

TITLE

Impact of SARS-CoV-2 Vaccines on Covid-19 Incidence and Mortality in the United States

Fang Fang¹, John David Clemens^{1,2,3}, Zuo-Feng Zhang^{1,4,5}, Timothy F. Brewer^{1,6}

1. Department of Epidemiology, Fielding School of Public Health, University of California at Los Angeles (UCLA), Los Angeles, CA, USA

2. International Centre for Diarrhoeal Disease Research, Bangladesh, Dhaka, Bangladesh

3. International Vaccination Institute (IVI), Seoul, the Republic of Korea

4. Jonsson Comprehensive Cancer Center, UCLA, Los Angeles, CA, USA

5. Center for Human Nutrition, Department of Medicine, UCLA David Geffen School of Medicine, University of California at Los Angeles (UCLA), Los Angeles, CA, USA

6. Division of Infectious Diseases, UCLA David Geffen School of Medicine, Los Angeles, CA, USA

Co-Correspondent Authors:

Timothy F. Brewer, MD, MPH

Professor of Epidemiology and Medicine

Division of Infectious Diseases

UCLA David Geffen School of Medicine

10833 Le Conte Ave

CHS 52-215

Los Angeles, CA 90095-1688

22 TBrewer@mednet.ucla.edu

23

24 Zuo-Feng Zhang, MD, PhD

25 Professor of Epidemiology and Medicine

26 UCLA Fielding Schools of Public Health and Medicine

27 650 Charles Young Drive, South

28 Los Angeles, CA 90095-1772

29 U.S.A.

30 zfzhang@ucla.edu

31

ABSTRACT

Background: Despite safe and effective vaccines to prevent Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) infections and disease, a substantial minority of the US remains resistant to getting vaccinated. It is imperative to know if expanding vaccination rates could reduce community-wide Coronavirus 2019 (COVID-19) disease, not just among those vaccinated.

Methods: Negative binomial models were used to estimate associations between U.S. county-level vaccination rates and county-wide COVID-19 incidence and mortality between April 23rd and September 30th, 2021. A two-week lag and a four-week lag were introduced to assess vaccination rate impact on incidence and mortality, respectively. Stratified analyses were performed for county vaccination rates >40%, and before and after Delta became the dominant variant.

Findings: Among 3,070 counties, each percentage increase in population vaccination rates reduced county-wide COVID-19 incidence by 0.9% (relative risk (RR) 0.9910 (95% CI: 0.9869, 0.9952)) and mortality by 1.9% (RR 0.9807 (95% CI: 0.9745, 0.9823)). Among counties with vaccination coverage >40%, each percentage increase in vaccination rates reduced COVID-19 disease by 1.5%, RR 0.9850 (95% CI: 0.9793, 0.9952) and mortality by 2.7% (RR 0.9727 (95% CI: 0.9632, 0.9823)). These associations were not observed among counties with <40% vaccination rates. Increasing vaccination rates from 40% to 80% would have reduced COVID-19 cases by 45.4% (RR 0.5458 (95% CI: 0.4335, 0.6873)) and deaths by 67.0% (RR 0.3305 (95% CI: 0.2230, 0.4898)). An estimated 5,989,952 COVID-19 cases could have been prevented and 127,596 lives saved had US population vaccination rates increased from 40% to 80%.

54 **Interpretations:** Increasing U.S. SARS-CoV-2 vaccination rates results in population-wide
55 reductions in COVID-19 incidence and mortality. Furthermore, increasing vaccination rates
56 above 40% has protective effects among non-vaccinated persons. Given ongoing vaccine
57 hesitancy in the U.S., increasing vaccination rates could better protect the entire community and
58 potentially reach herd immunity.

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INTRODUCTION

Since being recognized in December, 2019, the Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2) pandemic has caused almost 250 million cases and five million deaths worldwide.¹ The United States has been particularly affected, with more than 43 million Coronavirus 2019 (COVID-19) cases and 697,000 deaths reported as of September 30th, 2021.² Though a number of non-pharmacologic prevention initiatives (NPIs) have been introduced to slow SARS-CoV-2 transmission³, vaccines are now recognized as among the most effective means for preventing COVID-19 cases and deaths.⁴

Three vaccine preparations are authorized for use in the US. The BNT162b2 vaccine (Pfizer, Inc. and BioNTech), has full U.S. Food and Drug Administration (FDA) approval⁵, while mRNA-1273 (Moderna) and JNJ-78436735 (Janssen Pharmaceuticals) are available under an emergency use authorization. All three vaccines are effective in preventing SARS-CoV-2 infections and COVID-19 associated disease, hospitalizations, and deaths,⁶⁻⁸ though vaccine effectiveness wanes over time and breakthrough infections occur.^{4,9} Vaccine effectiveness also varies by SARS-CoV-2 variant, with higher rates of breakthrough infections or disease reported in vaccinated persons infected with Delta or Beta compared with other variants.^{8,10} With the recognition of waning vaccine immunity and the rise of Delta as the predominant SARS-CoV-2 variant in the U.S., the FDA has authorized the emergency use of a booster for COVID-19 vaccines, including the use of a heterologous booster.^{11,12}

Numerous studies have demonstrated that SARS-CoV-2 vaccines are effective in preventing COVID-19 infections and disease in individuals outside of clinical trials, including among health care workers, first responders, individuals attending ambulatory clinics, veterans, and in nursing homes.¹³⁻¹⁵ Despite the proven safety and effectiveness of these vaccines, a substantial minority of the adult US population remains resistant to getting vaccinated.¹⁶ To understand if the SARS-CoV-2 pandemic can be stopped, it is imperative to understand the impact of vaccination on community-wide SARS-CoV-2 cases and COVID-19 disease, not just among those vaccinated—a concept popularly referred to as “herd immunity”.¹⁷ To investigate the impact of population percentages of SARS-CoV-2 vaccination on community-wide COVID-19 case and mortality rates, we undertook an ecological analysis of U.S. county vaccination rates on reported county COVID-19 cases and deaths, controlling for socioeconomic, demographic, comorbid conditions, rural/urban, air pollution, hospital capacity, and related factors, the introduction of NPIs and the presence of Delta variant.

METHODS

Negative binomial models were used to estimate associations between U.S. county-level vaccination rates and county-wide COVID-19 incidence and mortality between April 23rd and September 30th, 2021. The dates represent when Delta was first recognized in the U.S. to the end of the study period. To account for the rise of Delta as the dominant U.S. variant, additional analyses were done dividing the study period into before (April 23rd – July 2nd) and after (July 3rd – September 30th) Delta was responsible for the majority of reported U.S. COVID-19 cases.

Both models were adjusted for the following potential confounders: annual average of ambient atmospheric particulate matter $<2.5 \mu\text{m}$ in diameter ($\text{PM}_{2.5}$) between 2000 and 2016, population density, poverty, education, proportions of White, proportions of male, proportion of population older than 65 years old, owner-occupied property, median house value, median household income, percentage of people under 65 years old without health insurance, prevalence of tobacco smoking, and obesity. All covariates were measured at the county level. State-level variables for NPIs policies (facemask mandates, stay home orders) also were included in both models. The mortality model additionally adjusted for the number of county hospital beds.

County-level COVID-19 case and mortality data were obtained from the Johns Hopkins University, Center for Systems Science and Engineering Coronavirus Resource Center (CSSE). CSSE collects county-level confirmed numbers of cases and deaths of 3,342 counties across the U.S. from the U.S. Centers for Disease Control and Prevention (CDC) as well as state departments of health since January 21st, 2020.²

County-level vaccine data were obtained from Covid Act Now. These data are derived from the U.S. Department of Health and Human Services, the CDC, the New York Times, and official state and county dashboards. Data on vaccinations initiated and vaccination regimens completed were available for all 50 states.¹⁸ To allow for the development of protective immunity after vaccination, a two-week lag was introduced after people were completely vaccinated (a person vaccinated on June 18th was considered fully protected by July 2nd). A two-week lag also was used to account for time between exposure and development of COVID-19 disease. To assess the

impact of vaccination on COVID-19 mortality, a four-week lag was used (vaccinated by September 2nd to assess the impact on mortality on September 30th).

County-level annual average of PM_{2.5} between the years 2000 and 2016, as well as county-level covariates, were available from a GitHub repository.¹⁹ County-level socioeconomic and demographic variables for 2018 were available from the US Census/American Community Survey. 2020 data on the prevalence of adult tobacco smoking and adult obesity were accessible through the County Health Rankings & Roadmaps program.²⁰ The number of county hospital beds were obtained from an ArcGIS Hub dataset.²¹ State averages were used to replace missing values for county-level prevalence for smoking, obesity, and numbers of hospital beds. U.S. Department of Agriculture 2013 rural and urban codes²² were used to identify whether a county was located in metropolitan areas. State-wide non-pharmacologic prevention policies, including facemask use and stay home orders, were obtained from the Boston University School of Public Health.²³

Counties with invalid Federal Information Processing Standards (n = 10), missing covariates (n = 236), missing vaccination status on June 4th (n = 4), and negative change in incidence (n = 22) or in mortality (n = 61) possibly due to data entry error were excluded. As a result, data from 3,070 counties in 49 states were available to investigate the association between population vaccination rates and county-wide COVID-19 incidence and 3,031 counties in 49 states to investigate the association between vaccination rates and COVID-19 mortality (Table 1).

As the average US county total population complete vaccination rate at the time of analysis was approximately 40%, further stratified analyses were performed investigating associations between counties where >40% of the total population was completely vaccinated with those with <40% complete population vaccination rates. The impact of 10% incremental increases in total population vaccine coverage was assessed in sensitivity analyses. To account for the correlation within each state, we applied the robust error estimation.²⁴ Relative risks (RR) and 95% confidence intervals (CI) are reported. Analyses were performed in SAS 9.4 (Cary, NC). To estimate the number of COVID-19 cases or deaths that could have been prevented during the study period by increasing county-wide vaccination rates, RRs were multiplied by the total at-risk US population. The at-risk population was estimated using the total 2021 U.S. population, subtracting the number of reported COVID-19 cases and deaths when estimating the population at risk for COVID-19 incidence and reported COVID-19 deaths only when estimating the population at risk for COVID-19 mortality.

RESULTS

Among the 3,070 counties across 49 states, the average county total population complete vaccination rate was 42.3% as of September 16th, 2021. Counties with >40% complete vaccination rates had more hospital beds, higher median house values, higher median household incomes, higher population density, and less uninsured population compared with counties with <40% vaccination rates. These counties also were more likely to be located in metropolitan areas and in states where a facemask policy was ever issued before September 30th, 2021 (Table 2).

Overall, each percentage increase in a county's total population vaccination rate between April 23rd and September 30th, 2021 was associated with a 0.9% reduction in county-wide COVID-19

cases (relative risk (RR) 0.9910 (95% CI: 0.9869, 0.9952)) and a 1.9% reduction in county-wide COVID-19 mortality (RR 0.9807 (95% CI: 0.9745, 0.9823)). County population vaccination was associated with greater protection against COVID-19 infection, RR of 0.9895 (95% CI: 0.9851, 0.9940), and mortality, RR 0.9742 (95% CI: 0.9670, 0.9804), when the analysis was limited to July 3rd to September 30th, corresponding to when Delta became the predominant SARS-CoV-2 variant in the U.S. (Table 3).

Among the 1,686 counties in 49 states with complete vaccination coverage >40% as of September 16th, each percentage increase in county complete vaccination rates reduced the county population RR of COVID-19 disease by 1.5%, RR 0.9850 (95% CI: 0.9793, 0.9952). However, in counties with <40% complete vaccination rates, the association became null, RR 1.0021 (95% CI: 0.9957, 1.0084). In the 1,442 counties in 49 states with vaccination rate >40% as of September 2nd, each percentage increase in the vaccination rate reduced county-wide COVID-19 mortality by 2.7% (RR 0.9727 (95% CI: 0.9632, 0.9823)). In contrast, increasing vaccination rates were not associated with reductions in county-wide COVID-19 mortality among counties with <40% population vaccination rates (RR 0.9938 (95% CI: 0.9849, 1.0027)). Similar results were observed before and after Delta became the most dominant U.S. variant, as well as when further stratifying by 10% incremental increases in vaccination rates (Table 3).

Compared to a county with 40% of its total population being completely vaccinated, increasing the population vaccination rate to 80% would have reduced COVID-19 cases by 45.4% (RR 0.5458 (95% CI: 0.4335, 0.6873)) between April 23rd and September 30th and COVID-19 deaths by 67.0% (RR 0.3305 (95% CI: 0.2230, 0.4898)). Given the at-risk US population, an estimated

5,989,952 COVID-19 cases could have been prevented and 127,596 lives saved had US population vaccination rates increased from 40% to 80% (Table 4 and Table 5).

DISCUSSION

Data from 3,070 counties across 49 states demonstrates that each percentage increase in people being completely vaccinated was associated with a 0.9% decrease in population-wide COVID-19 cases and a 1.9% reduction in COVID-19 mortality between April 23rd and September 30th, 2021 after adjusting for potential confounders. Limiting the analysis to between July 3rd and September 30th, when Delta was the predominant US variant, gave similar results; each percentage increase in population vaccination rates was associated with a 1.1% decrease in county-wide COVID-19 cases and a 2.6% reduction in COVID-19 deaths. Among the counties with vaccination rate >40%, an additional percentage increase in vaccination rate was associated with a 1.5% reduction in population COVID-19 cases and 2.7% decrease in COVID-19 mortality. In contrast, null associations were observed for counties with <40% coverage of complete vaccination rates. If a county increased its complete vaccination coverage from <40% to 80% during the study period, 45.4% infections and 67.0% deaths due to COVID-19 might have been prevented.

This study is among the first to demonstrate the impact of increasing SARS-CoV-2 vaccination rates on population-wide reductions in COVID-19 incidence and mortality. As the percentage reductions in population COVID-19 cases and deaths generally exceeded the percentage increases in population vaccination rates, these data suggest that increasing population vaccination rates has spillover protective effects among non-vaccinated persons. Moreover, these

spillover protective effects grow as population vaccination rates rise. Given ongoing vaccine hesitancy in the US, these results show how increasing vaccination rates could better protect the entire community and potentially reach herd immunity.

We observed clear reductions in COVID-19 cases and deaths with rising population SARS-CoV-2 vaccination rates among counties with >40% vaccination coverage, but not among those with <40% population vaccination rates. This observation was consistent with the Israeli study showing declined COVID-19 incidence as vaccination rates increased.²⁵ Similar results were found in the stratified analyses of 10% incremental increases in vaccination rates. Though these data do not enable us to determine the population vaccine rate necessary to achieve herd immunity, the results showed that at least a 40% population vaccine coverage rate is needed to see a protective impact of vaccination among the entire population.

The study was subject to several limitations. First, ecologic study designs are vulnerable to the ecologic fallacy. Therefore, caution is required when interpreting the study results, especially when extrapolating population findings to the individual level. In addition, we cannot rule out the possibility of residual confounding even after controlling for numerous county-level and state-level covariates. Using COVID-19 reported cases may underestimate of the number of actual infections due to under-testing of asymptomatic patients. However, alternative estimates for cumulative incidence, such as seroprevalence²⁶, also have limitations including sampling bias, test sensitivity and specificity, and the progress of the pandemic.²⁷ Our analysis was not able to assess the impact of the three different vaccines currently available in the U.S., which likely had

different efficacies. Although a detailed distribution of different variants in the U.S. was not available, we examined the associations before and after the Delta variant became the predominant strain. Therefore, our results represent the associations between vaccine rates overall and COVID-19 incidence and mortality in the U.S. for vaccines as actually deployed and SARS-CoV-2 variants as they circulated during the period of our analysis.

The differential impact of rising population vaccination rates between before and after the spread of Delta variant might be due to the proportion of counties achieving >40% complete vaccination coverage. Before July 3rd, <30% of counties reached 40% population vaccination rates; almost half of counties had >40% of their total population vaccinated by September 30th, 2021. Finally, there was limited power to assess impact in counties with vaccination rates <20% or >70%. As a result, counties were combined into either < or >40%, the approximate U.S. county average, to obtain sufficient power and to account for the heterogeneity.

Nevertheless, this study is the first to estimate the association between complete vaccination rates and COVID-19 incidence and mortality in the U.S. general population using county-level data. This nation-wide study covers 3,070 counties in 49 states across the entire country, showing the population-based impact of increasing complete vaccination rates. The proportion of the Delta variant surpassed the proportion of the Alpha variant and accounted for >50% of infection in the U.S. as of June 26th, 2021.¹² Our results indicated that increasing complete vaccination rates were associated with reduced COVID-19 incidence and mortality overall and after July 3rd, demonstrating the vaccine impact within communities against SARS-CoV-2

variants in the U.S. including the Delta variant. The population-wide protective associations observed only among counties with >40% vaccination rates urge the uptake of vaccines in all counties. Though we showed estimated COVID-19 incidence and mortality reductions with complete vaccination rates increasing above 40%, these results should be interpreted with caution since there were limited data for counties with very high vaccination coverage rates. Future research should examine the barriers to vaccine uptake, especially among under-privileged populations, as well as estimate the vaccination coverage needed to reach the herd immunity.

CONTRIBUTORS

ZF Zhang conceptualized and supervised the project. ZF Zhang and F Fang developed the methods. F Fang obtained the data, conducted the analysis and wrote the original draft. JD Clemens, TF Brewer and ZF Zhang provided feedback on the analyses and edited the draft. All authors reviewed and revised the manuscript for critical content.

DECLARATION OF INTERESTS

F Fang and TF Brewer held stock in Pfizer. All other authors declare no competing interests.

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283

Table 1. Summary of data sources

Sources	Description
Johns Hopkins University Center for Systems Science and Engineering Coronavirus Resource Center (CSSE) ²	Cumulative county-level confirmed cases and deaths up to September 30, 2021
Covid Act Now ¹⁸	Cumulative county-level number of people completely vaccinated up to September 16, 2021
GitHub repository ¹⁹	Annual average PM _{2.5} concentration between 2000 and 2016
The US Census/American Community Survey	County-level socioeconomic and demographic variables in 2018
The County Health Rankings & Roadmaps program ²⁰	County-level behavioral variables in 2020
ArcGIS hub ²¹	Numbers of hospital beds in each county
Economic Research Service ²²	Urban/rural code in 2013
Boston University of Public Health ²³	State-level policy of face masks mandates and stay home orders

287 **Table 2. Characteristics of counties (n = 3,070) in 49 states by vaccination rate as of 9/16**

	Total (n = 3,070 in 49 states)	Vaccination rate ³ on 9/16 ≤ 40% (n = 1,384 in 39 states)	Vaccination rate ³ on 9/16 > 40% (n = 1,686 in 49 states)
	Mean (SD)	Mean (SD)	Mean (SD)
Incidence of COVID-19 as of 9/30 (%) ¹	13.75 (3.84)	14.58 (3.94)	13.07 (3.63)
Incidence of COVID-19 as of 7/2 (%) ¹	10.25 (3.09)	10.50 (3.14)	10.04 (3.04)
Mortality of COVID-19 as of 9/30 (%) ²	0.24 (0.13)	0.27 (0.13)	0.22 (0.12)
Mortality of COVID-19 as of 7/2 (%) ²	0.21 (0.12)	0.22 (0.11)	0.19 (0.11)
Full vaccination rate as of 9/16 (%) ³	42.27 (10.59)	33.26 (5.28)	49.66 (7.74)
Full vaccination rate as of 9/2 (%) ³	40.60 (10.71)	31.56 (5.24)	48.01 (8.03)
Full vaccination rate as of 6/18 (%) ³	34.75 (10.24)	26.73 (5.30)	41.32 (8.48)
Full vaccination rate as of 6/4 (%) ³	32.95 (9.62)	25.55 (5.17)	39.03 (8.05)
Average ambient PM _{2.5} (µg/m ³) ⁴	8.41 (2.52)	8.30 (2.53)	8.51 (2.51)
Ever smokers (%)	17.45 (3.54)	18.35 (3.59)	16.71 (3.32)
Adult obesity (%)	32.88 (5.41)	33.89 (5.05)	32.05 (5.55)
Number of hospital beds	398.59 (1103.58)	175.30 (233.47)	581.89 (1448.76)
Population living in poverty (%)	15.63 (6.43)	16.97 (6.24)	14.53 (6.37)
Population density per square mile	267.33 (1817.39)	61.91 (171.05)	435.95 (2434.89)
Owner occupied properties (%)	71.60 (8.06)	72.61 (7.13)	70.77 (8.66)
Population 25 years old and older with less than high school education (%)	20.57 (6.09)	22.48 (5.94)	19.00 (5.75)
White Americans population (%)	83.51 (16.25)	84.43 (15.62)	82.75 (16.73)
African Americans population (%)	9.13 (14.57)	9.05 (13.95)	9.20 (15.07)
Hispanic population (%)	9.21 (13.76)	8.47 (12.08)	9.82 (14.97)
Median house value (×\$1,000)	145.80 (87.18)	114.56 (40.55)	171.45 (105.05)
Median household income (×\$1,000)	51.40 (13.56)	46.94 (9.94)	55.07 (14.97)
Population over 65 years old (%)	20.28 (4.81)	20.25 (4.48)	20.31 (5.08)
Male (%)	50.06 (2.14)	50.35 (2.44)	49.82 (1.82)
Uninsured population (%)	8.88 (3.97)	10.40 (3.97)	7.64 (3.52)
Metropolitan, n (%)			
Yes	1151 (37.49)	649 (31.43)	486 (55.16)
No	1919 (62.51)	1416 (68.57)	395 (44.84)
State stay-home order before 9/30, n (%)			
Ever issued	2709 (88.24)	1218 (88.01)	1491 (88.43)
Never issued	361 (11.76)	166 (11.99)	195 (11.57)
State facemask policy before 9/30, n (%)			
Ever issued	2297 (74.82)	867 (62.64)	1430 (84.82)
Never issued	773 (25.18)	517 (37.36)	256 (15.18)

¹COVID-19 cases out of total population in each county
²COVID-19 deaths out of total population in each county
³Number of people fully vaccinated out of total population in each county
⁴Annual average of PM_{2.5} between 2000 and 2016

288 **Table 3. Adjusted RRs of COVID-19 incidence and mortality associated with additional people**
 289 **fully vaccinated per 100 population by vaccination rates**

	RR		
	(95% CI with naïve standard error estimation)		
	(95% CI with robust standard error estimation)		
Incidence ¹ (n = 3,070 in 49 states)	4/23/2021 – 7/2/2021 ³	7/3/2021 – 9/30/2021 ⁴	4/23/2021 – 9/30/2021 ⁴
	0.9960	0.9895	0.9910
Overall	(0.9935, 0.9986)	(0.9875, 0.9915)	(0.9892, 0.9929)
	(0.9877, 1.0044)	(0.9851, 0.9940)	(0.9869, 0.9952)
Above 40%	0.9857	0.9836	0.9850
	(0.9795, 0.9920)	(0.9805, 0.9867)	(0.9821, 0.9878)
	(0.9768, 0.9947)	(0.9771, 0.9901)	(0.9793, 0.9907)
70% and above	NA	NA	0.9933
			(0.9525, 1.0360)
			(0.9506, 1.0380)
60% - 69%	NA	NA	0.9917
			(0.9729, 1.0107)
			(0.9706, 1.0131)
50% - 59%	NA	NA	0.9798
			(0.9679, 0.9918)
			(0.9682, 0.9915)
40% - 49%	NA	NA	0.9907
			(0.9825, 0.999)
			(0.9825, 0.999)
Below 40%	0.9968	1.0015	1.0021
	(0.9924, 1.0012)	(0.9963, 1.0068)	(0.9970, 1.0071)
	(0.9847, 1.0091)	(0.9951, 1.0080)	(0.9957, 1.0084)
30% - 39%	NA	NA	0.9976
			(0.9879, 1.0075)
			(0.9887, 1.0067)
20% - 29%	NA	NA	1.0268
			(1.0063, 1.0477)
			(1.0095, 1.0444)
Below 20%	NA	NA	1.0199
			(0.9580, 1.0858)
			(0.9622, 1.0809)
Mortality ² (n = 3,031 in 49 states)	4/23/2021 – 7/2/2021 ⁵	7/3/2021 – 9/30/2021 ⁶	4/23/2021 – 9/30/2021 ⁶
	0.9971	0.9742	0.9807
Overall	(0.9933, 1.0009)	(0.9706, 0.9779)	(0.9779, 0.9835)
	(0.9878, 1.0065)	(0.9670, 0.9815)	(0.9745, 0.9869)
Above 40%	0.9773	0.9685	0.9727
	(0.9651, 0.9897)	(0.9616, 0.9754)	(0.9679, 0.9775)
	(0.9613, 0.9936)	(0.9567, 0.9804)	(0.9632, 0.9823)
70% and above	NA	NA	1.0682
			(0.9594, 1.1894)

			(0.9882, 1.1547)
			1.0013
60% - 69%	NA	NA	(0.9676, 1.0362)
			(0.9675, 1.0363)
			0.9618
50% - 59%	NA	NA	(0.9434, 0.9806)
			(0.9440, 0.9800)
			0.9775
40% - 49%	NA	NA	(0.9634, 0.9917)
			(0.9612, 0.9940)
	1.0050	0.9899	0.9938
Below 40%	(0.9995, 1.0105)	(0.9820, 0.9978)	(0.9873, 1.0003)
	(0.9896, 1.0206)	(0.9792, 1.0007)	(0.9849, 1.0027)
			0.9849
30% - 39%	NA	NA	(0.9731, 0.9968)
			(0.9726, 0.9973)
			1.0189
20% - 29%	NA	NA	(0.9923, 1.0462)
			(0.9953, 1.0431)
			1.0947
Below 20%	NA	NA	(0.9843, 1.2174)
			(1.0388, 1.1536)

¹Models adjust for annual PM_{2.5} concentration between 2000 and 2016, percentage of adults smokers, percentage of obese adults, percentage of people living under poverty, population density, percentage of owner occupied properties, percentage of people with less than high school education, percentage of White population, median household income, median house value, percentage of population over 65 years old, percentage of male, percentage of population under 65 years old without an insurance, metropolitan status (yes/no), stay home orders before 9/30 (ever/never) and facemask mandate before 9/30 (ever/never)

²Model 2 adjusts for all covariates in model 1 + number of hospital beds

³Percentage of fully vaccinated population as of 6/18/2021, 877 counties in 47 states with complete vaccination rate above 40% and 2,193 counties in 42 states with complete vaccination rate below 40%

⁴Percentage of fully vaccinated population as of 9/16/2021, 1,686 counties in 49 states with complete vaccination rate above 40% (1,032 counties in 43 states with vaccination rate between 40% and 49%, 471 counties in 46 states with vaccination rate between 50% and 59%, 149 counties in 32 states with vaccination rate between 60% and 69%, and 34 counties in 20 states with vaccination rate of 70% and above) and 1,384 counties in 39 states with complete vaccination rate below 40% (36 counties in 14 states with vaccination rate below 20%, 260 counties in 32 states with vaccination rate between 20% and 29%, and 1,088 counties in 39 states with vaccination rate between 30% and 39%)

⁵Percentage of fully vaccinated population as of 6/4/2021, 684 counties in 47 states with complete vaccination rate above 40% and 2,347 counties in 44 states with complete vaccination rate below 40%

⁶Percentage of fully vaccinated population as of 9/2/2021, 1,442 counties in 49 states with complete vaccination rate above 40% (906 counties in 43 states with vaccination rate between 40% and 49%, 395 counties in 45 states with vaccination rate between 50% and 59%, 131 counties in 31 states with vaccination rate between 60% and 69%, and 29 counties in 19 states with vaccination rate of 70% and above) and 1,589 counties in 44 states with complete vaccination rate below 40% (43 counties in 15 states with vaccination rate of below 20%, 394 counties in 33 states with vaccination rate between 20% and 29%, and 1,172 counties in 40 states with vaccination rate between 30% and 39%)

Table 4. Estimated adjusted RRs, risk reductions of COVID-19 incidence and cases could have been prevented associated with complete vaccination rates between April 23 and September 30, 2021

	RR ¹ (95% CI with naïve standard error estimation) (95% CI with robust standard error estimation)	Cases per 100,000 population ² (95% CI with naïve standard error estimation) (95% CI with robust standard error estimation)	Cases could have been prevented ³ (95% CI with naïve standard error estimation) (95% CI with robust standard error estimation)
Counties with 40% complete vaccination rate	1.0000	4568.96	0
Counties with 50% complete vaccination rate (each 10% increase)	0.8595 (0.8352, 0.8846) (0.8114, 0.9105)	3927.02 (3816.00, 4041.70) (3707.25, 4160.04)	1,852,902 (1,521,886, 2,173,369) (1,180,319, 2,487,241)
Counties with 60% complete vaccination rate (each 20% increase)	0.7388 (0.6975, 0.7826) (0.6584, 0.8290)	3375.55 (3186.85, 3575.67) (3008.20, 3787.67)	3,444,684 (2,867,053, 3,989,345) (2,255,134, 4,504,992)
Counties with 70% complete vaccination rate (each 30% increase)	0.6350 (0.5825, 0.6923) (0.5343, 0.7548)	2901.29 (2661.42, 3163.09) (2441.20, 3448.65)	4,813,590 (4,057,922, 5,505,955) (3,233,677, 6,141,613)
Counties with 80% complete vaccination rate (each 40% increase)	0.5458 (0.4865, 0.6124) (0.4335, 0.6873)	2493.74 (2222.80, 2798.03) (1980.64, 3140.25)	5,989,952 (5,111,636, 6,771,995) (4,123,862, 7,470,955)
Counties with 90% complete vaccination rate (each 50% increase)	0.4692 (0.4063, 0.5418) (0.3518, 0.6258)	2143.76 (1856.37, 2475.46) (1607.36, 2859.26)	7,000,146 (6,042,703, 7,829,666) (4,934,918, 8,548,408)

¹Percentage of fully vaccinated population as of 9/16/2021; Models adjust for annual PM_{2.5} concentration between 2000 and 2016, percentage of adults smokers, percentage of obese adults, percentage of people living under poverty, population density, percentage of owner occupied properties, percentage of people with less than high school education, percentage of White population, median household income, median house value, percentage of population over 65 years old, percentage of male, percentage of population under 65 years old without an insurance, metropolitan status (yes/no), stay home orders before 9/30 (ever/never) and facemask mandate before 9/30 (ever/never)

²The average incidence among counties with less than 40% complete vaccination rates

³The at-risk population was estimated using the total 2021 U.S. population, subtracting the number of reported COVID-19 cases and the number of reported COVID-19 deaths

Table 5. Estimated adjusted RRs, risk reductions of COVID-19 mortality and deaths could have been prevented associated with complete vaccination rates between April 23 and September 30, 2021

	RR ¹ (95% CI with naïve standard error estimation) (95% CI with robust standard error estimation)	Deaths per 100,000 population ² (95% CI with naïve standard error estimation) (95% CI with robust standard error estimation)	Deaths could have been prevented ³ (95% CI with naïve standard error estimation) (95% CI with robust standard error estimation)
Counties with 40% complete vaccination rate	1.0000	57.39	0
Counties with 50% complete vaccination rate (each 10% increase)	0.7582 (0.7219, 0.7963) (0.6872, 0.8366)	43.51 (41.43, 45.70) (39.44, 48.01)	46,083 (38,822, 53,001) (31,141, 59,615)
Counties with 60% complete vaccination rate (each 20% increase)	0.5749 (0.5211, 0.6342) (0.4722, 0.6999)	32.99 (29.90, 36.40) (27.10, 40.17)	81,017 (69,716, 91,271) (57,194, 100,590)
Counties with 70% complete vaccination rate (each 30% increase)	0.4359 (0.3762, 0.5050) (0.3245, 0.5855)	25.02 (21.59, 28.98) (18.62, 33.60)	107,509 (94,339, 118,886) (78,997, 128,740)
Counties with 80% complete vaccination rate (each 40% increase)	0.3305 (0.2716, 0.4022) (0.2230, 0.4898)	18.97 (15.59, 23.08) (12.80, 28.11)	127,596 (113,931, 138,822) (97,236, 148,084)
Counties with 90% complete vaccination rate (each 50% increase)	0.2506 (0.1961, 0.3203) (0.1532, 0.4098)	14.38 (11.25, 18.38) (8.79, 23.52)	142,824 (129,540, 153,211) (112,483, 161,387)

¹Percentage of fully vaccinated population as of 9/2/2021; Models adjust for annual PM_{2.5} concentration between 2000 and 2016, percentage of adults smokers, percentage of obese adults, percentage of people living under poverty, population density, percentage of owner occupied properties, percentage of people with less than high school education, percentage of White population, median household income, median house value, percentage of population over 65 years old, percentage of male, percentage of population under 65 years old without an insurance, metropolitan status (yes/no), stay home orders before 9/30 (ever/never), facemask mandate before 9/30 (ever/never) and number of hospital beds

²The average mortality among counties with less than 40% complete vaccination rates

³The at-risk population was estimated using the total 2021 U.S. population, subtracting the number of reported COVID-19 deaths

REFERENCE

1. World Health Organization. COVID-19 Weekly Epidemiological Update. Geneva: World Health Organization, 2021.
2. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis* 2020; **20**(5): 533-4.
3. Fang F, Mu L, Zhu Y, Rao J, Heymann J, Zhang Z-F. Long-Term Exposure to PM2.5, Facemask Mandates, Stay Home Orders and COVID-19 Incidence in the United States. *International Journal of Environmental Research and Public Health* 2021; **18**(12): 6274.
4. Thompson MG, Burgess JL, Naleway AL, et al. Prevention and Attenuation of Covid-19 with the BNT162b2 and mRNA-1273 Vaccines. *N Engl J Med* 2021; **385**(4): 320-9.
5. U.S. Food and Drug Administration. FDA Approves First COVID-19 Vaccine. August 23, 2021 2021. <https://www.fda.gov/news-events/press-announcements/fda-approves-first-covid-19-vaccine> (accessed August 26, 2021 2021).
6. Polack FP, Thomas SJ, Kitchin N, et al. Safety and Efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020; **383**(27): 2603-15.
7. Doria-Rose N, Suthar MS, Makowski M, et al. Antibody Persistence through 6 Months after the Second Dose of mRNA-1273 Vaccine for Covid-19. *New England Journal of Medicine* 2021.
8. Sadoff J, Gray G, Vandebosch A, et al. Safety and Efficacy of Single-Dose Ad26.COV2.S Vaccine against Covid-19. *N Engl J Med* 2021; **384**(23): 2187-201.
9. Keehner J, Horton LE, Pfeffer MA, et al. SARS-CoV-2 Infection after Vaccination in Health Care Workers in California. *N Engl J Med* 2021.

- 322 10. Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and
323 Hospitalizations Among Adults, by Vaccination Status - New York, May 3-July 25, 2021.
324 *MMWR Morb Mortal Wkly Rep* 2021; **70**(37): 1306-11.
- 325 11. U.S. Food and Drug Administration. Coronavirus (COVID-19) Update: FDA Takes
326 Additional Actions on the Use of a Booster Dose for COVID-19 Vaccines. Silver Spring, MD;
327 2021.
- 328 12. Centers for Disease Control and Prevention. Variant Proportions. 2021.
329 <https://covid.cdc.gov/covid-data-tracker/#variant-proportions> (accessed July 3, 2021 2021).
- 330 13. Thompson MG, Stenehjem E, Grannis S, et al. Effectiveness of Covid-19 Vaccines in
331 Ambulatory and Inpatient Care Settings. *N Engl J Med* 2021; **385**(15): 1355-71.
- 332 14. Butt AA, Omer SB, Yan P, Shaikh OS, Mayr FB. SARS-CoV-2 Vaccine Effectiveness in
333 a High-Risk National Population in a Real-World Setting. *Ann Intern Med* 2021.
- 334 15. Cabezas C, Coma E, Mora-Fernandez N, et al. Associations of BNT162b2 vaccination
335 with SARS-CoV-2 infection and hospital admission and death with covid-19 in nursing homes
336 and healthcare workers in Catalonia: prospective cohort study. *Bmj* 2021; **374**: n1868.
- 337 16. Fisher KA, Bloomstone SJ, Walder J, Crawford S, Fouayzi H, Mazor KM. Attitudes
338 Toward a Potential SARS-CoV-2 Vaccine : A Survey of U.S. Adults. *Ann Intern Med* 2020;
339 **173**(12): 964-73.
- 340 17. Anderson RM, Vegvari C, Truscott J, Collyer BS. Challenges in creating herd immunity
341 to SARS-CoV-2 infection by mass vaccination. *Lancet* 2020; **396**(10263): 1614-6.
- 342 18. Covid Act Now. Covid Act Now API. 2021 ed; 2021.

19. Wu X, Nethery RC, Sabath MB, Braun D, Dominici F. Air pollution and COVID-19 mortality in the United States: Strengths and limitations of an ecological regression analysis. *Science Advances* 2020; **6**(45): eabd4049.
20. The County Health Rankings & Roadmaps program. Health Behaviors. 2020. <https://www.countyhealthrankings.org/explore-health-rankings/measures-data-sources/county-health-rankings-model/health-factors/health-behaviors>.
21. GeoPlatform ArcGIS Online. Hospitals. 2020. <https://hub.arcgis.com/datasets/geoplatform::hospitals/about> (accessed July 3, 2021 2021).
22. Economic Research Service. Rural-Urban Continuum Codes. 2020. <https://www.ers.usda.gov/data-products/rural-urban-continuum-codes/2021>).
23. Raifman J, Nocka K, Jones D, et al. COVID-19 US state policy database. 2020.
24. Gotway CA, Stroup WW. A Generalized Linear Model Approach to Spatial Data Analysis and Prediction. *Journal of Agricultural, Biological, and Environmental Statistics* 1997; **2**(2): 157-78.
25. Haas EJ, Angulo FJ, McLaughlin JM, et al. Impact and effectiveness of mRNA BNT162b2 vaccine against SARS-CoV-2 infections and COVID-19 cases, hospitalisations, and deaths following a nationwide vaccination campaign in Israel: an observational study using national surveillance data. *The Lancet* 2021; **397**(10287): 1819-29.
26. Byambasuren O, Dobler CC, Bell K, et al. Comparison of seroprevalence of SARS-CoV-2 infections with cumulative and imputed COVID-19 cases: Systematic review. *PLOS ONE* 2021; **16**(4): e0248946.
27. Accorsi EK, Qiu X, Rumpler E, et al. How to detect and reduce potential sources of biases in studies of SARS-CoV-2 and COVID-19. *Eur J Epidemiol* 2021; **36**(2): 179-96.

