Impact of Low Rates of Influenza on Next-Season Influenza Infections

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Introduction: Interventions to curb the spread of COVID-19 during the 2020−2021 influenza season essentially eliminated influenza during that season. Given waning antibody titers over time, future residual population immunity against influenza will be reduced. The implication for the subsequent 2021−2022 influenza season is unknown.

Methods: An agent-based model of influenza implemented in the Framework for Reconstructing Epidemiological Dynamics simulation platform was used to estimate cases and hospitalizations over 2 successive influenza seasons. The impact of reduced residual immunity owing to protective measures in the first season was estimated over varying levels of similarity (cross-immunity) between influenza strains over the seasons.

Results: When cross-immunity between first- and second-season strains was low, a decreased first season had limited impact on second-season cases. High levels of cross-immunity resulted in a greater impact on the second season. This impact was modified by the transmissibility of strains in the 2 seasons. The model estimated a possible increase of 13.52%−46.95% in cases relative to that in a normal season when strains have the same transmissibility and 40%−50% cross-immunity in a season after a very low one.

Conclusions: Given the light 2020−2021 influenza season, cases may increase by as much as 50% in 2021−2022, although the increase could be much less, depending on cross-immunity from past infection and transmissibility of strains. Enhanced vaccine coverage or continued interventions to reduce transmission could reduce this high season. Young children may have a higher risk in 2021−2022 owing to limited exposure to infection in the previous year.

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INTRODUCTION

Coronavirus disease 2019 (COVID-19) was declared a pandemic by the WHO on March 11, 2020. Cases were identified in the U.S. in early 2020, resulting in widespread interventions to reduce the spread of the virus, including school closure and measures to decrease social interactions. These interventions impacted not only COVID-19 transmission but also the transmission of other diseases that spread by the same mechanisms. Markedly decreased influenza activity was documented in many locations after the institution of COVID-19 interventions.[1−5] Little influenza activity was detected by the Centers for Disease Control and Prevention (CDC) in the U.S. during the 2020−2021 influenza season.[6]

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Previous-year vaccination is believed to provide little protection from subsequent-year influenza,[7] but natural infection appears to provide measurable immunity for several seasons, particularly if the circulating strains are close antigenic matches.[8] The limited number of influenza cases in the U.S. in 2020−2021 has raised concerns about the possibility of a higher burden of influenza illness in the 2021−2022 season owing to reduced immunity from previous-year natural infection. Children aged <2 years may be at increased risk after a season with limited influenza because they likely have never been exposed to natural infection and therefore have immunity only from vaccination.

Modeling has been applied to infectious diseases since the 1920s and is a well-established technique for analyzing and predicting influenza epidemics.[9] Historically, compartmental models were applied extensively to estimate values for the reproduction number in past epidemics and pandemics and to estimate the possible impact of interventions if applied to past and hypothetical future epidemics.[10−15] Agent-based and individual-based modeling of infectious diseases became more common when high-performance computing became available.[16−20] This type of model requires more computing resources but allows the setting of individual-based parameters and includes randomness so that a range of results are produced. Agent-based modeling can be used to perform highly detailed investigations of possible disease scenarios, for example, the effects of changes in strain transmissibility or the impact of vaccination.

The Framework for Reconstructing Epidemiologic Dynamics (FRED) simulation platform[21] is an agent-based modeling platform that was developed in response to the 2009 influenza pandemic and has been used for modeling influenza as well as other infectious and noninfectious conditions.[22−25] FRED models use census-based synthetic populations whose agents have realistic demographics, locations, and interaction patterns and rates, allowing for targeting of parameters by those factors. The FRED influenza model was formerly limited to simulating a single season. This study expands the pandemic model to include immunity from previous infection and from vaccination and to allow for modeling of multiple consecutive seasons of influenza. It therefore represents a novel expansion of modeling capabilities in this area and provides a starting point for more complex simulations.

To explore the impact of limited influenza activity on subsequent-year influenza burden, FRED was used to model 2-season influenza scenarios under a variety of assumptions on the impact of natural infection on second-year immunity and a variable degree of antigenic relatedness of first- and second-year circulating strains. Simulations estimated the impact of increased vaccination, continued interventions to reduce respiratory disease transmission, and the specific impact on the youngest age group in the population.

METHODS

The FRED simulation platform has been described in detail previously.[21] Details of simulations and the models used in this study as well as parameters used can be found in the Appendix (available online). A timeline is shown in Figure 1. FRED uses a transmissibility parameter to represent the infectious ability of a transmissible condition. The transmissibility parameter contributes to producing R_0 or R_e in a simulation. A higher transmissibility parameter will produce a larger outbreak if no other parameters in the model change. Simulations were run with a low transmissibility parameter value (0.6, R_0 ∼1.31, 95% CI=0.79, 1.83) and a high transmissibility parameter value (0.8, R_0 ∼1.75, 95% CI=1.13, 2.37). Base model results are included in Appendix Table 1 (available online).

Population

Simulations were performed on a population representing Allegheny County, a medium-sized county in the southwest of
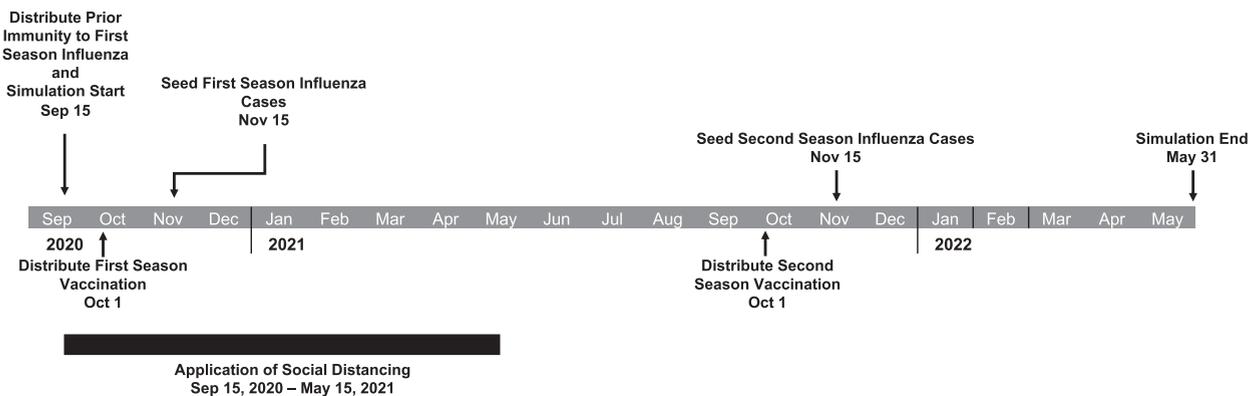
Figure 1. Timeline of influenza simulation.
Apr, April; Aug, August; Dec, December; Feb, February; Jan, January; Jul, July; Jun, June; Mar, March; Nov, November; Oct, October; Sep, September

Pennsylvania, with a population of approximately 1.2 million. It contains both urban and suburban areas and is large enough to capture the spread of influenza through a population. Simulations were performed with 100 repetitions to capture stochastic behavior.

Agents were immunized by age group as per CDC data using the following rates: age 0.5−17 years, probability=0.638; age 18−49 years, probability=0.384; age 50−64 years, probability=0.506; age ≥65 years, probability=0.698.[26] In the model, vaccination reduces susceptibility to influenza by 40% (vaccination efficacy in CDC studies ranges between 10% and 60%) (Appendix Table 2, available online).[27,28] Strain-specific vaccination occurs in October of the simulation year, and immunity wanes after vaccination at 7% per month.[29]

Immunity from previous infection was distributed by age group in the population using attack rates estimated by CDC for 2019−2020 (Appendix Table 2, available online).[30]

Reduced agent interactions at the population level were used to investigate the impact on second-season influenza cases. A simplified method of reducing contacts by isolating a proportion of agents in the simulation was used. Calibration runs with varied rates of isolation determined the percentage of the population needing to be isolated to prevent first-season influenza cases. Calibration results are in Appendix Section 7 (available online). The use of this method accomplishes the purpose of eliminating a first-season influenza epidemic. The method was not specifically focused on the impact of a particular social distancing intervention and does not address the nuances of various interventions (e. g., masking, work from home), which is not necessary for this study. Isolating 40% of the population was sufficient to reduce the first influenza epidemic to levels similar to those identified in the 2020−2021 influenza season (Appendix Section 7, available online, Model Validation Results). In 2-year simulations using the reduced interaction model, reductions were applied only in the first season. Additional simulations used a 40% reduction in the first season and lower levels of isolation (10% and 20%) in the second season.

To estimate the impact of increased vaccination, 1-year simulations with previous immunity were run with vaccination uptake by age group as reported by CDC and with 10% and 20% increases. Influenza vaccination levels as reported by CDC from 2010 to 2020 have increased by levels in the 10%−20% range.[31]

To orient the results to specific subtype/lineage scenarios in the modeled first and second influenza seasons, the level of reduction in susceptibility to infection by a subtype/lineage of influenza conferred by infection with the same or different subtype/lineage was estimated on the basis of discussions with experts in virology, influenza, and vaccination (Table 1). Support for expert opinion was identified in the literature.[32,33] These estimates represent the ranges of possible strain cross-immunity.

The University of Pittsburgh IRB determined that this study was not human subject research. It was therefore an exempt study design.

RESULTS

Model validation results are included in Appendix Section 7 (available online). In a 2-strain, 2-season model, normal first-season cases prevented second-season influenza cases and hospitalizations in all 4 transmissibility scenarios. A low first season would cause second-season case increases equal to the reductions caused by a normal first season. The impact varied by the transmissibility of the first- and second-year strains and by the similarity (cross-immunity) between those strains (Figure 2 and Appendix Table 4, available online). After waning, highly similar strains might have approximately 50%−60% cross-immunity (Table 1). Using 50% cross-immunity, if both season strains had lower transmissibility, the difference between second-season cases after a normal first season and a low first season was 26.29% (29.99% hospitalizations) (Figure 2A). A lower transmissibility strain in the first season had less impact on second-season cases when the second-season strain was more transmissible (difference of 3.83% cases and 4.31% hospitalizations) (Figure 2B). When the first-season strain had greater transmissibility than the second-season strain, there was a difference of 97.72% in cases (96.98% hospitalizations) (Figure 2C). When both the first-season and second-season strains were more transmissible, case difference in the second season was 49.47% for cases (56.81% hospitalizations) (Figure 2D). Higher transmissibility strains in the first season cause higher case numbers, contributing more to second-season immunity. When this immunity is removed, there is a larger increase in the second season. In the low transmissibility scenarios, R_e is approximately 1 in a model with previous immunity and vaccination;

Table 1. Theoretical Percent Cross-Immunity Between Influenza Subtypes/Lineages

Influenza subtype/lineage	Immunity to reinfection within the current year				Immunity to infection after 1-year waning[a]			
	H1N1	**H3N2**	**BYam**	**BVic**	**H1N1**	**H3N2**	**BYam**	**BVic**
H1N1	0.85–1.0	0	0	0	0.49–0.64	0	0	0
H3N2	0	0.65–1.0	0	0	0	0.29–0.64	0	0
BYam	0	0	0.90–1.0	0.40–0.60	0	0	0.54–0.64	0.04–0.24
BVic	0	0	0.40–0.60	0.90–1.0	0	0	0.04–0.24	0.54–0.64

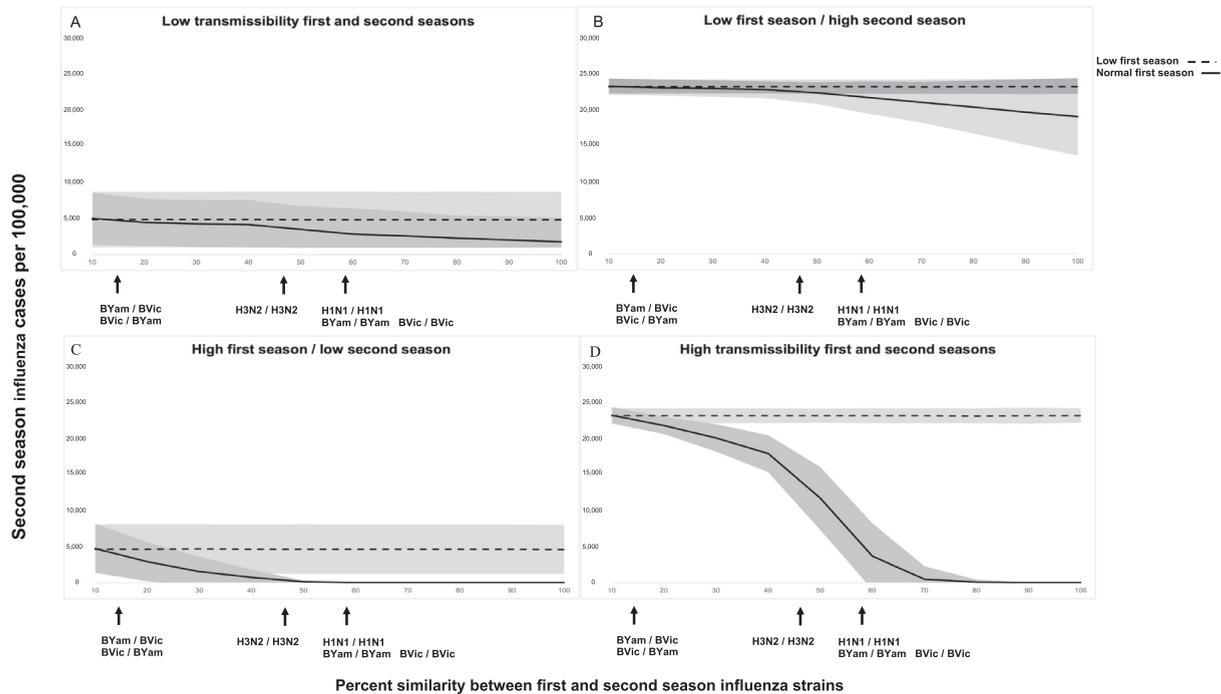[a]Waning is modeled at 3% per month, 36% between seasons.

Figure 2. Influence of cross-immunity between annual strains on second season influenza cases.

Note: Second-season cases per 100,000 are depicted by the burden of the first season (low versus normal) and by the amount of viral transmissibility (low versus high). x-axis is % cross-immunity between first- and second-year strains; y-axis is mean second season cases per 100,000. The *shaded area* represents 95% CIs of model results. *Arrows* indicate likely cross-immunity values for first-season/second-season strain pairs. For example, H1N1/H1N1 means that the first season and second season strains are both H1N1. The *dashed line* is second-season cases after a low first season. The *solid line* is second-season cases after a normal first season. The difference between *dashed* and *solid lines* indicates an increase in second-season cases when first-season cases are very low.

therefore, a greater impact of an intervention is not unexpected.

When agent interactions were reduced in the second season as well as in the first season (40% reduction first season), cases were reduced in the second season. Reduction of interactions by 20% in the second season resulted in a 98.6% reduction in cases (95% CI=98.5, 98.7) for the low transmissibility scenario and 85.3% reduction (95% CI=84.8, 85.8) for the high transmissibility scenario. Reduction of interactions by 10% resulted in a 68.6% reduction in cases (95% CI=67.7, 69.4) for the low transmissibility scenario and 32.1% reduction (95% CI=30.4, 33.9) for the high transmissibility scenario.

Increasing vaccination rates above those reported by CDC by 10% and 20% decreased the number of cases and hospitalizations in a single-season simulation. Increased vaccination rates had a greater impact on simulations with a lower transmissibility strain (10% increase in vaccination caused a 31.5% decrease in cases and 32.9% decrease in hospitalizations; 20% increase in vaccination caused a 45.5% decrease in cases and 47.4% decrease in hospitalizations). For simulations with a more transmissible strain, increased vaccination resulted

in a more modest effect (10% increase in vaccination caused a 2.3% decrease in cases and 3.3% decrease in hospitalizations; 20% increase in vaccination caused a 5.0% decrease in cases and 8.5% decrease in hospitalizations). In the low transmissibility scenario, increased vaccination rates may have a greater impact owing to vaccination levels reducing the reproduction number in that model to approximately 1 (R_e=0.93, 95% CI=0.57, 1.30 in a model including previous immunity and vaccination at CDC-reported rates). Relatively low vaccination effectiveness in this model (40%) may decrease the impact of vaccination in a high transmissibility scenario. Single-year simulations include previous immunity, as described in Methods and Appendix (available online).

The age group 0−4 years comprised 5.2% of the simulation population and accounted for approximately 6% of cases in the simulation (5.8%−6.2% of cases). Increasing vaccination coverage by 10% decreased cases in this age group by 31.7% in the lower transmissibility scenario but only 1.7% in a higher transmissibility scenario (Figure 3). A 20% increase in vaccination coverage resulted in 45.7% fewer cases for a lower transmissibility strain but only 4.1% fewer cases for a more transmissible
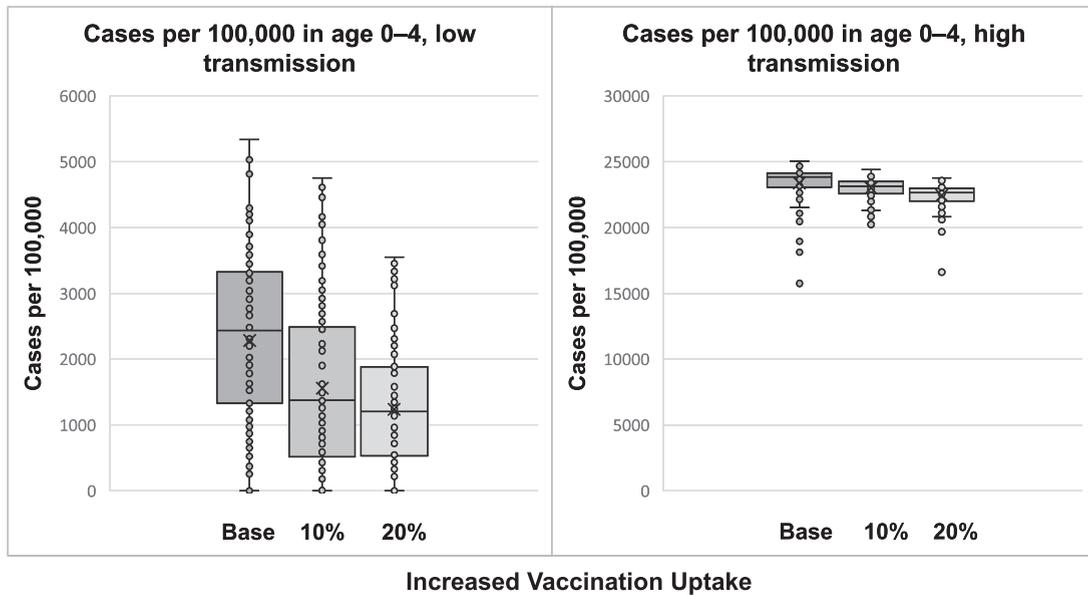
Figure 3. Change in total infections per 100,000 children aged 0−4 years with an increase in vaccination coverage rate in a single season simulation.

Note: Base vaccination from reported rates. Coverage rates were increased by 10% and 20%. A proportion of agents had immunity at the start of the simulation to reflect immunity from previous-year infection, as described in Methods and Appendix (available online).

strain. Hospitalizations decreased by similar amounts (for the low transmissibility scenario, 33.7% decrease with 10% uptake increase and 49.0% with 20% increase; for the high transmissibility scenario, 3.1% decrease with 10% uptake increase and 5.4% decrease with 20% increase). Low R_e may enhance the effects of vaccination in the low transmissibility scenarios.

Applying model results specifically to influenza subtypes/lineages, the greatest impacts would be expected for seasons in which the current predominant strain was closely related to the previous-year strain, and cross-immunity is generally high between strains in succeeding years. A 40%−50% reduction in susceptibility could be expected for similar strains in succeeding years in cases where strains share subtype/lineage. Strain transmissibility would be expected to be similar in highly similar strains. The model estimated an increase of 13.52% −46.95% in cases and 15.43%−56.81% in hospitalizations in strains with the same transmissibility and 40% −50% cross-immunity (Appendix Table 4, available online). In the population used for simulation (Allegheny County, PA, synthetic population of 1,218,695) these values correspond to an increase of 8,225 (95% CI=2,241, 14,209) to 139,205 (95% CI=98,836, 179,575) cases and 31 (95% CI=10, 53) to 369 (95% CI=610, 982) hospitalizations over the influenza season. Cases numbers include asymptomatic cases, which make up 25% of those occurring in the model.

DISCUSSION

Agent-based modeling was used to predict the impact of a light influenza season on infection rates in the following season. Results indicate that a light first season (such as 2020−2021) could result in a large, compensatory second season (such as what might occur in 2021−2022). This increase could be as large as a doubling of cases. Enhanced vaccine coverage could reduce but not eliminate this predicted severe season. Continuation of interventions to reduce infectious contacts in the population could have a larger impact.

Influenza immunity is complex. Strains are highly variable, with genetic drift antigens contributing to emergence of new variants that escape immunity and enable yearly seasonal outbreaks with widely varying case rates despite population immunity and vaccination.[34] Subtype switching of the predominant circulating strain is not consistently correlated with increases in infection rates.[35]

The northern hemisphere 2020−2021 season lacked the usual seasonal outbreak, likely because of COVID-19 interventions to reduce transmission. That outcome was beneficial because healthcare systems were already strained by the COVID-19 pandemic, but there is concern that the lack of residual immunity resulting from infection in 2020−2021 will cause a more severe influenza season in 2021−2022. Vaccination is an effective tool to prevent influenza, but vaccination rates are

typically suboptimal, and vaccination does not confer complete immunity to infection.

An agent-based model of influenza was used to help in understanding the impact of a very low influenza season on the succeeding season. Reductions in interactions in a proportion of the population were sufficient to essentially eliminate influenza. Normal interaction levels in a second season caused an increase in second-season cases beyond what was predicted using the same model with no first-year reduction in interactions.

The model accounts for situations in which highly related and less related strains circulate in successive seasons. With a low level of cross-immunity, similar to an influenza A subtype switch, a low first season has limited impact on second-season cases. If there is a good antigenic match between seasons (high level of cross-immunity), the model predicts a large impact on second-season cases from first-season infections.

Increased vaccination could help offset the reduced population immunity resulting from the lack of influenza in 2020−2021. This could be particularly important for young children, who may be especially at risk in 2021−2022. Very few very young children had influenza in 2020−2021, so essentially all immunity in that age group would be from vaccination, which wanes relatively quickly.

Several factors suggest that although cases may increase after a very low first season, disease burden will not reach pandemic levels. The most prevalent influenza subtype often switches from one season to the next—for example, H1N1 predominated in the 2013−2014 season, whereas H3N2 predominated in the 2 preceding seasons — and these influenza subtype switches do not always cause increased intensity.[36] Immunity owing to infection is believed to persist for 3−7 years, so substantial immunity can be expected to remain from previous seasons.[8] Immunity from exposure to infection early in life is believed to confer a level of lifetime immunity to related strains, possibly including some immunity to conserved epitopes,[37] and this could assist in limiting 2021−2022 influenza case rates.

Models are simplified representations of reality and therefore can never be perfect. Their intent is simply to provide useful and actionable information. The validity of a model is determined in part by how closely its design reflects reality and how accurately the parameters it uses are estimated. The FRED influenza model was designed to simulate pandemic influenza and has been used in previous studies to model influenza interventions, so model validity has been assessed in the past.[21][−23] The model now includes previous immunity in the first season and residual immunity from first-season infection in the second season and can be expanded to include an arbitrary number of seasons.

Limitations

Reliable and appropriate sources were used for parameter estimation; however, there are limitations on those estimates. Previous immunity is based on a CDC-modeled disease burden estimate,[29] which may be affected by fluctuations in disease reporting because of a variety of factors. Vaccination efficacy is estimated from surveillance data and may be an overestimate or underestimate. The parameters for the waning of both natural and vaccine immunity are based on the literature and expert opinion. Cross-immunity between strains of influenza is most difficult to quantitate when the strains differ by antigenic drift only, and this is a major source of uncertainty. The model uses a range of values to account for this uncertainty. Parameter uncertainty can cause model results to be higher or lower than what would be encountered in reality.

Transmission in this model is caused by the interaction of agents, specifically the geographic proximity of infectious and susceptible agents, simulating respiratory transmission. There is no inclusion of fomites or other nonrespiratory modes of transmission. Rates of interaction between agents are age dependent and were calibrated to match data from influenza studies.[21]

This set of simulations was designed to address a specific problem concerning the possible impact of loss of immunity because of a low influenza season on the following season. It assumes that the second season will behave as a normal influenza season, having no additional interventions. Additional simulations were performed to assess the impact of possible continued interventions and pandemic-induced changes in behavior on transmission. Other circumstances may also impact the 2021−2022 season. Low levels of circulating influenza worldwide and in the Southern Hemisphere may limit the seasonal introduction of influenza to the U.S., thereby limiting the season. The low level of influenza circulation since March 2020 may have limited influenza evolution in the interim; however, the circulation of influenza in animal hosts also provides the potential for the development and introduction of novel strains. These additional scenarios have not been modeled specifically. Model results must be interpreted in the context of model design, uncertainty in model parameters, and limitations of modeling in general.

CONCLUSIONS

Given the light 2020−2021 influenza season, the 2021−2022 season may see increased case rates of up to 50%, depending on cross-immunity from past infection and transmissibility of strains. Enhanced vaccine coverage as well as continued interventions and behaviors that

decrease population interactions could reduce this high season. Vaccination in the very young may be particularly important in 2021−2022, given the lack of immunity from previous infections in that age group.

ACKNOWLEDGMENTS

CREDIT AUTHOR STATEMENT

SUPPLEMENTAL MATERIAL

Supplemental materials associated with this article can be found in the online version at https://doi.org/10.1016/j.amepre.2021.11.007.

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