Association of Trends in SARS-CoV-2 Seroprevalence and State-Issued Nonpharmaceutical Interventions— United States, August 1, 2020 – March 30, 2021

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Running title: COVID-19 nonpharmaceutical interventions

Abstract

Objectives. To assess if state-issued nonpharmaceutical interventions (NPIs) are associated with reduced rates of SARS-CoV-2 infection as measured through anti-nucleocapsid (anti-N) seroprevalence, a proxy for cumulative prior infection that distinguishes seropositivity from vaccination).

Methods. Monthly anti-N seroprevalence during August 1, 2020 – March 30, 2021 was estimated using a nationwide blood donor serosurvey. Using multivariable logistic regression models, we measured the association of seropositivity and state-issued, county-specific NPIs for mask mandates, gathering bans, and bar closures.

Results. Compared with individuals living in a county with all three NPIs in place, the odds of having anti-N antibodies were 2.2 (95% CI: 2.0-2.3) times higher for people living in a county that did not have any of the three NPIs, 1.6 (95% CI: 1.5-1.7) times higher for people living in a county that only had a mask mandate and gathering ban policy, and 1.4 (95% CI: 1.3-1.5) times higher for people living in a county that had only a mask mandate.

Conclusions. Consistent with studies assessing NPIs relative to COVID-19 incidence and mortality, the presence of NPIs were associated with lower SARS-CoV-2 seroprevalence indicating lower rates of cumulative infections. Multiple NPIs are likely more effective than single NPIs.

Keywords: novel coronavirus, COVID-19, SARS-CoV-2, seroprevalence, nonpharmaceutical interventions

Introduction

Governments worldwide have used nonpharmaceutical interventions (NPIs), including mask mandates, gathering bans, and bar closures, to reduce the transmission of SARS-CoV-2, the virus that causes the novel coronavirus disease (COVID-19).[1-3] In the United States (U.S.), which has recorded over 79 million cases and 975,000 deaths associated with COVID-19 nationwide as of March 30, 2022,[4] studies examining NPIs (e.g., event studies of NPI's over a pre- and post-implementation timeframe)[5] have suggested that NPIs reduce COVID-19 cases[6] and hospitalizations.[7] No analyses have evaluated the association of NPIs in the U.S. and infections, including asymptomatic infections, through the use of COVID-19 seroprevalence data.

Longitudinal seroprevalence data can be used to estimate cumulative incidence for all infections.[8] For example, it captures data on different types of seropositivity: production of antibodies against the nucleocapsid (N) protein of the virus can differentiate past infection (anti-N antibodies and anti-spike [S] antibodies) from vaccine-induced seropositivity (anti-S antibodies only), a distinction that can capture mild and asymptomatic infections which may not be diagnosed or reported to public health officials or data systems and help supplement case data. This type of seroprevalence data may capture infections in persons more likely to experience no symptoms or mild symptoms, e.g., persons aged under 45 years who may be less likely to be tested and reported to public health compared with older persons[9,10], have higher contact rates than the general population,[11] and may contribute to increased community transmission rates. NPIs might reduce the number of close contacts or frequency of close contact exposures more for younger adults compared with older adults.[12] Seroprevalence data could thus be used to study NPIs.

The objectives of this study were to use seroprevalence data from a nationally representative serosurvey of blood donors[13] to examine (1) associations between the presence of continuous state-issued, county-specific NPIs with SARS-CoV-2 seroprevalence from August 1, 2020 – March 30, 2021 in the United States (including waves predominated by alpha, beta, and delta variants[14]) and (2) differences in the increase in seroprevalence among counties, stratified by differences in state-issued NPI status, in order to assess whether NPIs are associated with reduced transmission.

Methods

Human Participation Protection

Per policies and guidance of the University of California Institutional Review Board, study investigators certified that the seroprevalence study met the definition of research as defined in Code of Federal Regulations (C.F.R.) 46.102(l) but did not involve human subjects as defined in 46.103(e)(1); it was reviewed by CDC and conducted consistent with applicable federal regulations and CDC policy (45 C.F.R. part 46; 21 CFR part 56; 42 USC § 241(d), 5 USC § 552a, 44 USC § 3501).

Data Sources

Seroprevalence Data. Monthly anti-nucleocapsid (anti-N) seroprevalence during August 1, 2020 – March 30, 2021 was estimated using data from residual blood donation specimens from a nationwide blood donor seroprevalence study, which includes blood donor demographics and anti-N antibody results, which indicate previous SARS-CoV-2 infection. Eligibility criteria, donor selection, sampling methods, and data collection settings and locations have previously been described.[15] Blood collection organization laboratories performed the anti-N antibody testing using the Roche Elecsys Chemiluminescent Total Immunoglobulin Assay (Roche Diagnostics, Basel, Switzerland). Since July 2020, approximately 135,000 specimens per month were collected and tested for anti-N antibodies.[15,16]

Non-Pharmaceutical Interventions (NPIs) Data. County-specific data on state-issued mask mandates, bar closures, and gathering bans were obtained from executive and administrative orders identified on government websites (see appendix). In this analysis, "state" refers to the 50 states and the District of Columbia. Orders were catalogued and coded to extract mitigation policy variables for mask mandates, bar closures, and gathering bans, their effective dates and expiration dates, and the counties to which they applied when state-issued NPIs applied differently to counties within the state.

For each NPI, each county was categorized as having a continuous NPI for the entire study period or the absence of an NPI for the entire study period; those with intermittent NPIs were excluded (see appendix). State-issued mask mandates were defined as requirements for persons to wear a mask (1) anywhere outside of their home or (2) in retail businesses and in restaurants or food establishments. Bars were categorized as closed if the law prohibited on-site consumption in bars. Gathering bans were defined as the presence of any size gathering restriction, even if the size of prohibited gatherings changed within the study timeframe.

Study period and inclusion/exclusion criteria. The seroprevalence estimates used repeat cross-sectional data and lacked precision to estimate the incidence of SARS-CoV-2 infections over time. Antibody status can indicate that a blood donor has had a past infection but does not indicate when an infection occurred. We could not determine whether infections occurred after an NPI was issued or relaxed and investigated only states and counties with continuous policies in the date range August 1, 2020 – March 30, 2021, using the term “state-issued, county-specific” to refer to NPIs issued by the 50 states and District of Columbia. No territories or tribes were included in this analysis.

We use “state-issued, county-specific” to reflect the context in which NPI orders resulted: In the U.S., states-issued orders govern all counties within the state. However, a state-issued order may specify that the order applies differently to counties within the state, for instance based on a county’s COVID-19 case metrics. For example, a state-issued order may create different restriction categories and designate counties that fall in red, yellow, and green categories, defined by the county’s percent positivity and hospital capacity (e.g., Colorado[17]). This results in a state-issued order that applies differently at the county level. The legal data in this analysis accounts for these state-issued, county specific measures.

The selected study period was chosen by manually reviewing NPI policy data and maximizing the number of NPI policy categories with continuous NPI status over the longest possible duration. Out of 1972 counties with seroprevalence data, 1610 counties met inclusion criteria for the mask mandates, 1514 for bar closures, 1202 for gathering bans, and 752 for multiple policies.

Categorical variables. Counties were categorized in two mutually exclusive groups: the NPI was in place for the entire study period, and the NPI was never in place for the study period. Counties were also classified into the following multi-NPI categories: 1) presence of all three NPIs; 2) presence of mask mandate and gathering ban but permitted on-site consumption in bars; 3) presence of mask mandate but not gathering ban and permitted on-site consumption in bars; and 4) absence of all three NPIs (supplemental table 1). All other combinations of NPIs were limited to counties in fewer than three states and were not analyzed.

Statistical Analyses

Seroprevalence rates by NPI status. Monthly SARS-CoV-2 seroprevalence during August 1, 2020–March 30, 2021 was estimated and stratified by NPI status. Survey design weights were used in the construction of the seroprevalence estimates, to account for demographic differences between the sample of blood donors and the general population and for county population size. Associated 95% confidence intervals were computed using standard errors calculated with Jackknife replicate weights.[15] For each month, counties within the same NPI category (i.e. indicating sustained presence or absence of an NPI) were combined in order to compute a seroprevalence estimate. Regression analysis was performed if the trends between the categories had visually significant separation.

Multivariable logistic regression modeling. Association of seropositivity of individual blood donors with the effects of a continuously used NPI were estimated using four logistic regression models. Separate logistic regression models were developed to analyze effects for each NPI: (1) mask mandates, (2) bar closures, and (3) gathering bans, with the fourth logistic regression modeling effects for a (4) multi-NPI variable including combinations of all three NPIs. The model inputs were the same for each logistic regression, except for the NPI variables being analyzed.

Weights were incorporated into the model to account for survey design (see appendix). The model controlled for age, sex, race/ethnicity, rural/urban status, and spatio-temporal fixed effects including month and census region (supplemental Table 2). Donors with missing variables were excluded, including 3.0% due to missing race or ethnicity and <0.01% due to missing age. COVID-19 vaccination had been received by an unknown proportion of donors during December 2020—March 2021. Using unweighted estimates, first-time donors appear to have higher infection rates and lower vaccination rates. Repeat donors are more likely to be non-Hispanic White and older than first-time donors; we adjusted for these characteristics.

To estimate if vaccination rates might influence results, we conducted a sensitivity analysis restricting the analysis to December 2020, months prior to widespread vaccination.

Measures and outcomes. Adjusted odds ratios and 95% confidence intervals were estimated for the odds of being seropositive for an individual residing in a county with one or more continuous NPIs compared with living in a county with a continuous absence of an NPI during the entire study period. T-tests were used to determine significance, with $p < 0.05$ considered significant. All data preprocessing and formatting was performed in Python™ [18] with the Pandas™ [19] and NumPy© [20] libraries. Statistical analyses were executed in R (version 3.5.0). R's survey library was used to perform the regressions.

Results

Demographics

A median of 131,404 monthly donations were included in the study (range: 121,033–133,252). In total, 1,040,611 donations were included with 106,551 (10.2%) indicating past infection and 934,060 (89.8%) indicating no past infection. Among donors who donated during the study period, 50.9% were female, 86.3% were non-Hispanic White, 2.6% were non-Hispanic Black, 6.2% were Hispanic, 12.1% were aged 16–29 years, and 20.2% were aged ≥65 years

(Table 1). Approximately 87% of donations were from donors who had previously donated to the same blood organization.

Seroprevalence Trends By NPI

Multiple NPIs. In counties with all three NPIs (Figure 1(a)), seroprevalence increased from 3.8% (95% CI: 2.9-4.6%) in August 2020 to 12.0% (95% CI: 10.7-13.3%) in March 2021; in counties with zero NPIs, the seroprevalence increased from 1.7% (95% CI: 1.2-2.2%) to 26.5% (95% CI: 24.6-28.3%) (Figure 1(b), Table 2). Compared with people living in a county with all three state-issued NPIs, the odds of having anti-N antibodies were 2.2 (95% CI: 2.0-2.3) times higher for people living in a county that did not have any of the three state-issued NPIs and 1.6 (95% CI: 1.5-1.7) times higher for people living in a county that only had state-issued mask mandates and gathering bans, after controlling for other factors (Table 2).

Mask mandates. In counties with a state-issued mask mandate (Figure 1(c)), seroprevalence increased from 4.2% (95% CI: 4.0-4.5%) to 17.6% (95% CI: 17.1-18.0%); in counties without a state-issued mask mandate, the seroprevalence increased from 6.5% (95% CI: 6.0-7.0%) to 23.8% (95% CI: 23.0-24.6%) (Figure 1(d), Table 2). The odds of being seropositive for anti-N antibodies were 1.6 (95% CI: 1.5-1.6) times higher for people residing in counties without a state-issued mask mandate compared with people residing in counties with a state-issued mask mandate (Table 2).

Gathering bans. In counties with a state-issued gathering ban (Figure 1(e)), seroprevalence increased from 5.2% (95% CI: 4.8-5.6%) to 18.0% (95% CI: 17.5-18.6%); in counties without a state-issued gathering ban, the seroprevalence increased from 5.8% (95% CI: 5.3-6.4%) to 21.9% (95% CI: 21.1-22.8%) (Figure 1(f), Table 2). The odds of being seropositive for anti-N antibodies were 1.2 (95% CI: 1.2-1.3) times higher for people residing in counties without a state-issued gathering ban compared with people residing in counties with a state-issued gathering ban (Table 2).

Bar closures. In counties with state-issued bar closures (Figure 1(g)), seroprevalence increased from 3.4% (95% CI: 2.9-3.9%) to 17.1% (95% CI: 16.1-18.2%); in counties where the state permitted on-site consumption in bars, the seroprevalence increased from 5.0% (95% CI: 4.6-5.3%) to 21.2% (95% CI: 20.6-21.8%) (Figure 1(h), Table 2). The odds of being seropositive for anti-N antibodies were 1.5 (95% CI: 1.4-1.6) times higher for people residing in counties where the state permitted on-site consumption in bars compared with people residing in counties with state-issued bar closures (Table 2).

Impact of vaccination. The association of the presence of NPIs and lower SARS-CoV-2 seroprevalence was not impacted when restricting the study period to months prior to widespread COVID-19 vaccine administration (August–December 2020) (supplemental Tables 3 and 4).

<u>*Discussion*</u>

This is a unique study investigating the impact of NPI using national seroprevalence data. Mask mandates, gathering bans, and bar closures from August 1, 2020 – March 30, 2021 were associated with a lower anti-N seroprevalence, indicating lower rates of cumulative infections. Seroprevalence increased more in counties with no state-issued NPIs than in those with any state-issued NPI. The presence of any NPI was associated with a lower rate of anti-N seropositivity compared with counties with no state-issued NPIs, and while the presence of mask mandates had the largest impact on seroprevalence of any one NPI, the presence of all three NPIs was associated with the lowest anti-N seropositivity. These findings build upon research showing associations between NPIs and fewer COVID-19 cases[7] and can help quantify the potential burdens of infections (including asymptomatic infections) that could be averted through NPIs. Additionally, our model's consolidation of different combinations of policies both reflects the complexity of measuring the impact of multiple sustained policies[21] and demonstrates the potential benefits of employing the "Swiss Cheese Model" of using multiple measures to reduce community transmission.[22] Although the potential impacts of NPIs on social, mental, and economic health should be considered, the sustained use of NPIs and mass vaccination can reduce transmission and facilitate restoration of normal societal activities.

This study models effects of NPIs on decreasing cumulative incidence of SARS-CoV-2 infections over an extended period.[23] Other studies of case incidence or death do not capture all infections in the study population, resulting in significant under counts.[7,24] Although not all people may produce a detectable antibody response, use of serology data provides better capture of infections than reported case data. Pre/post NPI implementation analysis, as in previous studies,[5] was not possible in this study due to the heterogeneity of the NPI categories and the use of seroprevalence data, which cannot determine the specific time an infection occurred. However, a strength and novelty of the study was examining effects of the presence of continuous state-issued NPI policies over a sustained eight-month period with cumulative SARS-CoV-2 infection. Our study was consistent with prior U.S. and international studies that explored NPIs that found that community mask adherence,[21] mask mandates, and mass gathering bans[25] were associated with reduced COVID-19 hospitalization,[22] cases, and deaths[26-28] relative to the start and end of NPIs. This consistency both demonstrates seroprevalence data as a valuable metric for measuring NPI impact and validates prior studies that relied on reported case and death data to assess NPIs.[29]

Limitations

The findings of this study are subject to several limitations. First, states defined NPI categories differently, a potential source of misclassification and coding bias (see Appendix). Second, although seroprevalence estimates were adjusted for demographic differences between the sample of blood donors and the general population, other factors (e.g., eligibility or likelihood to donate) might influence the seroprevalence.[30,31] Thus, seroprevalence estimates might not be generalizable to the general population.[32-34] Third, seroprevalence data starting several months after the start of the pandemic (July 2020) limited the ability to conduct other types of analyses (e.g., analyzing trends in the first wave). Fourth, the analysis did not control for vaccination rates, but the results did not change when restricted to months prior to widespread administration. Only 19% of the U.S. population had completed a primary COVID-19 vaccine series by March 30, 2021.[4] Fifth, because blood donor personal identifiers were removed, individual blood donor data could not be analyzed longitudinally. Inclusion in the study sample of multiple specimens from an individual blood donor in a single month is expected to be rare. Results do not account for potential antibody waning.[35] Sixth, results might differ in the setting of other SARS-CoV-2 variants, which compared with previous strains may be more infectious.[36,37] Seventh, although our analysis shows an association between the presence of continuous state-issued NPIs and reduced anti-N SARS-CoV-2 seroprevalence, it cannot prove causation. Potential, unmeasured confounders include local methods of NPI implementation and enforcement, voluntary compliance with NPIs, and local culture around compliance.[29,38]

Populations that live in localities with continuous NPIs might voluntarily practice more strict social distancing or other mitigation measures. Eighth, in the multiple NPI analysis, NPI categories were represented by as few as three states because most states changed at least one NPI policy during the study period; this potentially limits generalizability.

Conclusion

The presence of continuous NPIs is associated with decreased SARS-CoV-2 seroprevalence. Data suggest that multiple NPIs are more effective than single NPIs. A sustained, layered approach to NPIs, including implementation of multiple NPIs, may help prevent infections. The combined use of NPI and seroprevalence data can inform long-term strategic approaches to limiting disease transmission. The interaction and efficacy of NPIs and vaccination should continue to be evaluated, including studies using longitudinal seroprevalence data. Future studies could examine vaccination and mask use in localities with continuous NPIs to investigate vaccination rates and cumulative rates of infection.

NOTES

Acknowledgements

The authors thank members from Vitalant Research Institute, Westat, the American Red Cross, each of the 17 participating blood collection organizations and 10 testing laboratories, Max Gakh, University of Nevada, Las Vegas, CDC's COVID-19 Mitigation Policy Analysis Unit and Public Health Law Program, and Alexandra Ramirez and Jordan Chandler from Georgia Tech Research Institute for their assistance on this study.

Disclaimer:

The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of CDC/ATSDR.

Funding

This study was funded by the CDC. CDC employees contributed to the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Conflicts of Interest

MPB reports being an employee of Vitalant Research Institute and serving on the medical advisory board for Creative Testing Solutions; Vitalant Research Institute receives research funds and reagents for studies from Ortho and Roche and Dr. Busch has presented on behalf of both companies at meetings in the past with travel support but does not receive personal compensation from these or other SARS-CoV-2 test manufacturing companies. They are also the President Elect of the International Society of Blood Transfusions (ISBT). SLS reports receiving payments or honoraria from Cerus Corporation, Roche Molecular Systems, and Grifols and participates on a data safety board or advisory board with Creative Testing Solutions and Hema-Quebec. JDO, CD, GPG, CH, GS, DF, KENC, AH, TJB, RM, SJ, NF, MHW, KB, MJM, AVG, AH, JMJ, and AM have no conflicts to report. No other disclosures were reported.

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Tables (2)

Table 1. MASS-D donor demographics stratified by past infection status — United States, August 2020 – March 2021.

	Donors With No Past Infections (N = 934,060)	**Donors With Past Infections (N = 106,551)**	**Overall Number of Donors (N = 1,040,611)**
Age Group			
--16-29 years	106,570 (11.4%)	19,586 (18.4%)	126,156 (12.1%)
--30-49 years	286,045 (30.6%)	37,437 (35.1%)	323,482 (31.1%)
--50-64 years	344,641 (36.9%)	36,522 (34.3%)	381,163 (36.6%)
--65+ years	196,804 (21.1%)	13,006 (12.2%)	209,810 (20.2%)
Race/Ethnicity			
--Asian	28,770 (3.1%)	1,890 (1.8%)	30,660 (2.9%)
--Black	23,146 (2.5%)	3,579 (3.4%)	26,725 (2.6%)
--Hispanic	54,033 (5.8%)	10,764 (10.1%)	64,797 (6.2%)
--Other	18,688 (2.0%)	2,139 (2.0%)	20,827 (2.0%)
--White	809,423 (86.7%)	88,179 (82.8%)	897,602 (86.3%)
Sex			
--Men	459,816 (49.2%)	51,527 (48.4%)	511,343 (49.1 %)
--Women	474,244 (50.8%)	55,024 (51.6%)	529,268 (50.9%)
Region			
--Northeast	172,526 (18.5%)	13,183 (12.4%)	185,709 (17.8%)
--Midwest	204,616 (21.9%)	28,745 (27.0%)	233,361 (22.4%)
--South	293,666 (31.4%)	39,555 (37.1%)	333,221 (32.0%)
--West	263,252 (28.2%)	25,068 (23.5%)	288,320 (27.7%)

Table 2. SARS-CoV-2 seroprevalence in August 2020, seroprevalence in March 2021, and change in seroprevalence among U.S. blood donors in August 2020 – March 2021.

		Seroprevalence (%) (95% confidence interval)			
Model	**NPI Category**	*August 2020*	*March 2021*	**Absolute change in seroprevalence[a] (percentage points, 95% confidence interval)**	**Adjusted Odds ratio (95% confidence interval)**
Single NPI models	Mask Mandate	4.2 (3.96, 4.45)	17.6 (17.13, 18.02)	13.4 (12.86, 13.88)	ref
	No Mask Mandate	6.5 (6.01, 7.02)	23.8 (23.00, 24.60)	17.3 (16.34, 18.24)	1.6 (1.51, 1.60)
	Gathering Ban	5.2 (4.85, 5.57)	18.0 (17.50, 18.58)	12.8 (12.18, 13.48)	ref
	No Gathering Ban	5.8 (5.29, 6.38)	21.9 (21.08, 22.81)	16.2 (15.08, 17.13)	1.2 (1.20, 1.28)
	Bar closure/no on-site consumption	3.4 (2.92, 3.88)	17.1 (16.08, 18.16)	13.7 (12.58, 14.86)	ref
	No bar closure/on-site consumption	5.0 (4.62,	21.2 (20.64,	16.2 (15.58, 16.90)	1.5 (1.45, 1.56)

		5.31)	21.77)		
Multiple NPI Model	All Policies	3.8 (2.89, 4.63)	12.0 (10.66, 13.29)	8.2 (6.63, 9.79)	ref
	Mask Mandate and Gathering Ban Only	6.5 (5.89, 7.01)	20.2 (19.42, 20.93)	13.7 (12.78, 14.66)	1.6 (1.52, 1.73)
	Mask Mandate Only	2.2 (1.44, 3.00)	17.3 (15.93, 18.70)	15.1 (13.51, 16.69)	1.4 (1.31, 1.54)
	No Policies	1.7 (1.18, 2.20)	26.5 (24.64, 28.32)	24.8 (22.88, 26.69)	2.2 (2.00, 2.33)

[a] This number reflects the absolute change in seroprevalence from August 2020 – March 2021 as a percentage.

Figures (1)

Figure 1 (multi-panel). Seroprevalence of SARS-CoV-2 in individuals with a past infection in counties with multiple NPIs ***(a, b)*** or single NPIs (mask mandates ***(c, d)***; gathering bans ***(e, f)*****;** on-site consumption in bars ***(g, h)*** compared to reference groups in counties with fewer or zero NPIs in place (August 1 ,2020 – March 30, 2021).

1(a) State-issued NPIs in effect August 2020 – March 2021 by type and combination[a] (map) and ***(b)*** seroprevalence over time by NPI categories included in analysis (all policies, no policies, mask mandate and gathering ban, mask mandate only) (August 2020-March 2021) (line graph).

[a] The multi-NPI variable had eight unique categories (supplemental Table 1). On the map in Figure 1(a), the category all policies (mask mandate, gathering ban, and bar closures) included three states (including DC), all policies (some counties) one state, mask mandate ("mask") and gathering ban ("GB") seven states, mask mandate ("mask") and gathering ban ("GB") (some counties) one states, mask mandate only ("mask only") three states, gathering ban only ("GB only") one state, no policies four states, and intermittent policies 31 states. Supplemental Table 1 lists these categories as "combination 1-8," and in the same order as they are presented in the legend and map.

1(c) Continuous state-issued mask mandates August 2020 – March 2021 (map) and ***(d)*** seroprevalence over time by absence or presence of continuous mask mandate (August 2020-March 2021) (line graph).[b]

[b]Continuous mask mandates were present in 32 states (including DC), and 11 states did not have a mask mandate at any time in the study period.

1(e) Continuous state-issued gathering bans by state August 2020 – March 2021. (map) and ***(f)*** seroprevalence over time by gathering ban status (August 2020 – March 2021) (line graph).[c]

[c]Legend: The gathering ban variable had four categories. The category gathering ban included 18 states (including DC), gathering ban (some counties) two states, no gathering ban 11 states, no gathering ban (some counties) one state.

1(g) Continuous state-issued bar closure policies (map) and ***(h)*** seroprevalence over time by bar closure status (August 2020 – March 2021) (line graph).[d]

[d]The no on-site consumption variable had four categories. The category no on-site consumption included four states (including DC), no on-site consumption (some counties) three states, on-site consumption 28 states, no on-site consumption (some counties) four states.

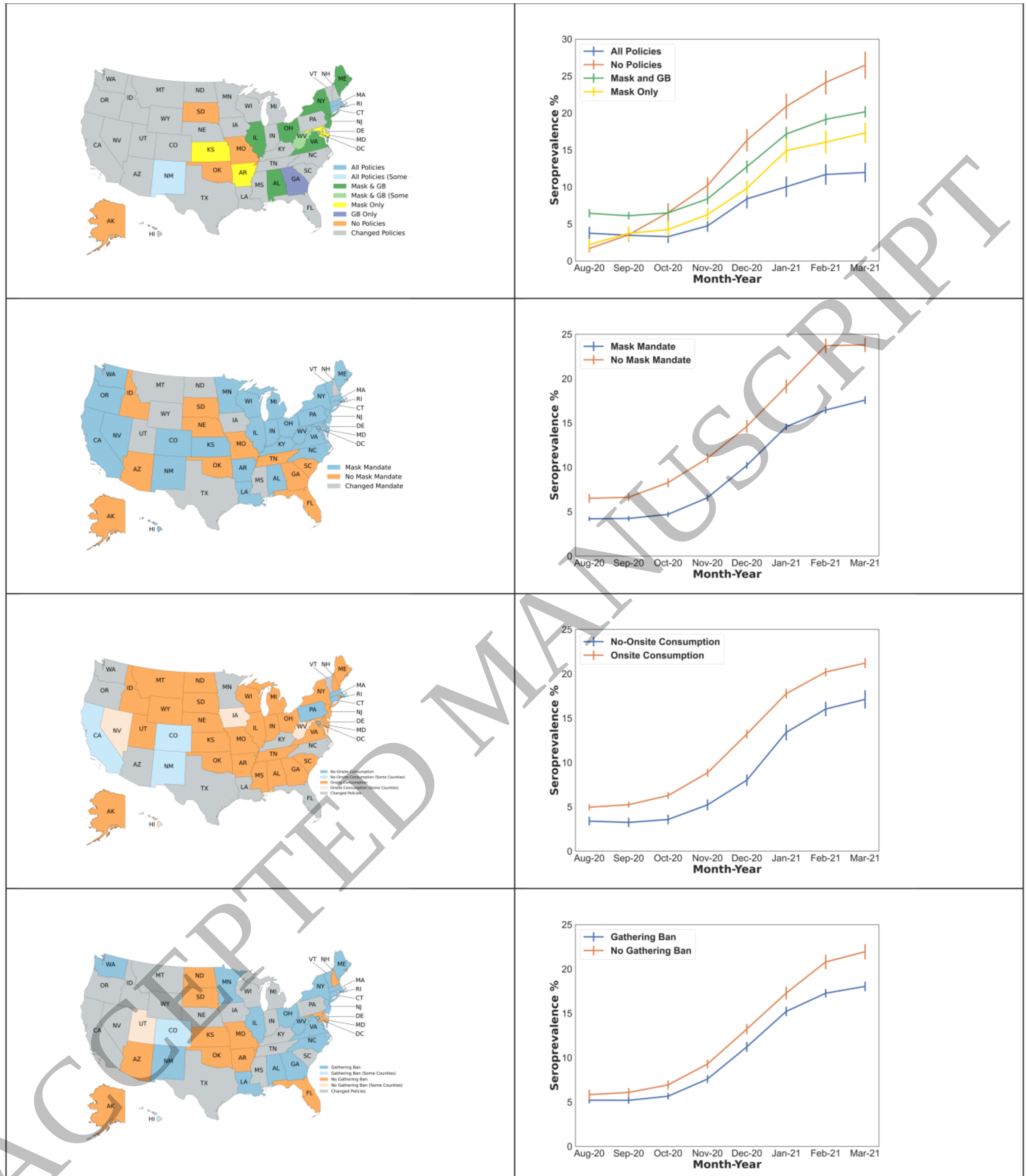

Figure 1

165x190 mm (69 x DPI)