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Public Health Impact of Coronavirus Disease Vaccines in the United States: An Observational Study

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Summary box

What is already known on this topic: The public health impact of scaling up Coronavirus Disease (COVID-19) vaccines remains largely uncharacterized.

What this study adds: In this observational study, including nearly 80% of U.S. counties and 300 million persons, higher vaccination coverage was associated with lower rates of population-level COVID-19 mortality and incidence. Vaccines should be deployed strategically with public health and social measures based on on-going levels of transmission.

Abstract (279 words)

Background: Although previous studies have examined Coronavirus Disease (COVID-19) vaccines at the individual-level, studies evaluating the impact at the population-level are limited.

Objective: We evaluated the impact of vaccine scale-up on population-level mortality and incidence in the United States (U.S.).

Design, Setting, and Participants: In this U.S. observational study, we included county-level case surveillance and vaccine administration data reported from December 14, 2020 – December 18, 2021.

Interventions: We estimated the impact of a 10% improvement in county vaccination coverage (defined as at least one dose of a COVID-19 vaccine amongst adults ≥ 18 years of age) on mortality and incidence rates during the first year of vaccine scale-up. For impact estimates during the eras of Alpha and Delta predominance we evaluated the impact of low (10-39%), medium (40-69%), and high vaccination coverage (≥70%) versus very low coverage (0-9%) on mortality and incidence rates.

Main outcome measures: We calculated county mortality rates (i.e. deaths/100K population/county-week) as our primary outcome and incidence (i.e. cases/100K population/county-week) as our secondary outcome. Incidence rate ratios (IRR) were used to compare rates across vaccination coverage levels.

Results: 2,558 counties from 48 U.S. states were included. In total, there were 30,643,878 COVID-19 cases and 439,682 COVID-19–associated deaths over 132,791 county-weeks. A 10% improvement in vaccination coverage was associated with an 8% reduction in mortality rates (95% confidence interval [CI], 8%-9%) and a 7% reduction in incidence (95% CI, 6%-8%). Compared to very low coverage, low, medium, and high vaccination coverage were associated with reduced mortality and incidence rates during the eras of Alpha and Delta variant predominance.

Conclusions: Higher vaccination coverage is associated with lower rates of population-level COVID-19 mortality and incidence in the U.S.

Background

As of February 11, 2022 there have been 404,910,528 COVID-19 cases and 5,783,776 COVID-19 deaths reported globally and 77,516,009 COVID-19 cases and 915,425 COVID-19 deaths reported in the United States (U.S.).[1,2] The U.S. death toll recently surpassed the 1918 Spanish Flu as the deadliest pandemic in recent history.[3] In addition to COVID-related deaths, the pandemic also has indirect effects on other health conditions. These effects are captured in excess mortality and life expectancy estimates. Domestically, life expectancy decreased by 1.5 years from 2019 to 2020, representing the largest reduction since World War II.[4]

Messenger RNA (mRNA) COVID-19 vaccines developed by Pfizer-BioNTech and Moderna, and an adenovirus COVID-19 vaccine developed by Johnson & Johnson, have become valuable tools to combat this pandemic. Clinical trials evaluating efficacy against symptomatic infection found that the Pfizer-BioNTech vaccine was 95.0% effective, the Moderna vaccine was 94.1% effective, while the Janssen vaccine (Johnson & Johnson) was 66.3% effective.[5-7] The U.S. Food and Drug Administration (FDA) granted emergency use authorization (EUA) for mRNA vaccines in December 2020 and the Janssen vaccine in February 2021. FDA approval for the Pfizer and Moderna vaccines were granted in August 2021 and January 2022, respectively.[8] EUA was further granted to third doses of the mRNA vaccines for the immunocompromised and for certain populations.[8] As of February 11, 2022 there have been nearly 550 million vaccine doses administered in the U.S. and over 10 billion vaccine doses administered globally [1,2] By mid-2022, the World Health Organization target is to vaccinate 70% of the world's population.[9]

Across countries, the real-world effectiveness of the COVID-19 vaccines has largely been consistent with efficacy estimates observed in clinical trials.[10-12] In addition to the individual-level effect on disease risk and progression, vaccines may also have secondary benefits on slowing spread and reducing onward transmission and its associated morbidity and mortality.[13] Population-level data and analyses have been limited.[14,15] We aimed to estimate how increasing county coverage of vaccines affected population-level mortality and incidence.

Methods

Study design

We conducted an observational study of the U.S. population using national, county-level surveillance data. In the United States, counties are a geographic administrative unit below states and territories, and is inclusive of the nation's capital, Washington D.C. The U.S Centers for Disease Control and Prevention (CDC) currently receives surveillance data from 3,224 counties (or county-equivalents) in the United States. We included and analyzed county COVID-19 cases, deaths, and vaccines reported to CDC. We tracked mortality as our primary outcome and incidence (using reported probable and confirmed COVID-19 cases) as our secondary outcome. County-level incidence was calculated by standardizing reported county cases and deaths per 100,000 population over a week.[2]

Study definitions

We defined a case as one which meets the Council of State and Territorial Epidemiologists' surveillance case definitions as confirmed or probable and a death as those that were COVID-related as determined or reported by jurisdictions. Deaths are defined as those that were determined or reported by jurisdictions as being COVID-related.[16,17] Each vaccine dose administered was attributed to the county in which the person resides.[18] The county vaccination coverage is defined as the number of people aged ≥ 18 years old who received at least one dose of COVID-19 vaccine among the total number of people aged ≥ 18 years old residing in that county.[2]

Data sources

For case and death counts disaggregated by county and week, we utilized the CDC-managed case surveillance dataset which includes the most recent numbers reported by states, territories, and other jurisdictions. This dataset is populated by routine reporting from jurisdictions to CDC.[19] To document new cases, jurisdictions may use the date that a case was reported to the health department, a person took a COVID-19 test, a laboratory confirmed a COVID-19 test as positive, or a person was diagnosed with COVID-19 by a clinician. For death reporting, jurisdictions may use the date when the death was reported to the health department or the date of COVID-19 associated death.[2] Counts of COVID-19 vaccine doses administered by week and county were retrieved from the CDC-managed vaccine dataset. This dataset includes COVID-19 vaccination data (including the date of vaccine administration, the number of doses administered, county of residence, amongst other variables) reported to CDC by jurisdictions, pharmacies and federal

entities through Immunization Information Systems, Vaccine Administration Management System, or direct submission of vaccination records.[20] The population data, used for denominators to measure vaccination coverage, was from the vintage 2019 U.S. population estimates.[21] To prevent confounding related to community social vulnerability and movement, these variables were included in the model.[22,23] The CDC and Agency for Toxic Substances and Disease Registry's Social Vulnerability Index (SVI) encompasses socioeconomic status (i.e., poverty rates, unemployment rates, income levels, and education levels), household composition and disability (i.e., ages, disability, and single-parent households), minority status, language capability, and housing type and transportation (multi-unit structures, mobile homes, crowding levels, vehicle ownership, and group housing) into a single measure.[24] Google's Community Mobility Reports help measure changes in community mobility related to COVID-19.[25]

Inclusion criteria

We included case surveillance and vaccine administration data from December 14, 2020 to December 18, 2021. Persons at least eighteen years of age with a valid county of residence in one of the states or territories that received at least one COVID-19 vaccination were included. Given that population benefits may extend beyond the primary vaccine recipient, we included case and mortality data across all ages. Data completeness was an inclusion criterion for analysis. We used a 70% threshold for data completeness of reporting county of residence across all data sources. Specifically, a jurisdiction was excluded if more than 30% of the case, death, and/or vaccination data for the jurisdiction was contributed by unspecified or unknown counties of residence.[1] In addition, any county-week missing covariate information used in regression models was excluded.

Data analysis

[1] Texas and Hawaii were excluded due to vaccination data being unavailable at county-level. County-equivalents in territories except for Puerto Rico and Guam were excluded either because the county-level population data of adults ≥18 years old was unavailable (U.S. Virgin Islands) or because the county-equivalent vaccination data was unavailable (all other territories). In addition, eight counties in California with a population of fewer than 20,000 people were excluded since California does not report the vaccination data of counties with under 20,000 people. The Kusilvak Census Area in Alaska was excluded due to unavailable vaccination data and the Valdez-Cordova Census Area in Alaska was excluded because the case and mortality data were unavailable. The District of Columbia, villages in Guam, and municipalities in Puerto Rico were excluded due to a lack of mobility data. Finally, Rio Arriba County in New Mexico was excluded due to missing the social vulnerability index.

County of residence case and first dose COVID-19 vaccination data were aggregated by MMWR week beginning with MMWR week 2020-51 (December 13-19, 2020) and ending with MMWR week 2021-50 (December 12-18, 2021).[26] Generalized linear mixed models assuming a negative binomial outcome distribution were utilized to assess associations between vaccination coverage and death and case rates using continuous estimates.[27] A first-order autoregressive correlation structure was used to account for multiple observations per county and for potential autocorrelation. County-level population was included as an offset and SVI category and mobility data were included as covariates. To account for cases occurring during the period of developing immunity, a county remained in the lower vaccination category for two weeks before moving to the next vaccination category.

We calculated estimates during the period of Alpha predominance and the period of Delta predominance (starting when the national Delta prevalence was estimated to be at least 50%, i.e. the week of June 20, 2021 onward) categorically.[28,29] We defined four different categories for county vaccination coverage: very low coverage (0-9% of the county had been vaccinated), low coverage (10-39% of the county had been vaccinated), medium coverage (40-69% of the county had been vaccinated), and high coverage (≥70% of the county had been vaccinated). As with the continuous analyses, to account for cases occurring during the period of developing immunity, a county remained in the lower vaccination category for two weeks before moving to the next vaccination category. Given the inadequate number of county-weeks accrued with very low vaccination coverage during the era of Delta predominance, we used the mortality and incidence rates for very low vaccination coverage from the Alpha era as a referent for all categorical analyses.

Sensitivity analyses

We conducted three sensitivity analyses with the continuous analyses. The first sensitivity analysis was to compare definitions of vaccination being at least one dose to only including fully vaccinated individuals (i.e., at least two mRNA doses or a single adenovirus dose). The second was to compare how using a stringency level for data completeness of 70% compared to 90%. The third was to compare estimates with and without the two-week lag period.

Results

First year of vaccine roll-out

Data from a total of 2,558 counties in 48 U.S. states were included. In total, there were 30,643,878 COVID-19 cases and 439,682 COVID-19–associated deaths observed over 132,791 county-weeks (Table 1). Every 10% improvement in vaccination coverage was associated with an 8% reduction in mortality rates (95% CI, 8%-9%, Figure 1) and with a 7% reduction in case incidence (95% CI, 6%-8%, Figure 1).

Era of Alpha variant predominance

In total, there were 15,493,299 COVID-19 cases and 263,873 COVID-19–associated deaths observed over and 70,189 county-weeks. Compared to very low coverage, low (IRR 0.40, 95% CI 0.39-0.42), medium (IRR 0.25, 95% CI 0.23-0.26), and high (IRR 0.19, 95% CI 0.16-0.22) vaccination coverage categories had lower rates of mortality (Figure 2). Compared to very low coverage, low (IRR 0.43, 95% CI 0.41-0.44), medium (IRR 0.30, 95% CI 0.29-0.32), and high (IRR 0.20, 95% CI 0.18-0.22) vaccination coverage categories had lower incidence rates (Figure 2).

Era of Delta variant predominance

In total, there were 15,150,579 COVID-19 cases and 175,809 COVID-19–associated deaths observed over and 62,602 county-weeks. Compared to very low coverage, low (IRR 0.16, 95% CI 0.07-0.36), medium (IRR 0.10, 95% CI 0.04-0.22), and high (IRR 0.07, 95% CI 0.03-0.17) vaccination coverage categories had lower rates of mortality (Figure 3). Compared to very low coverage, low (IRR 0.30, 95% CI 0.18-0.50), medium (IRR 0.21, 95% CI 0.13-0.36), and high (IRR 0.14, 95% CI 0.08-0.24) vaccination coverage categories had lower incidence rates (Figure 3).

Sensitivity analyses

We observed sustained reductions in county mortality and incidence rates when only including fully vaccinated individuals within the vaccination coverage categories, when increasing our data stringency level, and when removing the two-week immunity lag period (Figure 4).

Discussion

Using data from 2,558 counties – representing nearly 300 million persons and 80% of the U.S. population – we found that increasing the vaccination coverage in counties was associated with a reduced incidence of COVID-related mortality and cases. We observed decreasing trends in mortality and case incidence associated with higher levels of vaccination coverage across both the eras of Alpha and Delta variant predominance. This impact was robust to various changes conducted in sensitivity analyses, which improves prediction and confidence in these findings.

COVID-associated mortality remains one of the most important clinical outcomes to guide public health decision making, measure pandemic severity, and evaluate mitigation efforts. As such, it was our primary outcome. In the U.S., death registration rates, and cause of death ascertainment, remain high. This suggests that U.S. mortality surveillance systems have, and will continue, to be useful for COVID-19 mortality surveillance. Previous vaccine studies have proven individual-level benefits on survival.[30] We observed that these benefits may extend to the population-level, with high coverage counties having over an 80% reduction in mortality rates compared to very low coverage counties. Given that infection fatality rates for COVID-19 increase with age, counties with a higher proportion of elderly persons may have more COVID-19 mortality and stand to benefit from high coverage of COVID-19 vaccines.[31]

We used reported cases as a proxy for incidence for our secondary outcome. Although reliable, available across jurisdictions, and reported continuously, reported cases may not reflect true transmission rates because of variation in when people seek out testing.[32] For example, asymptomatic people may not actively seek out testing on their own accord, but may be important to test for gauging disease transmission. Due to more recent re-opening requirements for workplaces, restaurants, entertainment venues, schools, and outgoing international air travel more asymptomatic individuals may be seeking out testing as of late.[33] These requirements, and their uptake, may vary across states and counties. Nonetheless, the reduction in incidence observed with increasing vaccination coverage is consistent with surveillance data from other countries that have achieved high vaccination coverage and emerging evidence on transmission from contact tracing programmes.[1,34]

Increasing vaccination coverage may play a role in mitigating the effects of the Delta and Omicron variants and reduce the emergence of future variants.[35,36] By June 27, 2021 the Delta variant made up 50% of circulating variants in the U.S. and nearly 100% by September 21, 2021.[2] More recently, the Omicron variant was first reported December 1, 2021 and comprised 95% of circulating variants by January 1, 2022.[2] The Delta variant had increased transmissibility and possible increased virulence compared to earlier COVID-19 strains.[37,38] In our study, by the time the Delta variant predominated, counties with very low vaccination coverage (i.e., 0-9%) were rare making comparisons to very low coverage counties more difficult. Nonetheless, our findings of continued protection against death during the period of Delta predominance appear consistent with literature on vaccine effectiveness.[30,39-41] Additional studies aimed at population vaccine impact during the period of Delta predominance merit consideration for validating our observations. Although our study period did not include the period of Omicron predominance, data suggesting reduced vaccine effectiveness are emerging and may lead to changes in population vaccine impact that merit exploration.[42,43] Continuing to monitor the Delta and Omicron variants, and the emergence of other variants of interest, is critical and will require on-going genomic surveillance.

Clinical studies indicate that a single dose of an mRNA vaccine provides a lower level of protection compared to two doses.[44] Furthermore, two mRNA doses appears more effective than a single adenovirus dose against symptomatic infection.[45] We defined individuals with at least one dose of vaccine as being vaccinated for the purposes of vaccination coverage. Given our study design utilized population surveillance data, changing our coverage definition to include solely fully vaccinated individuals would place people with a single dose of mRNA vaccine in our referent, the very low coverage category. This may introduce bias in the incidence and mortality estimates. Indeed, when we changed our definition of vaccination coverage to being fully dosed during sensitivity analysis, we did not find increased effect sizes, as would be expected from clinical studies.[44] On-going vaccine studies continue to evaluate the comparative effectiveness of vaccines by manufacturer.[10] Furthermore, as of September 2021 the FDA began recommending a third dose for specific populations.[8] Given that only individuals 18 and older were eligible for vaccination across vaccines during most of our study period, we used this age threshold to define vaccination coverage. Pediatric studies will be a welcome contribution to understanding the effects of vaccines

on younger age groups, when feasible. Further studies may benefit from evaluating the population impact of vaccination coverage using different definitions and eligibility scenarios.

There are several limitations to consider when interpreting these data. We chose vaccination coverage thresholds based on programmatic experience; exploring coverage thresholds above 70% may be worth examining in future research once more counties have achieved these levels for extended periods of time. There were some jurisdictions that were excluded based on not having county-level information on immunizations, cases, and deaths for at least 70% of their counties. Additional markers of disease severity, such as hospitalizations, were not explored in this study due to possible differences in ascertainment and reporting coverage across jurisdictions. Given the limited number of variables that were (1) known to affect mortality and incidence, (2) collected at the county-level, and (3) available on a weekly basis we did not control for masking, physical distancing, or other similar potential confounding variables in this study. Furthermore, given the limited number of county-weeks we lacked power to stratify by time periods, and to include a contemporaneous Delta referent group, and cannot rule out the possibility of temporal confounding. Finally, given that we used aggregate case surveillance data to have the most complete case and death data available, other characteristics of cases, such as demographics and comorbidities, were not available. States, territories, and jurisdictions adapt national guidance on which date to use for case reporting.[17] In this study we collated county data across these geographic areas. There may be a time difference depending on which date a health department uses; however, this is unlikely to be substantial enough to affect which week a case or death occurs. Naturally acquired immunity resulting from COVID-19 infection may have affected the reduced case incidence observed during the study period. These are limitations of our study. Nonetheless, reductions in incidence and death observed in emerging U.S. data using alternative data sources and study designs give us confidence in the directionality and magnitude of our estimates.[46,47]

In addition to individual-level benefits, we observed that vaccines protect communities against severe disease and incidence. Higher coverage of vaccines appeared to confer greater levels of community benefits. Given community benefits are rooted in individual benefits, for which vaccine effectiveness has been established in countries around the world, these data may be generalisable to other countries. Future research may benefit from evaluating macroeconomic

effects of improving population health, such as changes in employment rates and GDP resulting from re-opening society. Vaccines should be deployed strategically with public health and social measures based on on-going levels of transmission.

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Table 1. Characteristics of included counties

Variable	13/12/20-12/12/21	Alpha (13/12/20-27/6/21)	Delta (28/6/21-12/12/21)
Sample size (counties, weeks)	2558, 132791	2557, 70189	2543, 62602
Vaccination coverage (Median, range)	46.4 (0.0, 100.0)	24.9 (0.0, 100.0)	58.8 (2.1, 100.0)
Vaccination coverage 0-9.9% (Number, %)	21312 (16.0)	21238 (30.3)	74 (0.1)
Vaccination coverage 10-39.9% (Number, %)	31838 (24.0)	28138 (40.1)	3700 (5.9)
Vaccination coverage 40-69.9% (Number, %)	65473 (49.3)	19513 (27.8)	45960 (73.4)
Vaccination coverage 70%+ (Number, %)	14168 (10.7)	1300 (1.9)	12868 (20.6)
Population Size (Median, range)	24538 (1074, 7894557)	24541 (1074, 7894557)	24696 (1404, 7894557)
SVI, Quartile 1 (Number, %)	620 (24.2)	620 (24.2)	614 (24.1)
SVI, Quartile 2 (Number, %)	666 (26.0)	666 (26.0)	662 (26.0)
SVI, Quartile 3 (Number, %)	655 (25.6)	654 (25.6)	652 (25.6)
SVI, Quartile 4 (Number, %)	617 (24.1)	617 (24.1)	615 (24.2)
% of adults aged ≥ 25 years without a high school diploma (Median, range)	11.8 (1.6, 42.4)	11.8 (1.6, 42.4)	11.8 (1.7, 42.4)
% Below Federal Poverty Level (Median, range)	14.8 (2.3, 55.1)	14.8 (2.3, 55.1)	14.8 (2.3, 55.1)
Per capita income (Median, range)	26256 (10148, 72832)	26256 (10148, 72832)	26262 (10148, 72832)
Unemployment rate (Median, range)	5.6 (0.7, 25.8)	5.6 (0.7, 25.8)	5.6 (0.7, 25.8)
% Aged 17 or younger (Median, range)	22.3 (7.3, 40.3)	22.3 (7.3, 40.3)	22.3 (7.3, 40.3)
% Aged 65 or older (Median, range)	17.9 (3.8, 55.6)	17.9 (3.8, 55.6)	17.8 (3.8, 55.6)
% Older than age 5 with a disability (Median, range)	15.5 (3.8, 33.7)	15.5 (3.8, 33.7)	15.5 (3.8, 33.7)
% racial or ethnic minority (Median, range)	15.1 (0.3, 95.7)	15.1 (0.3, 95.7)	15.1 (0.3, 95.7)
% Single-parent households (Median, range)	8.2 (1.9, 25.6)	8.2 (1.9, 25.6)	8.2 (1.9, 25.6)
% with limited English proficiency (Median, range)	0.7 (0.0, 21.7)	0.7 (0.0, 21.7)	0.7 (0.0, 21.7)
% Households without a vehicle (Median, range)	5.8 (0.5, 77.0)	5.8 (0.5, 77.0)	5.8 (0.5, 77.0)
% Housing in structures with ≥ 10 units (Median, range)	3.2 (0.0, 89.4)	3.2 (0.0, 89.4)	3.2 (0.0, 89.4)
% in mobile homes (Median, range)	10.7 (0.0, 54.8)	10.7 (0.0, 54.8)	10.7 (0.0, 54.8)
% Occupied housing units where people exceed rooms (Median, range)	1.8 (0.0, 35.4)	1.8 (0.0, 35.4)	1.8 (0.0, 35.4)
% People in institutionalized group residencies (Median, range)	2.0 (0.0, 36.2)	2.0 (0.0, 36.2)	2.0 (0.0, 36.2)
% Change in mobility for groceries (Median, range)	4.6 (-91.0, 206.7)	-0.7 (-91.0, 140.0)	8.0 (-80.0, 206.7)

% Change in mobility for home (Median, range)	4.1 (-23.2, 41.8)	6.0 (-4.0, 41.8)	3.3 (-23.2, 15.4)
% Change in mobility for parks (Median, range)	33.0 (-84.6, 490.0)	10.4 (-84.6, 433.0)	58.7 (-81.3, 490.0)
% Change in mobility for retail (Median, range)	-1.4 (-88.0, 304.9)	-7.1 (-88.0, 163.4)	2.6 (-85.0, 304.9)
% Change in mobility for transit (Median, range)	-6.6 (-85.4, 280.1)	-14.4 (-82.0, 258.6)	3.1 (-85.4, 280.1)
% Change in mobility for offices (Median, range)	-18.4 (-85.4, 65.7)	-18.4 (-79.8, 32.4)	-18.4 (-85.4, 65.7)

SVI, social vulnerability index

Figure 1. Impact of vaccination coverage on county COVID-19 mortality ('A') and incidence ('B') during the first year of vaccine roll-out

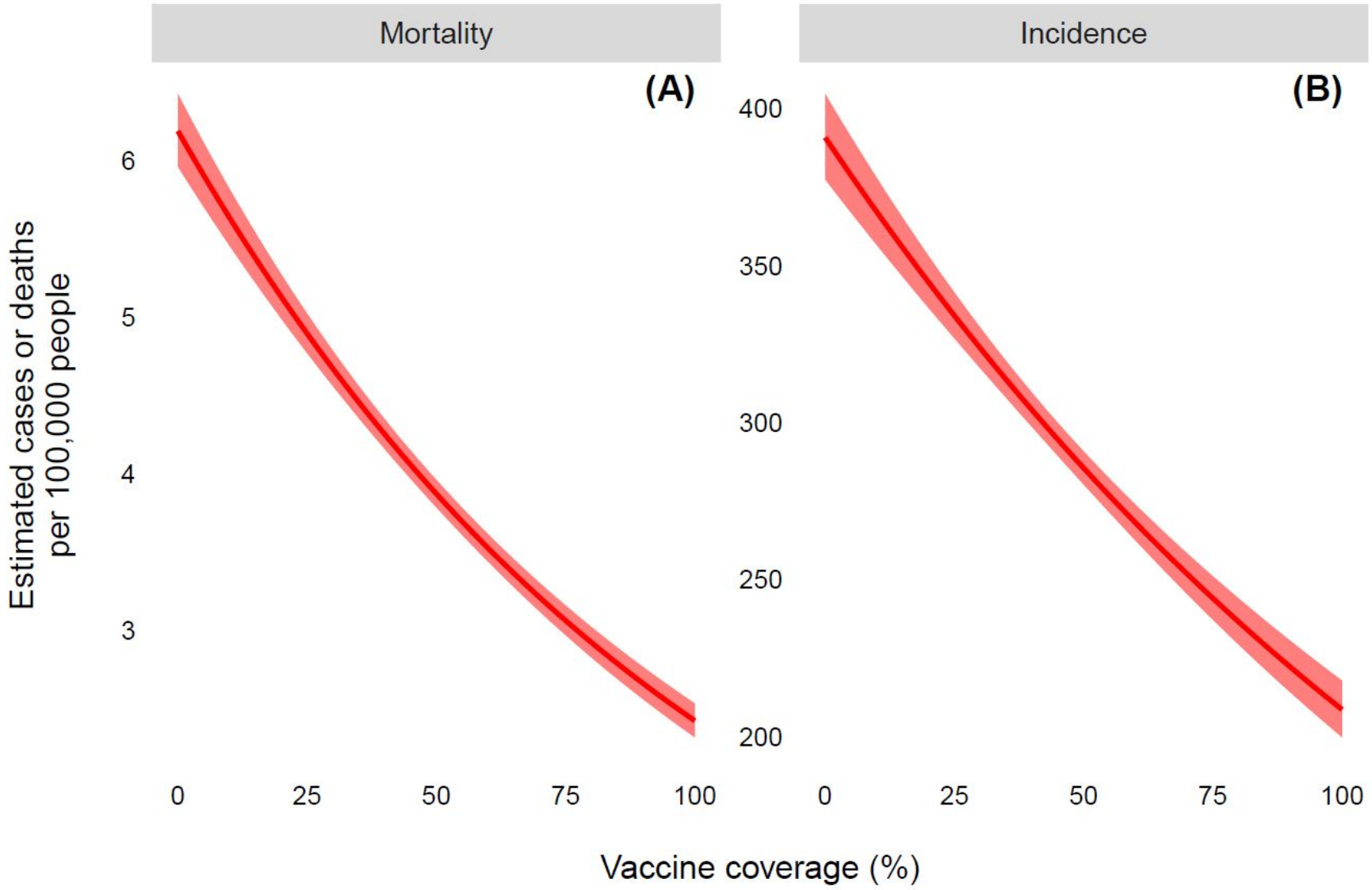
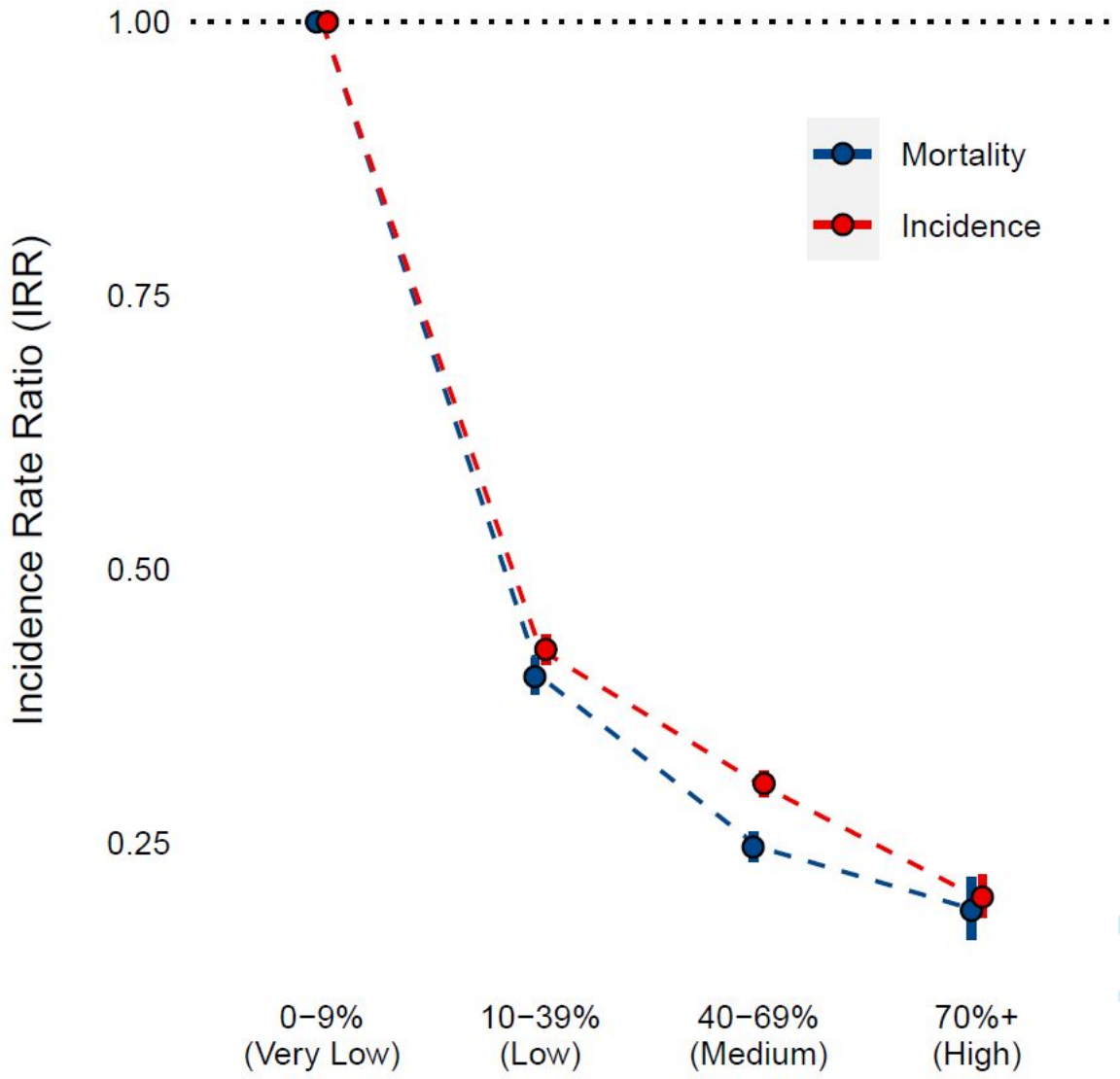
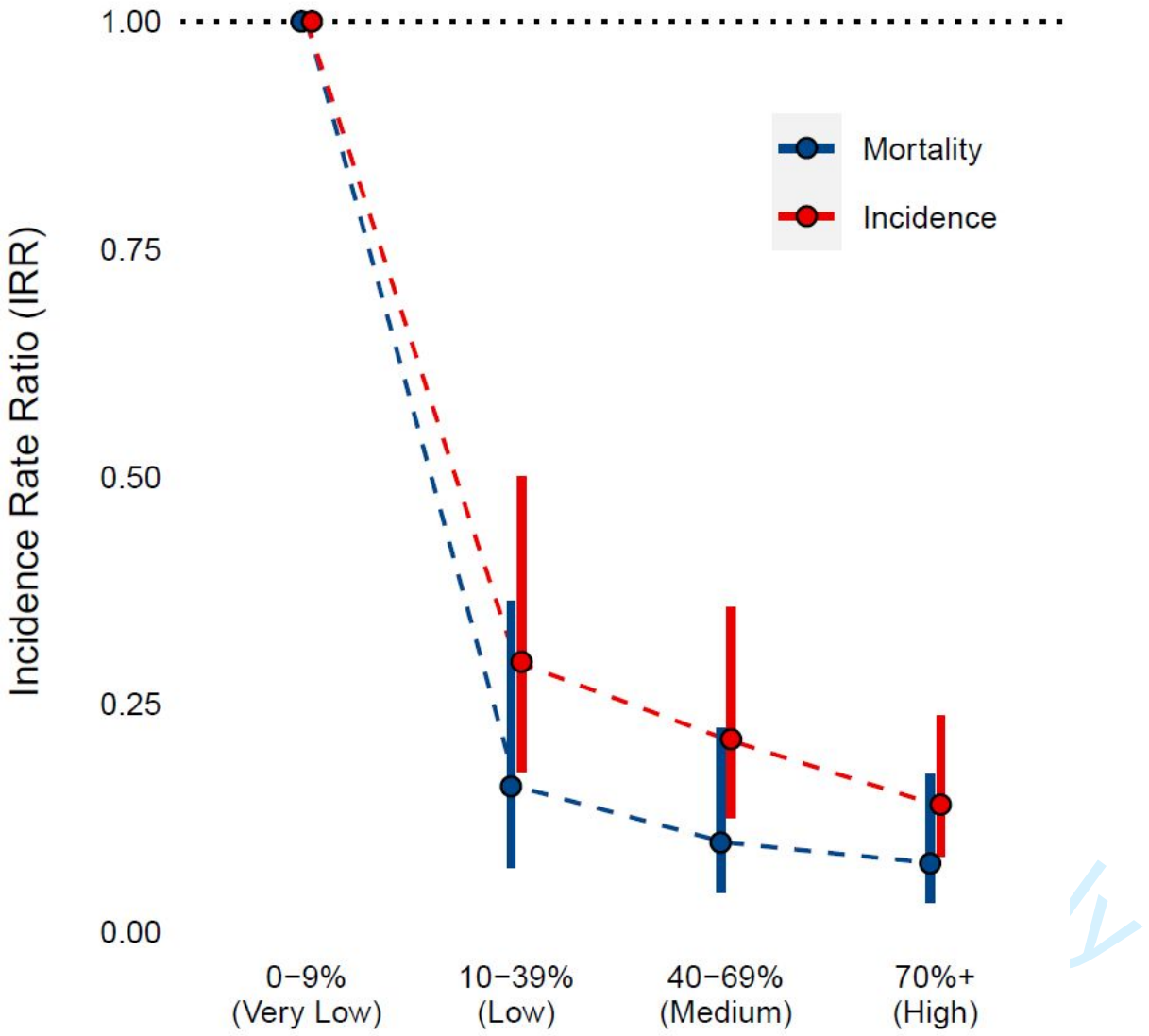


Figure 2. Impact of vaccination coverage on county COVID-19 mortality and incidence during the era of Alpha predominance



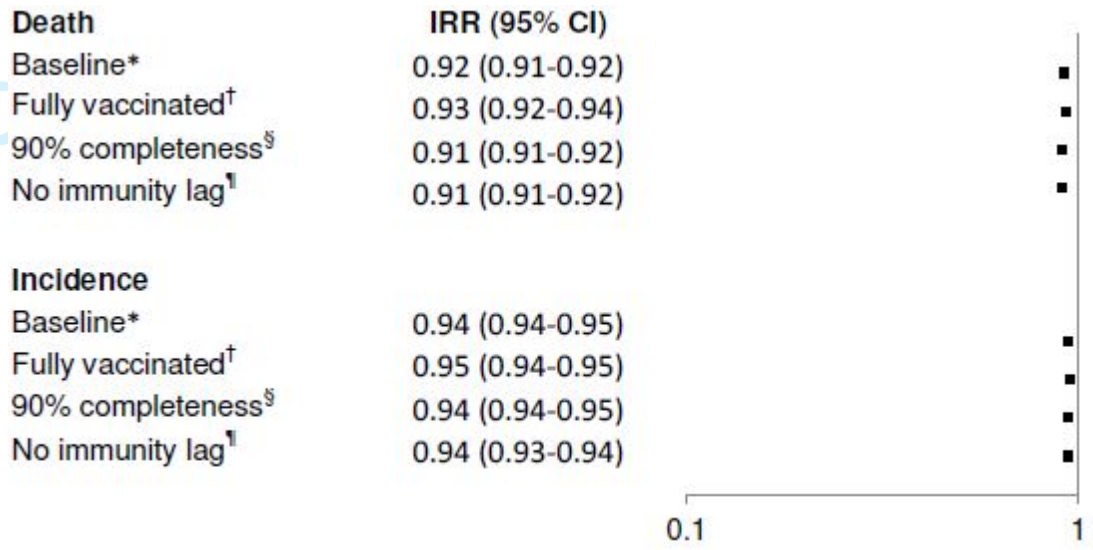
Note: Analyses are from 2,557 counties in 48 U.S. jurisdictions

Figure 3. Impact of vaccination coverage on county COVID-19 mortality and incidence during the era of Delta predominance



Note: Analyses are from 2,543 counties in 48 U.S. jurisdictions

Figure 4. Sensitivity analyses of including only fully vaccinated individuals, increasing data stringency requirements, and removing the two-week immunity lag period



*In the baseline group, the vaccination coverage refers to coverage of at least one dose of vaccine, the 2,558 counties and 48 U.S. jurisdictions included had ≥70% completeness rates of reporting county of residence, and the study period was December 14, 2020 – December 18, 2021

†Vaccination coverage refers to coverage of fully vaccinated individuals

§, The 2,164 counties and 42 U.S. jurisdictions included had ≥90% completeness rates of reporting county of residence

¶The two-week immunity period was removed

References

1. World Health Organization. WHO Coronavirus (COVID-19) Dashboard. (https://covid19.who.int/).
2. Centers for Disease Control and Prevention. COVID Data Tracker. (https://covid.cdc.gov/covid-data-tracker/#datatracker-home).
3. Centers for Disease Control and Prevention. 1918 Pandemic (H1N1 virus). (https://www.cdc.gov/flu/pandemic-resources/1918-pandemic-h1n1.html).
4. Arias E, Tejada-Vera B, Ahmad F, Kochanek KD. Provisional Life Expectancy Estimates for 2020. Vital Statistics Rapid Release 2021(15) (https://www.cdc.gov/nchs/data/vsrr/vsrr015-508.pdf).
5. 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):2603-2615. DOI: 10.1056/NEJMoa2034577.
6. Baden LR, El Sahly HM, Essink B, et al. Efficacy and Safety of the mRNA-1273 SARS-CoV-2 Vaccine. N Engl J Med 2021;384(5):403-416. DOI: 10.1056/NEJMoa2035389.
7. 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):2187-2201. DOI: 10.1056/NEJMoa2101544.
8. U.S. Food & Drug Administration. COVID-19 Vaccines. (https://www.fda.gov/emergency-preparedness-and-response/coronavirus-disease-2019-covid-19/covid-19-vaccines).
9. World Health Organization. Strategy to Achieve Global COVID-19 Vaccination by mid-2022. (https://cdn.who.int/media/docs/default-source/immunization/covid-19/strategy-to-achieve-global-covid-19-vaccination-by-mid-2022.pdf).
10. Self WH, Tenforde MW, Rhoads JP, et al. Comparative Effectiveness of Moderna, Pfizer-BioNTech, and Janssen (Johnson & Johnson) Vaccines in Preventing COVID-19 Hospitalizations Among Adults Without Immunocompromising Conditions - United States, March-August 2021. MMWR Morb Mortal Wkly Rep 2021;70(38):1337-1343. DOI: 10.15585/mmwr.mm7038e1.
11. Hall VJ, Foulkes S, Saei A, et al. COVID-19 vaccine coverage in health-care workers in England and effectiveness of BNT162b2 mRNA vaccine against infection (SIREN): a prospective, multicentre, cohort study. Lancet 2021;397(10286):1725-1735. DOI: 10.1016/S0140-6736(21)00790-X.
12. 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. Lancet 2021;397(10287):1819-1829. DOI: 10.1016/S0140-6736(21)00947-8.
13. The COVID-19 Scenario Modeling Hub Team. COVID-19 Scenario Modeling Hub. (https://covid19scenariomodelinghub.org/viz.html).
14. Haas EJ, McLaughlin JM, Khan F, et al. Infections, hospitalisations, and deaths averted via a nationwide vaccination campaign using the Pfizer-BioNTech BNT162b2 mRNA COVID-19 vaccine in Israel: a retrospective surveillance study. Lancet Infect Dis 2021. DOI: 10.1016/S1473-3099(21)00566-1.
15. McNamara LA, Wiegand RE, Burke RM, et al. Estimating the early impact of the US COVID-19 vaccination programme on COVID-19 cases, emergency department visits,

hospital admissions, and deaths among adults aged 65 years and older: an ecological analysis of national surveillance data. Lancet 2022;399(10320):152-160. DOI: 10.1016/S0140-6736(21)02226-1.
16. Centers for Disease Control and Prevention. About CDC COVID-19 Data. (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/about-us-cases-deaths.html).
17. Council of State and Territorial Epidemiologists. Update to the standardized surveillance case definition and national notification for 2019 novel coronavirus disease (COVID-19). (https://cdn.ymaws.com/www.cste.org/resource/resmgr/21-ID-01_COVID-19_updated_Au.pdf).
18. Centers for Disease Control and Prevention. Reporting COVID-19 Vaccinations in the United States.
19. Centers for Disease Control and Prevention. CDC COVID-19 Data. (https://www.cdc.gov/coronavirus/2019-ncov/covid-data/about-us-cases-deaths.html).
20. Centers for Disease Control and Prevention. COVID-19 Vaccine Delivered and Administration Data. (https://www.cdc.gov/coronavirus/2019-ncov/vaccines/distributing/about-vaccine-data.html).
21. The United States Census Bureau. Datasets. (https://www2.census.gov/programs-surveys/popest/datasets/2010-2019/).
22. Islam SJ, Nayak A, Hu Y, et al. Temporal trends in the association of social vulnerability and race/ethnicity with county-level COVID-19 incidence and outcomes in the USA: an ecological analysis. BMJ Open 2021;11(7):e048086. DOI: 10.1136/bmjopen-2020-048086.
23. Wellenius GA, Vispute S, Espinosa V, et al. Impacts of social distancing policies on mobility and COVID-19 case growth in the US. Nat Commun 2021;12(1):3118. DOI: 10.1038/s41467-021-23404-5.
24. Centers for Disease Control and Prevention. CDC SVI 2018 Documentation – 1/31/2020. (https://www.atsdr.cdc.gov/placeandhealth/svi/documentation/SVI_documentation_2018.html).
25. Google. COVID-19 Community Mobility Reports. (https://www.google.com/covid19/mobility/).
26. Centers for Disease Control and Prevention. MMWR weeks ending log 2020-2021. (https://stacks.cdc.gov/view/cdc/84011/).
27. Hilbe JM. Negative binomial regression: Cambridge University Press, 2011.
28. Paul P, France AM, Aoki Y, et al. Genomic Surveillance for SARS-CoV-2 Variants Circulating in the United States, December 2020-May 2021. MMWR Morb Mortal Wkly Rep 2021;70(23):846-850. DOI: 10.15585/mmwr.mm7023a3.
29. Lambrou AS, Shirk P, Steele MK, et al. Genomic Surveillance for SARS-CoV-2 Variants: Predominance of the Delta (B.1.617.2) and Omicron (B.1.1.529) Variants — United States, June 2021–January 2022. Morbidity and Mortality Weekly Report 2022;71(6):206-211.
30. Scobie HM, Johnson AG, Suthar AB, et al. Monitoring Incidence of COVID-19 Cases, Hospitalizations, and Deaths, by Vaccination Status - 13 U.S. Jurisdictions, April 4-July 17, 2021. MMWR Morb Mortal Wkly Rep 2021;70(37):1284-1290. DOI: 10.15585/mmwr.mm7037e1.
31. Levin AT, Hanage WP, Owusu-Boaitey N, Cochran KB, Walsh SP, Meyerowitz-Katz G. Assessing the age specificity of infection fatality rates for COVID-19: systematic review,

meta-analysis, and public policy implications. Eur J Epidemiol 2020;35(12):1123-1138. DOI: 10.1007/s10654-020-00698-1.

32. Suthar AB, Schubert S, Garon J, Couture A, Brown AM, Charania S. COVID-19 case definitions, diagnostic testing criteria, and surveillance across the pandemic's 25 highest burden countries. Emerging Infectious Diseases 2021.

33. Centers for Disease Control and Prevention. Community, Work, and School: Information for Where You Live, Work, Learn, and Play. (https://www.cdc.gov/coronavirus/2019-ncov/community/index.html).

34. Eyre DW, Taylor D, Purver M, et al. Effect of Covid-19 Vaccination on Transmission of Alpha and Delta Variants. N Engl J Med 2022. DOI: 10.1056/NEJMoa2116597.

35. Christie A, Brooks JT, Hicks LA, et al. Guidance for Implementing COVID-19 Prevention Strategies in the Context of Varying Community Transmission Levels and Vaccination Coverage. MMWR Morb Mortal Wkly Rep 2021;70(30):1044-1047. DOI: 10.15585/mmwr.mm7030e2.

36. Walensky RP, Walke HT, Fauci AS. SARS-CoV-2 Variants of Concern in the United States-Challenges and Opportunities. JAMA 2021;325(11):1037-1038. DOI: 10.1001/jama.2021.2294.

37. Ong SWX, Chiew CJ, Ang LW, et al. Clinical and virological features of SARS-CoV-2 variants of concern: a retrospective cohort study comparing B.1.1.7 (Alpha), B.1.315 (Beta), and B.1.617.2 (Delta). Clin Infect Dis 2021. DOI: 10.1093/cid/ciab721.

38. Twohig KA, Nyberg T, Zaidi A, et al. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. Lancet Infect Dis 2021. DOI: 10.1016/S1473-3099(21)00475-8.

39. Rosenberg ES, Holtgrave DR, Dorabawila V, et al. New COVID-19 Cases and Hospitalizations Among Adults, by Vaccination Status - New York, May 3-July 25, 2021. MMWR Morb Mortal Wkly Rep 2021;70(37):1306-1311. DOI: 10.15585/mmwr.mm7037a7.

40. Fowlkes A, Gaglani M, Groover K, et al. Effectiveness of COVID-19 Vaccines in Preventing SARS-CoV-2 Infection Among Frontline Workers Before and During B.1.617.2 (Delta) Variant Predominance - Eight U.S. Locations, December 2020-August 2021. MMWR Morb Mortal Wkly Rep 2021;70(34):1167-1169. DOI: 10.15585/mmwr.mm7034e4.

41. Lopez Bernal J, Andrews N, Gower C, et al. Effectiveness of Covid-19 Vaccines against the B.1.617.2 (Delta) Variant. N Engl J Med 2021;385(7):585-594. DOI: 10.1056/NEJMoa2108891.

42. Collie S, Champion J, Moultrie H, Bekker LG, Gray G. Effectiveness of BNT162b2 Vaccine against Omicron Variant in South Africa. N Engl J Med 2021. DOI: 10.1056/NEJMc2119270.

43. Johnson AG, Amin AB, Ali AR, et al. COVID-19 Incidence and Death Rates Among Unvaccinated and Fully Vaccinated Adults with and Without Booster Doses During Periods of Delta and Omicron Variant Emergence - 25 U.S. Jurisdictions, April 4-December 25, 2021. MMWR Morb Mortal Wkly Rep 2022;71(4):132-138. DOI: 10.15585/mmwr.mm7104e2.

44. Pilishvili T, Fleming-Dutra KE, Farrar JL, et al. Interim Estimates of Vaccine Effectiveness of Pfizer-BioNTech and Moderna COVID-19 Vaccines Among Health

Care Personnel - 33 U.S. Sites, January-March 2021. MMWR Morb Mortal Wkly Rep 2021;70(20):753-758. DOI: 10.15585/mmwr.mm7020e2.

45. !!! INVALID CITATION !!! 5-7.

46. Fang F, Clemens JD, Zhang Z-F, Brewer TF. Impact of SARS-CoV-2 Vaccines on Covid-19 Incidence and Mortality in the United States. medRxiv 2021 (https://www.medrxiv.org/content/10.1101/2021.11.16.21266360v1.full).

47. McLaughlin JM, Khan F, Pugh S, Swerdlow DL, Jodar L. County-Level Vaccination Coverage and Rates of COVID-19 Cases and Deaths in the United States. SSRN 2021 (https://papers.ssrn.com/sol3/papers.cfm?abstract_id=3908476).

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