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Intermediate levels of vaccination coverage may minimize seasonal influenza outbreaks

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Abstract

For most pathogens, vaccination reduces the spread of the infection and total number of cases; thus, public policy usually advocates maximizing vaccination coverage. We use simple mathematical models to explore how this may be different for pathogens, such as influenza, which exhibit strain variation. Our models predict that the total number of seasonal influenza infections is minimized at an intermediate (rather than maximal) level of vaccination, and, somewhat counter-intuitively, further increasing the level of the vaccination coverage may lead to higher number of influenza infections and be detrimental to the public interest. This arises due to the combined effects of: competition between multiple co-circulating strains; limited breadth of protection afforded by the vaccine; and short-term strain-transcending immunity following natural infection. The study highlights the need for better quantification of the components of vaccine efficacy and longevity of strain-transcending cross-immunity in order to generate nuanced recommendations for influenza vaccine coverage levels.

Introduction

Influenza A remains a widespread disease that continues to circulate worldwide with more than 200,000 people in the US hospitalized annually for illnesses associated with seasonal influenza virus infections [1]. Vaccination is considered to be a chief preventive tool against influenza, and the Centers for Disease Control and Prevention encourages maximal vaccination coverage by recommending that all individuals 6 months and older receive an influenza vaccine annually [2].

The influenza vaccine in general use is an inactivated virus vaccine that targets the strains of influenza A and B predicted to circulate in the population during the current season. Many studies have measured the efficacy of the vaccine (we use “efficacy” to include estimates from...
both randomized and observational studies). Early studies of influenza vaccine efficacy in the military [3], as well as Tecumseh and Hutterite communities studies [4, 5] and studies in Japan [6] showed that the inactivated influenza vaccine provides reasonable levels of protection against the current circulating strain of influenza and may interrupt virus transmission. Meta-analyses in ten randomized controlled trials revealed pooled efficacy of trivalent inactivated vaccine (TIV) as 59% (95% CI 51-67) [7], while for one of the component of TIV vaccine, influenza A subtype H3N2, a meta-analysis of 56 test-negative design studies reported a much lower pooled vaccine efficacy of 33% (95% CI 26-39) [8]. The main challenge in vaccination against influenza is that antigenic drift of the virus in response to population level immunity generates virus strains that are not covered by the vaccine, and this requires frequent reformulation of the vaccine to include the drifted strains.

Vaccination against H3N2 subtype typically shows lower vaccine efficacy in comparison to H1N1, so we will focus on H3N2. If during a given season only one strain, drifted from a previous season strain of a given subtype, would be in circulation, the situation would be relatively simple. In reality, phylogenetic analysis of HA genes from circulating H3N2 strains revealed extensive genetic diversity with multiple clades and subclades co-circulating (see CDC report for the current 2017-2018 season [9]). Multiple co-circulating strains generate potentially complex dynamics with ongoing replacement of older strains by newer ones. Consider, for example, the spread of influenza A (H3N2) in the US during the 2014-2015 season, where the H3N2 subtype dominated. Cases analyzed just prior to the onset of that influenza season showed that 42% were caused by strains antigenically similar to the strain included in that season’s influenza vaccine [10]. Characterization of the limited number of confirmed H3N2 cases during the seasonal outbreak is shown in Fig 1. We see that the fraction of H3N2 cases caused by the
vaccine-like strains gradually declined, and the proportion of cases due to strains not targeted by the vaccine increased. By the end of the season, virtually all new cases were due to strains not targeted by the vaccine, and over the entire season 81% of the cases were caused by non-vaccine strains [11].

The circumstance described above is not unique. For example, by the final week of the 2007-2008 influenza season in US, 21% of reported cases were caused by the H3N2 strain included in the vaccine, 65% cases were caused by its known antigenic variant, and 14% showed somewhat reduced titers to antisera produced by any of these two strains [12].

To better understand the nature of the phenomenon described above, we briefly discuss how influenza varies and the epidemiological and immunological consequences of this variation. Infection with a given strain of influenza results in the generation of a long-lived antibody response specific for hemagglutinin (HA) and neuraminidase (NA), the virus surface proteins that are the major targets of the humoral immunity [13]. The influenza virus responds to pre-existing immunity in the host population by antigenic changes through mutations in HA and NA. In addition to long-lived strain-specific immunity mentioned above, infection induces strain-transcending immunity that is of a shorter duration. This short-term strain-transcending immunity has been demonstrated in a number of immunological studies and is also invoked in epidemiological studies that describe the circulation of different influenza strains. Immunological studies in mouse and ferret model systems have shown that infection with one strain induces temporary strain-transcending immunity with a relatively short duration on the scale of one or a few months [14–19]. The mechanisms for this strain-transcending immunity, or cross-immunity, following natural infection are the subject of much current work and could arise due to temporary non-specific antiviral immunity [14] or T cells specific for internal epitopes which are typically conserved between strains [15–19]. In contrast to natural infection, the trivalent inactivated vaccine (TIV) primarily induces humoral strain-specific immunity directed against HA and NA included in the vaccine and does not generate broad cross-immunity against mismatched strains. Epidemiological studies also indicate the presence of temporary strain-transcending immunity [20–23]. Observations of infection of humans over the course of a single season show that infection with one strain significantly reduces the risk of infection with an antigenically different strain [23]. Short-term cross-immunity was used to explain the limited diversity of circulating influenza strains [20, 21], though other studies suggest alternative explanations [24–26].

We extend prior studies that use mathematical models to analyze the dynamics of pathogens exhibiting strain variation [22, 27–31]. We extend these models to analyze how the size of seasonal outbreaks of influenza depends on vaccination coverage in a simple scenario with two antigenically distinct co-circulating strains and vaccination which targets one of these strains. This allows us to explore how the optimal vaccination strategy depends on factors such as the initial relative prevalence of the two strains and the duration of cross-immunity generated by natural infection with influenza. Our results suggest that high levels of influenza vaccination coverage may lead to the replacement of the dominant strain targeted by the vaccine with another co-circulating mismatched strain that would otherwise be suppressed from the cross-immunity generated in the population by natural infection with the dominant strain. We show that increasing vaccination coverage above an optimal level may, in fact, lead to a higher total number of influenza cases (attack rate).

The goal of this study is not to come up with definitive recommendations for vaccination policy, but to explore the complex consequences of vaccination for pathogens that exhibit strain variation, with a focus on influenza. In doing so, we bring attention to possible unexpected consequences of high vaccination coverage, and identify key factors that need to be
evaluated when considering the optimal vaccine coverage that minimizes the attack rate from influenza.

**Model**

The model incorporates the following biological features: (i) two co-circulating antigenically distinct influenza strains; (ii) natural infection with either strain induces long-term immunity specific for that strain and short-term strain-transcending immunity (i.e. cross-immunity) to the other strain; (iii) vaccination induces protection only against the strain included in the vaccine.

Our model is based on the widely used Susceptible-Infectious-Recovered (SIR) framework for disease transmission, which puts individuals in the population into compartments based on their immune and infection status [32–34]. The SIR framework has been extended to model strain variation in influenza in a number of different ways [20, 22, 26, 35–37]. We incorporate two co-circulating influenza strains using a status-based approach (Fig 2) [22, 35]. A two-letter code is used to describe the ten possible states for each individual in the population, where the first and second letters reflect the status with respect to the first and second influenza virus strains. For example, SS denotes individuals susceptible to the infection with both strains and SR represents an individual susceptible to the first strain but recovered from the second strain and immune to it. Infection of susceptible individuals (SS) with the first strain moves them to the IS state at a rate that depends on the infectiousness of the first strain and the prevalence of infection caused by it. Infectious individuals recover and move to RC state, which indicates that they have long-term immunity to the first strain (R) and short-term cross-immunity (C) to the second strain. These individuals lose immunity to the second strain at rate \( \sigma \) and move to the RS state. Individuals in the RS state can be infected only by the second strain, and this would result in movement to the RI state and, subsequently, after recovery, to the RR state. We note that the state space variables are the fractions of the total population in each state and, consequently, we are not modeling a population of any particular size. The model variables and parameters are summarized in Table 1. We chose the basic reproductive number of seasonal influenza to be 1.6 [38, 39]. The average duration of infection (reciprocal of \( \gamma \)) was defined as the viral shedding period of an infected adult and was set to 5 days [40]. The duration of cross-immunity was varied from 60 days to 1 year [20].

Fig 2. Scheme for SIR-based model with two strains. Ten different states corresponding to model variables in eqs (1)–(10) characterize the status of individuals with respect to the first and second strains of the virus. The first and second letters in the two-letter code show the individual’s status of infection with respect to the first and second strain. We use the conventional notation “S” for susceptible, “I” for infected, and “R” for recovered with long-term immunity and “C” for recovered with short-term cross-immunity.

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The model equations are:

\[
\frac{dSS}{dt} = -\beta(IS + IR + SI + RI)SS
\] (1)
\[
\frac{dIS}{dt} = \beta(IS + IR)SS - \gamma IS
\] (2)
\[
\frac{dSI}{dt} = \beta(SI + RI)SS - \gamma SI
\] (3)
\[
\frac{dRC}{dt} = \gamma IS - \sigma RC
\] (4)
\[
\frac{dCR}{dt} = \gamma SI - \sigma CR
\] (5)
\[
\frac{dRS}{dt} = \sigma RC - \beta(SI + RI)RS
\] (6)
\[
\frac{dSR}{dt} = \sigma CR - \beta(IS + IR)SR
\] (7)
\[
\frac{dRI}{dt} = \beta(SI + RI)RS - \gamma RI
\] (8)
\[
\frac{dIR}{dt} = \beta(IS + IR)SR - \gamma IR
\] (9)
\[
\frac{dRR}{dt} = \gamma(IR + RI)
\] (10)

The two strains have similar parameters except for their initial prevalences that determine the degree of initial dominance of the first strain. We changed the degree of dominance by altering the time of introduction ($\Delta T$) of the second strain. Higher values of $\Delta T$ result in a
higher degree of dominance of the first strain. An alternative way of changing the degree of dominance is to introduce the two strains simultaneously (at $t = 0$) at different frequencies. We have shown that it did not alter the qualitative outcomes of the model (see Model Robustness section).

Because the duration of one epidemic season is short, we did not include births and deaths or migration in our model. Different studies showed a wide range in estimated vaccine efficacy (16 to 76% for adults 18–64 years old, see Table 2 in [7]). In our model, we assume that the vaccine provides all-or-none protection from infection, and define the vaccine efficacy ($V_E$) as the fraction of individuals who are protected. We introduced vaccination by moving $fV_E$ of individuals from $SS$ to $RS$ prior to the season, where $f$ is a fraction of vaccinated people. We assume that infection, but not vaccination, induces short-term strain-transcending immunity—this is consistent with the shift from the vaccine strain to the mismatched strain over the course of the season shown in Fig 1.

We first considered the case where individuals are resistant to superinfection, i.e. individuals can only be infected by a single strain at a given time. We then explored the robustness of our model by considering scenarios that include superinfection, simple age-structure and where infection results in long-term cross-immunity in a fraction of individuals (see Figs A–C in S1 Text).

## Results

### Dynamics of strain competition

We consider the dynamics of two co-circulating influenza strains and how it is changed by vaccination. Fig 3 shows the dynamics of two strains of influenza and how it is affected by the degree of initial dominance of the first strain, the duration of cross-immunity and the extent of vaccination. The degree of dominance was modeled by delaying the time of introduction of the second strain by $\Delta T$. The prevalence of a given strain was defined as a fraction of the total population that is infected with that strain and is shown by the dashed and solid lines for the first and second strains, respectively.

Competition between the two strains is mediated by cross-immunity induced following infection with either strain. Fig 3 Panel A illustrates that in the absence of vaccination, the extent to which the first (dominant) strain can suppress the second strain increases with the extent of initial dominance of the first strain (i.e. suppression of the second strain is higher when it is introduced later). Fig 3 Panel B shows in more detail how the suppression of the second strain depends not only on the degree of initial dominance of the first strain but also on the duration of cross-immunity ($1/\sigma$). The attack rate of the second strain (i.e. the total number of cases with the second strain) during the outbreak is reduced by increases in the degree of dominance of the first strain $\Delta T$ from 0 to 100 days, and if we increase the duration of cross-immunity $1/\sigma$ from 0 to 180 days. For Fig 3 Panels B, D, and F, the attack rate is calculated for one influenza season which we assume to last for about six months (180 days in our simulations). In the absence of competition between the two strains (light grey lines for “no cross-immunity” condition), the attack rate for the second strain does not depend on the vaccination against the first strain (Fig 3 Panels B, D, and F).

As the level of vaccination against the dominant strain increases, its prevalence decreases and, consequently, the extent to which it suppresses the second strain falls. This is seen in Fig 3 Panel C, where the size of the outbreaks due to the second strain is much higher than the corresponding outbreaks in the absence of vaccination shown in Fig 3 Panel A. Finally, when the vaccination coverage is sufficiently high, it eliminates the outbreak with the first strain, and it is replaced by the outbreak with the second strain (Fig 3 Panel E). In this case, the
The magnitude of the outbreak with the second strain becomes independent of both the degree of dominance of the first strain and the level of infection-induced cross-immunity (Fig 3 Panel F). The timing of the outbreak depends on the time of introduction of the second strain (Fig 3 Panel E).

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Vaccination changes the total attack rate

Fig 3 shows that the dynamics of strain competition is affected by three key parameters: (i) extent of vaccination coverage; (ii) duration of cross-immunity \((1/\sigma)\); and (iii) degree of initial dominance of the first strain \((\Delta T)\). We would like to know how the total attack rate due to influenza is affected by the level of vaccination coverage. The total attack rate is the sum of the attack rates with the first and the second strains over the season. In Fig 4A the degree of dominance of the first strain is kept constant (the second strain is introduced at day 60) and the total attack rate is plotted as a function of the vaccination coverage against the first strain and the duration of cross-immunity \(1/\sigma\). In Fig 4B the duration of cross-immunity is held constant (at \(1/\sigma = 180\) days) and the total attack rate is plotted as a function of the extent of vaccination and the degree of dominance (i.e. the time delay \(\Delta T\)).

Increasing the vaccination coverage initially decreases the total attack rate. However, for a large parameter regime, after a critical level of vaccination, further increases in the vaccination coverage lead to an increase in the total attack rate. The initial decrease in the attack rate is expected because of the decrease in the prevalence of the dominant strain that is targeted by the vaccine. The subsequent increase in the total attack rate at high levels of vaccination coverage occurs because of strain replacement described in Fig 3. The feedback between the prevalence of each strain and the extent of competitive suppression between the two strains determines the magnitude of the total attack rate and the level of vaccination coverage at which the total attack rate is minimized (see Discussion on the “overshoot” effect).

This result (i.e. the total attack rate being minimized at intermediate levels of vaccination against one strain) does not require cross-immunity induced by infection to be complete. Previous studies considered a range for the duration of cross-immunity between three months and two years [20], and our results hold for an even wider range of cross-immunity as shown

Fig 4. The total attack rate depends on the vaccination coverage, the duration of infection-induced cross-immunity \((1/\sigma)\) and the degree of dominance \((\Delta T)\). Panel A shows how the total attack rate depends on the level of vaccination coverage and the duration of cross-immunity \((\sigma)\). The time of introduction to the second strain is kept fixed at 60 days. Panel B shows how the total attack rate depends on the vaccination coverage as well as the degree of dominance (the time delay \(\Delta T\) between introduction of the first and second strains). The parameter for the duration of cross-immunity after influenza infection \(1/\sigma = 180\) days. All other model parameters are in Table 1.

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This result also requires a degree of dominance $\Delta T >$ about 20 days (Fig 4B), and vaccination against the dominant strain. If we assume that at the early stages the dominant strain grows exponentially, then a time delay $\Delta T \approx 20$ corresponds to the case where the first strain would have a relative prevalence of $e^{(R_0S-1)\Delta T/\gamma} \approx 10$ fold higher than that of the second strain.

**Optimal vaccination coverage**

Finally, we asked how the optimal level of vaccination coverage depends on both the level of cross-immunity as well as the time of the second strain’s introduction. Each panel in Fig 5 corresponds to a different level of vaccination and shows how the total attack rate depends on the level of cross-immunity and the degree of dominance. For a given level of cross-immunity and dominance (i.e. position on the graph) we can see how changing the level of vaccination changes the attack rate by comparing the attack rate moving from the plots on the left (low vaccination) to the plots on the right (high vaccination).

Fig 6A plots the optimal vaccination level, and Fig 6B shows how much benefit it produces in comparison to the case of complete vaccine coverage. From Fig 6A we can see that complete
vaccination coverage is desirable only if the duration of cross-immunity is very low and provided that the dominance $\Delta T$ of the first strain is less than 60 days. For a substantial region of parameter space we find that a relatively modest vaccination coverage (between 10 and 50%) is optimal. From Fig 6B we also can see that for a large parameter regime there is only a modest difference in the outcome with the degree of vaccination coverage. The benefit of optimal vaccination vs vaccinating the total population can be relatively large (between 25-40%) when the cross-immunity and dominance is relatively high.

Model robustness
We have checked the robustness of our model by determining how the results are affected by introduction of a number of changes. First, we added superinfection to the model and consider the opposite limiting case by allowing someone infected with one strain ($IS$ or $SI$) to be infected with the other strain (become $II$) at the same rate $\beta$ as the $SS$ individuals (Fig A in S1 Text). Contrasting the two extreme scenarios for incorporating superinfection into the model, we demonstrated that superinfection does not play a significant role in the observed dynamics (Fig D in S1 Text). Second, we added heterogeneity to the model by modifying it to include two age groups, children and adults, with higher levels of transmission and slower recovery for children (Figs B and E in S1 Text). This allowed us to incorporate a higher level of transmission in children and lower level of transmission in adults as has been described earlier [41]. Third, we changed the structure of our model to incorporate a different formulation for cross-immunity. In the current model, after recovery from natural infection, the level of cross-immunity gradually wanes. We changed this to allowing a fraction of hosts to have permanent cross-immunity after infection with either strain (Figs C and F in S1 Text). Fourth, we added seasonality into the model as has been previously done [22] by changing the parameter $\beta$ as a function of time so that $\beta(t) = \beta(1 + \beta_s \sin(2\pi t/365))$ (Fig G in S1 Text). Fifth, we changed the way we introduced the two strains. Previously we introduced the subdominant strain at a later time, and here we considered the effect of introducing the two strains at the same time (at $t = 0$) but at different frequencies (Fig H in S1 Text). Sixth, we changed the $R_0$ to a higher value which might occur following larger antigenic changes in the virus. In Fig I S1 Text we show that increasing $R_0$ from 1.6 to 2.0 did not alter the main qualitative result—the optimal reduction in the attack rate occurs at intermediate levels of vaccination, though there was a modest increase in the optimal level of vaccination coverage. Seventh and finally, we considered a scenario where there were additional strains not targeted by the vaccine. It can be shown that if cross-immunity lasts for the duration of a season then the multi-strain model can be reduced to our two strain model with the multiple strains which are not targeted by the vaccine combined together. The more complex scenario where cross-immunity does not last an entire season is illustrated for a three strain model in Figs J and K S1 Text. The qualitative results are similar to those of the two strain model shown in Fig 4.

The details of these changes and corresponding models equations are shown in S1 Text. We note that none of the changes or additions to the model altered the qualitative results, indicating the robustness of the basic results of our model.

Discussion
We considered the dynamics of two co-circulating influenza strains, and how it is changed by vaccination. This allowed us to explore how vaccination affects the total attack rate, and we showed that an intermediate level of vaccination minimizes the total attack rate. We also showed that our simple model is robust to inclusion of complexities such as superinfection,
seasonality, and heterogeneity in transmission in subpopulations, as well as a different way of describing strain dominance.

We explored the problem of vaccination against pathogens, such as influenza, that exhibit ongoing strain variation. Our study builds on previous work on vaccination and strain replacement in *Streptococcus pneumoniae* [28], and multi-strain models of influenza [22]. The model of Lipsitch [28] describes the situation when vaccination against the targeted serotypes may cause an increase in carriage of non targeted serotypes in the case of *S. pneumoniae* and *Haemophilus influenzae*, which have multiple well defined strains and relatively slowly changing strain structure compared with influenza. The potential for large-scale vaccination campaigns to alter the competitive landscape between influenza subtypes has been mentioned before [42], and we integrate and expand on all of these earlier studies.

The model makes the novel prediction that increasing influenza vaccination coverage beyond an optimal level may lead to a higher total attack rate. The finding that the maximal level of vaccination coverage may not always be the optimal solution has been reported previously in other very different scenarios [43, 44].

Our result for the optimal level of vaccination can be intuitively explained with the help of the "overshoot" effect [45] that describes the observation that the total attack rate of an epidemic is much larger than the fraction of immune or recovered individuals needed to prevent an epidemic (Fig 7 Panels A and B). Consider the limiting case when the degree of dominance is high and short-term cross-immunity is high. In this case, the optimal level of vaccination

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**Fig 7. Illustration of the "overshoot" effect.** Panel A shows the number of susceptibles and infecteds during an outbreak with $R_0 = 2$. The initial growth phase of the epidemic is approximately characterized by an exponential increase in the number of infecteds, accompanied by a decline of susceptibles. The dashed horizontal line indicates the threshold level of susceptibles below which population immunity prevents further outbreaks for this given set of parameters. Once the number of susceptibles crosses a threshold level, the average number of new infections caused by an infected person falls below 1 and the epidemic wanes. The arrow indicates the difference between the number of susceptibles at the end of the outbreak and the threshold line. This difference was termed as the "overshoot" [45]. Panel B shows how the magnitude of overshoot depends on $R_0$. For the simple SIR model, the number of prevented infections is found to be highest for intermediate values of $R_0 \sim 2$. Panel C considers the optimal level of vaccination for the limiting case which is easy to analyze. We choose an infection with $R_0 = 2$, high degree of dominance (second strain is introduced at day 150) and high cross-immunity which does not wane on this timescale. We plot the cumulative number of infections by either strain (as a fraction of the total population) as a function of time. The optimal level of vaccination (fraction vaccinated = 0.209, solid black line) against the first strain results in the fraction of susceptibles to the second strain declining to $\frac{1}{2} \frac{1}{R_0} = 0.5$. This level of herd immunity just prevents the second strain from spreading. At a lower level of vaccination (fraction vaccinated = 0.16, blue dotted line) leads to more infections with the first strain (and also prevents the second strain spreading). A higher level of vaccination (fraction vaccinated = 0.26, green dotted line) leads to fewer infections with the first strain but allows the second strain to spread and generate an overshoot.

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for the first strain is such that the number of individuals recovered from infections with the first strain \((1 - 1/R_0)\) is just sufficient to prevent the second strain from spreading (and this eliminates the "overshoot") (Fig 7 Panel C). The situation is more complex when the degree of dominance is lower but the basic result is that a single large outbreak (either with a vaccine-matched strain in the absence of vaccination or the mismatched strain when the vaccine prevents the outbreak of the vaccine-matched strain) can result in a greater attack rate than the total attack rate from a smaller outbreak of the vaccine-matched strain that generates sufficient cross-immunity to blunt the subsequent outbreak with the vaccine mismatched strain. Similar scenarios can also occur for the use of antivirals and drug sensitive and resistant strains [46–48]. At the optimal level of vaccination, the effective reproductive numbers and overshoot are reduced for both strains. This occurs because of direct targeting of the dominant strain by vaccination and indirect targeting of the second strain by strain-transcending immunity after influenza infection.

We now discuss the assumptions and limitations of our model, and how the model would need to be extended to accurately capture the dynamics of circulating influenza strains. The first set of assumptions is that influenza exhibits strain variation, and that multiple strains co-circulate at the same time. As discussed in the introduction, this is not uncommon for the H3N2 influenza subtype. The model is a relatively simple deterministic compartmental model and includes only two influenza virus strains of a given subtype, one which is targeted by the vaccine and one which has substantially reduced titers to the immune response induced by vaccination. In reality, there is likely to be a number of strains with a more graded response to vaccine-induced immunity. If there are only two strains, then it might be best to include both strains in the vaccine, and this has been suggested by [49]. However, we would expect the problem described here to re-emerge, if there is an additional strain not targeted by the vaccine, and this is regardless of the number of strains included in the vaccine. In such a scenario, we would once again expect the lowest total attack rate to happen at an intermediate level of vaccine coverage, and complete vaccine coverage to be counterproductive. If only one strain is included in the vaccine, addition of more not targeted by a vaccine strains will not change the result qualitatively, as described in the section on the robustness of the model and illustrated in Figs J and K in S1 Text.

Another set of assumptions concerns the specificity and longevity of immunological memory induced by vaccination vs. natural infection. The model assumes that both natural infection and vaccination generate immunity that lasts at least the entire season to the specific strain included in the vaccine and, thus, in the model this immunity does not wane in this period. We additionally assume that natural infection, but not vaccination with the inactivated virus such as TIV, generate shorter-term strain-transcending immunity. These assumptions are similar to those used in earlier models [20, 22]. Our model covers a broad range for the longevity of cross-immunity lasting between two months to over a year as in a previous study [20]. Both innate immunity [14] and CD8 T cell responses to conserved virus epitopes [15–19] could provide strain-transcending immunity following influenza infections. Innate immunity, however, would be expected to last for a relatively short-duration of a few weeks [50], while elevated levels of resident memory T cells may be maintained in the respiratory tract for months [19], and would be more relevant to short-term cross-immunity [51–53].

We assume that vaccine generates all-or-none immunity that renders half vaccinated individuals resistant to infection. Changing \(V_E\) does not change the qualitative results but just scales how the results depend on vaccine coverage \(f\), and this is because the results depend on the product \(fV_E\). If we were to use a "leaky" vaccine model, then we would also need estimates of the effect of the vaccine on infectiousness and pathogenicity, which are other components
of the efficacy of the vaccine, and are not readily available. An important next step will be to obtain more accurate estimates of these different components of vaccine efficacy and incorporate them into the model.

Going from the simple qualitative results of our paper to quantitatively accurate predictions will require more detailed models such as individual based models which incorporate more complex and realistic contact networks, spatial structure, and stochasticity. These models will need to account for seeding of seasonal outbreaks and a quantitative understanding of cross-immunity between the responses to different viruses [54–57]. The models assume all individuals in the population have identical immunity generated by exposure to influenza in the past. They will also need to taking into account the prior immune history to influenza infection that may lead to mild and/or asymptomatic infections, mild infection as a result of the vaccination and effect of influenza vaccine on secondary bacterial infections [58–61]. Finally, we have assumed that there is no inherent fitness difference in the two strains (in the absence of immunity) and need to consider the process of generation of variation and how vaccination can change the tempo of antigenic evolution which has been considered in a recent paper [62].

The paper uses simple conceptual models to explore the consequences of the increased vaccination coverage on the dynamics of the co-circulating strains and total influenza attack rate. The surprising prediction of the model is that for a wide range of biologically reasonable parameters the maximum reduction in the total attack rate occurs at the intermediate level of vaccine coverage, and, somewhat counter-intuitively, further increasing the level of the vaccination coverage may lead to higher number of influenza infections and be detrimental to the public interest. Bringing the models predictions into contact with epidemiological data will be the subject of subsequent studies. It will require taking into account factors such as the match between the vaccine and the dominant strain and the frequencies of vaccine matched and mismatched strains at the beginning of the season, as well as more realistic contact networks and other factors mentioned in the previous paragraph.

While we focus on antigenic drift, the model can also be applied to a scenario involving an antigenic shift that causes pandemics. This is because of the high degree of conservation of T cell epitopes on influenza virus internal proteins not only for strains of a given subtype but also for strains of different virus subtypes [63, 64]. In this case, vaccination which reduces the prevalence of the seasonal strain may decrease the level of cross-immunity generated by infection with a seasonal strain and, thus, weaken a protection against the shifted (pandemic) strain. As pandemic strain often has higher transmissibility in comparison to a seasonal strain [65], vaccination may facilitate its spread. This might suggest that vaccination against the currently circulating seasonal influenza should be halted following the emergence of a pandemic strain, which is consistent with the report that people vaccinated against seasonal influenza strain had a higher rate of infection with pandemic strain and more severe disease during that season [66]. It is also consistent with the study showing that infection with H3N2 was negatively associated with a subsequent risk of infection with H1N1 during the same influenza season [23].

In summary, our models suggest that more detailed surveillance of the relative prevalence of co-circulating strains, and measurements of parameters such as the duration of cross-immunity and their integration with more sophisticated models for the spread of influenza, may allow for more nuanced recommendations for coverage levels that minimize the attack rate of both seasonal and pandemic influenza in the future. Such consideration may prove useful until the development of a universal vaccine that could provide long-duration strain-transcending immunity [67, 68].
Supporting information

S1 Text. Model robustness. We have checked the robustness of our model by determining how the results are affected by introduction of a number of changes: addition of superinfection; addition of age structure; alternative introduction of cross-immunity into the model; addition of seasonality; introduction of the two strains at the same time (at $t = 0$) but at different frequencies; increase in $R_0$; and addition of the third strain. These changes did not alter the basic result shown in Fig 4—for a large range of parameters the lowest attack rate occurs at intermediate levels of vaccine coverage.

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