 minus the ratio of the odds of infection for unvaccinated hosts in a population vaccinated at a given rate relative to the odds in an unvaccinated population (eq. [5]). The social benefit thus measures the relative reduction in the odds of infection due to vaccination in the population. We define the private benefit as 1 minus the odds of infection having been vaccinated relative to the risk of infection having not been vaccinated in a population vaccinated at the given rate (eq. [7]). These metrics are the same as the direct (standardly reported as vaccine effectiveness; Osterholm et al. 2012; McLean et al. 2014; Skowronski et al. 2017) and indirect effects of vaccination (Halloran et al. 1991).

Across all levels of coverage, the evolutionary impact of vaccination increases its social benefit. For example, when vaccination affects antigenic evolution, at 10% annual vaccination coverage, unvaccinated hosts are 49.1% (95% CI = 48.0%–50.1%) less likely to be infected in a vaccinated compared with an unvaccinated population (fig. 4; table S3). When vaccination cannot affect antigenic evolution, an unvaccinated host in a population vaccinated at the same rate is only 21.7% (95% CI = 20.7%–22.8%) less likely to become infected (fig. 4; table S3). The same trend holds from 5% to 30% vaccination coverage. At 1% vaccination coverage, the reduction in incidence from vaccination is so small that the impact of evolution on social benefits is indiscernible.

As the social benefit rises, the private benefit falls. This is due to a mechanical relationship between the social and

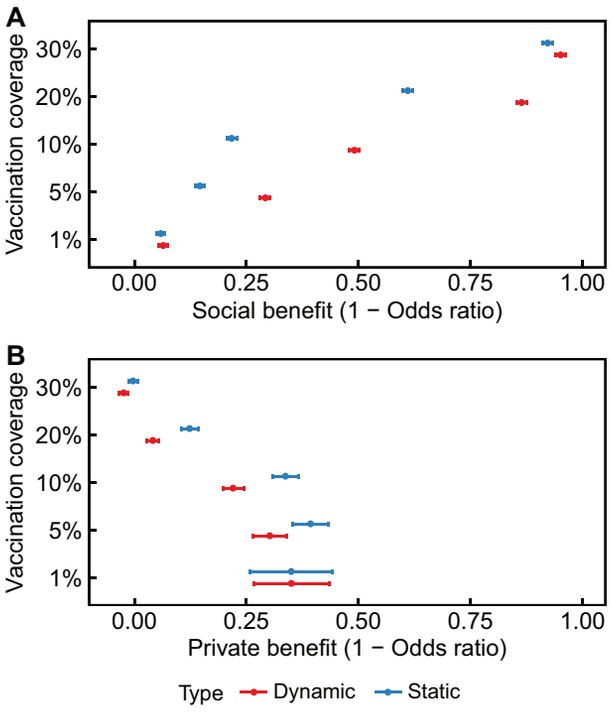


Figure 4: Comparison of the social (*A*) and private (*B*) benefits of vaccination when vaccination can or cannot affect antigenic evolution at 1%, 5%, 10%, 20%, and 30% annual vaccination coverages. Odds ratios are calculating using coefficients from a linear panel model fitted to the last 17 years of simulated hosts' infection and vaccination histories (eq. [4]; table S3). Vaccination continues at the same rate after extinction, with no new infections. 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). Points are jittered vertically for visualization.

private benefit. A large social benefit implies a large reduction in incidence. However, as incidence falls, the marginal reduction in the risk of infection that an individual gains from being vaccinated decreases. At 10% annual vaccination coverage, vaccinated hosts are 22.0% (95% CI = 19.7%–24.4%) less likely to be infected relative to unvaccinated hosts when vaccination does affect evolution, compared with 33.7% (95% CI = 30.8%–36.6%) less likely when vaccination does not affect evolution (fig. 4; table S3). Again, the same trend holds from 5% to 30% vaccination coverage. Although in theory improved antigenic match between the vaccine and circulating strains at high vaccination coverage (fig. S17) could increase the private benefit at higher vaccination coverage, we find that the overall evolutionary impact of vaccination reduces the private benefit.

We find similar results when calculating the social benefit directly from incidence (fig. S16). The general patterns are also similar with a vaccine that has half the breadth of natural immunity ($b = 0.5$; table S3).

Discussion

We found that vaccination against an influenza-like pathogen typically slows its rate of antigenic evolution and thereby reduces disease burden beyond the immediate impact of vaccination on transmission. This is a previously unrecognized potential benefit of vaccination against antigenically evolving pathogens that could lower the threshold for eradication. The evolutionary effects of vaccination on antigenic evolution affect private and social benefits differently. Evolutionary effects increase the social benefit of vaccination and concomitantly decrease the private benefit compared with when evolutionary effects are omitted. Thus, while the evolutionary effects of vaccination may yield a large public health benefit by further reducing incidence, they may decrease personal incentives to vaccinate.

The model is calibrated to reproduce epidemiological and evolutionary features of influenza A/H3N2, but we expect these results to generalize to other fast-evolving pathogens. For instance, SARS-CoV-2 and previously endemic human coronaviruses mutate more slowly than influenza A viruses and show evidence of antigenic evolution (Edridge et al. 2020; Dejnirattisai et al. 2021; Eguia et al. 2021; Kistler and Bedford 2021; Madhi et al. 2021; Starr et al. 2021; Yadav et al. 2021). It has been suggested that vaccination strategies that do not confer nearly perfect protection against COVID-19 could increase the emergence and spread of SARS-CoV-2 variants due to heightened selection within hosts from partial immune pressure (Bieniasz 2021; Saad-Roy et al. 2021). A contrasting hypothesis posits that within-host selection for SARS-CoV-2 and other acute respiratory viruses, including influenza, is inefficient (Cobey et al. 2021). Instead, the overriding evolutionary effect of vaccination is to slow adaptation by reducing the emergence and spread of antigenic variants, which are assumed unable to escape vaccine-induced immunity completely. Our results provide support for this hypothesis. New strains in our model are extremely unlikely to be perfect escape mutants (i.e., have large antigenic distance from all prior strains), resulting in a decline in incidence and prevalence, and we find that viral adaptation is reliably slowed for all but the narrowest breadths of vaccine-induced immunity. This result is largely consistent with expectations from population genetics that the rate of adaptation should decline with total population size (Desai and Fisher 2007; Good et al. 2012). However, our model makes the simplifying assumption that the rate of mutant generation scales linearly with prevalence. It thus cannot investigate scenarios where partially immune hosts might facilitate unusually

high rates of antigenic evolution. Other models suggest that at least for influenza, such within-host dynamics are not a driving force in global evolution (Morris et al. 2020).

Although our simulations show vaccines typically slow evolution and drive extinction of an influenza-like pathogen, other models predict faster evolution or higher incidence under different assumptions. Immune pressure can accelerate antigenic evolution when some consequences of finite population sizes and constraints on escape are ignored (Boni et al. 2006). In contrast, stochastic extinctions in our agent-based model weaken selection in small viral populations. Vaccines can also accelerate antigenic evolution locally when the generation of mutants occurs independently of population size or vaccination status, for example, when antigenic variants are introduced at a fixed rate (Subramanian et al. 2016; Zarnitsyna et al. 2018; Saad-Roy et al. 2021). In our model, strains can emerge only stochastically by mutation in infected hosts, so novel strains are less likely to appear when prevalence is low. In summary, the stochastic and individual-based features of our model allow for open-ended evolutionary outcomes. Mechanisms that slow down and speed up evolution interact simultaneously, with the net effect of vaccination being slower antigenic evolution.

While our simple model is intended to test general hypotheses, practical aspects of vaccination complicate the translation of our model to real-world applications. We highlight three illustrative examples for influenza. First, influenza vaccination is concentrated in a few temperate populations (e.g., in the United States and Europe) rather than in the populations that contribute most to influenza's evolution (East Asia, South Asia, and Southeast Asia; Bedford et al. 2010, 2015; Palache et al. 2015). Consequently, current vaccination likely has limited impact on influenza's persistence because the populations that sustain influenza circulation are mostly unvaccinated. Second, the influenza vaccine appears to protect only partially against infection, even when there is a good antigenic match between vaccine and circulating strains (Skowronski et al. 2017; Cobey et al. 2018; Lewnard and Cobey 2018). Thus, the effective amount of vaccine-induced protection in a population is probably lower than coverage estimates would suggest, and protection is lower still if vaccination reduces disease (the typical end point for vaccine effectiveness studies) more than transmission. This implies higher coverage or a more immunogenic vaccine might be necessary to achieve the impacts described here. Third, a different model might be needed if some fraction of vaccinated or infected individuals have distinctly different immune responses (e.g., some individuals fail to respond to the vaccine or have especially strong immune responses; Nakajima et al. 2000; Cobey and Pascual 2011; Lewnard and Cobey 2018; Georgieva et al. 2019).

Improved understanding of a pathogen's fine-scale evolutionary and immunological dynamics might shift the expected impact of vaccination. For instance, the rate of vaccine-driven evolution is sensitive to transmission rates and the distribution of mutation sizes (Wen et al. 2016). We chose transmission and mutation parameters such that the simulated epidemiological and evolutionary dynamics match those of H3N2 (Bedford et al. 2012; Wen et al. 2016). Increasing the mutation rate, skewing the distribution of mutation sizes toward large mutations, and increasing the transmission rate each increase the rate of antigenic evolution and the tendency for viral populations to diversify (Bedford et al. 2012; Wen et al. 2016). While our model assumes that an individual's immune responses against multiple infections or vaccinations are independent, immunity from prior influenza infection or vaccination affects subsequent immune responses (Smith et al. 1999). Consistent with this hypothesis, there is evidence that influenza vaccination history (McLean et al. 2014; Skowronski et al. 2017) and recipient age (also a proxy for infection history; McLean et al. 2015) affect vaccine efficacy and cross-reactivity. Heterogeneity in adaptive immune responses could require more complex representations of pathogen evolution in strain space (e.g., multiple antigenic maps; Cobey and Hensley 2017).

We found that vaccination against an influenza-like pathogen is unlikely to accelerate evolution, assuming that the breadth of vaccine-induced immunity is similar to that of natural immunity. In simulations, vaccine-driven accelerated antigenic evolution occurs only when the breadth of vaccine-induced immunity is much narrower than that of natural infection, and then only at low vaccination coverage. The relative breadths of vaccine-induced and natural immunity are uncertain, especially since the basis of protection from infection is not precisely known. For influenza, vaccines and natural infection induce similarly broad antibody responses to the top of the hemagglutinin surface protein (i.e., as measured by serum HI), suggesting comparable breadth of immunity (Fonville et al. 2014), although vaccines typically do not match circulating strains at (or sometimes even contain) the neuraminidase. However, unlike infection, inactivated vaccines cannot induce cross-reactive $CD8^+$ T cell responses (He et al. 2006), which would suggest narrower breadth of vaccine-induced immunity. Immune memory affects the specificity of responses to influenza antigens (Davenport and Hennessy 1956, 1957; Linderman et al. 2014; McLean et al. 2014; Cobey and Hensley 2017; Zost et al. 2017; Kwong et al. 2020; Lindley et al. 2020), including the breadth of vaccine-induced and natural immunity, in ways that are still challenging to predict.

In theory, universal vaccines that immunize against all strains necessarily slow antigenic evolution by not discriminating between antigenic variants (Arinaminpathy

et al. 2012). Our results, however, suggest that conventional vaccines against antigenically evolving pathogens already have this potential. For influenza, increasing seasonal vaccine immunogenicity and coverage, especially in populations that contribute substantially to influenza's evolution, could help realize similar evolutionary benefits. However, if vaccination further reduces disease burden, people may require more incentives to get vaccinated (Chapman and Coups 1999; Brewer et al. 2007; Galvani et al. 2007).

Acknowledgments

This work was completed in part with resources provided by the University of Chicago Research Computing Center. F.T.W. and S.C. were supported by the National Institute of Allergy and Infectious Disease of the National Institutes of Health under award DP2AI117921. F.T.W. was also supported by the National Institute of General Medical Sciences under award T32GM007281. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health. We thank Ed Baskerville for programming guidance and Mercedes Pascual and Greg Dwyer for insightful comments. We have no competing interests.

Statement of Authorship

A.M. and S.C. conceived the study. F.T.W. performed the analysis and wrote the first draft of the manuscript. All of the authors contributed to and approved the final version.

Data and Code Availability

The source code for the model can be found at https://github.com/cobeylab/antigen-vaccine (https://doi.org/10.5281/zenodo.5295715). All data and code used to generate the results are available at https://github.com/cobeylab/vaccine-manuscript (https://doi.org/10.5281/zenodo.5295719).

Literature Cited

Alizon, S., and M. van Baalen. 2005. Emergence of a convex tradeoff between transmission and virulence. American Naturalist 165:E155–E167.

———. 1992. Infectious diseases of humans: dynamics and control. Oxford University Press, Oxford.

Arevalo, P., H. Q. McLean, E. A. Belongia, and S. Cobey. 2020. Earliest infections predict the age distribution of seasonal influenza A cases. eLife 9:e50060.

Arinaminpathy, N., O. Ratmann, K. Koelle, S. L. Epstein, G. E. Price, C. Viboud, M. A. Miller, and B. T. Grenfell. 2012. Impact of cross-protective vaccines on epidemiological and evolutionary dynamics of influenza. Proceedings of the National Academy of Sciences of the USA 109:3173–3177.

Atkins, K. E., A. F. Read, N. J. Savill, K. G. Renz, A. F. Islam, S. W. Walkden-Brown, and M. E. J. Woolhouse. 2013. Vaccination and reduced cohort duration can drive virulence evolution: Marek's disease virus and industrialized agriculture. Evolution 67:851–860.

Axelsen, J. B., R. Yaari, B. T. Grenfell, and L. Stone. 2014. Multiannual forecasting of seasonal influenza dynamics reveals climatic and evolutionary drivers. Proceedings of the National Academy of Sciences of the USA 111:9538–9542.

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

Bedford, T., A. Rambaut, and M. Pascual. 2012. Canalization of the evolutionary trajectory of the human influenza virus. BMC Biology 10:38.

Bedford, T., S. Riley, I. G. Barr, S. Broor, M. Chadha, N. J. Cox, R. S. Daniels, et al. 2015. Global circulation patterns of seasonal influenza viruses vary with antigenic drift. Nature 523:217–220.

Bedford, T., M. A. Suchard, P. Lemey, G. Dudas, V. Gregory, A. J. Hay, J. W. McCauley, C. A. Russell, D. J. Smith, and A. Rambaut. 2014. Integrating influenza antigenic dynamics with molecular evolution. eLife 3:e01914.

Belongia, E. A., M. D. Simpson, J. P. King, M. E. Sundaram, N. S. Kelley, M. T. Osterholm, and H. Q. McLean. 2016. Variable influenza vaccine effectiveness by subtype: a systematic review and meta-analysis of test-negative design studies. Lancet Infectious Diseases 16:942–951.

Bieniasz, P. D. 2021. The case against delaying severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) mRNA vaccine boosting doses. Clinical Infectious Diseases 73:1321–1323.

Boni, M. F., J. R. Gog, V. Andreasen, and M. W. Feldman. 2006. Epidemic dynamics and antigenic evolution in a single season of influenza A. Proceedings of the Royal Society B 273:1307–1316.

Brewer, N. T., G. B. Chapman, F. X. Gibbons, M. Gerrard, K. D. McCaul, and N. D. Weinstein. 2007. Meta-analysis of the relationship between risk perception and health behavior: the example of vaccination. Health Psychology 26:136–145.

CDC (Centers for Disease Control and Prevention). 2015. FluVaxView. CDC, Atlanta.

Chapman, G. B., and E. J. Coups. 1999. Predictors of influenza vaccine acceptance among healthy adults. Preventive Medicine 29:249–262.

Charu, V., C. Viboud, L. Simonsen, K. Sturm-Ramirez, M. Shinjoh, G. Chowell, M. Miller, and N. Sugaya. 2011. Influenza-related mortality trends in Japanese and American seniors: evidence for the indirect mortality benefits of vaccinating schoolchildren. PLoS ONE 6:e26282.

Cobey, S., S. Gouma, K. Parkhouse, B. S. Chambers, H. C. Ertl, K. E. Schmader, R. A. Halpin, et al. 2018. Poor immunogenicity, not vaccine strain egg adaptation, may explain the low H3N2 influenza vaccine effectiveness in 2012–2013. Clinical Infectious Diseases 67:327–333.

Cobey, S., and S. E. Hensley. 2017. Immune history and influenza virus susceptibility. Current Opinion in Virology 22:105–111.

Cobey, S., D. B. Larremore, Y. H. Grad, and M. Lipsitch. 2021. Concerns about SARS-CoV-2 evolution should not hold back efforts to expand vaccination. Nature Reviews Immunology 21:330–335.

Cobey, S., and M. Pascual. 2011. Consequences of host heterogeneity, epitope immunodominance, and immune breadth for strain competition. Journal of Theoretical Biology 270:80–87.

Davenport, F. M., and A. V. Hennessy. 1956. A serologic recapitulation of past experiences with influenza A; antibody response to monovalent vaccine. Journal of Experimental Medicine 104:85–97.

———. 1957. Predetermination by infection and by vaccination of antibody response to influenza virus vaccines. Journal of Experimental Medicine 106:835–850.

Day, T., and S. R. Proulx. 2004. A general theory for the evolutionary dynamics of virulence. American Naturalist 163:E40–E63.

Dejnirattisai, W., D. Zhou, P. Supasa, C. Liu, A. J. Mentzer, H. M. Ginn, Y. Zhao, et al. 2021. Antibody evasion by the P.1 strain of SARS-CoV-2. Cell 184:2939–2954.e9.

Demicheli, V., T. Jefferson, E. Ferroni, A. Rivetti, and C. Di Pietrantonj. 2018. Vaccines for preventing influenza in healthy adults. Cochrane Database of Systematic Reviews 2:CD001269.

Desai, M. M., and D. S. Fisher. 2007. Beneficial mutation–selection balance and the effect of linkage on positive selection. Genetics 176:1759–1798.

Du, X., A. A. King, R. J. Woods, and M. Pascual. 2017. Evolution-informed forecasting of seasonal influenza A (H3N2). Science Translational Medicine 9:eaan5325.

Edridge, A. W., J. Kaczorowska, A. C. Hoste, M. Bakker, M. Klein, K. Loens, M. F. Jebbink, et al. 2020. Seasonal coronavirus protective immunity is short-lasting. Nature Medicine 26:1691–1693.

Eguia, R., K. H. Crawford, T. Stevens-Ayers, L. Kelnhofer-Millevolte, A. L. Greninger, J. A. Englund, M. J. Boeckh, and J. D. Bloom. 2021. A human coronavirus evolves antigenically to escape antibody immunity. PLoS Pathogens 17:e1009453.

Feikin, D. R., E. W. Kagucia, J. D. Loo, R. Link-Gelles, M. A. Puhan, T. Cherian, O. S. Levine, C. G. Whitney, K. L. O'Brien, and M. R. Moore; Serotype Replacement Study Group. 2013. Serotype-specific changes in invasive pneumococcal disease after pneumococcal conjugate vaccine introduction: a pooled analysis of multiple surveillance sites. PLoS Medicine 10:e1001517.

Fonville, J. M., S. H. Wilks, S. L. James, A. Fox, M. Ventresca, M. Aban, L. Xue, et al. 2014. Antibody landscapes after influenza virus infection or vaccination. Science 346:996–1000.

Fox, J. W., D. Vasseur, M. Cotroneo, L. Guan, and F. Simon. 2017. Population extinctions can increase metapopulation persistence. Nature Ecology and Evolution 1:1271–1278.

Frank, S. A. 1996. Models of parasite virulence. Quarterly Review of Biology 71:37–78.

Galvani, A. P., T. C. Reluga, and G. B. Chapman. 2007. 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 of the USA 104:5692–5697.

Gandon, S., M. J. Mackinnon, S. Nee, and A. F. Read. 2001. Imperfect vaccines and the evolution of pathogen virulence. Nature 414:751–756.

Geoffard, P.-Y., and T. Philipson. 1997. Disease eradication: private versus public vaccination. American Economic Review 87:222–230.

Georgieva, M., C. O. Buckee, and M. Lipsitch. 2019. Models of immune selection for multi-locus antigenic diversity of pathogens. Nature Reviews Immunology 19:55–62.

Gog, J. R., and B. T. Grenfell. 2002. Dynamics and selection of many-strain pathogens. Proceedings of the National Academy of Sciences of the USA 99:17209–17214.

Good, B. H., I. M. Rouzine, D. J. Balick, O. Hallatschek, and M. M. Desai. 2012. Distribution of fixed beneficial mutations and the rate of adaptation in asexual populations. Proceedings of the National Academy of Sciences of the USA 109:4950–4955.

Gupta, V., D. J. Earl, and M. W. Deem. 2006. Quantifying influenza vaccine efficacy and antigenic distance. Vaccine 24:3881–3888.

Hadfield, J., C. Megill, S. M. Bell, J. Huddleston, B. Potter, C. Callender, P. Sagulenko, T. Bedford, and R. A. Neher. 2018. Nextstrain: real-time tracking of pathogen evolution. Bioinformatics 34:4121–4123.

Halloran, M. E., M. Haber, J. Ira M Longini, and C. J. Struchiner. 1991. Direct and indirect effects in vaccine efficacy and effectiveness. American Journal of Epidemiology 133:323–331.

Hanage, W. P., J. A. Finkelstein, S. S. Huang, S. I. Pelton, A. E. Stevenson, K. Kleinman, V. L. Hinrichsen, and C. Fraser. 2010. Evidence that pneumococcal serotype replacement in Massachusetts following conjugate vaccination is now complete. Epidemics 2:80–84.

He, X.-S., T. H. Holmes, C. Zhang, K. Mahmood, G. W. Kemble, D. B. Lewis, C. L. Dekker, H. B. Greenberg, and A. M. Arvin. 2006. Cellular immune responses in children and adults receiving inactivated or live attenuated influenza vaccines. Journal of Virology 80:11756–11766.

Hurwitz, E. S., M. Haber, A. Chang, T. Shope, S. Teo, M. Ginsberg, N. Waecker, and N. J. Cox. 2000. Effectiveness of influenza vaccination of day care children in reducing influenza-related morbidity among household contacts. Journal of the American Medical Association 284:1677–1682.

Kimura, M. 1979. The neutral theory of molecular evolution. Scientific American 241:98–129.

Kistler, K. E., and T. Bedford. 2021. Evidence for adaptive evolution in the receptor-binding domain of seasonal coronaviruses OC43 and 229E. eLife 10:1–35.

Kucharski, A., and J. R. Gog. 2012. Influenza emergence in the face of evolutionary constraints. Proceedings of the Royal Society B 279:645–652.

Kung, H. C., K. F. Jen, W. C. Yuan, S. F. Tien, and C. M. Chu. 1978. Influenza in China in 1977: recurrence of influenzavirus A subtype H1N1. Bulletin of the World Health Organization 56:913–918.

Kwong, J. C., H. Chung, J. K. Jung, S. A. Buchan, A. Campigotto, M. A. Campitelli, N. S. Crowcroft, et al. 2020. The impact of repeated vaccination using 10-year vaccination history on protection against influenza in older adults: a test-negative design study across the 2010/11 to 2015/16 influenza seasons in Ontario, Canada. Eurosurveillance 25:1900245.

Ladhani, S. N., S. Collins, A. Djennad, C. L. Sheppard, R. Borrow, N. K. Fry, N. J. Andrews, E. Miller, and M. E. Ramsay. 2018. Rapid increase in non-vaccine serotypes causing invasive pneumococcal disease in England and Wales, 2000–17: a prospective national observational cohort study. Lancet Infectious Diseases 18:441–451.

Levin, S., and D. Pimentel. 1981. Selection of intermediate rates of increase in parasite-host systems. American Naturalist 117:308–315.

Lewnard, J., and S. Cobey. 2018. Immune history and influenza vaccine effectiveness. Vaccines 6:28.

Linderman, S. L., B. S. Chambers, S. J. Zost, K. Parkhouse, Y. Li, C. Herrmann, A. H. Ellebedy, D. M. Carter, et al. 2014. Potential antigenic explanation for atypical H1N1 infections among middle-aged adults during the 2013–2014 influenza season. Proceedings

of the National Academy of Sciences of the USA 111:15798–15803.

Lindley, M. C., A. Srivastav, M. Hendrich, H. Fisun, K. Nguyen, O. Pedraza, H. Razzaghi, J. A. Singleton, and W. W. Williams. 2020. Early-season influenza vaccination uptake and intent among adults—United States, September 2020. Centers for Disease Control and Prevention, https://www.cdc.gov/flu/fluvaxview/nifs-estimates-sept2020.htm.

Loeb, M., M. L. Russell, L. Moss, K. Fonseca, J. Fox, D. J. D. Earn, F. Aoki, et al. 2010. Effect of influenza vaccination of children on infection rates in Hutterite communities: a randomized trial. Journal of the American Medical Association 303:943–950.

Madhi, S. A., V. Baillie, C. L. Cutland, M. Voysey, A. L. Koen, L. Fairlie, S. D. Padayachee, et al. 2021. Efficacy of the ChAdOx1 nCoV-19 Covid-19 vaccine against the B.1.351 variant. New England Journal of Medicine 384:1885–1898.

McLean, H. Q., M. G. Thompson, M. E. Sundaram, B. A. Kieke, M. Gaglani, K. Murthy, P. A. Piedra, et al. 2015. Influenza vaccine effectiveness in the United States during 2012–2013: variable protection by age and virus type. Journal of Infectious Diseases 211:1529–1540.

McLean, H. Q., M. G. Thompson, M. E. Sundaram, J. K. Meece, D. L. McClure, T. C. Friedrich, and E. A. Belongia. 2014. Impact of repeated vaccination on vaccine effectiveness against influenza A(H3N2) and B during 8 seasons. Clinical Infectious Diseases 59:1375–1385.

Morris, D. H., V. N. Petrova, F. W. Rossine, E. Parker, B. T. Grenfell, R. A. Neher, S. A. Levin, and C. A. Russell. 2020. Asynchrony between virus diversity and antibody selection limits influenza virus evolution. eLife 9:e62105.

Nakajima, K., U. Desselberger, and P. Palese. 1978. Recent human influenza A (H1N1) viruses are closely related genetically to strains isolated in 1950. Nature 274:334–339.

Nakajima, S., E. Nobusawa, and K. Nakajima. 2000. Variation in response among individuals to antigenic sites on the HA protein of human influenza virus may be responsible for the emergence of drift strains in the human population. Virology 274:220–231.

Newland, M., D. Durham, J. Asher, J. J. Treanor, J. Seals, R. O. Donis, and R. A. Johnson. 2021. Improving pandemic preparedness through better, faster influenza vaccines. Expert Review of Vaccines 20:235–242.

Ohta, T. 1992. The nearly neutral theory of molecular evolution. Annual Review of Ecology and Systematics 23:263–286.

Osterholm, M. T., N. S. Kelley, A. Sommer, and E. A. Belongia. 2012. Efficacy and effectiveness of influenza vaccines: a systematic review and meta-analysis. Lancet Infectious Diseases 12:36–44.

Otto, S. P., and M. C. Whitlock. 1997. The probability of fixation in populations of changing size. Genetics 146:723–733.

Palache, A., A. Abelin, R. Hollingsworth, W. Cracknell, C. Jacobs, T. Tsai, and P. Barbosa. 2017. Survey of distribution of seasonal influenza vaccine doses in 201 countries (2004–2015): the 2003 World Health Assembly resolution on seasonal influenza vaccination coverage and the 2009 influenza pandemic have had very little impact on improving influenza control and pandemic preparedness. Vaccine 35:4681–4686.

Palache, A., V. Oriol-Mathieu, M. Fino, and M. Xydia-Charmanta; Influenza Vaccine Supply Task Force (IFPMA IVS). 2015. Seasonal influenza vaccine dose distribution in 195 countries (2004–2013): little progress in estimated global vaccination coverage. Vaccine 33:5598–5605.

Park, A. W., J. M. Daly, N. S. Lewis, D. J. Smith, J. L. N. Wood, and B. T. Grenfell. 2009. Quantifying the impact of immune escape on transmission dynamics of influenza. Science 326:726–728.

Pebody, R. G., H. K. Green, and N. Andrews. 2015. 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. Eurosurveillance 20:1560–7917.

Pilishvili, T., C. Lexau, M. M. Farley, J. Hadler, L. H. Harrison, N. M. Bennett, A. Reingold, et al. 2010. Sustained reductions in invasive pneumococcal disease in the era of conjugate vaccine. Journal of Infectious Diseases 201:32–41.

Principi, N., S. Esposito, P. Marchisio, R. Gasparini, and P. Crovari. 2003. Socioeconomic impact of influenza on healthy children and their families. Pediatric Infectious Disease Journal 22:S207–S210.

Ranjeva, S., R. Subramanian, V. J. Fang, G. M. Leung, D. K. M. Ip, R. A. P. M. Perera, J. S. M. Peiris, B. J. Cowling, and S. Cobey. 2019. Age-specific differences in the dynamics of protective immunity to influenza. Nature Communications 10:1660.

Read, A. F., S. J. Baigent, C. Powers, L. B. Kgosana, L. Blackwell, L. P. Smith, D. A. Kennedy, S. W. Walkden-Brown, and V. K. Nair. 2015. Imperfect vaccination can enhance the transmission of highly virulent pathogens. PLoS Biology 13:e1002198.

Rozo, M., and G. K. Gronvall. 2015. The reemergent 1977 H1N1 strain and the gain-of-function debate. mBio 6:e01013-15.

Saad-Roy, C. M., S. E. Morris, C. J. E. Metcalf, M. J. Mina, R. E. Baker, J. Farrar, E. C. Holmes, et al. 2021. Epidemiological and evolutionary considerations of SARS-CoV-2 vaccine dosing regimes. Science 372:363–370.

Skowronski, D. M., C. Chambers, G. De Serres, S. Sabaiduc, A.-L. Winter, J. A. Dickinson, J. B. Gubbay, et al. 2017. 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 215:1059–1099.

Smith, D. J., S. Forrest, D. H. Ackley, and A. S. Perelson. 1999. Variable efficacy of repeated annual influenza vaccination. Proceedings of the National Academy of Sciences 96:14001–14006.

Smith, D. J., A. S. Lapedes, J. C. de Jong, T. M. Bestebroer, G. F. Rimmelzwaan, A. D. M. E. Osterhaus, and R. A. M. Fouchier. 2004. Mapping the antigenic and genetic evolution of influenza virus. Science 305:371–376.

Starr, T. N., A. J. Greaney, A. S. Dingens, and J. D. Bloom. 2021. Complete map of SARS-CoV-2 RBD mutations that escape the monoclonal antibody LY-CoV555 and its cocktail with LY-CoV016. Cell Reports Medicine 2:100255.

Subramanian, R., A. L. Graham, B. T. Grenfell, and N. Arinaminpathy. 2016. Universal or specific? a modeling-based comparison of broad-spectrum influenza vaccines against conventional, strain-matched vaccines. PLoS Computational Biology 12:e1005204-17.

Tam, J. S., M. R. Z. Capeding, L. C. S. Lum, T. Chotpitayasunondh, Z. Jiang, L.-M. Huang, B. W. Lee, et al.; Pan-Asian CAIV-T Pediatric Efficacy Trial Network. 2007. Efficacy and safety of a live attenuated, cold-adapted influenza vaccine, trivalent against culture-confirmed influenza in young children in Asia. Pediatric Infectious Disease Journal 26:619–628.

Uscher-Pines, L., A. Mulcahy, J. Maurer, and K. Harris. 2014. The relationship between influenza vaccination habits and location of vaccination. PLoS ONE 9:e114863.

Waight, P. A., N. J. Andrews, S. N. Ladhani, C. L. Sheppard, M. P. E. Slack, and E. Miller. 2015. Effect of the 13-valent pneumococcal conjugate vaccine on invasive pneumococcal disease in England and Wales 4 years after its introduction: an observational cohort study. Lancet Infectious Diseases 15:535–543.

Weinberger, D. M., R. Malley, and M. Lipsitch. 2011. Serotype replacement in disease after pneumococcal vaccination. Lancet 378:1962–1973.

Wen, F., T. Bedford, and S. Cobey. 2016. Explaining the geographical origins of seasonal influenza A (H3N2). Proceedings of the Royal Society B 283:20161312–20161319.

Wen, F., S. Bell, T. Bedford, S. Cobey, F. T. Wen, S. M. Bell, T. Bedford, and S. Cobey. 2018. Estimating vaccine-driven selection in seasonal influenza. Viruses 10:509.

WHO (World Health Organization). 2014. Influenza fact sheet. WHO, Geneva.

Witter, R. L. 1997. Increased virulence of Marek's disease virus field isolates. Avian Diseases 41:149–163.

Yadav, P. D., G. N. Sapkal, P. Abraham, R. Ella, G. Deshpande, D. Y. Patil, D. A. Nyayanit, et al. 2021. Neutralization of variant under investigation B.1.617 with sera of BBV152 vaccinees. Clinical Infectious Diseases, https://doi.org/10.1093/cid/ciab411.

Zarnitsyna, V. I., I. Bulusheva, A. Handel, I. M. Longini, M. E. Halloran, and R. Antia. 2018. Intermediate levels of vaccination coverage may minimize seasonal influenza outbreaks. PLoS ONE 13:e0199674.

Zost, S. J., K. Parkhouse, M. E. Gumina, K. Kim, S. Diaz Perez, P. C. Wilson, J. J. Treanor, A. J. Sant, S. Cobey, and S. E. Hensley. 2017. Contemporary H3N2 influenza viruses have a glycosylation site that alters binding of antibodies elicited by egg-adapted vaccine strains. Proceedings of the National Academy of Sciences of the USA 114:12578–12583.

References Cited Only in the Online Enhancements

Anderson, R. M., and R. M. May. 1982. Coevolution of hosts and parasites. Parasitology 85:411–426.

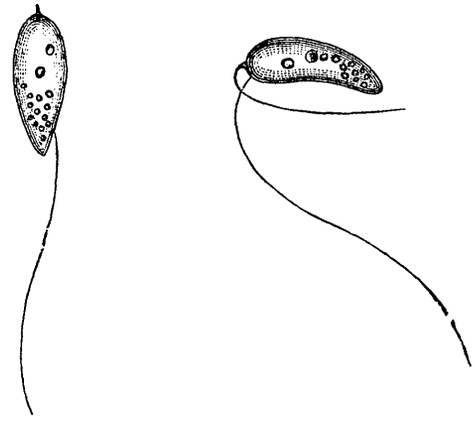
Biggerstaff, M., S. Cauchemez, C. Reed, M. Gambhir, and L. Finelli. 2014. Estimates of the reproduction number for seasonal, pandemic, and zoonotic influenza: a systematic review of the literature. BMC Infectious Diseases 14:1–20.

Carrat, F., E. Vergu, N. M. Ferguson, M. Lemaitre, S. Cauchemez, S. Leach, and A.-J. Valleron. 2008. Time lines of infection and disease in human influenza: a review of volunteer challenge studies. American Journal of Epidemiology 167:775–785.

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

United Nations. 2013. World population prospects: the 2012 revision. United Nations, Department of Economic and Social Affairs, Population Division, New York.

Associate Editor: Matthew J. Ferrari
Editor: Daniel I. Bolnick



"The creature, when in a healthy or comfortable condition, is very slightly if at all changeable in shape. . . . The motion of the Heteromita when swimming is rapid and oscillating, being a forward movement by short zig-zags, the animal at the same time rotating on its longitudinal axis." Figured: "*Heteromita putrina*." From "Notes on Some Apparently Undescribed Infusoria from Putrid Waters" by Alfred C. Stokes (*The American Naturalist*, 1884, 18:133–140).