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MAJOR ARTICLE

Estimating the Impact of Low Influenza Activity in 2020 on Population Immunity and Future Influenza Seasons in the United States

Kyueun Lee,[1,2] Hawre Jalal,[1,2] Jonathan M. Raviotta,[3] Mary G. Krauland,[1,2] Richard K. Zimmerman,[3] Donald S. Burke,[2,4] and Mark S. Roberts[1,2]

[1]Department of Health Policy and Management, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA, [2]Public Health Dynamics Laboratory, University of Pittsburgh Graduate School of Public Health, Pittsburgh, Pennsylvania, USA, [3]Department of Family Medicine, University of Pittsburgh School of Medicine, Pittsburgh, Pennsylvania, USA, and [4]Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh, Pittsburgh, Pennsylvania, USA

Background. Influenza activity in the 2020–2021 season was remarkably low, likely due to implementation of public health preventive measures such as social distancing, mask wearing, and school closure. With waning immunity, the impact of low influenza activity in the 2020–2021 season on the following season is unknown.

Methods. We built a multistrain compartmental model that captures immunity over multiple influenza seasons in the United States. Compared with the counterfactual case, where influenza activity remained at the normal level in 2020–2021, we estimated the change in the number of hospitalizations when the transmission rate was decreased by 20% in 2020–2021. We varied the level of vaccine uptake and effectiveness in 2021–2022. We measured the change in population immunity over time by varying the number of seasons with lowered influenza activity.

Results. With the lowered influenza activity in 2020–2021, the model estimated 102 000 (95% CI, 57 000–152 000) additional hospitalizations in 2021–2022, without changes in vaccine uptake and effectiveness. The estimated changes in hospitalizations varied depending on the level of vaccine uptake and effectiveness in the following year. Achieving a 50% increase in vaccine coverage was necessary to avert the expected increase in hospitalization in the next influenza season. If the low influenza activity were to continue over several seasons, population immunity would remain low during those seasons, with 48% of the population susceptible to influenza infection.

Conclusions. Our study projected a large compensatory influenza season in 2021–2022 due to a light season in 2020–2021. However, higher influenza vaccine uptake would reduce this projected increase in influenza.

Keywords. epidemic; influenza; mathematical model; vaccine.

In response to public health measures for preventing coronavirus disease 2019 (COVID-19) transmission including social distancing, school closure, and mask wearing, and due to reduced international travel, influenza activity was unprecedently low during the influenza season in 2020–2021 globally [1–3]. Because influenza virus is primarily transmitted through droplets, reduced in-person interactions and reduced emissions of virus-laden droplets due to COVID-19 nonpharmaceutical interventions can substantially decrease influenza transmission. In the United States, according to Centers for Disease Control and Prevention surveillance, the cumulative rate of influenza-associated hospitalization by May in 2021 was <4 per 100 000 [4]. In contrast, during the same period in 2020, the cumulative hospitalization rate had been 70 per 100 000. Total influenza-related deaths decreased by 95% in the 2020–2021 season, compared with the previous season.

Although low influenza activity resulted in fewer influenza-related hospitalizations and deaths in the 2020–2021 season, the potential impact on the subsequent season is unknown. Those who have never been infected with influenza before (normally infants and children) obtain their first immunity against influenza virus through maternal immunity during pregnancy, natural infection, or vaccination [5–8]. The obtained immunity can provide protection against a specific strain of influenza virus beyond the year of infection. During the season with low influenza activity in 2020–2021, the population missed the opportunity to establish or boost their immunity for the future influenza season.

The missed opportunities for enhanced immunity during a low influenza season raise concerns of a resurgence of influenza in the following season when public health measures are lifted and viral transmission resumes. As COVID-19 containment

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Correspondence: Kyueun Lee, MS, PhD, Public Health Building #7137, 130 De Soto St, Pittsburgh, PA 15261 (KEL171@pitt.edu).

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measures are relaxed around the world, cases of other respiratory viruses whose activity was suppressed under COVID-19 measures in 2020–2021 have started to make a resurgence. For example, epidemics of the respiratory syncytial virus (RSV) in children from Western Australia, which normally peak in June, began to increase after the county relaxed social distancing measures [9]. By the end of December 2020, the number of RSV cases was far higher than past seasonal peaks. Similarly, Hong Kong had an increased number of outbreaks of acute upper respiratory tract infection after reopening schools [10]. The study showed that the total number of school outbreaks involving >20 persons from late October to November 2020 was about 7 times the total number of outbreaks from 2017 to 2019. RSV cases began to rise in the United States in the summer of 2021, well ahead of the normal pattern [11]. However, the pattern and the severity of future outbreaks of respiratory viruses after relaxing COVID-19 measures depend on many factors including viral transmissibility, rate of waning immunity, vaccine uptake, and vaccine effectiveness.

A mathematical model that considers immunity over multiple years is required to estimate the burden of seasonal influenza as a consequence of low influenza activity in 2020–2021. Baker and colleagues used an epidemic model to estimate the impact of COVID-19 nonpharmaceutical interventions on the future dynamics of RSV and influenza in the United States [12]. However, the impact of countermeasures such as increasing the coverage and effectiveness of seasonal influenza vaccination on the future of the epidemic has not yet been evaluated. COVID-19 pandemic and public health measures may have affected the uptake of the influenza vaccine [13]. On the other hand, because vaccine composition is determined based on surveillance data, low influenza activity may prevent an accurate prediction of strains in the following season [14]. Hence, this study aimed to estimate the impact of low influenza activity in 2020–2021 on the population immunity and burden of influenza in the following season under various scenarios of vaccine uptake and effectiveness.

METHODS

Multiyear, Multistrain Seasonal Influenza Model

We built a non-age-structured susceptible-exposed-infected-recovered (SEIR) model that simulated influenza epidemics and consequent population immunity over multiple influenza seasons. We modeled the entire population without stratifying age because we are primarily interested in estimating the overall burden of flu epidemics and because of the computational complexities. We adapted the model structure developed by Hill et al. [15] and reproduced the model in R. In brief, the model simulates 4 main strains of influenza (H1N1, H3N2, B/Yamagata, B/Victoria) starting from 2009. We assumed a perfectly susceptible population in the beginning of the 2009–2010 season. After 2009–2010, the model links epidemiological outcomes in the prior season to the population immunity in the beginning of the "current" season. Exposure history in the past season such as infection with the same strain of influenza, infection with the other B lineage, or vaccination reduced the susceptibility to a specific strain of influenza in a subsequent season. We assumed that vaccine-induced immunity provides protection only for the year of vaccination [16]. Because there are not sufficient data on the duration of infection-induced immunity by substrain and clade in the modern era and given that natural infection stimulates stronger immune reaction than the vaccine, we assumed that infection-induced immunity lasts for 2 influenza seasons [17]. We provided details of the structure of the seasonal influenza model and implementation of immunity propagation in the model in Supplementary Appendix 1. Flu vaccine uptake rates and vaccine effectiveness from 2009–2010 to 2019–2020 in the United States are presented in Supplementary Tables 1 and 2, respectively.

Model Calibration

We conducted Bayesian calibration to estimate the uncertain model parameters related to immunity propagation. Calibration parameters include influenza virus transmissibility by strain (β_s), multipliers for the reduced susceptibility among those who have an exposure history of infection with the same strain and other B lineages (a, b). In addition, to compare the model's outcome with the observed influenza-related hospitalization rate, we estimated the proportion of total influenza cases that led to hospitalization (ε_y) by season. We set up the prior distribution of model parameters based on the mean of those parameters from another modeling study in the United Kingdom [15]. Given the difference in influenza transmission and population immunity between the 2 countries, we employed uniform distributions as a prior distribution and set the uncertainty range from 0.5 to 1.5 times the mean of the identified parameters. We describe the prior distribution of inferred parameters and the value of fixed parameters in Table 1.

As a calibration target, we compared the model's outcomes to the annual rate of influenza hospitalization from 2012–2013 to 2019–2020 in the United States [4, 18, 19] after simulating a burn-in period from 2009–2010 to 2011–2012. We elaborate the details of how we calculated the annual and strain-specific rate of hospitalization from the lab surveillance and total influenza-like illness data in Supplementary Table 3.

Because it was computationally expensive to repeatedly run an SEIR model over multiple seasons, we instead implemented a meta-model for model calibration. A meta-model describes the relationship between the simulation model's inputs (eg, transmission rates, duration of infectiveness) and outputs (eg, strain-specific rate of influenza hospitalization) [20]. Among many forms of meta-model, the artificial neural-network (ANN) meta-model works well when the output of an original model

Table 1. Model Parameters

Description	Notation	Prior	Posterior Mean [95% CI]
Inferred parameters			
Transmission rates for strain s	β_s	Uniform (0.27, 0.80)	
H1N1			0.425 [0.419–0.431]
H3N2			0.409 [0.403–0.415]
B/Yamagata			0.391 [0.387–0.396]
B/Victoria			0.388 [0.383–0.392]
Modified susceptibility given natural infection with the same strain in prior season (multiplier)	a	Uniform (0.5, 1)	0.725 [0.706–0.743]
Modified susceptibility given natural infection with type B influenza in prior season and consequent cross-reactivity (multiplier)	b	Uniform (0.5, 1)	0.683 [0.581–0.789]
Hospitalization rate in season y	ε_y	Uniform (0, 0.01)	
2012–2013			0.007 [0.006–0.008]
2013–2014			0.005 [0.004–0.006]
2014–2015			0.004 [0.003–0.005]
2015–2016			0.003 [0.002–0.004]
2016–2017			0.004 [0.004–0.005]
2017–2018			0.007 [0.006–0.008]
2018–2019			0.005 [0.004–0.006]
2019–2020			0.003[0.003–0.004]
Fixed parameters	Notation	Value	Reference
Duration latency for influenza A subtypes	$1/_A$	1.4 d	[15]
Duration latency for influenza B lineages	$1/_B$	0.6 d	[15]
Duration of infectivity	$1/\delta$	3.8 d	[15]
Proportion of vaccine effectiveness propagated to the next influenza season	k	0	Assumed
Time-varying parameters			
Monthly vaccine uptake rate	μ	Supplementary Table 1	[28]
Vaccine effectiveness in season y	e	Supplementary Table 2	[29]

is a nonlinear function of its inputs. This method of adopting the ANN meta-model for a complex simulation model is called BayCANN [21]. We trained an ANN meta-model using independent samples of inputs and corresponding outputs from the SEIR model and validated the trained ANN meta-model with the test data set. In Supplementary Appendix 2, we describe the methods and results of training and validating the ANN in detail. We then implemented the ANN framework within Stan, which is a probabilistic language that performs Hamiltonian Monte-Carlo Markov chains [22]. We evaluated the likelihood of the observed target data given a sampled input parameter to identify distribution of input parameters that can produce model outcomes close to the target. Details of implementing BayCANN with Bayesian calibration using Stan are demonstrated in Supplementary Appendix 3.

Examining the Change in Influenza Epidemics in 2021–2022 in Response to the Reduced Transmission in 2020–2021

We simulated lowered influenza activity by reducing the transmission rate by 10%, 15%, and 20% in 2020–2021 and examined the change in influenza epidemic in 2021–2022. We also estimated the number of influenza-related hospitalizations in the following season under different scenarios of vaccine uptake and effectiveness. In this scenario analysis, we assumed that public health measures to contain COVID-19 transmission reduced the influenza activity by 20% in 2020–2021, which produced a season close to the observed activity.

In the status quo scenario or "historic" scenario, we assumed as the counterfactual case that there had been no effect of public health measures on influenza activity in 2020–2021 and projected influenza epidemics in 2020–2021 and 2021–2022 with the historic influenza transmission rate. In the base case scenario, the influenza transmission rate was decreased by 20% in 2020–2021 and returned to the historic influenza transmission rate (0.425, 0.409, 0.391, 0.388 for H1N1, H3N2, B/Yamagata, B/Victoria, respectively) in 2021–2022. In both the historic and base case scenarios, we assumed that the vaccine uptake rate and effectiveness would be the average of these corresponding measures in the past influenza seasons from 2009–2010 to 2019–2020. Hence, by comparing the number of hospitalizations in 2021–2022 between 2 scenarios, we examined the expected increase in influenza-related hospitalizations in 2021–2022, after low influenza activity in 2020–2021 if there were no change in vaccine uptake rate or effectiveness in the 2021–2022 season. We further evaluated the sensitivity of the estimated increase in hospitalizations with varying levels of

vaccine uptake and effectiveness in the 2021–2022 season. We simulated influenza epidemics in 2021–2022 with 25% and 50% increased or decreased vaccine uptake and effectiveness from baseline (average of vaccine uptake and effectiveness in the past influenza season). We first varied 1 measure at a time while fixing the other variable at baseline. We then varied both variables simultaneously and measured the change in the number of hospitalizations compared with the historic scenario.

Examining the Change in Exposure History by the Number of Low Influenza Seasons

The ongoing COVID-19 pandemic may impose public health and social measures in the long term. We examined how the population's immunity would change if the low influenza season were to continue for 1, 2, or 3 years after 2020. In the beginning of influenza seasons in 2021, 2022, and 2023, we mapped the entire population into 4 groups based on their exposure history in the prior year: naïve, natural infection, vaccination, and both. The "naïve" group had no immunity because they did not have infection or vaccination in the prior season, whereas the "natural infection," "vaccination," and "both" groups indicated those who had exposure histories with infection, vaccination, or both, respectively, in the prior season.

RESULTS

Calibrated Seasonal Influenza Model

Bayesian calibration of the seasonal influenza model identified model parameters for which empirical data are insufficient (Table 1). The transmission rates of 4 influenza strains that were estimated in the historic influenza seasons in the United States ranged from 0.391 to 0.425. The estimated transmission rates for the subtype A lineages tend to be higher than the transmission rates of the B lineages. Calibration identified that infection with the same strain of influenza or the other B lineage in the prior season reduces susceptibility on average by 27.5% (95% CI, 25.7%–29.4%) and 31.7% (95% CI, 21.1%–41.9%) for the next season. In calibrations, we estimated the hospitalization rate among all influenza cases to be 0.3%–0.7% over the 2012–2013 to 2019–2020 seasons. Prior and posterior distributions of parameters are compared in Supplementary Figure 1. In model validation, the calibrated seasonal influenza model reproduced past epidemics; specifically, the model simulated the annual rate of flu hospitalization from 2012–2013 to 2019–2020 close to the corresponding data observed over the same time period (Supplementary Figure 2). The calibrated model also replicated the dominant influenza strain of each season (Supplementary Figure 3) and the seasonal peak (Supplementary Figure 4) in most historic influenza seasons.

Change in Influenza Epidemics in Response to the Reduced Transmission in 2020–2021

The lowered influenza activity in the 2020–2021 season leads to higher and earlier epidemic peaks in subsequent seasons, compared with normal influenza activity in 2020–2021 (Figure 1). With a 10% reduced transmission rate, we estimated the seasonal peak (defined as when the prevalence of infection is the highest) in 2021–2022 to be 0.017 on January 19, 2022. This is 10% higher and 5 days earlier than the estimated seasonal peak without the change in influenza activity (0.016). With the 15% and 20% reduced influenza activity in 2020–2021, the seasonal peaks in 2021–2022 increased by 19.7% and 37.7% and were 7 and 9 days earlier than the epidemics modeled with the historic influenza pattern.

Expected Increase in the Number of Influenza-Related Hospitalizations in the 2021–2022 Season

With lowered influenza activity in 2020–2021, the ensuing influenza season is expected to surge, with ~610 000 (95% CI, 500 000–728 000) hospitalizations if vaccine uptake and effectiveness remain stable (Figure 2A). This is 102 000 (95% CI, 57 000–152 000) more hospitalizations compared with the counterfactual case where influenza activity remained same as historic influenza seasons in 2020–2021. If the vaccine uptake rate in 2021–2022 decreased by 25% and 50% from the average rate in past influenza seasons, the model estimated the number of influenza hospitalizations in 2021–2022 to be as high as 709 000 (95% CI, 587 000–842 000) and 808 954 (95% CI, 680 000–950 000) hospitalizations, respectively. The number of hospitalizations in 2021–2022 could be lower if the vaccine uptake level were to reach higher than the average of past vaccine uptake levels. If the vaccine uptake level were 25% and 50% higher than in the prior seasons, the number of hospitalizations could decrease to 511 000 (95% CI, 428 000–600 000) and 402 000 (95% CI, 346 000–462 000), respectively. The result was very similar to the varying levels of vaccine efficacy in 2021–2022 (Figure 2B).

In the worst-case scenario, where both vaccine uptake and efficacy were half of the baseline values, our model projected an even greater increase in the number of hospitalizations in the next influenza season (409 000 additional hospitalizations; 95% CI, 337 000–490 000) (Figure 2C). Achieving a 50% increase in 1 of 2 measures (1.5X vaccine uptake with 1X vaccine efficacy or 1.5X vaccine efficacy with 1X vaccine uptake) was necessary to avert the expected increase in hospitalization in the next influenza season. Increases in both measures by 25% also averted the expected increase in influenza hospitalizations.

Change in Exposure History by Number of Influenza Seasons

Our model demonstrates that if the influenza seasons with low activity persistently recur, population immunity for influenza would remain low (Figure 3). If there had been no effect of the COVID-19 public health measures on influenza activity in 2020–2021 ("no COVID effect"), 75% of the population would have acquired immunity through infection, vaccination, or both in the beginning of the 2021–2022 season. The percentage

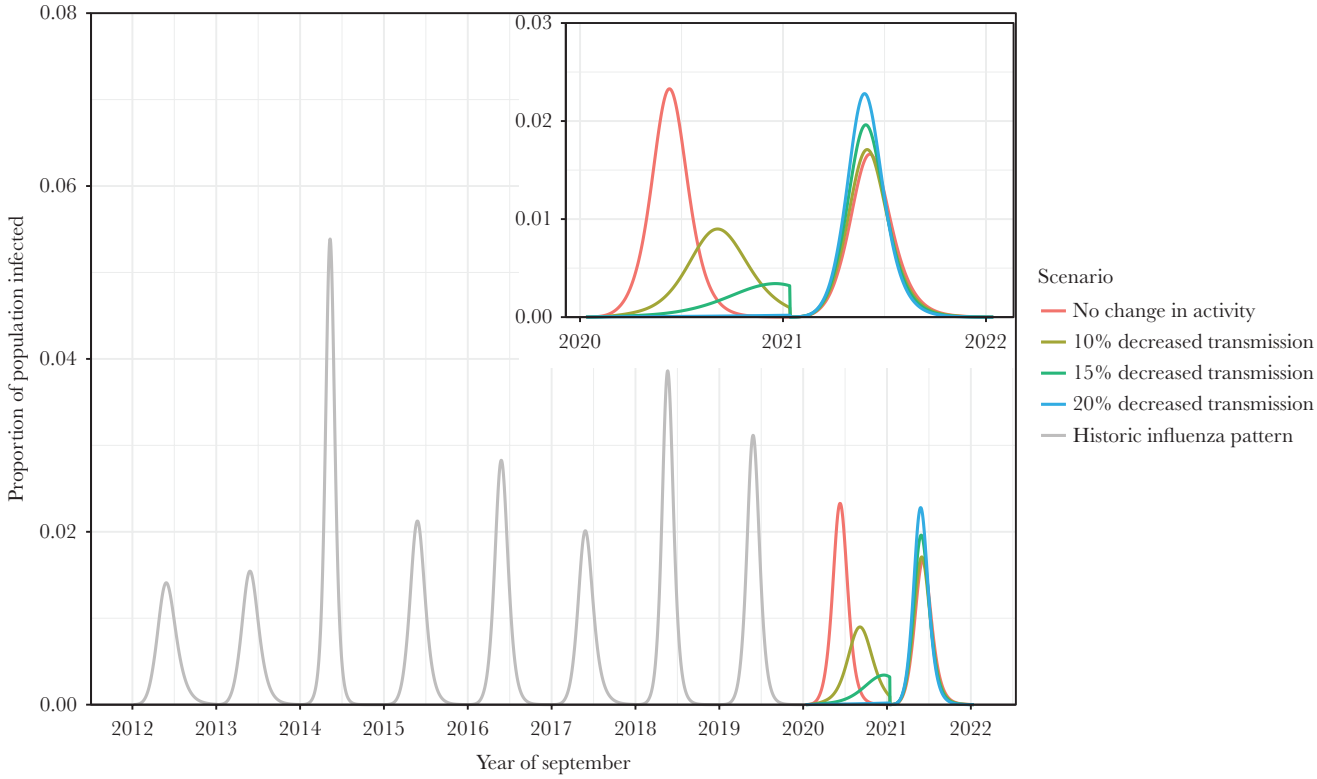

Figure 1. Change in influenza epidemics in response to the reduced transmission in 2020–2021. Influenza seasons from 2012 to 2020 were simulated using transmission rates that represent historic influenza patterns ("historic influenza pattern" in gray). The future influenza epidemics from 2020 to 2022 were simulated with the same transmission rates ("no COVID-19 effect" in red) or with 10% (olive), 15% (green), and 20% (blue) decreased transmission rates. Trends in 2020–2022 are zoomed in a window. Abbreviation: COVID-19, coronavirus disease 2019.

of the population that is immune to at least 1 strain of influenza remained high afterwards. On the other hand, if influenza activity was low in 2020–2021 ("1-year effect"), the percentage of the population with immunity would decrease to 52%, and the rest (48%) would have no immunity in the beginning of the following season. The decrease in population immunity was due to the decrease in natural infection in the prior season. As the number of years with lowered influenza activity increased ("2-year effect" and "3-year effect"), the population immunity remained low (52%), until influenza activity returned back to normal and the population obtained immunity through infection.

DISCUSSION

By using a seasonal influenza model that considers immunity propagated over multiple influenza seasons, we estimated the expected increase in the number of influenza-related hospitalizations when transmission returns to a typical level, given reduced residual immunity. Under the assumptions in this specific model, the model estimated 102 000 more hospitalizations, namely a 20% increase above the average number of hospitalizations in past influenza seasons. If both low vaccine uptake and vaccine effectiveness were to occur in the upcoming season, the model projected the increase to be as high as 400 000. While our study explored a specific scenario where flu activity is fully recovered in 2021, the possibility of a worse flu season in 2021 depends on many unknown factors including viral transmissibility with relaxed and ongoing social distancing measures, baseline population immunity to the strains that circulate, vaccine uptake, and vaccine effectiveness.

We also estimated that if the number of seasons with lowered influenza activity was extended, residual immunity in the population would decrease. If social distancing measures and school closure continue, and if influenza activity remains low for multiple seasons, then the susceptible population will accumulate over time, which could lead to a large outbreak in a subsequent season. In another modeling study, Baker and colleagues also found that longer periods of decreased infection are followed by higher and earlier epidemic peaks, due to the increase in susceptibility in the population [12].

Our study highlights the importance of increased influenza vaccination in order to prevent a major outbreak. Achieving a large 50% increase in either vaccine uptake or vaccine efficacy or a 25% increase in both measures was necessary to avert the expected increase in hospitalization in the next influenza season. During the COVID-19 pandemic, awareness of flu vaccination may have increased and people who have not received

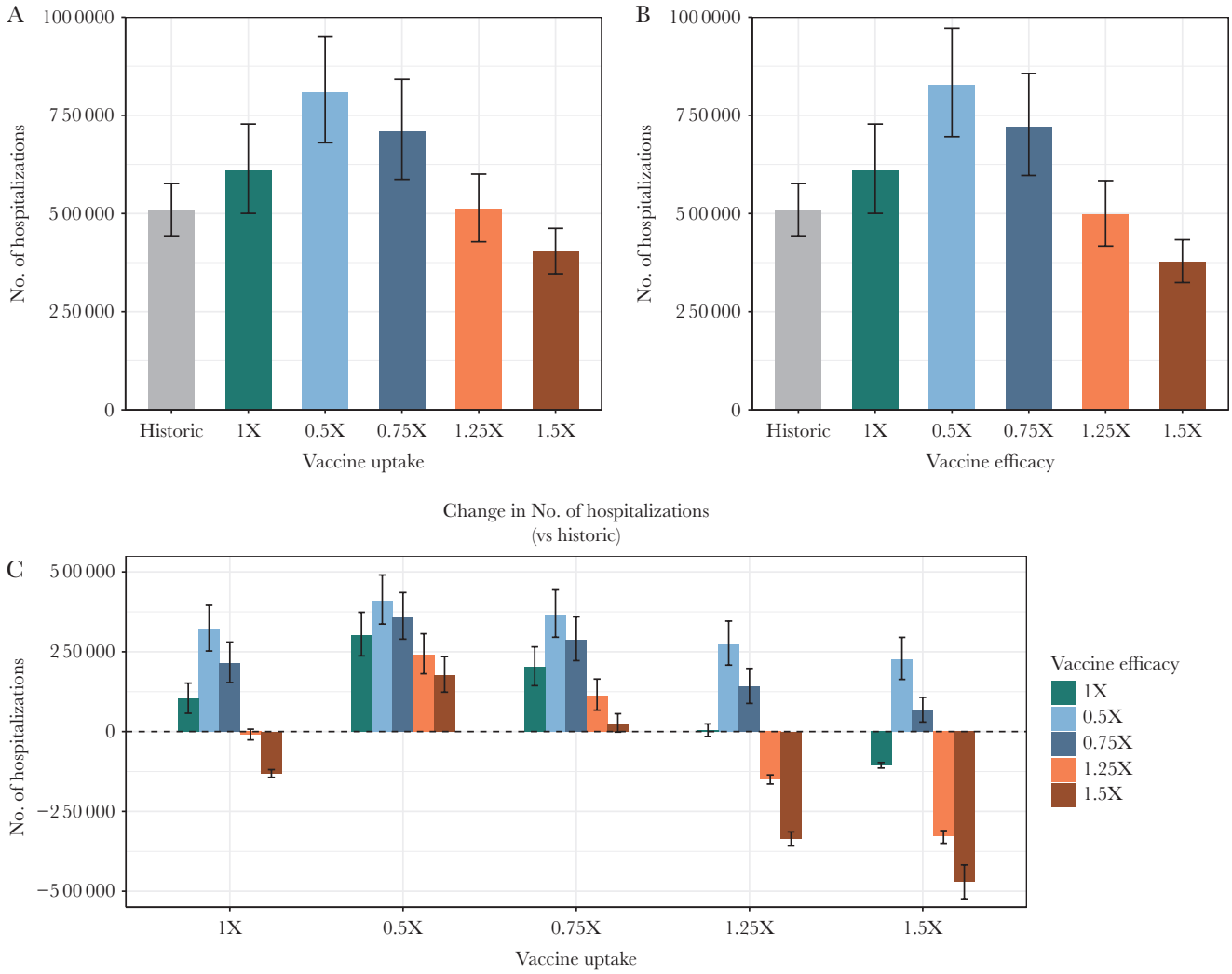

Figure 2. Expected increase in the number of influenza-related hospitalizations in the 2021–2022 season. "Historic" scenario is the status quo scenario where the influenza activity in 2020–2021 remained the same as the activity in the historic influenza seasons from 2012–2013 to 2019–2020. Other scenarios (0.5X–1.5X) assumed low influenza activity in 2020–2021 with varying levels of vaccine uptake and effectiveness. The label of those scenarios indicates the change in vaccine uptake or effectiveness in 2021–2022 from the baseline (defined as the average of measures in the past influenza seasons). A, The number of influenza-related hospitalizations in the 2021–2022 season with varying levels of vaccine uptake in the 2021–2022 season, while the level of vaccine efficacy remained at baseline. B, The number of influenza-related hospitalizations in the 2021–2022 season with varying levels of vaccine efficacy in the 2021–2022 season, while the levels of vaccine uptake remained at baseline. C, The expected increase in the number of hospitalizations with varying levels of vaccine uptake and efficacy, compared with the number of hospitalizations in the "historic" scenario.

the flu vaccine before may be more willing to receive the influenza vaccine this year [13]. Preparedness for the potential resurgence of respiratory diseases after COVID-19 measures are relaxed is important. If other infectious diseases whose activity was suppressed under COVID-19 measures resurge in the subsequent year simultaneously, along with the ongoing COVID-19 pandemic, this could overwhelm the capacity of the health care system.

This study has several limitations. We only considered immunity from infection to last 2 years. It is possible that immunity built through infection can last longer than 2 years [23]. Uncertainty in the duration of immunity can lead to a large variation in the estimated size of epidemics [24]. If infection-induced immunity lasts longer than 2 years, the estimated size of third and fourth seasons would be smaller than our estimates. On the other hand, the impact of low influenza activity would be extended beyond the following season, because the reduction in population immunity from infection can alter the susceptibility farther into future influenza seasons. In addition, our model made a simplifying assumption that the effectiveness of vaccination lasts only for 1 year. This parameter could have been inferred in model calibration. There are 2 reasons why this parameter was excluded in calibration: first, because the calibration problem becomes unidentifiable with too many uncertain parameters, given the scope of calibration targets, and second, because there was enough evidence on the shorter duration of vaccine-induced immunity compared with infection-induced immunity [16, 25]. Lastly, we modeled and estimated

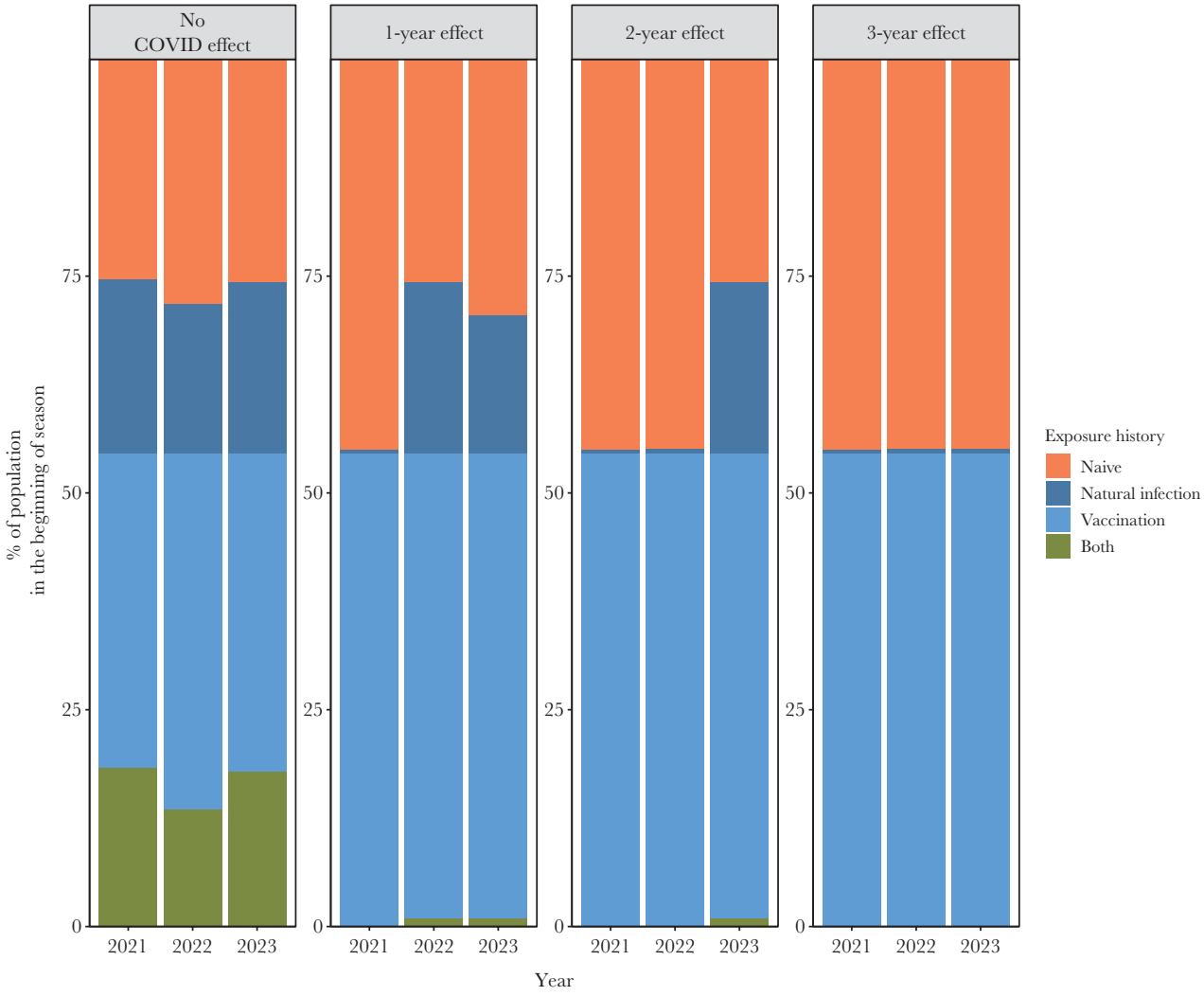

Figure 3. Change in exposure history by the number of influenza seasons with low activity. With no low influenza activity ("no COVID effect"), or 1 year, 2 years, or 3 years of low influenza activity since 2020–2021 ("1-year effect," "2-year effect," "3-year effect"), population immunity in the beginning of seasons starting from 2021 was mapped to 4 groups: naïve, natural infection, vaccination, and both. Abbreviation: COVID, coronavirus disease.

the overall burden of influenza epidemics without stratifying by different age or risk groups. Upcoming influenza epidemics could disproportionately affect subpopulations, with variation by age in waning immunity, risk behaviors, and access to health care. Future iterations of the model can be developed to provide age- or risk group–specific estimates of the expected increase in influenza hospitalizations in the following season.

The strengths of this study include both a multiyear evaluation and modeling multistrains; such a multiyear, multistrain model is an advance in the field over single-year or single-strain models. There are few studies in the current literature that have calibrated an influenza model against the observed epidemiological data in the United States [26, 27]. By combining an artificial neural network meta-model and a calibration technique, our study inferred uncertain model parameters relevant to viral transmission and immunity propagation that have driven the seasonal influenza epidemics for the past 11 years in the US population. Lastly, while the previous modeling study investigated the change in the patterns of future flu epidemics after implementing COVID-19 interventions in terms of the prevalence of infection over time, our projections of increases in the number of hospitalizations as a consequence of the low influenza activity in 2020 and its variability with vaccine coverage and effectiveness can provide valuable information for the preparedness for the upcoming influenza season [12].

Our study concludes that reduced influenza activity due to public health preventive measures in 1 season can result in a larger influenza epidemic in the following season if vaccination rates remain stable. Thus, higher influenza vaccine uptake is necessary to reduce the projected increase in burden of influenza in the second season due to reduced residual immunity from lack of seasonal infection in the first season.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

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Ethics approval. As all data used in this study were publicly available, ethics approval was not required.

Patient consent. Our study does not include factors necessitating patient consent.

Availability of data. All the data used for this analysis are publically available. Data from the Center for Disease Control and Prevention for influenza are available at https://www.cdc.gov/flu/index.htm.

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