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Increasing child vaccination coverage can reduce influenza cases across age groups: An agent-based modeling study

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Abstract

Objectives: Availability of caregiver-administered nasal spray live attenuated influenza vaccine (LAIV) raises the potential for increased influenza vaccine uptake. Direct and indirect benefits (decreased influenza cases and hospitalizations) of increased uptake among school-age children may be realized across the age spectrum. We used an agent-based model to determine the extent to which increased vaccination of children might affect overall influenza epidemiology.

Methods: The Framework for Reproducing Epidemiological Dynamics (FRED) uses a population based on the US census and accounts for individual characteristics to estimate the effect of changes in parameters including vaccine uptake, on outcomes. We modeled increases in vaccine uptake among school-age children 5–17 years old on influenza cases and hospitalizations by age group.

Results: Increasing vaccination rates in school-aged children by 5%–15% decreased their symptomatic influenza cases by 3.2%–10.9%, and among all age groups by 3.3%–11.6%, corresponding to an estimated annual reduction in cases of 522,867–1,810,170 among school-age children and of 1,394,687–4,945,952 overall. Annual U.S. hospitalizations could decrease by as much as 49,977, with the greatest impact (23,258) in those ages 65 years and over.

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Human participant protection statement

The University of Pittsburgh Institutional Review Board determined that this study was not human subject research.

Conclusions: The opportunity to increase vaccination coverage in school-age children using LAIV can have a positive impact across all ages.

Keywords

Influenza; Human; Vaccination; Disease transmission; Infectious; Epidemiological models; School age population

Introduction

Annual influenza vaccination is recommended for everyone age 6 months and older in the U.S. to reduce influenza infections, medical visits, hospitalizations and deaths in children and adults.¹⁻⁴ Children have the highest annual influenza attack rate,⁵ are believed to play a leading role in influenza transmission,⁶ and severe illness in children is not uncommon. For example, during the 2022–23 and 2023–24 influenza seasons, influenza-associated pediatric hospitalizations reached their highest rates in over a decade (82.5 and 86.5 per 100/000 in respective seasons in ages 0–4 years).⁷ In 2023–24, 199 children died from influenza matching the high reached in 2019–20.⁸ Many of these recent deaths occurred in children who were not fully vaccinated.⁸

In addition to reducing hospitalizations and deaths in children, influenza vaccination of children may provide benefits related to herd immunity, thereby protecting other vulnerable groups, specifically high-risk adults and those age 65 years and over.^{9,10} Vaccination of young children has been associated with reducing influenza infections, primary care visits, and hospitalizations in unvaccinated adults.¹¹⁻¹⁴ A U.S.-based program specifically focused on vaccinating school children in Texas using LAIV was associated with direct and indirect protection from symptomatic influenza infections in children and adults,¹⁵ and medically attended acute respiratory illness among adults in the community.¹⁶ In Japan, a successful mandatory vaccination program for school children prevented 1 death for every 420 children vaccinated, and when this program was stopped, excess mortality from influenza began to rise.¹⁷ More recently in England, vaccine programs with LAIV targeting healthy children have reduced influenza-related illness across the population.^{13,14} Thus, vaccinating children against influenza has broad effects and maximizing vaccine coverage (VC) in this age group would be expected to have significant public health impact.

U.S. influenza VC of children under age 2 years approaches 70%, but rates progressively decline with age of the child.¹⁸ Parental hesitancy regarding influenza vaccination in the U.S. (25.8%) is higher than for other childhood vaccinations (6.1%),¹⁹ and is reflected in declining influenza VC in children since the COVID-19 pandemic.^{18,20,21} There are several other potential barriers to influenza vaccination among children including needle phobia²² and lack of convenient access.²³ For example, the influenza vaccination season occurs largely during the school year, with most child influenza vaccinations occurring in a doctor's office, health center, or pharmacy, that are primarily open for vaccination services during the school or workday.²⁰ Thus, in many cases, influenza vaccination would require missing school and/or parental work time. Recently, the U.S. Food and Drug Administration (FDA) approved self- (ages 18–49 years) or caregiver (ages 2–17 years) administration of LAIV,

which is estimated to be available as soon as 2025.²⁴ This change in policy means that parents could administer influenza vaccine at a time more convenient to them, there is no needle involved and there is the potential for mass vaccination clinics to be held on-site at schools. Administration of LAIV outside of a healthcare setting offers an opportunity to increase influenza VC.

The purpose of this study was to determine the potential impact of increased options for LAIV availability assuming that it results in increased VC in school-age children. We used an agent-based model, the Framework for Reconstructing Epidemiological Dynamics (FRED) to estimate the effect on symptomatic influenza cases and hospitalizations in all ages, but especially children and older adults. Because efforts to increase VC in children would require efforts of parents and possibly schools, secondary outcomes of reductions of missed days of school for children²⁵ and missed days of work for caregivers²⁶ were also considered. We also explored the impact of a slight increase in vaccine effectiveness (VE) in school-age children that might be expected by the change from quadrivalent to trivalent influenza vaccine for the 2024–2025 season. Historically, quadrivalent LAIV (LAIV4) was reformulated after it was found to have lower VE than trivalent LAIV (LAIV3) and data suggest that LAIV3 may in some cases be more effective than trivalent injected inactivated influenza vaccine (IIV).^{27,28}

Methods

FRED has been used to model influenza and other diseases and conditions as described in detail previously.^{29–40} In FRED, diseases such as influenza are defined as a series of health states (susceptible, exposed, infected, recovered) through which individuals can progress based on probabilities and time periods to evaluate health state changes. This study used a modified Susceptible-Exposed-Infectious-Recovered (SEIR) model to describe influenza (Fig. 1),^{31,37,40} with transmission parameters defined in Appendix Table 1. The susceptible state for each individual agent incorporated immunity from prior season's infection, current season vaccination, and waning of immunity. Agents were assigned a susceptibility of 1 across all age groups, which was correspondingly reduced based on immunity from prior influenza infection or seasonal vaccination. To capture immunity from prior year infections on simulation start, agents in the model were randomly assigned 50% immunity to influenza at age-specific rates based on CDC-reported influenza infections for the 2019–20 season, as previously described.^{37,40,41} The exposed state represented a latent period for infection. Within the infected state, symptomatic (Is) and asymptomatic (Ia) states incorporated agent level of infectiousness and behaviors related to staying home (i.e., not interacting with other agents at schools, workplaces, or neighborhoods). A 24-hour Pre-symptomatic (Ps) state during which agents continued their daily activities and were fully infectious preceded the Is state. Agents moved from the Ps to the Is, in which they remained fully infectious, and half of these agents stayed home. Agents in the Ia state represented a milder form of infection, were half as infectious as the Ps and Is states, and continued their usual interactions (school, workplace, neighborhood). The model was calibrated to CDC estimates of 2019–20 age-specific rates of symptomatic influenza illnesses as previously described.⁴⁰ Age-specific hospitalization was assigned by CDC estimates of 2019–20 hospitalizations relative to estimated illness rates.⁴¹

The base model simulated age-based influenza VC per CDC 2021–22 reporting, including four age categories for children (Table 1),²⁰ chosen because they were the most recent data available at the time of analysis. (April 2023 through September 2024). Within age groups, agents were randomly assigned vaccination and received one influenza vaccine dose beginning September 1 over a mean vaccination season of 45 ± 14 days. Baseline VE was set at 40% [i.e., a 40% reduction in susceptibility to infection, based on reported VE in 2004–05 to 2019–20 seasons⁴²] for all ages beginning two weeks after vaccination. Waning of vaccine protection was set at 7% per month for ages < 65 years and 10% per month for ages ≥ 65 years.^{43,44}

A single influenza season was modeled from August 15 through May 31 and was started by seeding 50 symptomatic cases (a standard seeding size within FRED for similar sized populations) into the population on October 15, resulting in mid-February peak cases. The reproduction number, or number of secondary cases per infection, was not fixed but was a product of the model's transmissibility parameter, the characteristics of the infection (e.g., infectious period) and the characteristics of the population, such as prior immunity level, age structure, and vaccination-induced immunity. The effective reproductive rate across models was 1.26 ± 0.19 (Mean $\pm$ SD). The simulation included a single strain of influenza, similar to type A(H1N1). To reproduce the seasonal timing of influenza,⁴⁵ a seasonal transmissibility parameter that depends on how far the current day is from the winter solstice was included.⁴⁶ This seasonal transmissibility parameter is intended to account for factors that may influence transmissibility across a range of seasons due to variability in factors such as temperature, humidity, and changes in contact rates.⁴⁷

For this study, FRED tracked the urban and suburban population of Allegheny County, PA for which age-based calibrations for symptomatic influenza cases have been previously reported.⁴⁰ The Allegheny County population distribution by age is comparable to the 2020 US population (Appendix Table 2), and model results were extrapolated to the US population.⁴⁸ Because FRED models are stochastic, each model was run 100 times per scenario to produce mean values.

Corresponding estimates of potentially prevented school and work absenteeism due to increased VC were estimated as follows: 1) School absenteeism estimates were based on 1 to 2.5 missed school days for each symptomatic illness in children,^{25,49} if absenteeism is limited to the approximately half of symptomatic school-age children who were to seek medical care⁴¹; 2) Work absenteeism estimates were based on 50% of symptomatic school-age children requiring a caregiver to miss 1–2 days of work.²⁶

The Institutional Review Board determined that this study was not human subject research.

Results

Increased vaccination coverage in children

The benefits of increased vaccine coverage in school-age children only, assuming moderate VE of 40% (Table 2a) resulted in a reduction in symptomatic influenza cases in that age group by 956 cases per 100,000, representing a 3.2% overall decrease in cases. The benefit

of reduced cases extended beyond the school-age children to all other age groups. Preschool children ages 0–4 years had 522 fewer cases per 100,000 (3.1% decrease). Adults aged 65 and older had the lowest overall reduction in symptomatic cases (121 per 100,000), but this represented the largest percentage reduction in cases (3.7%). The low number of hospitalizations due to influenza precluded age-group analyses, but overall hospitalizations declined by 3.4% as a result of a 5% increase in VC among school-age children. As VC in school-age children was increased by 10% and by 15%, cases and hospitalizations declined proportionally.

We then extrapolated these rates of averted cases and hospitalizations to the entire U.S. population by age group (Fig. 2, solid fill). At all levels of increased VC among school-age children, averted cases were highest among those ages 5–17 and 18–49 years; whereas, averted hospitalizations were highest among those ≥ 65 years old.

Extrapolation to missed days of school for children and days of work for adults

Increasing VC of school-age children by 5% reduces symptomatic influenza cases by 522,867. Assuming that half of children with symptomatic influenza (261,434) miss 1 to 2.5 days of school, this small increase in VC would reduce missed school days by 261,434 to 653,585 for the US population, corresponding to 52,287 to 130,717 missed 5-day weeks of school. If half of symptomatic school age children who miss school (130,716) require a parent to miss 1–2 days of work to care for them, 130,716 to 261,434 missed workdays would be prevented with a 5% increase in VC. (Data not shown.).

Increased vaccine effectiveness

The next series of analyses explored the impact of a small, 5% increase in VE as might occur by the change in formulation of LAIV from quadrivalent (LAIV4) to trivalent (LAIV3) vaccine. This change in VE was applied to school-age children only because it is this age group whose VC is assumed to increase with use of LAIV. VE is assumed to be unchanged in other age groups. Without a change in VC in children ages 5–17 years, an increased VE to 45% resulted in 2265 per 100,000 fewer symptomatic cases (7.5%) within this age group (Table 2b). This increase in VE resulted in 7.3% fewer cases of influenza across all age groups with the largest reduction of cases observed among people ≥ 65 years. Progressive increases in VC in school-age children (5%, 10%, 15%) assuming 45% VE in this group resulted in additional reductions in symptomatic cases in all age groups ranging from 4.9% to as high as 17.2%.

Discussion

Agent-based modeling was used to predict the impact of increased influenza VC in school age children, a group that may potentially benefit from the enhanced availability of LAIV for caregiver administration. Results indicate that a modest increase in VC of 5% could reduce symptomatic influenza cases not only in the LAIV recipient group, but that all age groups could benefit, especially the most vulnerable age groups of preschool children and adults aged 65 years and older. This additional protection is noteworthy because VC in these groups is already approaching the Healthy People 2030 goal of 70% and unlikely

to increase further.⁵⁰ Depending on the level of increased vaccination coverage attained, increased effectiveness translates into a reduction of millions of US influenza cases and tens of thousands fewer hospitalizations in a season of moderate severity, as presented herein.

In the US, a randomized control trial of over 12,000 students in grades kindergarten through 5 (approximate ages 5–11 years) in Western New York over a period of two years showed that influenza VC was 6–16% higher when influenza vaccinations were offered by schools, with the odds of vaccination being 50%–60% higher for students in schools with influenza vaccination programs.⁵¹ Intranasal influenza vaccines and H1N1 pandemic response vaccines have been the primary influenza vaccines administered through school programs in published reports, with higher VC achieved in elementary compared to high school students.⁵² Logistics of such programs include obtaining parental consent as well as insurance coverage if vaccine is not provided free of charge by an outside source (e.g., local health department). Benefits are 1) that loss of class time to receive a vaccine has been reported to be only 10 min; and 2) faculty and staff in some cases have been able to receive influenza vaccination from school-located programs.⁵² A more recent school-located influenza vaccination program in Oakland, California showed that increased VC varied by race. In intervention districts where all students were eligible to be vaccinated regardless of their insurance status, the impact on increased vaccination coverage was highest among White students (21.0%) and lowest among Black students (5.9%).⁵³ In addition, fewer all-age and older adult influenza hospitalizations were observed in some years in the intervention districts.⁵³ The differences in raced-based impact in this study suggest that additional measures to address vaccine hesitancy are needed to provide equitable improvements in vaccine coverage.

Several aspects of LAIV use in school-age children may be leveraged to compound its benefits. The nasal, needle-free route of administration may improve acceptance of influenza vaccine among children who are averse to receiving shots, with fear of needles serving as a primary reason for an estimated 8% of vaccine non-compliance.²² Secondly, the availability of self- and caregiver administration provides more convenient access to the vaccine for parents and opens the possibility of school-based vaccination clinics, thereby reducing a common barrier to vaccine uptake. School-based influenza vaccination offering only LAIV has been successfully used in the UK since 2013,⁵⁴ and pilot areas for ages 5–11 years achieved VC of 57.9% (range 43.6–72.0%).¹³ Thirdly, if trivalent LAIV is more effective than quadrivalent LAIV, the potential impact of both increased VE and VC is huge. We have shown that substantial public health benefits i.e., reduced influenza cases, could result from a 5% higher VE combined with a 5% increase in VC, with proportionally higher benefits as VC is increased.

The costs of influenza include both the direct costs of medical visits, over-the-counter and prescription medications, hospitalizations and death, and hidden costs such as missed school days for children and workdays for parents who stay home to care for them. Influenza is the number one cause of school absenteeism,²⁵ and children with respiratory illnesses miss an average of 1–2.5 days of school, with 53% of families requiring an adult to miss work to care for the ill child.^{25,26,49} Our numbers may underestimate the potential benefit of increased vaccination, as we assumed only half of symptomatic children stayed

home. The high influenza attack rate among children⁶ coupled with higher rates of viral shedding found in children,^{55,56} and the fact that many symptomatic children continue to attend school,⁵⁷ makes school-age children an ideal target for increasing influenza vaccine uptake through LAIV campaigns. School-located vaccination in the US can result in higher vaccination coverage, decreased laboratory-confirmed influenza, lower influenza hospitalization rates, provide indirect protection in unvaccinated children, and improve school attendance.^{53,58} Thus, increasing VC among school-age children has significant benefits.

The primary models presented assume VE would remain consistent if VC were increased, due to increased availability of LAIV3 for children. LAIV3 was first released in 2003,⁵⁹ and because LAIV3 VE may be higher in children than IIV3 VE^{27,28} a modest increase in VE of 5% in school age children was also considered. Even without a change in VC, a modest increase in VE reduced cases and hospitalizations in all age groups. However, VE varies annually and the VE of future LAIV3 formulations has yet to be determined. LAIV4 was not recommended for use in the 2016–17 and 2017–18 seasons, based on lower LAIV4 VE in the U.S. against A/H1N1pdm09 in 2013–14 compared to IIV, corresponding to the year that LAIV3 became quadrivalent. It should be noted that LAIV4 VE estimates in 2013–14 in other countries were comparable to previous seasons and markedly higher than those observed in the U.S.⁵⁹

A potential limitation of this study is that modeling results were based on the Allegheny County population representing a single season and influenza strain and then extrapolated to the US population. The actual impact of increased vaccination in a given season may be influenced by additional factors including the circulating influenza strain, the extent to which a seasonal vaccine matches the circulating strain(s), and the age distribution of the population. We present model output as symptomatic cases and hospitalizations calibrated to CDC estimates.^{41,60} In our model, the symptomatic state is included in the infectious state which comprises presymptomatic, symptomatic, and asymptomatic states. These states represent ranges of behavioral actions such as staying home (50% of symptomatic agents) and transmissibility (50% less infectious if asymptomatic) that served as the basis for model calibration of symptomatic influenza cases by age.^{40,41} Asymptomatic cases are not estimated at the population level, and clinical definitions can range from viral shedding in the absence of symptoms to not meeting a symptomatic case definition of influenza-like illness.⁶¹ Actual influenza infections have variable dynamics related to symptoms and shedding.^{62–65}

In summary, the availability of LAIV for self-administration offers a potential opportunity to offer influenza vaccination more widely and conveniently in settings outside the standard locations of doctors' offices and pharmacies. This increased flexibility could be suitable for efforts to increase vaccination coverage in school-age children. The success of past studies using LAIV in school children and school-based vaccination programs can serve as a model for making vaccination more readily available to children. The benefits of increasing vaccination in children, fewer symptomatic infections in children and adults, fewer missed days of work and school, and reduced hospitalizations in seniors justify consideration of such efforts.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Roberts, MS reports financial support was provided by Centers for Disease Control and Prevention. Nowalk, MP reports a relationship with Sanofi Pasteur that includes: funding grants. Zimmerman, RK reports a relationship with Sanofi Pasteur that includes: funding grants. Harrison, LH has consulted with Sanofi Pasteur, GSK, Pfizer, and Merck without compensation. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

All models and data used for this study will be made available upon request to the corresponding author.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:[10.1016/j.jinf.2025.106443](https://doi.org/10.1016/j.jinf.2025.106443).

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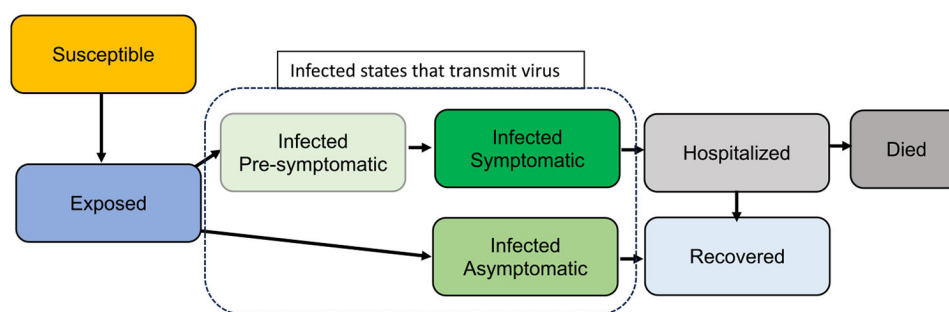
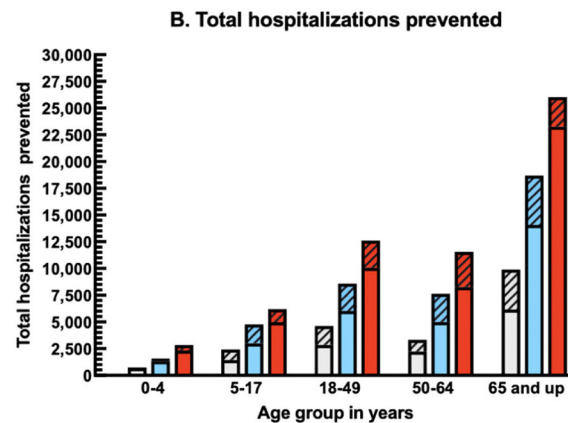
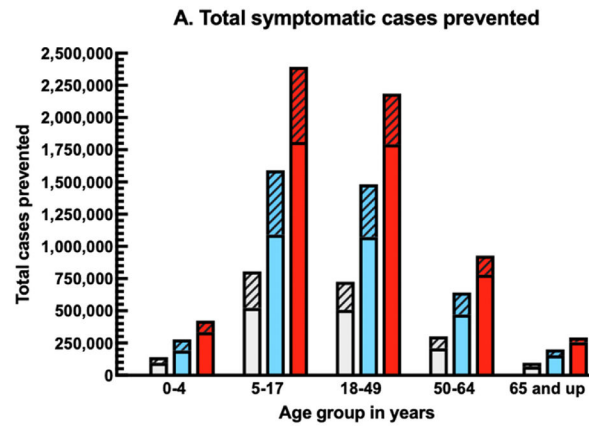


Fig. 1. Influenza Model Schematic. Infected Symptomatic and Hospitalized represent states presented in data tables.



Increase in vaccination coverage in ages 5-17 years: 5% 10% 15%
 Diagonal lines represent 45% vaccine effectiveness in 5-17-year-olds

Fig. 2.

Estimation of reduction in total symptomatic influenza cases and hospitalizations in the US population with 5%, 10%, and 15% increased vaccination coverage in children ages 5-17 years and 40% vaccine effectiveness (VE). Diagonal shading represents additional benefit of 45% VE in ages 5-17 years.

Table 1

Vaccination coverage (VC) by age used in models.

Age, years	Baseline	Increase in VC in age 5-17 years*			
		5%	10%	15%	
0.5-1	70.3				
2-4	64.3				
5-12	58.4	63.4	68.4	73.4	
13-17	49.8	54.8	59.8	64.8	
18-49	37.1				
50-64	52.4				
65+	73.9				

Source: Centers for Disease Control and Prevention Website. Flu Vaccination Coverage, United States, 2021–22 Influenza Season updated September 4, 2024. Available from: <https://www.cdc.gov/fluavaxview/coverage-by-season/2021-2022.html>

*Coverage in remaining age groups was unchanged from baseline throughout the models.

Table 2a

Reduction in symptomatic cases/100,000 due to increased vaccination coverage in school age children, ages 5–17 years assuming 40% vaccine effectiveness in all.

	Increase in vaccination coverage in ages 5–17 years		
	5%	10%	15%
Age group, years	Cases, n (%)	Cases, n (%)	Cases, n (%)
0–4	522 (3.1)	1042 (6.2)	1812 (10.7)
5–17	956 (3.2)	1994 (6.6)	3309 (10.9)
18–49	366 (3.2)	776 (6.8)	1295 (11.4)
50–64	327 (3.5)	734 (7.9)	1215 (13.0)
65 and up	121 (3.7)	277 (8.4)	459 (13.8)
Total	421 (3.3)	895 (7.1)	1492 (11.6)
	Hospitalized	Hospitalized	Hospitalized
Overall	4 (3.4%)	9 (7.6%)	15 (12.4%)

Table 2b

Reduction in symptomatic cases/100,000 due to increased vaccination coverage in school age children, ages 5–17 years assuming 45% vaccine effectiveness in ages 5–17 years and 40% in all others.

	Increase in vaccination coverage in ages 5-17 years			
	0% ^a	5%	10%	15%
Age group, years	Cases, n (%)	Cases, n (%)	Cases, n (%)	Cases, n (%)
0–4	1200 (7.1)	765 (4.9)	1515 (9.6)	2307 (14.7)
5–17	2265 (7.5)	1475 (5.3)	2908 (10.4)	4375 (15.6)
18–49	784 (6.9)	524 (4.9)	1072 (10.1)	1579 (14.9)
50–64	717 (7.7)	471 (5.5)	1001 (11.6)	1447 (16.8)
65 and up	269 (8.1)	173 (5.7)	359 (11.7)	526 (17.2)
Total	944 (7.3)	620 (5.2)	1256 (10.5)	1862 (15.6)
	Hospitalized	Hospitalized	Hospitalized	Hospitalized
Overall	9 (7.4)	6 (5.7)	13 (11.2)	18 (16.0)

^aRepresents reduction compared to 40% VE in all agents with no increase in vaccination coverage. All other numbers in Table 2b represent reduction in cases with increasing vaccination coverage compared to baseline for the vaccine effectiveness state.