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Estimating COVID-19 associated hospitalizations, ICU admissions, and in-hospital deaths averted in the United States by 2023-2024 COVID-19 vaccination: A conditional probability, causal inference, and multiplier-based approach

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Abstract

COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths averted from 2023-2024 COVID-19 vaccination from the weeks of October 1, 2023, through April 21, 2024, were estimated via a novel multiplier model that utilized causal inference, conditional probabilities of hospitalization, and correlations between data elements in Monte Carlo simulations. Median COVID-19-associated hospitalizations averted were 68,315 (95% uncertainty interval [UI] 42,831 – 97,984), ICU admissions averted were 13,108 (95% UI 4,459 – 25,042), and in-hospital deaths averted were 5,301 (95% UI 101 – 14,230). Averted COVID-19-associated burden was highest in adults aged 65 years and older (hospitalizations averted 57,665, 95% UI 35,442 – 84,006; ICU admissions averted 10,878, 95% UI 3,104 – 21,591; in-hospital deaths averted 4,779, 95% UI 0 – 13,132). Expanding the analytic period to comprise the weeks of September 24, 2023, through August 11, 2024, resulted in 107,197 COVID-19-associated hospitalizations averted (95% UI 80,692 – 137,643), 18,292 COVID-19-associated ICU admissions averted (95% UI 10,062 – 28,436), and 6,749 COVID-19-associated in-hospital deaths averted (95% UI 2,077 – 13,557). Older adults had the highest COVID-19-associated averted burden and potential to reduce burden further through increased vaccine coverage. 2023-2024 COVID-19 vaccinations reduced the burden of COVID-19-associated severe disease.

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Author Contributions Statement

REW supervised the project, performed the burden averted analyses, and prepared the manuscript. OD and HTF performed modeling and queries of COVID-NET data. FPH and CAT provided supervision for COVID-NET activities. REW, OD, MW, IROS, DK, DLM, LER, IT, KEFD, FPH, and CAT contributed to the study design, discussed the results, read the manuscript and supplement, and provided critical feedback.

Declaration of interests

The authors declare no conflicts of interest.

Keywords

COVID-19; disease burden; epidemiological models; vaccines

Introduction

Estimating the national burden of COVID-19 averted by vaccinations is an important component of understanding the impact of vaccinations on the United States population. The number of SARS-CoV-2 infections,(1, 2) COVID-19-associated symptomatic illnesses,(3) cases,(4–6) hospitalizations,(1–4) and deaths (1–4) averted by prior formulations of COVID-19 vaccinations have been estimated for the United States or for smaller U.S. jurisdictions. The U.S. Centers for Disease Control and Prevention’s Advisory Committee on Immunization Practices (ACIP) has used estimates of the potential benefits and risks to inform vaccine policy decisions,(7) and burden averted estimates can be used to evaluate vaccine policy.

Burden averted estimates have been produced by multiple methods, including multiplier,(1) agent-based,(2) decision tree,(3) compartmental,(4) regression,(5) and nested mean (6) models. Causal inference was used in a subset of these studies (1, 5, 6). Our causal inference framework was based on counterfactual reasoning, also known as potential outcomes, which forms the basis of the Rubin causal model (8) where an observed outcome for an individual is compared to an unobserved outcome under a different set of conditions. With empirical data and assumptions,(9) we can make predictions about the causal effect of an intervention by comparing the aggregate differences between outcomes with and without the presence of the intervention (e.g. probability of hospitalization with and without COVID-19 vaccination).

Vaccine effectiveness (VE) (1–4) or vaccine efficacy (2) estimates were used as input parameters in some of these models to represent the ability of vaccination to prevent COVID-19 outcomes. VE estimates are often only produced once or twice a season from large networks due to sample size constraints,(10) meaning burden averted modeling may only be able to use one or two VE estimates per season. Waning infection- and vaccination-induced protection and changing gross attack rates over a season may create bias in burden averted estimates when using aggregate VE estimates. Finally, population level hospitalization rates should depend on vaccination coverage since an effective vaccination should reduce hospitalizations, yet models may not account for this dependence.

We endeavored to incorporate causal inference and conditional probabilities into a multiplier model estimating the number of COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths averted by 2023-2024 COVID-19 vaccination in the United States from the week beginning on October 1, 2023, through the week of April 21, 2024, for a seasonal estimate to align with other respiratory viruses and the weeks of September 24, 2023, through August 11, 2024, for an annual estimate. The analysis focused on the population that received 2023-2024 COVID-19 vaccination and had no COVID-19-associated hospitalizations and estimated the number that would have been hospitalized had they not been vaccinated. Instead of using VE estimates against hospitalization to represent

the ability of COVID-19 vaccination to protect against COVID-19-associated outcomes, we utilized a novel approach that leveraged conditional probabilities of COVID-19 vaccination given COVID-19-associated hospitalization. Since the conditional probabilities were updated monthly, this might provide an estimate of the ability of COVID-19 vaccination to protect against COVID-19-associated hospitalization that is more sensitive to variations in a vaccine's effectiveness due to waning and changes in SARS-CoV-2 variants over a season. Finally, simulated data incorporated correlations between model inputs since some data (e.g., COVID-19 vaccination coverage and the likelihood of COVID-19-associated hospitalization) were likely to be correlated. Monte Carlo simulations were then implemented to produce estimates of the averted burden of multiple COVID-19-associated outcomes.

Methods

We designed and analyzed an age-specific multiplier-based inference model that compares two vaccine effectiveness-influenced scenarios, a factual (with 2023-2024 COVID-19 vaccinations) versus the counterfactual (no 2023-2024 COVID-19 vaccination), to estimate the averted COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths averted by 2023-2024 COVID-19 vaccination in the US. For this purpose, a causal inference framework for each age group with or without immunocompromising conditions was set to account for COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths within the factual and counterfactual scenarios. The model incorporates potential outcomes and conditional probabilities of hospitalization to estimate the COVID-19 burden averted by 2023-2024 COVID-19 vaccination. Performed sensitivity analyses were mainly focused on correlation parameters and the likelihood of a COVID-19-associated hospitalization among people with a 2023-2024 COVID-19 vaccination who did not experience a COVID-19-associated hospitalization.

Primary data sources

Two analytic periods were used. First, seasonal estimates used the week of October 1, 2023, through the week of April 21, 2024, to align with burden averted estimates of other respiratory viruses.(11) Second, annual estimates utilized an expanded analytic period of September 24, 2023, through the week of August 11, 2024, since SARS-CoV-2 circulates year round. The dates for the annual estimates were chosen based on ACIP recommendation dates: the week of September 24, 2023, was chosen as the start of the analytic period to allow for a minimum of a week after 2023-2024 COVID-19 vaccinations were recommended(12) and the week of August 11, 2024, was the last full week before 2024-2025 COVID-19 vaccinations were approved by the U.S. Food and Drug Administration.(13)

Population data comes from the U.S. Census 2022 national estimates.(14) Age was categorized into the following five groups: 6 months-4 years; 5-17 years; 18-49 years; 50-64 years; and 65 years and older.

Estimates of the national count of COVID-19-associated hospitalizations were derived based on surveillance data of hospitalizations with confirmed SARS-CoV-2 infection collected in

the COVID-19–Associated Hospitalization Surveillance Network (COVID-NET) platform. (15) COVID-NET is an active sentinel surveillance system that produces population-based rates of COVID-19-associated hospitalizations among residents of defined surveillance catchment areas across 98 counties in 12 states. COVID-19-associated hospitalizations are defined as those among persons who have received a positive SARS-CoV-2 reverse transcription–polymerase chain reaction (RT-PCR) or rapid antigen detection test result during or within the 14 days preceding hospitalization. Estimates of national COVID-19-associated hospitalizations were extrapolated from data collected in the COVID-NET sentinel surveillance system using a hierarchical Bayesian modeling approach.(16) This modeling approach incorporated temporal trends in the reported counts as well as unmeasured differences among sites reporting data to the COVID-NET system and variation in SARS-CoV-2 testing frequency and accuracy. In addition, the modeling approach enabled estimation of the uncertainty in the estimated age group-specific hospitalization counts due to extrapolation from the COVID-NET catchment areas to the national population.

Using previously described methods,(15) the prevalence of intensive care unit (ICU) admission and in-hospital death were abstracted from medical records from an age- and site-stratified random sample of hospitalizations. The prevalence of receipt of COVID-19 vaccination was obtained from state immunization information systems. Specific measures included the likelihood that a COVID-19-associated hospitalized person received a 2023-2024 COVID-19 vaccination, $\Pr(V|H)$, the probability of a COVID-19-associated ICU admission given a COVID-19-associated hospitalization, $\Pr(ICU|H)$, and the probability of a COVID-19-associated in-hospital death given a COVID-19-associated hospitalization, $\Pr(IHD|H)$, where $\Pr(\square)$ denotes a probability. For sampled data, unweighted case counts and weighted percentages to better represent the hospitalized population of the catchment area are presented. Monthly estimates were used, except in situations where the weighted sample size was less than 20; in those situations, a quarterly estimate was used instead. For a week split across two months, the estimate from the month with the most days in that week was used.

National, weekly 2023-2024 COVID-19 vaccination coverage estimates were from the National Immunization Survey (NIS) for adults (17) and children.(18) NIS defined vaccination coverage with the 2023-2024 COVID-19 vaccination as receipt of at least one COVID-19 vaccination since September 14, 2023. Thus, COVID-19 vaccination coverage does not take into account the second dose of individuals aged 65 years or older who received a second 2023-2024 COVID-19 vaccine doses after ACIP’s recommendation in February 2024.(19) Analyses of Annual estimates carried forward vaccination coverage estimates from the week of May 5, 2024, for the weeks of May 12, 2024, through August 11, 2024.

COVID-19-associated hospitalizations averted

To estimate the number of COVID-19-associated hospitalizations averted by 2023-2024 COVID-19 vaccination, we compared the total number of people with a COVID-19-associated hospitalization in the presence of 2023-2024 COVID-19 vaccinations (referred to as “factual”) to the hypothetical total number of people with a COVID-19-associated

hospitalization without the presence of 2023-2024 COVID-19 vaccinations (referred to as the “counterfactual”) (Figure 1). In mathematical form, this was represented as

$$C(HA) = C(\widehat{H}) - C(H) \quad (1)$$

where H denoted a person with a COVID-19-associated hospitalization in the factual condition, $\widehat{H}$ indicated a COVID-19-associated hospitalized person in the counterfactual condition, HA represented the number of COVID-19-associated hospitalizations averted, and $C(\square)$ was a function for the count of people. We categorized the U.S. population into four mutually exclusive groups where V denoted people with a 2023-2024 COVID-19 vaccination, NV signified people without a 2023-2024 COVID-19 vaccination, H is a person with a COVID-19-associated hospitalization, and NH represented people without a COVID-19-associated hospitalization (Figure S1). We made the following assumptions about each population subset:

- people without a 2023-2024 COVID-19 vaccination who did not have a COVID-19-associated hospitalization, $C(NV, NH)$, did not have a COVID-19-associated hospitalization in the counterfactual scenario;
- people with a 2023-2024 COVID-19 vaccination who did not have a COVID-19-associated hospitalization, $C(V, NH)$, could have had a COVID-19-associated hospitalization in the counterfactual scenario;
- people without a 2023-2024 COVID-19 vaccination who had a COVID-19-associated hospitalization, $C(NV, H)$, had a COVID-19-associated hospitalization in the counterfactual scenario; and
- people with a 2023-2024 COVID-19 vaccination who had a COVID-19-associated hospitalization, $C(V, H)$, had a COVID-19-associated hospitalization in the counterfactual scenario since their protection level will be the same or decreased.

The only subset of the population which could have contained COVID-19-associated averted hospitalizations was $C(V, NH)$, people with a 2023-2024 COVID-19 vaccination who did not have a COVID-19-associated hospitalization. Persons who did not have a 2023-2024 COVID-19 vaccination and a COVID-19-associated hospitalization, $C(NV, NH)$, nor those who already experienced a COVID-19-associated hospitalization, $C(NV, H)$ and $C(V, H)$, could, therefore, have a 2023-2024 COVID-19 vaccination-averted COVID-19-associated hospitalization. Thus, our goal was estimating the subset of $C(V, NH)$ that would have a COVID-19-associated hospitalization in the comparison condition (Figure S2). We can represent this as

$$C(HA) = C(V, NH) * \gamma \quad (2)$$

where γ is a probability denoting the likelihood of a person with a 2023-2024 COVID-19 vaccination and no COVID-19-associated hospitalization would have had a COVID-19-associated hospitalization in the comparison scenario. γ is an unknown parameter and we considered multiple approaches for estimating this parameter, details of which are in the supplementary materials. We assumed that $\gamma = \Pr(H | V)$ in equation (2) and

$$C(HA) = C(V, NH) * \Pr(H | V), \quad (3)$$

because people who obtained or with the intention to obtain a COVID-19 vaccination have been more likely to engage in risk prevention behaviors than people without the intention to obtain a COVID-19 vaccination.(20, 21)

COVID-19-associated hospitalizations averted accounting for immunocompromising conditions

Multiple studies indicated that COVID-19 vaccinated people with immunocompromising conditions are more likely to experience a SARS-CoV-2 or COVID-19 outcome than COVID-19 vaccinated people without immunocompromising conditions.(22–28) Our approach modified formula (3) by incorporating dependence of this probability on immunocompromise status, i.e.,

$$C(HA_{IC}) = C(IC, V, NH) * \Pr(H | IC, V) + C(NIC, V, NH) * \Pr(H | NIC, V), \quad (4)$$

where IC and NIC indicated immunocompromised and not immunocompromised, respectively, and $C(HA_{IC})$ were the COVID-19-associated hospitalizations averted by 2023-2024 COVID-19 vaccination accounting for immunocompromise condition (Figure S3). We were unable to find national estimates of $\Pr(H | IC, V)$ and $\Pr(H | NIC, V)$, meaning we relied on estimates outside the U.S. or on subsets of the U.S. population.(26–28) To account for differences in $\Pr(H | V)$ between data sources, we adapted equation (4) to

$$C(HA_{IC}) = C(IC, V, NH) * \left[\Pr(H | V) * \frac{\Pr(H_A | IC_A, V_A)}{\Pr(H_A | V_A)} \right] + C(NIC, V, NH) * \left[\Pr(H | V) * \frac{\Pr(H_A | NIC_A, V_A)}{\Pr(H_A | V_A)} \right], \quad (5)$$

where the subscript A represented an alternate data source. Probabilities of COVID-19-associated hospitalization of people with a 2023-2024 COVID-19 vaccination with and without immunocompromising conditions were taken from multiple sources.(26–28) (Table S1) For a data source to be included, the source needed $C(V_A)$ and $C(H_A, V_A)$ to estimate $\Pr(H_A | V_A)$, $C(NIC_A, V_A)$ and $C(H_A, NIC_A, V_A)$ to estimate $\Pr(H_A | NIC_A, V_A)$, and $C(IC_A, V_A)$ and $C(H_A, IC_A, V_A)$ to estimate $\Pr(H_A | IC_A, V_A)$. Results presented are from Evans et al. (28) with results from other sources (26, 27) included in the supplementary materials.

Estimating averted COVID-19-associated ICU admissions and in-hospital deaths

The number of COVID-19-associated ICU admissions averted was calculated using the following formula

$$C(IA) = C(HA) * \Pr(ICU|H) \quad (6)$$

where $C(IA)$ is the number of COVID-19-associated ICU admissions averted and $\Pr(ICU|H)$ is the probability of an COVID-19-associated ICU admission given a COVID-19-associated hospitalization. The number of COVID-19-associated in-hospital deaths were estimated similarly,

$$C(DA) = C(HA) * \Pr(IHD|H) \quad (7)$$

where $C(DA)$ is the number of COVID-19-associated in-hospital deaths averted and $\Pr(IHD|H)$ is the probability of an COVID-19-associated in-hospital death given a COVID-19-associated hospitalization.

The supplementary materials also include sensitivity analyses to the parameter values of the averted burden estimates. In sum, burden averted results were sensitive to changes in key parameter values except for the probability of COVID-19 vaccination and, when considering immunocompromising conditions, the probability of immunocompromise (Figures S4, S5). For the former, this is due to the implicit assumption that parameters depend on each other, i.e., changing $\Pr(V)$ will affect other parameters, such as $\Pr(H)$ and $\Pr(H|V)$. If changes in the burden averted arose directly from $\Pr(V)$, we might be double counting averted burden due to $\Pr(V)$. Additionally, the direct effect of changes to $\Pr(V)$ may be diminished because $\Pr(H|V)$ is used in both the calculation of $C(V, NH)$ and $C(HA)$.

Comparison formula

We utilized a modified formula from the ACIP benefit-risk assessment framework for COVID-19 vaccine policy decisions (7) to calculate COVID-19-associated burden averted estimates. The original formula calculated the COVID-19-associated hospitalizations prevented as the product of the COVID-19 hospitalization rates, analytic time horizon, the number of COVID-19 vaccination doses administered, and an estimate of the VE against COVID-19 hospitalization. We modified this formula to

$$C(HA_B) = \Pr(H) * C(V) * VE \quad (8)$$

where $C(V)$ is the number of COVID-19 vaccinated people and VE was an estimate of the vaccine effectiveness against COVID-19-associated hospitalization of the 2023-2024 COVID-19 vaccination compared to people without a 2023-2024 COVID-19 vaccination. Results from equation (8) were compared to results from equation (3). Estimates of VE

against COVID-19-associated hospitalization of the 2023-2024 COVID-19 vaccination compared to people without a 2023-2024 COVID-19 vaccination were taken from the VISION platform.(29)

Averted COVID-19-associated burden calculations

Monte Carlo simulations were used to generate the number of COVID-19 hospitalizations, 2023-2024 COVID-19 vaccination coverage, the probability that a COVID-19-associated hospitalized person received a 2023-2024 COVID-19 vaccination, the probability of a COVID-19-associated ICU admission given a COVID-19-associated hospitalization, the probability of a COVID-19-associated in-hospital death given a COVID-19-associated hospitalization, and VE against COVID-19-associated hospitalization. Data were generated by age group and week for COVID-19 hospitalizations and 2023-2024 COVID-19 vaccination coverage, monthly for all probabilities, and seasonal for VE. Data were generated from multivariate standard Gaussian distributions based on estimated means and standard deviations. A correlation matrix was created to incorporate potential correlations within and between data elements (Table S2). 10,000 Monte Carlo simulations were generated. Full details about the estimation of averted COVID-19-associated burden due to 2023-2024 COVID-19 vaccinations including the assumed correlations among modeling elements and logical values used for truncation are presented in the supplementary materials.

For each simulation, the estimated number of COVID-19-associated hospitalizations was converted to $\Pr(H)$ by dividing by the census population. Then, using the calculated $\Pr(H)$ and the simulated values of $\Pr(V)$ and $\Pr(V|H)$, $\Pr(H | V)$ was calculated using Bayes Theorem. For each simulation, $C(V, NH)$ was calculated by the product of the population size, $\Pr(V)$, and $1 - \Pr(H)$ and $C(HA)$ from the formula above. Age group estimates were created by summing across all months for an age group by simulation and then computing the median of 10,000 simulations. Uncertainty intervals were the 2.5th and 97.5th quantiles of the 10,000 simulations. Overall estimates were computed by summing over all months and age groups by simulation and are summarized by the median and 2.5th and 97.5th quantiles.

Sensitivity analyses

Additional sensitivity analyses for averted COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths were performed. For analyses without accounting for immunocompromising conditions, we varied the correlation structure, correlation parameter, and the likelihood that people with a 2023-2024 COVID-19 vaccination and no COVID-19-associated hospitalization would experience a COVID-19-associated hospitalization in the counterfactual condition. Other parameters varied included the probability of a COVID-19-associated hospitalization in the counterfactual (see supplemental materials for details). For analyses that accounted for immunocompromising conditions, we varied the correlation structure, correlation parameter(s), and the probability of COVID-19-associated hospitalization of people with a 2023-2024 COVID-19-associated vaccination with and without immunocompromising conditions.(26–28)

Results

COVID-19-associated hospitalizations averted

Seasonal COVID-19 hospitalizations averted by 2023-2024 COVID-19 vaccination without accounting for immunocompromising conditions was 68,315 (95% uncertainty interval [UI]: 42,831 – 97,984) or 98 COVID-19-associated hospitalizations averted per 100,000 2023-2024 COVID-19 vaccinated people (95% UI 61 - 141) (Figure 2 panel A, Table S3). The annual estimate of hospitalizations averted was 107,197 (95% UI 80,692 – 137,643) (Figure 2 panel B, Table S4).

The seasonal COVID-19-associated hospitalizations averted by 2023-2024 COVID-19 vaccination was 724 (95% UI 177 – 1,527) for people aged 6 months to 4 years, which was approximately 71 (95% UI 17 - 156) COVID-19-associated hospitalizations averted per 100,000 2023-2024 COVID-19 vaccinated people aged 6 months to 4 years. COVID-19-associated hospitalizations averted by 2023-2024 COVID-19 vaccination was 453 (95% UI 44 – 1,917) for people aged 5 to 17 years, 2,467 (95% UI 992 - 4,197) for people aged 18-49 years, 6,770 (95% UI 2,564 - 11,761) for people aged 50-64 years, and 57,665 (95% UI 35,442 - 84,006) for people aged 65 years and older. COVID-19-associated hospitalizations averted per 100,000 people with a 2023-2024 COVID-19 vaccination was lower for people aged 6 months to 4 years compared to all age groups except people aged 65 years and older.

After accounting for immunocompromising conditions, estimated COVID-19 hospitalizations averted by 2023-2024 COVID-19 vaccination was 58,540 (95% UI 36,669 - 83,987) (Table S5). This was approximately 14% fewer COVID-19-associated hospitalizations averted compared to the results that did not account for people with immunocompromising conditions. Age group estimates accounting for immunocompromising conditions ranged from 11% to 17% fewer COVID-19-associated hospitalizations averted compared to results that did not account for people with immunocompromising conditions. Similar differences were found for annual estimates after accounting for immunocompromising conditions (Table S6).

COVID-19-associated ICU admissions averted

An estimated 13,108 (95% UI 4,459 – 25,018) seasonal COVID-19-associated ICU admissions were averted by 2023-2024 COVID-19 vaccination without accounting for immunocompromising conditions (Figure 3 panel A, Table S7). This translated to approximately 19 COVID-19-associated ICU admissions averted per 100,000 2023-2024 COVID-19 vaccinated people (95% UI 6 - 36). Our annual estimate was 18,292 COVID-19-associated ICU admissions averted (95% UI 10,062 – 28,436) (Figure 3 panel B, Table S8).

Age-based, seasonal estimates were 175 (95% UI 38 - 418) COVID-19-associated ICU admissions averted for people aged 6 months to 4 years, 93 (95% UI 3 - 392) for people aged 5 to 17 years, 307 (95% UI 39 - 776) for people aged 18 to 49 years, 1,499 (95% UI 321 – 3,503) for people aged 50 to 64 years, and 10,878 (95% UI 3,104 – 21,591) for people aged 65 years and older (Table S7). Seasonal COVID-19-associated ICU admissions averted by 2023-2024 COVID-19 vaccination accounting for immunocompromise status was 11,237

(95% UI 3,815 – 21,461) (Table S9) and annual ICU admissions averted were 15,673 (95% UI 8,629 - 24,386) (Table S10).

COVID-19-associated in-hospital deaths averted

Without accounting for immunocompromising conditions, a seasonal estimate of 5,301 (95% UI 101 – 14,230) COVID-19-associated in-hospital deaths were averted by 2023-2024 COVID-19 vaccination (Figure 4 panel A, Table S11); annually, that estimate increases to 6,749 in-hospital deaths (95% UI 2,077 - 13,557) (Figure 4 panel B, Table S12). Seasonally, COVID-19-associated in-hospital deaths averted were 2 (95% UI 0 - 17) for people aged 6 months to 4 years, 6 (95% UI 0 - 59) for people aged 5 to 17 years, 36 (95% UI 0 - 185) for people aged 18 to 49 years, 412 (95% UI 0 - 1,447) for people aged 50 to 64 years, and 4,779 (95% UI 0 - 13,132) for people aged 65 years and older (Table S11). After accounting for immunocompromising conditions, the model estimated 4,538 (95% UI 88 – 12,166) COVID-19-associated in-hospital deaths were averted by 2023-2024 COVID-19 vaccination (Table S13) or 5,774 (95% UI 1,776 - 11,613) COVID-19-associated in-hospital deaths averted annually (Table S14).

Sensitivity analyses

Point estimates for annual COVID-19-associated hospitalization, ICU admissions, and in-hospital deaths using the conditional probability multiplier model were lower than estimates generated from the formula adapted from the ACIP benefit-risk assessment framework (107,197, 95% UI 80,692 - 137,643, versus 116,026, 95% UI 93,253 - 141,078 when using the benefit-risk formula), but the uncertainty intervals overlapped between the two methods (Table S15).

In formula (2), the number of hospitalizations averted is the product of the number of people with a 2023-2024 COVID-19 vaccination who were not hospitalized and a probability. For our main analyses, we chose that probability to be the probability that people with a 2023-2024 COVID-19 vaccination were hospitalized. In sensitivity analyses, we found the choice of that probability affected the averted COVID-19-associated hospitalization burden (Table S16), with most probabilities resulting in a higher averted COVID-19-associated hospitalization burden compared to the benefit-risk assessment framework formula. Otherwise, the correlation structure and assumed correlation values (ρ) had minimal impact on the point estimates of COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths averted (Tables S17–S22). For most probability values, the uncertainty interval width increased with increasing correlation for both the autoregressive and compound symmetric correlation structures. When accounting for immunocompromising conditions, there were large differences in the point estimates when using different data sources (Tables S18, S20, S22) with the values from Evans et al. (28) providing the highest averted burden of COVID-19-associated hospitalizations, followed by Suleyman et al. (27), and Smits et al. (26) with the lowest, approximately 45% less than Evans et al. (28).

Discussion

Utilizing counterfactual reasoning and conditional probabilities our model estimated that 2023-2024 COVID-19 vaccination prevented thousands of COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths from the week of October 1, 2023, through the week of April 21, 2024. Specifically, 2023-2024 COVID-19 vaccination averted 68,315 (95% UI 42,831 – 97,984) COVID-19-associated hospitalizations, 13,108 (95% UI 4,459 – 25,018) COVID-19-associated ICU admissions, and 5,301 (95% UI 101 – 14,230) COVID-19-associated in-hospital deaths. These estimates were substantially higher if additional summer months were also included in the analysis, where averted COVID-19-associated hospitalizations increased by 57%, COVID-19-associated ICU admissions increased by 40%, and COVID-19-associated in-hospital deaths increased by 27%. These estimates highlight the ongoing disease burden the United States experiences from COVID-19 and the additional burden that is experienced beyond the typical respiratory virus season.

Older adults achieved the largest 2023-2024 COVID-19-associated averted burden and the greatest potential for additional averted burden of COVID-19-associated outcomes. This is due to higher COVID-19-associated hospitalization rates in adults aged 65 years or older compared to other age groups (Figure S6); adults aged 65 years or older accounted for between 80% and 90% of the averted COVID-19-associated hospitalizations, ICU admissions, and in-hospital deaths. Though, adults aged 65 years or greater also have the potential to reduce COVID-19-associated outcomes since the percentage of people aged 65 years or greater with at least one 2023-2024 COVID-19 vaccination coverage by the week of May 5, 2024, is slightly below 41%, suggesting more older adults obtaining COVID-19 vaccinations would further reduce COVID-19-associated outcomes.

Increased 2023-2024 COVID-19 vaccination rates would reduce COVID-19-associated outcomes in other age groups as well, as suggested from estimates of VE against COVID-19 hospitalization for 2023-2024 COVID-19 vaccination.(29) The percentage of people with at least one 2023-2024 COVID-19 vaccination by the week of May 5, 2024, was 25% in people aged 50-64 years and < 15% in age groups younger than 50 years.(17, 18) The model estimated a high number of COVID-19-associated hospitalizations averted per 100,000 2023-2024 COVID-19 vaccinated people aged 6 months to 4 years, albeit with higher uncertainty than other age groups. Children less than 4 years old are the least likely to possess infection-induced immunity and, as these estimates suggest, increased vaccination coverage has the potential to decrease their COVID-19-associated burden.

These results suggest that 2023-2024 COVID-19 vaccination prevented a similar number of hospitalizations as annual influenza vaccination, when comparisons are limited to the traditional respiratory virus season, i.e., October-April. The hospitalizations averted by 2023-2024 COVID-19-associated vaccinations from October 2023 through April 2024 were 68,315 (95% UI 42,831 - 97,984), which was similar to influenza hospitalizations averted from influenza vaccination in the 2022-2023 flu season from October 2022 from April 2023 (64,950, 95% UI 34,744-96,011).(30) However, since 2020, SARS-CoV-2 has circulated year-round with peaks in both winter and summer. The annual COVID-19-

associated hospitalizations averted increased by 57% when incorporating the summer months, suggesting that the full averted burden of COVID-19-associated hospitalizations from 2023-2024 COVID-19 vaccination may exceed that of annual influenza vaccination.

The results accounting for immunocompromising conditions demonstrated the importance of accounting for key factors in averted burden estimates. Splitting the COVID-19-associated burden calculations into people with and without immunocompromising conditions decreased the averted burden estimates from 2023-2024 COVID-19 vaccination by between 9% and 15% depending on the outcome. People with a COVID-19 vaccination and immunocompromising conditions were more likely to have a COVID-19-associated hospitalization than people with a COVID-19 vaccination and without an immunocompromising condition.(26–28) For instance, in 2022, 4% of people in the United Kingdom had an immunocompromising condition, but 22% of COVID-19 hospitalizations were from individuals with an immunocompromising condition.(28) From the same study, (28) approximately 7 of 100 people with a 2023-2024 COVID-19 vaccination and without a COVID-19-associated hospitalization were immunocompromised whereas approximately 25 of 100 people with a 2023-2024 COVID-19 vaccination and with a COVID-19-associated hospitalization were immunocompromised. These results suggest that the group of people with a 2023-2024 COVID-19 vaccination and without a COVID-19-associated hospitalization will have a smaller proportion of people with an immunocompromising condition compared to those with a 2023-2024 COVID-19 vaccination and a COVID-19-associated hospitalization, and, thus, will be less likely to experience a COVID-19-associated hospitalization in the hypothetical scenario where 2023-2024 COVID-19 vaccinations were not available. Though, the results accounting for immunocompromising conditions were sensitive to the data used to calculate the probabilities of COVID-19-associated hospitalization dependent on immunocompromise status. Robust information on the likelihood of COVID-19-associated hospitalization dependent on COVID-19 vaccination and immunocompromise status will be needed to provide estimates of the burden averted when taking into account immunocompromising conditions.

In addition, COVID-19-associated burden averted estimates using conditional probabilities were lower than a modified formula that used COVID-19 VE,(7) but higher than annual results from economic analyses presented at ACIP.(31) Using results per 100,000 vaccinated people by 2023-2024 COVID-19 vaccination, conditional probability estimates were higher for people aged 18-49 years (20 [95% UI 12 – 28] versus 16), aged 50-64 years (67 [95% UI 44 – 95] versus 55), and aged 65 years or more (369 [95% UI 279 – 471], versus 274). A potential reason for these differences were that VE estimates have the limitation of covering a half or full season. Conditional probabilities can provide more granular time-based estimates and, potentially, help account for waning protection from vaccination since the probability of hospitalization in vaccinated people may mirror the aggregate level of protection in the population. The probability of hospitalization in vaccinated people may be robust with a smaller sample size, but further evaluation is needed to establish this. Differences with the economic model may be due to different model assumptions and data inputs, such as the economic model using hospitalization data from October 2022 to September 2023. These differences highlight that the bias and robustness properties of the conditional probability approach are unclear. Further research is needed to understand the

advantages and disadvantages of using conditional probability for vaccine effectiveness to estimate burden averted, especially compared to common methods, such as agent-based, decision-tree, and compartmental models.

These analyses are subject to multiple limitations. We did not account for the February 2024 ACIP recommendation of a second dose of 2023-2024 COVID-19 vaccination for adults aged 65 years or older. Vaccine effectiveness was not directly a part of the calculations, as has been done in other multiplier models. Estimated COVID-19 deaths averted only reflect people who died as an inpatient and did not include COVID-19-associated deaths that occurred among those who died after hospital discharge nor those who were never admitted. These estimates did not directly incorporate vaccine- or infection-induced waning and did not incorporate any indirect effects, though conditional probabilities may incorporate the waning effects. Nevertheless, some indirect effects cannot be included, such as the impact of maternal vaccination on infants under 6 months of age. In addition, the COVID-NET surveillance system catchment area includes approximately 10% of the U.S. population and may not be able to capture fluctuations in hospitalizations that occurred outside of the COVID-NET coverage area.⁽¹⁶⁾ The probabilities of ICU admission and in-hospital death given hospitalization were estimated from all COVID-19-associated hospitalized participants, and not from people without a 2023-2024 COVID-19 vaccination since this would have decreased the robustness of these results. Therefore, the ICU admissions and in-hospital deaths are likely underestimates since we expect the probability of ICU admission and in-hospital death given a COVID-19-associated hospitalization and no 2023-2024 COVID-19 vaccination would be higher than the probabilities used. The Monte Carlo simulation procedure may have had inaccuracies, such as the assumed correlations between data elements, the multivariate normal distributions may not optimally represent parameter distributions, and small, systematic biases across data elements may have led to a larger bias in averted estimates.

Conclusion

These results support the ACIP recommendation for everyone 6 months and older to receive an updated COVID-19 vaccination (12) and that updated vaccination is especially important for adults aged 65 years or older, given their increased risk of COVID-19-associated hospitalization, ICU admission and death compared to younger age groups. Utilizing causal inference and conditional probabilities into multiplier model estimates provide an alternative approach that may improve COVID-19 burden averted estimates without computational complexity. Further research is needed to understand the methodological properties.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Reality (what we observed during the weeks October 1, 2023-April 21, 2024)	Comparison (assumptions about what could have happened without updated (2023- 2024 Formula) COVID-19 vaccination)
No 2023-2024 COVID-19 vaccination, no COVID-19-associated hospitalization	No COVID-19-associated hospitalization (no change in hospitalization risk)
2023-2024 COVID-19 vaccination, no COVID-19-associated hospitalization	?
No 2023-2024 COVID-19 vaccination, COVID-19-associated hospitalization	COVID-19-associated hospitalization (no change in hospitalization risk)
2023-2024 COVID-19 vaccination, COVID-19-associated hospitalization	COVID-19-associated hospitalization (hospitalization risk same or increased)

Figure 1:
Categories of the U.S. population by 2023-2024 COVID-19 vaccination status in factual and assumptions made in the counterfactual scenario.

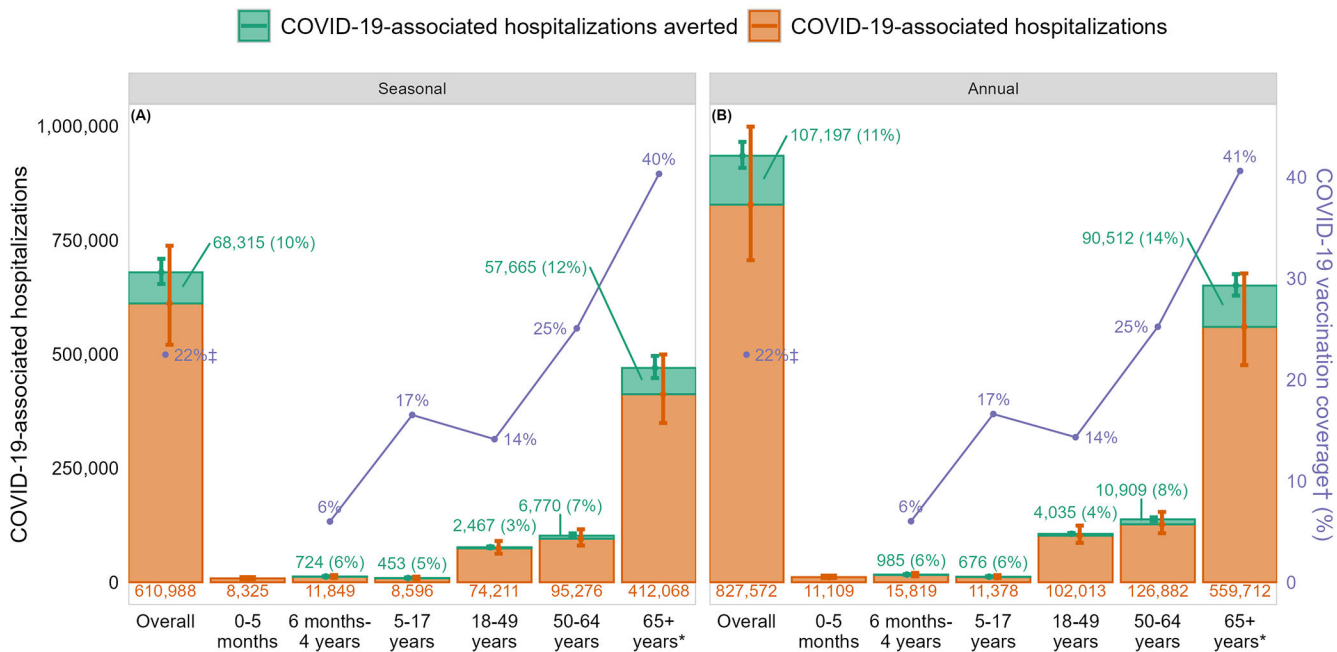


Figure 2: Seasonal and annual estimates of COVID-19-associated hospitalizations and hospitalizations averted by 2023-2024 COVID-19 vaccination, United States. Error bars represent 95% uncertainty intervals for COVID-19-associated hospitalizations averted calculated from Bayesian random effects model and Monte Carlo simulations. Seasonal estimates include the weeks of October 1, 2023, through April 21, 2024, and annual estimates include the weeks of September 24, 2023, through August 11, 2024. †Cumulative 2023-2024 COVID-19 vaccination coverage is through the week of April 21, 2024, for seasonal and through May 5, 2024, for annual. *Based on having at least one dose of 2023-2024 COVID-19 vaccination. ‡Coverage is in people aged 18+ years.

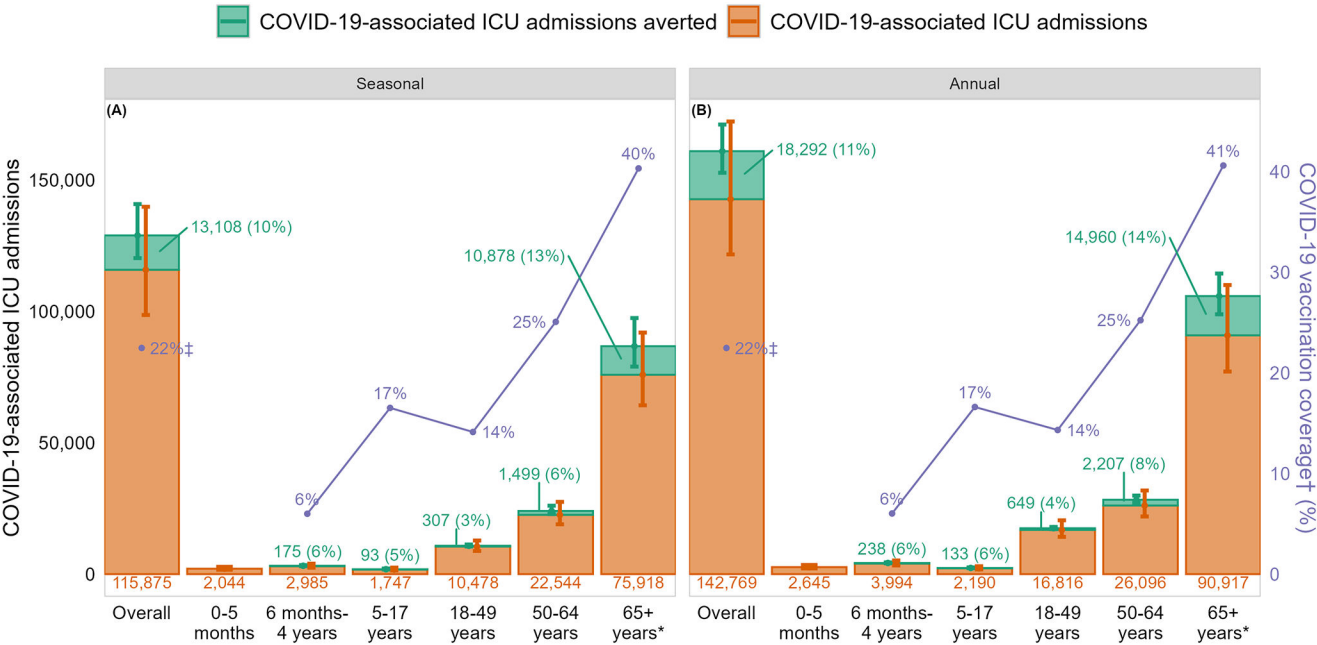


Figure 3: Seasonal and annual estimates of COVID-19-associated ICU admissions and ICU admissions averted by 2023-2024 COVID-19 vaccination, United States. Error bars represent 95% uncertainty intervals for COVID-19-associated ICU admissions averted that are calculated from Bayesian random effects model and Monte Carlo simulations. Seasonal estimates include the weeks of October 1, 2023, through April 21, 2024, and annual estimates include the weeks of September 24, 2023, through August 11, 2024. †Cumulative 2023-2024 COVID-19 vaccination coverage is through the week of April 21, 2024, for seasonal and through May 5, 2024, for annual. *Based on having at least one dose of 2023-2024 COVID-19 vaccination. ‡Coverage is in people aged 18+ years.

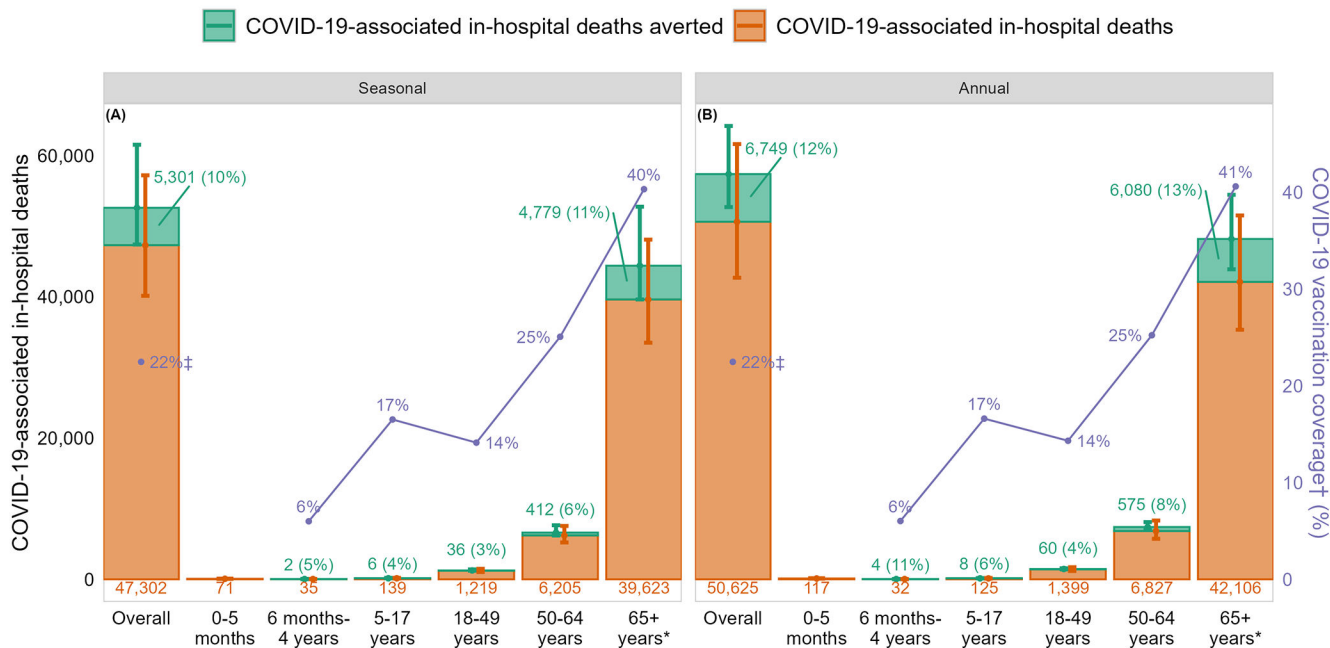


Figure 4: Seasonal and annual estimates of COVID-19-associated in-hospital deaths and in-hospital deaths averted by 2023-2024 COVID-19 vaccination, United States. Error bars represent 95% uncertainty intervals for COVID-19-associated in-hospital deaths averted that are calculated from Bayesian random effects model and Monte Carlo simulations. Seasonal estimates include the weeks of October 1, 2023, through April 21, 2024, and annual estimates include the weeks of September 24, 2023, through August 11, 2024. †Cumulative 2023-2024 COVID-19 vaccination coverage is through the week of April 21, 2024, for seasonal and through May 5, 2024, for annual. *Based on having at least one dose of 2023-2024 COVID-19 vaccination. ‡Coverage is in people aged 18+ years.