Pandemic Preparedness and COVID-19: lessons learned from national and subnational response, what we can learn from existing preparedness metrics, and how to prepare for novel threats

Erin Hulland Frame, MPH

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Reading committee:

David M. Pigott, Chair

Joseph L. Dieleman

Robert C. Reiner

Christopher Adolph

Cyrus Shahpar

Thomas J. Bollyky

Program authorized to offer degree:

Global Health

Thomas J Bollyky*, Erin N Hulland*, Ryan M Barber, James K Collins, Samantha Kiernan, Mark Moses, David M Pigott, Robert C Reiner Jr, Reed J D Sorensen, Cristiana Abbafati, Christopher Adolph, Adrien Allorant, Joanne O Amlag, Aleksandr Y Aravkin, Bree Bang-Jensen, Austin Carter, Rachel Castellano, Emma Castro, Suman Chakrabarti, Emily Combs, Xiaochen Dai, William James Dangel, Carolyn Dapper, Amanda Deen, Bruce B Duncan, Lucas Earl, Megan Erickson, Samuel B Ewald, Tatiana Fedosseeva, Alize J Ferrari, Abraham D Flaxman, Nancy Fullman, Emmanuela Gakidou, Bayan Galal, John Gallagher, John R Giles, Gaorui Guo, Jiawei He, Monika Helak, Bethany M Huntley, Bulat Idrisov, Casey Johanns, Kate E LeGrand, Ian D Letourneau, Akiaja Lindstrom, Emily Linebarger, Paulo A Lotufo, Rafael Lozano, Beatrice Magistro, Deborah Carvalho Malta, Johan Månsson, Ana M Mantilla Herrera, Fatima Marinho, Alemnesh H Mirkuzie, Ali H Mokdad, Lorenzo Monasta, Paulami Naik, Shuhei Nomura, James Kevin O'Halloran, Christopher M Odell, Latera Tesfaye Olana, Samuel M Ostroff, Maja Pasovic, Valeria Maria de Azeredo Passos, Louise Penberthy, Grace Reinke, Damian Francesco Santomauro, Maria Inês Schmidt, Aleksei Sholokhov, Emma Spurlock, Christopher E Troeger, Elena Varavikova, Anh T Vo, Theo Vos, Rebecca Walcott, Ally Walker, Simon D Wigley, Charles Shey Wiysonge, Nahom Alemseged Worku, Yifan Wu, Sarah Wulf Hanson, Peng Zheng, Simon I Hay, Christopher J L Murray, and Joseph L Dieleman.

*Joint first authors, contributed equally.

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Abstract

Pandemic Preparedness and COVID-19: lessons learned from national and subnational response, what we can learn from existing preparedness metrics, and how to prepare for novel threats

Erin Hulland Frame

Chair of the Supervisory Committee: David Pigott

Department of Global Health

The COVID-19 pandemic has been one of the most catastrophic health emergencies of all time, leading to millions of deaths and hundreds of millions of infections worldwide. Yet, a global pandemic impacting all of humanity was not unforeseen, with countless studies articulating the spillover potential of various pathogens into humans and the ability for such viruses to replicate. Similarly, pandemic preparedness frameworks and metrics existed pre-COVID to quantify pandemic risks and vulnerabilities for a given country to emphasize both strong existing capacities as well as areas for improvement for emerging outbreaks and pandemics of international concern.

The unprecedented scale of COVID-19 has renewed focus on pandemic preparedness and response. This research aims to understand the drivers of differential COVID-19 outcomes across various countries and within key countries and to quantify how current preparedness indices of immunization measure up against retrospective COVID-19 vaccination uptake. In the first aim, we consider whether existing pandemic preparedness indicators nationally were informative of better COVID-19 outcomes, and investigate what other political, social, health or demographic covariates influenced heterogeneities in COVID-19 across the globe. In the second aim, we focus our analyses subnationally to investigate drivers of within-country heterogeneities, and again investigate whether pre-pandemic preparedness was informative of COVID-19 outcomes, and whether national patterns were persistent subnationally. In the third aim, we build on our findings from the first and second aim that pandemic preparedness composite

measures were not predictive of COVID-19 successes, and decompose such metrics to investigate one specific indicator of routine immunization in order to understand whether our measurement of vaccine readiness was truly informative of pandemic vaccine delivery.

In the first aim *Pandemic preparedness and COVID-19: an exploratory analysis of infection and fatality rates, and contextual factors associated with preparedness in 177 countries, from Jan 1, 2020, to Sept 30, 2021*, we used multi-stage log-log regression models to understand drivers of cross-country differences in COVID-19 infections and mortality from January 2020 through September 2021, expanding on previous research looking at COVID-19 outcomes in relation to pandemic preparedness scores. We first controlled for immutable factors including daily seasonality and age profile, and secondly controlled for baseline risk factors like age profile, seasonality, density, and BMI. Following these adjustments, we modeled our standardized COVID-19 infections and infection fatality rates against policy-amenable factors, including pandemic preparedness indicators, health care readiness, and social and political characteristics. We found that the largest drivers of reduced COVID-19 infections were not associated with existing pandemic preparedness metrics, but instead to higher trust in the government and in other people. As trust is an essential driver of effective risk communication and behavioral modification such as vaccine uptake or social distancing, improving trust prior to the next pandemic is essential.

In the second aim *An exploratory analysis of improved COVID-19 outcomes in subnational locations across two countries: the United States and Brazil, January 2020 through May 2022*, we again used multi-stage log-log regression models to understand within-country drivers of COVID-19 outcomes in Brazil and the United States. These two countries were chosen for their high overall COVID-19 burdens, but also for heterogeneous COVID-19 burdens, responses, and high political polarization. This time, our analysis ran from January 2020 through May 2022, and we controlled for daily seasonality and variant prevalence in the first stage, followed by a standardization for baseline risk factors. We again modeled these standardized estimates versus policy-amenable factors, including pandemic preparedness indicators,

health care readiness, and social and political characteristics, though many of the covariates from the first chapter were not available at the state-level and either had to be modeled or omitted. Although there were observable differences within these countries, we identified no significant policy-amenable drivers of COVID-19 differences within countries following baseline standardization, though hospital beds per capita were found to be significantly related to higher infections. Trust was not a key driver of COVID-19 outcomes in Brazil and the United States, though the sample sizes of our trust variables were small and had wide confidence intervals. Similarly, modeled pandemic preparedness indicators were not predictive of improved COVID-19 outcomes subnationally. Our research additionally suggests that access to high quality health care is a potential avenue to explore to reduce the burden of disease in future pandemics. Within-country efforts to prepare for the next pandemic may be best focused on improving access to care and reducing existing burdens of comorbidities such as obesity and cancer which drive not only high mortality in general but are exacerbated in pandemics like COVID-19 where undue morbidity and mortality were observed among the chronically ill and elderly, and to improve estimates of trust and pandemic preparedness at a local level to better understand true disparities nationally.

In the final aim *Considering measles containing vaccine as a proxy for pandemic preparedness in the context of COVID-19: are we truly measuring what matters?*, we look at a country's routine measles containing vaccine (MCV) coverage – a proxy for immunization readiness and vaccine delivery in preparedness metrics like the Joint External Evaluation (JEE) – and model it against at least one dose COVID-19 vaccination between December 1, 2020 and December 1, 2022 for national and subnational locations separately. Vaccination has been an incredible tool throughout the COVID-19 pandemic in reducing morbidity and mortality, but has been highly inequitable in its distribution, so we wanted to understand how closely heterogeneities in MCV as a routine measure mapped to those seen in COVID-19 vaccine uptake. Moreover, composite scores of pandemic preparedness proved non-informative of COVID-19 outcomes, and so we sought to understand whether specific indices were beneficial in

understanding specific aspects of the COVID-19 pandemic, such as immunization. In each location, we consider the time to various thresholds of coverage (1%, 5%, and 10%) to understand the relationship between pre-pandemic immunization and speed of novel vaccine roll out, controlling for pre-pandemic vaccine hesitancy and percentage of the population over 65 years of age. We consider the maximum number of persons vaccinated in a single day (smoothed and averaged over a one-month period to adjust for noisy data) as a measure of speed of scale-up and separately estimate the maximum level of coverage achieved for at least one dose COVID-19 vaccination coverage. We model these additional COVID-19 vaccine outcomes against MCV as well, again controlling for vaccine hesitancy and percentage of the population over 65 years of age. Our research suggests that the level of pre-pandemic one-dose measles vaccine coverage across 134 countries was successful in predicting the time to vaccine roll out at varying thresholds and the overall vaccination level achieved. In the subnational model, we found no significant relationships between routine immunization coverage and one-dose COVID-19 vaccine delivery, a relationship that persisted across all data subsets and additional indicators of routine immunization. While composite metrics of pandemic preparedness are not effective at predicting pandemic COVID-19 outcomes, specific, targeted indicators have stronger predictive validity than the composites. Specifically, this analysis demonstrates that measles vaccine coverage is an effective metric for quantifying immunization readiness at the national level, and can provide utility for considering equitable delivery of vaccines and therapies for future threats.

This dissertation takes a comprehensive look at pandemic preparedness measures and assess their validity with a COVID-19 lens. We find that pre-pandemic composite scores held little validity for predicting better COVID-19 outcomes across the globe, nor within two key countries. However, when drilling down to individual components of these composite scores, we found a correlation between pre-pandemic immunization readiness and pandemic vaccine delivery at a national level, suggesting the possibility of wider validity of individual indicators for various facets of pandemic preparedness and

response. Trust in other people and in the government was identified as a key driver of lower COVID-19 infections in the national analysis, though lack of focused, high-quality subnational data limited the extension of these findings in the second, subnational aim. Considering trust as an essential tool to build prior to subsequent pandemics and monitor on an ongoing basis, as well as focusing dedicated resources and efforts to better quantify and understand trust nationally and subnationally will have extensive payoffs in better understanding current patterns of trust, as well as improving messaging and adherence for novel threats.

COVID-19 was the first of what is likely to be many outbreaks and pandemics in our lifetimes given a growing number of interactions between humans and wildlife due to climate change and urbanization, allowing for spillover of novel and re-emerging pathogens into human populations. Lessons learned from this dissertation would be useful for guiding pandemic preparedness plans to consider how to reformat existing metrics to be most suited for planning for a multitude of different diseases in the future, and to ensure that subnational capacities and vulnerabilities are thoroughly addressed.

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CHAPTER 1: INTRODUCTION

The COVID-19 pandemic has been one the most catastrophic health emergencies in human history, leading to millions of deaths and hundreds of millions of infections, many with lingering morbidities, and untold economic effects.[1] Yet, a global pandemic impacting all of humanity was not unforeseen, with countless studies articulating the spillover potential of various pathogens into humans and the ability for such viruses to replicate.[2–4] Similarly, pandemic preparedness frameworks and metrics existed pre-COVID to quantify pandemic risks and vulnerabilities for a given country to emphasize both strong existing capacities as well as areas for improvement.[5,6] While some metrics, like the Global Health Security Index (GHSI) were designed to quantify a country's readiness through a composite weighting of various health care, administrative, and governmental indicators, others like the Joint External Evaluation (JEE) were calculated as part of a larger objective to develop National Action Plans for Health Security where vulnerabilities were addressed and prioritized.[5,6] Recent efforts have considered the JEE in particular measures can be more informative for improved pandemic detection and response, with a recent emphasis on timely detection, reporting, and treatment, yet other important facets of the JEE, GHSI remain unexplored.[7] As we move into the post-vaccination phase of the pandemic in many locations, understanding how existing preparedness metrics performed, and what other covariates were most predictive of improved outcomes, is necessary to understand how to best prepare for, and respond to, the next outbreak.

A major part of retrospective analyses of the COVID-19 pandemic is understanding what we as public health experts – globally and locally – can do differently to mitigate not only disease spread but subsequent morbidity and mortality. Prior to the COVID-19 pandemic, many high-income countries ranked highly in their preparedness capacities, suggesting that countries like the United States, Spain, and the United Kingdom would have been the most effective in preventing, detecting, and responding to COVID-19. In reality, these countries were often among those heavily burdened with high fatality and infection rates.[8,9] Moreover, existing preparedness plans do not consider subnational preparedness, allowing for pockets of under-preparedness to persist even where national level readiness is high. Given that an outbreak can spread rapidly within a country, national level preparedness is insufficient to gauge a country's true ability to prevent, detect, and respond to a novel threat. While COVID-19 was the first pandemic in most of our lifetimes, it is unlikely to be the last. Climate change, deforestation and urbanization, and human population growth are all increasingly driving interactions between wildlife and human populations, leading to increased possibility for spillover events of new or re-emerging zoonoses into human populations.[4,10,11]

Responses have been varied across the globe, but no country was wholly prepared for COVID-19, suggesting a need to better evaluate and prepare countries for future pandemics. This dissertation aims to evaluate what made countries more successful in handling COVID-19 including both political, social, and existing preparedness covariates, within-country differences to better understand how local decision-making impacts COVID-19 outcomes and differs between selected countries, and to quantify the utility of pre-pandemic immunization preparedness metrics on vaccine delivery to understand if we are accurately quantifying national and subnational immunization readiness, and, more importantly, to refocus efforts and resources to quickly and equitably distribute vaccines and therapies in future pandemics.

SPECIFIC AIMS

AIM 1: UNDERSTAND CROSS-COUNTRY VARIATION IN COVID-19 OUTCOMES

The first aim of this dissertation sought to understand what was predictive of better COVID-19 outcomes among 177 countries via infection and infection fatality rates and builds on existing literature in two key ways: we first consider a larger number of countries across the globe, and second use both estimated infections triangulated from a multitude of data sources including serosurveys and deaths adjusted for underreporting via excess mortality calculations. We first standardized outcomes for baseline risk factors including demographic, health, and socioeconomic covariates. Following this standardization, we used log-log linear models to examine health care, political, social, and pandemic preparedness drivers with policy implications. Lastly, we explored covariates identified as significant and explored pathway by which these covariates may influence COVID-19 outcomes including through vaccination uptake, mobility changes, and mandate application.

AIM 2: UNDERSTAND VARIABLES MOST RELEVANT TO BETTER COVID-19 OUTCOMES AT A SUBNATIONAL LEVEL, COMPARING ACROSS COUNTRIES AND BETWEEN SUBNATIONAL UNITS.

In my second aim, I sought to replicate the methods of the cross-country analysis to investigate whether national-level drivers were also significant at a subnational level or whether there were more localized predictors of success. We again considered estimated infections triangulated from a multitude of data sources, and deaths accounting for underreporting. We focused on two large countries with highly heterogenous COVID-19 outcomes and heavy burdens of COVID-19 – Brazil and the United States – and modeled state level COVID-19 infections and infection fatality rates. We again standardized for key baseline risk factors, this time including variant prevalence, and considered policy, preparedness, and health capacity indicators in our policy analysis. Where covariates were not available at the state-level, we triangulated available data and created models to estimate state-level indicators, including all subnational pandemic preparedness indicators.

AIM 3: UNDERSTAND THE RELATIONSHIP BETWEEN THE PANDEMIC PREPAREDNESS MEASURE OF VACCINATION READINESS (VIA MEASLES VACCINATION COVERAGE) AND COVID-19 VACCINE DISTRIBUTION, NATIONALLY AND SUBNATIONALLY.

In my third aim I sought to investigate the utility of routine one-dose measles containing vaccine (MCV) coverage as a measure of pandemic immunization readiness and vaccine delivery by modeling it versus at least one-dose COVID-19 vaccination from December 2020 through December 2022. We looked at three distinct phases of vaccine delivery: initial roll out, maximum distribution at scale up, and overall coverage achieved and modeled each of these versus one-dose MCV coverage, controlling for the percentage of the population over 65 years of age and pre-pandemic vaccine hesitancy. Each of these periods represents important elements of vaccine delivery, from how quickly doses can get out the door and into arms, to how expedient delivery can be with concentrated resources, and to how much of the population can be reached. We additionally explored these variables subnationally across six countries to investigate how these results hold up locally. We considered alternate subsets of data including the first six months of delivery to prevent confounding of booster administration or doses to children and teens and considered only those countries not meeting routine immunization targets to understand this relationship among countries historically underserved by routine immunization. Lastly, we considered using different routine immunization metrics including three-dose Diphtheria-Tetanus-Pertussis vaccination, three-dose poliovirus vaccination, one-dose Bacille Calmette-Guérin vaccination, and including governmental trust as a control variable.

CHAPTER 2: PANDEMIC PREPAREDNESS AND COVID-19: AN EXPLORATORY ANALYSIS OF INFECTION AND FATALITY RATES, AND CONTEXTUAL FACTORS ASSOCIATED WITH PREPAREDNESS IN 177 COUNTRIES, FROM JAN 1, 2020, TO SEPT 30, 2021

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SUMMARY

Background

National rates of COVID-19 infection and fatality have varied dramatically since the onset of the pandemic. Understanding the conditions associated with this cross-country variation is critical to guiding investment in more effective preparedness and response for future pandemics.

Methods

Daily SARS-CoV-2 infections and COVID-19 deaths for 177 countries and territories and 181 subnational locations were extracted from the Institute for Health Metrics and Evaluation's modelling database. Cumulative infection rate and infection-fatality ratio (IFR) were estimated and standardized for environmental, demographic, biological, and economic factors. For infections, these included factors associated with environmental seasonality (measured as the relative risk of pneumonia), population density, gross domestic product (GDP) per capita, proportion of the population living below 100 meters, and a proxy for pre-exposure to other beta coronaviruses. For IFR, these included age distribution of the population, mean body-mass index (BMI), exposure to air pollution, smoking rates, the proxy for pre-exposure to other beta coronaviruses, population density, age-standardized prevalence of chronic obstructive pulmonary disease (COPD) and cancer, and GDP per capita. Standardized national cumulative infection rates and IFR were tested for associations with 12 pandemic preparedness indices, seven health-care capacity indicators, and ten other demographic, social, and political conditions. To investigate pathways by which important factors might affect infections with SARS-CoV-2 (the virus that causes COVID-19), we also assessed the relationship between interpersonal and governmental trust and corruption and changes in mobility patterns and COVID-19 vaccination rates.

Findings

The conditions that explained the most variation in SARS-CoV-2 cumulative infection rates between January 1, 2020, and September 30, 2021, included the proportion of infections attributable to seasonality (2.1% [95% UI 1.7–2.7] of variation), the proportion of the population living below 100 meters (5.4% [4.0–7.9] of variation), and GDP per capita (4.2% [1.8 – 6.6] of variation). The majority of cross-country variation in cumulative infection rates could not be explained. The conditions that explained the most variation in COVID-19 IFR over the same period were the age profile of the country (46.7.0% [18.4–67.6] of variation), GDP per capita (3.1% [0.3 – 8.6] of variation), and national mean BMI (1.1% [0.2–2.6] of variation). Some 44.4.2% (29.2–61.7) of cross-national variation in IFR could not be explained. Pandemic preparedness indices, which aim to measure health security capacity, were not meaningfully associated with standardized infection rates or IFR. Measures of trust in the government and interpersonal trust, as well as less government corruption, had larger, statistically significant associations with lower standardized infection rates. High levels of government and interpersonal trust, as well as less government corruption, were also associated with higher COVID-19 vaccine coverage among middle- and high-income countries where vaccine availability was more widespread, and lower corruption was associated with greater reductions in mobility. If these modelled associations were to be causal it would suggest that an increase in trust such that all countries had the amount of interpersonal trust or trust in their government as that of the 75th percentile would be associated with a reduction in global infections

of 40.3% (24.3-51.4) and 12.9% (5.7–17.8), respectively. Similarly, if all countries had a national BMI equal to or less than that of the 25th percentile, our analysis suggests global standardized IFR would be 11.1% lower.

Interpretation

Current metrics used for assessing pandemic preparedness were largely non-informative of COVID-19 outcomes, including infections and fatalities after standardizing for several risk factors including BMI and age. This manuscript suggests that trust in other people and in one's government may be the key to improving pandemic outcomes, and methods to improve governmental risk communication and build trust in communities and in the government should be considered as ways to prepare for future pandemic threats.

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INTRODUCTION

While the world remains in the grip of COVID-19, critical efforts are already underway to begin learning from the pandemic response and prepare for future threats.[12–19] Policy responses such as mask mandates and social distancing measures have been critical to shaping outcomes.[20–22] But it is also important to identify the contextual factors associated with lower infection and fatality rates in order to guide the long-term path to addressing future threats.

COVID-19 has been called an "epidemiological mystery."[23] Reported incidence and mortality from SARS-CoV-2 (the virus that causes COVID-19) have not followed the pattern of many other communicable diseases; wealthier countries with more health-care resources have experienced greater burden from COVID-19 than low-income countries with more limited health-care resources. Upper-middle-income and high-income countries have 48% of the global population but 53% of the total estimated excess mortality-adjusted cumulative deaths from COVID-19 as of September 30, 2021, despite having much higher COVID-19 vaccination rates since December 2020.[24,25] Moreover, countries that experts believed before the pandemic to be most prepared to mitigate the effects of a deadly pandemic have not been the most successful at doing so.[12] Some prior research has attempted to explain variation in country experiences controlling SARS-CoV-2 infections and averting mortality. To date, most of these analyses have either been commentaries on why preparedness metrics are useful despite not being predictive of COVID-19 pandemic outcomes, or have focused on specific regions,[26] used relatively limited analyses,[27,28] focused exclusively on cumulative deaths,[29] or had small sample sizes and missing data.[30] One analysis investigated some political, social, and governmental correlates with cumulative deaths per capita,[31] and another found a relationship between trust in government and lower death rates.[32] Our analysis builds on this research by incorporating results from the Institute for Health Metrics and Evaluation (IHME) on estimated infections built from hospitalizations, reported cases, and deaths accounting for excess mortality due to the COVID-19 pandemic,[24,25] and additional covariates of interest such as metrics of health system and pandemic preparedness and response capacity. In addition, we more fully control for key covariates associated with age structure of the population and environmental seasonality, among other factors.[9,33] Without controlling for these factors, an analysis risks confounding from other deterministic drivers that remain outside the control of policy makers. In addition, we differentiate between infection rates and infection-fatality ratios (IFRs) in order to assess the differences in prevention and treatment of COVID-19. Finally, we incorporate subnational data where available.

The aim of this research was to complete an exploratory analysis of potential correlates of COVID-19 prevention and treatment across 177 countries and territories. We investigated these correlates in relation to both SARS-CoV-2 infections and IFRs to disentangle the factors that prevented the spread of the virus from the health-system factors that prevented death from disease. We controlled for known factors of SARS-CoV-2 infection and mortality that are generally considered outside the control of policy makers (such as altitude, age profile, and seasonality of the disease) and explored associations with 28 factors that policy makers can control. Variables explored were associated with pandemic preparedness indices; health system capacity indicators; governance variables; and measures of economic inequality and societies' trust in their government, science, and their communities.

METHODS

Overview

In this research, the outcomes of interest were infections per capita and IFRs. Both were calculated from estimates produced by IHME's ongoing COVID-19 project.[9,33] This research was conducted in three stages. In stage 1, we standardized the national infection rates and IFRs by estimating what the infection rate and IFR would be if each country had the global mean value of key, known drivers of infection and IFR. This

process included adjusting national infection rates for environmental seasonality, altitude and income, among other factors, and standardizing IFRs to the global age distribution and the prevalence of competing risks. In Stage 2, we measured the cross-country association of these standardized infection rates and IFR against health system policy variables, such as measures of pandemic preparedness, health system capacity, governance factors, and several measures of social and governmental trust, to determine which policy factors. In Stage 3, we investigated how reduction in mobility and vaccine coverage might be pathways for more distal policy variables to impact infection rates and IFR. For stages 1 and 2, we assessed two time periods. To assess the full span of the pandemic (until present), we assessed cumulative infection and IFR for January 1, 2020, through September 30, 2021. As a sensitivity analysis, we also assessed the time period before vaccines and disease variants were known to have spread, January 1, 2020, through October 15, 2020. All analyses were conducted using R version 4.0.3.[34]

This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix section 2.1).[35] Code used to produce this analysis is available online.

COVID-19 infection and mortality estimates

Daily estimated infections and death counts were extracted from the IHME modelling database. These estimates span from January 1, 2020, to September 30, 2021, and exist for 177 countries and 181 subnational locations.[9] To estimate the number of COVID-19 deaths, IHME extracted data from the Johns Hopkins University Center for Systems Science and Engineering COVID-19 database, supplemented these with additional data from national and subnational ministries and departments of health, and adjusted them to correct for missing data and reporting lags. The resulting mortality rates were then adjusted for under-reporting based on the ratio of excess deaths attributable to COVID-19 versus reported deaths, a ratio that was modelled using spatial correlation and additional covariates.[9] To estimate the number of SARS-CoV-2 infections, IHME estimated infections from the number of deaths, hospitalizations, and reported cases occurring in each location, again extracted from the Johns Hopkins COVID-19 database and adjusted for missing data and reporting lags. The infections estimate was based on IFR, infection-hospitalization ratios, and infection-detection ratios, respectively, estimated for each population. Ratio observations were derived by matching the parameter (eg, deaths) to the number of infections occurring in the population according to seroprevalence surveys, the results of which have been adjusted for waning sensitivity of antibody tests and other known biases. The IFR, infection-hospitalization ratio, and infection-detection ratio were then modelled as a function of covariates to obtain predictions for all locations and days. Underlying data uncertainty and modelling uncertainty were propagated at each stage and incorporated into the quantification of the estimates' uncertainty. Full details of the modelling approaches are provided elsewhere.[9,24,25,36]

For this study, cumulative infections were calculated by summing up the total estimated daily infections for each national or subnational location over the entire time period (and also for the shorter time period – January 1, 2020, through October 15, 2020), and were divided by the 2019 estimated population in each location to get the cumulative infections per capita.[37] The IFRs were calculated by applying a nine-day lag to our daily infections to account for the delay between infection and death, calculating the sum of infections and deaths, and then dividing the cumulative deaths over the cumulative lagged infections.

Variable selection

In stage 1, we included demographic, biological, comorbid, economic, and environmental factors known or believed to have influenced infection rates or IFR. Most of these background variables are generally not factors subject to direct policy maker control, such as population density, GDP, altitude, and

seasonality—factors that may increase transmission; and age, age-standardized chronic obstructive pulmonary disease (COPD) prevalence, and age-standardized cancer prevalence—factors that may increase morbidity or mortality from infection; and previous exposure to coronaviruses—a factor that may influence both subsequent transmission probability and mortality outcomes. A few biological and environmental factors considered at stage 1 are related to health and are policy-amenable, such as BMI, smoking, and air pollution, which may cause higher IFR. We used a theoretical, rather than empirical, approach for including these covariates, assessed for multicollinearity (appendix sections 2.3, 2.4, and 2.5), and generated standardized infection rates and IFRs that hold these values constant across countries.

In stage 2, we sought to test associations between the standardized infection rates and standardized IFRs and key measures of pandemic preparedness, health-care capacity, and government effectiveness and social conditions that are subject to policy maker control (see Table 1). The pandemic preparedness measures included were the JEE and GHSI, as well as their subcomponents. The health-care capacity and spending measures included the universal health coverage (UHC) effective coverage index and two UHC index subcomponents (non-communicable diseases and communicable, maternal, and neonatal disease), Healthcare Access and Quality Index, hospital beds per capita, governmental health expenditure per capita, and health spending per capita. For governance and social measures, we included factors that may affect government capacity, priorities, and responsiveness in a pandemic (such as electoral democracy, government effectiveness, populism, state fragility, and corruption), as well as social factors that may affect the willingness of a population to comply with government or health mandates (income inequality and trust in the government, science, and other members of that population).

Stage 1: Standardizing infection rates and IFRs

To improve comparability across countries, we used regression analyses to standardize the effects of COVID-19 determinants that were not directly related to our research questions. For infections, we regressed infection rates on the time-varying relative risk of pneumonia, and then predicted infection rates holding all countries constant at the global mean, generating seasonally adjusted infection rates. We then used a multivariate generalized linear regression to model the association between seasonality-adjusted infections per capita and GDP per capita, a proxy for previous exposure to beta coronavirus host bat species (further described in appendix section 3.2), fraction of the population living below 100 meters (a factor meant to capture variability in incidence of pneumonia and other lower respiratory infections that vary by altitude[38–40]), and population density. We produced standardized infection rates by generating the seasonally adjusted infection rates for each location had each had the global mean of each of these factors.

For IFR, we used indirect age-standardization to remove the effects of different age profiles across locations. We then used a multivariate regression model to assess the relationships between the age-standardized IFR and national income per capita, a proxy for previous exposure to beta coronavirus host bat species, population density, mean body-mass index (BMI), age-standardized COPD prevalence, age-standardized cancer prevalence, air pollution, and smoking prevalence. Among five disease prevalences believed to be related to IFR[41] (COPD, cancer, diabetes, cardiovascular disease, and chronic kidney disease), the age-standardized rates of chronic kidney and diabetes were correlated, and cardiovascular disease and diabetes were correlated with BMI, leading to multicollinearity. Consequently, age-standardized prevalence of chronic kidney disease, age-standardized cardiovascular disease, and age-standardized diabetes (the factors with the largest variance inflation factors) were removed from the model.

All models were linear regressions, with dependent and independent variables natural-log-transformed using a "pad" of 5% of the median value for covariates with estimated zeros. To account for within-country correlations and avoid any one country's estimate from unduly impacting our parameter estimates, we down-weighted subnational locations corresponding to their proportion of the country's population. To estimate the fraction of variance explained by each covariate, we performed a Shapley decomposition of the R-squared. Variation accounted for by adjusting for seasonality or age was calculated by comparing the sum of squares of the standardized values (cumulative infections per capita and IFRs) to their respective raw values. In addition, we used regressions estimated in Stage 1 to conduct counterfactual analyses. These analyses are presented in Table 2 and denote reductions in IFR had risk factors (ie, BMI) been at the 25th percentile across countries, and reductions in infections had trust variables (ie, government trust and interpersonal trust) been at the 75th percentile across countries.

Stage 2: Exploring health care, governance, and social associations with standardized COVID-19 outcomes

Standardized infection rates and standardized IFR from Stage 1 (measured for all 177 countries) were used as the dependent variable in Stage 2. We regressed these on the 28 health-care, governance, and social indicators previously described and which are outlined in table 1.

For comparisons, all covariates were centered and scaled to have a standard deviation of. Because these indicators are highly correlated with other indicators, and some have a great deal of missingness (appendix sections 2.2, 2.3, 2.4, & 2.5), we used bivariate linear regression models to assess each association independent of all the other indicators. To address the issue of testing multiple hypotheses, we adjusted our p-value threshold using a Bonferroni correction for each of our Stage 2 covariates (n=28) and a desired alpha of 0.05, resulting in a significance cut-off of 0.0018. For trust in the government and government corruption, there were multiple data sources with varying degrees of variable completeness and coverage by location, so we conducted a principal component analysis (PCA) and extracted the first component to create a summary indicator. We used a PCA method (missMDA package in R)[42] that imputed values for countries with missing information (see appendix section 3.3 for more detail). To estimate the fraction of variance explained by each indicator, we noted the sum of squares explained by each factor and combined each value with the raw sum of squares of cumulative infections per capita or of IFR.

Stage 3: The association between key factors and intermediate health outputs

To explore two potential pathways connecting the governance and social factors identified as statistically associated with COVID-19 outcomes in Stage 2, we assessed the relationship between these variables—interpersonal trust, government trust, and government corruption—and the most extreme country-specific reduction in mobility observed at any point in 2020 or 2021, relative to a pre-pandemic baseline based on a composite metric extracted from smartphone data,[43] and the maximum achieved vaccine coverage (at least one dose) as of September 30, 2021. Given the lack of access to vaccinations and vaccine supplies in many low-income and lower-middle-income countries during our study period, the analysis of vaccine coverage was only on upper-middle- and high-income countries.

Uncertainty and sensitivity analyses

To capture uncertainty associated with the input data and uncertainty associated with our linear models, we completed our analysis 100 times independently, each on a separate draw produced previously by IHME for estimating infection rates and IFR uncertainty.[9,33] In addition, for each draw and each linear regression we took a random sample draw from the estimated variance-covariance matrix in order to incorporate model uncertainty. Similarly, the PCA-based summary indicators were completed 100 times

to capture uncertainty from the imputation process. Here we report the mean of the 100 estimates, with uncertainty intervals (UIs) spanning for the 2·5th and 97·5th percentiles of the 100 estimates.

To assess the impact of our modelling choices, we completed sensitivity analyses using centered and scaled data rather than log-transformed covariates in Stage 1, and also using a 1% of the median pad rather than 5%. To assess the impact of imperfect input data, we completed sensitivity analyses using only national and subnational locations where we had seroprevalence survey data (n=303, appendix section 5.4), and completed our analysis without incorporating IHME's technique for adjusting for within-country excess mortality. To assess the role that novel variants and vaccine coverage might have on our analysis, we completed a sensitivity analysis including variant spread as a stage 1 covariate and ran our analyses using a subset of the data from the pre-vaccine, pre-variant era that extended from January 1, 2020, to October 15, 2020.

RESULTS

Between January 1, 2020, and September 30, 2021, there was substantial cross-country variation in SARS-CoV-2 infection rates (Figure 1a). While the global infection rate was 432.6 per 1000 persons (95% UI 393.4–493.2), country-specific estimates ranged from 0.7 per 1000 (0.4–1.4) in China to 1013.3 per 1000 persons (507.0–1111.2) in Afghanistan. Excess relative risk of infection associated with seasonality explained 2.1% (1.7–2.7) of the variation in cross-country daily infection rates (Table 2). Countries such as Romania, the Bahamas, and Suriname were most negatively impacted by excess risk associated with seasonality. A further 5.4% (4.0–7.9) of the cross-country variation was explained by controlling for population living below 100 meters in altitude, followed by GDP per capita (4.2% [1.8 – 6.6] of variation).. Population density and our proxy measure of previous exposure to beta coronaviruses from bat hosts were not significantly associated with infection. The majority of cross-country variation (60.6% [55.6–65.2]) in cumulative infection rates could not be explained by the covariates presented to the analysis.

Like infection rates, COVID-19 IFR varied dramatically across countries during the first 21 months of the pandemic (January 2020–September 2021, Figure 1b). While the global IFR was 3.4 (95% UI 2.4–4.8) per 1000 infections, country-specific estimates ranged from 0·5 (0·3–0·6) in Singapore to 15.9 (9.3–26.8) in Portugal. Age was a clear contributor to this cross-country variation, explaining 46.70% (18.1–67.6) of cross-country variation. The countries that saw the largest decreases due to age standardization (ie, the countries with relatively old populations) were Japan, Portugal, and Spain. The countries with the largest increases in IFR due to age standardization (ie, the countries with relatively young populations) were Afghanistan, Mozambique, and Zambia. After adjusting for age, variation in BMI and GDP per capita were significantly associated with age-standardized IFR, accounting for 1.1% (0.2–2.6) and 3.1% (0.3–8.6), respectively. Some 44.4% (29.2–61.7) of cross-national variation in IFR could not be explained. A 10% increase of BMI was associated with an increase in age-standardized IFR of 17.4% (6.5–32.0%) (p<0·0001). If these associations prove to be causal and all countries had national BMI that was equal to or less than that of the global 25th percentile, these associations suggest global standardized IFR could be 11.1% (2.1–20.6) lower.

A great deal of cross-country infection rates and IFR variation persisted, even after standardizing for key factors such as seasonality, age, BMI, and other factors described above (Figure 2). Between January 1, 2020, and September 30, 2021, countries such as Iceland and Singapore had relative success in preventing infection and treating those infected. On the contrary, countries such as India, Bolivia, and Peru are examples of countries that had high standardized infection rates and high IFR. Taiwan and Vietnam had relative success in preventing infections yet had high IFR. Meanwhile, Georgia and Qatar had the opposite experience, with less relative success preventing infection, but low IFR.

Traditional pandemic preparedness indices, such as the JEE and GHS Index (and their components), were not associated with standardized infection rates or standardized IFR (Figure 3). Similarly, health-care capacity indicators were not favorably associated with standardized infection rate or IFR (Figure 3). More government corruption was associated with higher levels of standardized infections throughout the pandemic, and no other governance variables were associated with standardized IFR. Finally, trust in government and interpersonal trust were associated with standardized infection rates, for both the first ten months of the pandemic and the entire pandemic through September 30, 2021. Moreover, the magnitude of these associations was substantive and persistent across nearly all of the sensitivity analyses conducted (appendix sections 4 & 5). If our modelled associations prove to be causal, an increase in trust of governments such that all countries had societies that attained at least the amount of trust in government or interpersonal trust measured in Denmark, which is in the 75th percentile across these spectrums, global infections might have been 12.9% (95% UI 5.7–17.8) and 40.3% (24.3–51.4) lower, respectively.

To assess how government trust, interpersonal trust, and government corruption might have contributed to reductions in infection rates, we assessed the association between these factors and COVID-19 vaccine coverage rates and reductions in mobility (Figure 4). More interpersonal trust, more government trust, and less government corruption were associated with greater COVID-19 vaccine coverage (as of September 30, 2021; p-values = <0.001 p=0.006, and < 0.001, respectively). Less government corruption was also associated with greater reduction in mobility (p-value <0.001).

Discussion

There are several main conclusions that are drawn from this analysis. First, we find that many of the baseline risk factors were strongly related to COVID-19 outcomes. For infections, this was seasonality, population living below 100m altitude, and GDP per capita and for IFR this was age profile of the country, average BMI, and again GDP per capita. However, these factors are largely not policy amenable in the short term, and therefore not helpful for emergency response. While we can encourage improved behaviors for reducing obesity such as imposition of sugar taxes or improving access and cost of fruits, vegetables, nuts, and grains, [44–46] or banning smoking in public places to reduce prevalence of smoking and second hand smoke inhalation,[47–49] the temporal impact of these changes is much more distal. Other factors like seasonality, age profile, altitude, population density, GDP per capita, and baseline exposure to betacoronavirus bats are altogether relatively immutable. Our study suggests that for infections, the majority of variation across the countries was unexplained (60.6% (UCI: 55.6 – 65.2%)), followed by altitude, GDP per capita, and seasonality explaining 5.4% (4.0 – 7.9%), 4.2% (1.8 – 6.6%), and 2.1% (1.7 – 2.7%) of variability, respectively. For seasonality and altitude, it is suggested that these influence COVID-19 outcomes due to atmospheric changes like humidity or through behavioral changes such as increasing time spent indoors.[38–40] For IFR, age structure of the population explained by and large the most variation (46.7% (18.1-67.6%)) in the study – not counting unexplained variation – with those with older populations in general having higher IFRs. While relatively immutable, this study emphasizes the need for public health and pandemic preparedness policies that consider the population at risk and additionally prioritize and protect the most vulnerable populations for each pathogen; for COVID-19, this included the elderly and immunocompromised. Following age structure, GDP per capita, population density, cancer prevalence, and BMI explained the largest percentage of variation at 3.1% (0.3 – 8.6%), 1.7% (0.3 – 5.6%), 1.6% (0.1 – 4.8%), and 1.1% (0.2 – 2.6%), respectively, adding to the evidence that those most at risk (older age, higher BMI, comorbidities) had higher fatality rates once infected.[33,50,51] It is important to note that the risk profile for various pathogens of pandemic potential will inevitably vary: for SARS-CoV-2, elderly patients with comorbidities were at highest risk, but for other pathogens like Zika, neonates and

pregnant women faced the higher burden of disease. Preparedness plans should consider multiple frameworks of populations at risk across a wide array of pathogens rather than focusing on the most recent threat, in this case, COVID-19.

Second, this study suggests that those variables related to pre-pandemic health care access and capacity as well as pandemic preparedness such as the GHSI score, JEE score, UHC estimate, and the HAQI score were not related to improved COVID-19 outcomes. Pre-pandemic, both the JEE and GHSI suggested that the United States would have been the most prepared for detecting and responding to a pandemic. We have seen since that the United States has among the highest death rates.[8,9,24] In contrast, some other countries with relatively low GHSI and JEE scores such as Burundi, the Philippines, and the Dominican Republic, all fared relatively well in terms of IFR and infections per capita. This suggests that these preparedness and health care indices were not well suited for understanding a country's success in preventing, detecting, and responding to a novel threat. Moreover, they failed to account for lack of uptake of prescribed policies or therapies due to lack of trust in the government's messaging, or communities of non-support.[52–54] It is important to emphasise that the JEE, GHS Index, and measures of UHC are intended to be tools for identifying gaps in national capacity in order to direct financial and political support appropriately and were never intended to predict pandemic outcomes. JEEs were developed as a mechanism to identify gaps in a country's preparedness for developing National Action Plans and were not designed for cross-country comparability; in addition, the aggregate measure is a weighting of the components and was not scored by the countries themselves. More than 100 nations have undertaken voluntary Joint External Evaluations, and more than 60 countries developed National Action Plans for Health Security; the benefits of such exercises extend beyond preparing for the current pandemic. Similarly, the 2019 GHS Index focuses critically on a national capacity and preparedness to limit epidemic spread, with what it measures potentially having benefits associated with future pandemics. Measures assessed by these metrics, such as laboratory capacity, that have not yet proven to drive outcomes in a pandemic, may well prove important against future emerging disease threats, as they were not intended to predict outcomes for any one specific pandemic. Additional research understanding key risk profiles for various pathogens is essential for targeted preparedness and understanding how specific indicators performed will help inform necessary resources and capacity building for novel threats.

Third, we identified from our bivariate analyses (Figure 3) that trust – in the federal government and in other people – was highly correlative of lower infections in the full time period; trust was not significant in the correlations of IFR. This is consistent with previous research suggesting that trust in governmental bodies promotes prosocial, protective behaviors like handwashing, mask wearing, and social distancing, reduces non-necessary activities, and encourages vaccine uptake.[52–56] No other health care or pandemic preparedness, social, or governance indicators were significantly related to improved COVID-19 outcomes. Our counterfactual analyses considered what the world may have been like if all countries had trust at the 75th percentile – similar to that of Denmark for governmental trust – and found that there would have been 40% fewer and 13% fewer infections at the 75th percentile for interpersonal and governmental trust, respectively.

One mechanism by which trust may influence COVID-19 infections is through vaccination. In this analysis, we found that higher interpersonal trust and lower governmental corruption were both correlated with significantly higher vaccination coverage levels (Figure 4). In addition, lower governmental corruption levels were also correlated with higher reductions in mobility. Previous research has shown that pre-pandemic trust is correlative of higher vaccine uptake,[56] while the COVID-19 pandemic has demonstrated that the vaccine hesitancy movement has marked impacts on vaccine uptake.[57] Improving trust in the government and medical professions now, before the next pandemic, via improved transparency and

clear communication,[58] addressing misinformation and disinformation,[59] and increasing accountability among leadership,[58] may have large implications for future outbreaks.

Limitations

This analysis has a number of limitations. First, the explanatory variables come from a variety of sources that include population-based opinion surveys, a survey of expert opinions, reported government statistics, and modelled estimates. The findings for each explanatory variable should be assessed considering the quality of the data source. Second, while we attempted to propagate sources of uncertainty into the final results by running the analysis on each of 100 samples, an estimate of uncertainty was not available for most explanatory variables. Third, we prioritized explanatory value when deciding how to specify the functional forms of the models. Stage 1 and Stage 2 variables are assumed to have log-log relationships with their respective outcomes, and the variables in Stage 1, Stage 2, and Stage 3 are assumed to be independent. It is likely that a fuller model could result in the use of interactions and non-linear effects, but we chose relatively simple models by design and due to limitations in data. Fourth, we did not include country-specific response variables such as mask use, changes in mobility, testing, vaccination, and mandate imposition in our primary analysis of infections and IFR, given the challenges in identifying causal relationships using cross-sectional models. We included these variables in our supplementary analyses (appendix section 5.1) and in our Stage 3 analysis but note that the temporality of these associations is not fully understood. Future research using time series methods is needed to better understand how response measures influenced COVID-19 outcomes. Fifth, we adjusted for underlying influences on COVID-19 outcomes, including age structure and seasonality, but were unable to adjust for differentials in outcomes by sex given data limitations; future work is needed to better understand the degree of variability in outcomes due to differing sex population structures. Sixth, we include the most up-to-date information on variants and the most recent data but note that continually changing circumstances of the pandemic may influence these results. Seventh, while Stage 1 was completed using subnational and national data, we focused our reporting and Stage 2 and 3 analyses at the national level in order to focus on factors that could be influenced by national policy. Additional research is needed to better understand within-country variability, which is likely equally important in understanding differences in COVID-19 outcomes. Finally, this is an ecological analysis and was not designed to provide information about the causes of COVID-19 variation. While we hope these results will spur discussion about the drivers of COVID-19 outcomes, a causal analysis would require more data and a different study design.

Conclusions

This study suggests not only that previous measures of pandemic preparedness were not predictive of COVID-19 success, but that those countries with the highest pre-pandemic scores were some of the worst-faring countries throughout the COVID-19 pandemic. Our finding that governmental trust and interpersonal trust were so influential on reduced infections suggests that improving trust pre-pandemic may pay dividends in improving pandemic outcomes. Investments into better risk communication, improved accountability or community engagement strategies are effective ways to improve current trust in federal officials and can be fostered before the next threat to improve confidence in leaders and public health officials. However, our variables of trust were limited by small sample sizes and few surveys, resulting in wide confidence intervals and limited interpretations. Similarly, the definition of trust is not understood equivalently across all contexts and cultures.[60,61] We therefore call for additional research into trust into various groups – other people, the government, scientists – to better understand these patterns as well as to further qualify – and quantify - how trust is interpreted in local and regional contexts. Importantly, however, is that trust is not static and varies substantially over time; ongoing,

dynamic assessments are essential to understand both the current state of trust and changing patterns in response to political, social, natural, or medical crises.

This research has identified that several baseline risk factors influencing poorer COVID-19 outcomes, including obesity and comorbidities. While some pandemic threats may target children or young adults, the shifting epidemiologic profile in many countries towards older populations exhibiting a larger burden of non-communicable diseases puts more and more countries at risk for diseases like COVID-19 that impact elderly and comorbid groups. Preparedness efforts focused on reducing obesity, smoking, and chronic illnesses will help in reducing the burden of those diseases targeting these risk groups and prevent additional countries from facing the burden faced by many higher income countries like the United States and Italy during the COVID-19 pandemic. However, for both outcomes, there were high degrees of unexplained variation that remained even after accounting for all covariates of interest, which highlights future avenues for research. This analysis also identified trust in the government and in other people as a key avenue for reducing pandemic morbidity and mortality; resources directed at building trust now via clear risk communication, reduction of mis- and dis-information, and transparency by elected officials have the potential to improve the rapidity and degree of uptake for pandemic response measures for future threats.

List of Tables and Figures

TABLE 1: COVARIATES USED IN STAGE 1 AND STAGE 2 ANALYSES

Stage	Grouping	Name	Units	Temporal Coverage	Spatial Coverage	Data Source	Notes
1	-	Pneumonia RR	Relative risk of death from pneumonia divided by the average risk of death from pneumonia	2013-2019	National and subnational	Modeling COVID-19 scenarios for the United States[43]	Varies weekly
1	-	Age	Age structure of the population (5 year age bins)	2020	National and subnational	Global Burden of Disease Study 2019[62]	
1	-	Altitude	% of population living below 100m	2015	National and subnational	Global Burden of Disease Study 2019[62]	
1	-	Population Density	% of population living above 1,000 people / km^2	2020	National and subnational	Modeling COVID-19 scenarios for the United States[43]	
1	-	Air Pollution	PM 2.5 air pollution concentration (mg/m^3)	2019	National and subnational	Global Burden of Disease Study 2019[62]	
1	-	Smoking Prevalence	Age-standardized tobacco smoking prevalence	2019	National and subnational	Global Burden of Disease Study 2019[62]	
1	-	Cancer prevalence	Age-standardized cancer prevalence	2019	National and subnational	Global Burden of Disease Study 2019[62]	

		COPD prevalence	Age-standardized chronic obstructive pulmonary disease prevalence	2019	National and subnational	Global Burden of Disease Study 2019[62]	
1	-	Bats	Average number of Beta-Coronavirus host bat species in a given location	2021 Bats & Ranges	National only	IUCN[63] & Verena Consortium[64]	See appendix section 3.2 for more details of methodology
1	-	Gross Domestic Product per Capita	2019 US dollars	2019	National and subnational	Global Burden of Disease Study 2019[62]	
1	-	BMI	Population-adjusted body mass index	2019	National and subnational	Global Burden of Disease Study 2019[62]	
2	Preparedness indicators	Joint External Evaluation Components and Prevent Epidemics' Preparedness overall score	Index	2016-2021	National only	WHO and Prevent Epidemics[65]	Only places that have completed a JEE; overall score is a summary variable of JEE components created by Prevent Epidemics
2	Preparedness indicators	Global Health Security Index Components and Overall Score	Index	2019	National only	Global Health Security Index 2019[6]	Weighted average of the other components
2	Healthcare capacity indicators	Universal Health Coverage	Index	2019	Nationals	Global Burden of Disease Study 2019[62], Measuring Universal Health Coverage[66]	Included 2 subcomponents – communicable and non-communicable
2	Healthcare capacity indicators	Healthcare Accessibility and Quality Index	Index	2019	National only	Global Burden of Disease Study 2019[62]	
2	Healthcare capacity indicators	Government health spending per capita	2019 US dollars	2020	National only	Global Burden of Disease Health Financing Collaborator Network[67]	Mean value
2	Healthcare capacity indicators	Beds per Capita	Number of hospital beds per capita before start of the pandemic	2019	National and subnational	Global Burden of Disease Study 2019[62]	
2	Healthcare capacity indicators	Health spending per capita	2019 US dollars	2020	National only	Global Burden of Disease Health Financing Collaborator Network[67]	Mean value

2	Governance Indicators	Government corruption – PCA	Index		National only	Transparency International[68] Varieties of Democracy Institute, Version 10 [69,70]	Principal components analysis of V-Dem Public sector corruption and the Transparency International's Corruptions Perceptions Index; see appendix section 3.3 for more details of methodology
2	Governance Indicators	Electoral Populism	Populism-based campaign run		National only	Populism in Power[74] & Bosancinau[31]	Whether a democratically elected head of government ran a populist campaign
2	Governance Indicators	Government Effectiveness	Index		National only	World Bank Indicators[71] & Bosancinau[31]	Perceived quality of public services, its provision and providers
2	Governance Indicators	State Fragility	Index		National only	State Fragility Index[72]& Bosancinau[31]	Incapacity to provide essential public goods and services and cope with shocks
2	Governance Indicators	Electoral Democracy Index	Index	2020	National only	Varieties of Democracy Institute, Version 11[73,74]	Aggregate indicator combining free and fair elections, free association, freedom of expression and access to alternative information, suffrage, and elected officials
2	Social indicators	Interpersonal Trust	Trust in Other People	2017-2021	National only	WORLD VALUES SURVEY WAVE 7[75]	Trust coded as those who answered "most people can be trusted on Q57"
2	Social indicators	Trust in Science		2018	National only	Wellcome Global Monitor Survey[76]	Those that answered 'A lot' to trusting science
2	Social indicators	Trust in government - PCA	Index	2017-2021	National only	WORLD VALUES SURVEY WAVE 7[75],; Gallup World Poll[73]	Principal components analysis of Gallup's Politics and Government variable Confidence in National government and

							World Values Survey (Wave 7s) question on confidence in government ; see appendix section 3.3 for more details of methodology
2	Social indicators	GINI	Gini Index		National only	SWIID v8.2[77] & Bosancinau[31]	

Further references for data sources given in the appendix (p 4). BMI=body-mass index. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. COPD=chronic obstructive pulmonary disease. JEE=Joint External Evaluation. PCA=principal component analysis. SWIID=Standardized World Income Inequality Database.

This table presents the stage and category, unit of measure, data source, temporal and spatial coverage, and notes on the covariates used in the stage 2 analyses.

TABLE 2: FACTORS ASSOCIATED WITH VARIATION IN CROSS-COUNTRY CUMULATIVE INFECTIONS PER CAPITA, IFR, AND HYPOTHETICAL LEVELS OF TRUST AND PREVALENCE OF RISK FACTORS

	Percentage of cross country observed infection per capita variation explained by each factor	Percentage of cross country observed IFR variation explained by each factor	Reduction in global infections if trust in all countries exceeded 75th percentile for all countries	Reduction in global mortality if risk factors were less than 25th percentile for all countries
Seasonality	**2.1% (1.7 - 2.7%)**	-	-	-
Age structure	-	**46.7% (18.1 - 67.6%)**	-	-
GDP per capita	**4.2% (1.8 - 6.6%)**	**3.1% (0.3 - 8.6%)**	-	-
Population density	1.8% (0.8 - 3.2%)	1.7% (0.3 - 5.6%)	-	-
Altitude	**5.4% (4.0 - 7.9%)**	-	-	-
Pre-exposure to beta corona virus	2.1% (1.1 - 3.1%)	0.7% (0.1 - 2.1%)	-	-
Body mass index	-	**1.1% (0.2 - 2.6%)**	-	**11.1% (2.1 - 20.6%)**
Smoking prevalence	-	0.3% (0.1 - 3%)	-	-
Air pollution	-	0.3% (0.1 - 2.1%)	-	-
COPD prevalence	-	0.2% (0.0 - 0.7%)	-	-
Cancer prevalence	-	1.6% (0.1 - 4.8%)	-	-
Trust in government*	**7.4% (5.4 - 9.6%)**	-	**12.9% (5.7 - 17.8%)**	-
Interpersonal trust*	**16.5% (12.3 - 19.5%)**	-	**40.3% (24.3 - 51.4%)**	-
Unexplained variation	60.6% (55.6 - 65.2%)	44.4% (29.2 - 61.7%)	-	-

*These covariates are assumed to be independent from each other and all other covariates. Further, a limited number of countries had incomplete reporting of these covariates. Corresponding figures reflect those countries where the respective covariate was present. Bold entries have estimated parameters that are statistically different from zero.

BMI=body-mass index. COPD=chronic obstructive pulmonary disease. IFR=infection-fatality ratio. UI=uncertainty interval.
* Estimated parameters that are statistically different from zero.
† These covariates are assumed to be independent from each other and all other covariates. Further, a few countries had incomplete reporting of these covariates. Corresponding figures reflect those countries where the respective covariate was present.

The range of values in the parentheses represent 95% uncertainty intervals. IFR=infection-fatality ratio.

FIGURE 1A: DECOMPOSITION OF THE DIFFERENCE BETWEEN CUMULATIVE AND STANDARDIZED CUMULATIVE SARS-COV-2 INFECTIONS PER CAPITA

		Marginal effect of standardizing to the global mean					
Country	Raw infections per 1000 population	Seasonality	Altitude	GDP per capita	Population density	Previous betacoronavirus exposure	Adjusted infections per 1000 population
Central Europe, Eastern Europe, and Central Asia							
Armenia	908	+25	-255	-13	-9	-62	594
Azerbaijan	900	+13	+ 108	+ 48	+ 3	-13	1060
Georgia	833	+20	-34	-9	-3	-68	740
Kazakhstan	814	+13	-70	+ 107	+ 17	+132	1014
Kyrgyzstan	934	+ 4	-251	-148	+ 9	+ 8	556
Mongolia	410	+25	-137	+ 6	-1	+ 70	373
Tajikistan	782	+13	-208	-132	+ 4	-5	454
Uzbekistan	628	+10	-78	-40	+ 5	+ 38	562
Albania	870	+17	+ 94	+ 21	-9	-73	921
Bosnia and Herzegovina	717	+15	-91	+ 11	+ 21	-60	612
Bulgaria	636	+21	-49	+ 64	+ 5	-64	613
Croatia	457	+ 9	+ 10	+ 65	+ 2	-44	499
Czech Republic	658	+ 2	-206	+ 121	-1	-43	531
Hungary	483	+ 3	+ 21	+ 84	-3	-49	540
North Macedonia	838	+12	-225	+ 32	+ 14	-66	604
Montenegro	915	+23	-43	+ 79	+ 30	-78	926
Poland	405	+ 2	+ 17	+ 72	-1	-25	469
Romania	550	+50	+ 81	+ 84	-6	-50	709
Serbia	552	+28	+ 28	+ 27	-1	-51	582
Slovakia	193	+ 3	-48	+ 33	+ 1	-16	166
Slovenia	374	+ 7	-64	+ 70	+ 1	-36	351
Belarus	492	+13	-142	+ 7	-3	-11	354

Estonia	233	+12	+ 57	+ 48	-4	+ 5	351
Latvia	345	+19	+ 69	+ 58	-1	-8	483
Lithuania	548	+29	+ 63	+ 108	+ 4	-21	730
Moldova	634	+16	+ 38	-72	+ 11	-38	588
Russia	828	+30	+ 31	+ 123	-7	+160	1165
Ukraine	500	+25	+ 16	-23	-2	-13	503
High-income							
Brunei	58	+ 9	+ 15	+ 22	+ 0	-12	92
Japan	46	+ 0	+ 8	+ 12	-1	+ 1	67
South Korea	18	+ 1	+ 3	+ 5	+ 0	+ 1	28
Singapore	35	+ 9	+ 9	+ 16	-1	-8	59
Australia	9	+ 2	+ 2	+ 3	+ 0	+ 3	18
New Zealand	1	+ 0	+ 0	+ 0	+ 0	+ 1	3
Andorra	462	+ 1	-152	+ 140	-5	-42	405
Austria	180	+ 2	-57	+ 42	+ 0	-14	153
Belgium	281	+ 3	+ 55	+ 79	-2	-19	397
Cyprus	133	+ 1	+ 13	+ 28	-2	-8	164
Denmark	102	+ 1	+ 26	+ 33	-1	+ 4	166
Finland	119	+ 4	+ 23	+ 36	+ 1	+ 20	204
France	294	+ 1	+ 36	+ 75	-2	-27	376
Germany	141	+ 2	+ 14	+ 42	-1	-9	188
Greece	129	+ 3	+ 13	+ 21	-2	-10	154
Iceland	63	+ 2	+ 9	+ 24	+ 0	+ 39	136
Ireland	156	+ 5	+ 35	+ 65	-2	+ 2	261
Israel	247	+ 4	+ 37	+ 56	-6	-10	328
Italy	224	+ 0	+ 22	+ 51	-4	-19	273

Luxembourg	226	+ 2	-77	+ 79	-1	-14	214
Malta	151	+ 1	+ 33	+ 40	-4	+ 15	236
Netherlands	224	+ 1	+ 56	+ 74	-4	-8	344
Norway	190	+ 3	+ 12	+ 76	-1	+ 31	311
Portugal	210	+ 1	+ 25	+ 40	-3	-19	255
Spain	242	+ 0	+ 11	+ 54	-4	-19	284
Sweden	225	+ 1	+ 48	+ 73	-3	+ 24	368
Switzerland	190	+ 2	-62	+ 52	-2	-16	164
UK	252	+ 8	+ 53	+ 69	-7	-1	374
Argentina	638	+ 2	+ 104	+ 55	-12	+ 99	887
Chile	332	+ 2	-36	+ 48	-6	+ 79	420
Uruguay	329	+ 1	+ 74	+ 43	-9	+ 34	472
Canada	202	+ 6	+ 21	+ 64	-5	+ 59	346
USA	328	+ 8	+ 33	+ 119	-5	+ 62	545
Latin America and Caribbean							
Antigua and Barbuda	258	+28	+ 67	+ 46	+ 3	+ 30	433
The Bahamas	437	+53	+ 124	+ 99	-9	+136	839
Barbados	97	+31	+ 21	+ 8	-1	+ 19	175
Belize	392	+18	+ 68	-24	+ 24	-18	460
Cuba	201	+ 7	+ 33	-11	+ 0	+ 5	235
Dominican Republic	321	+ 3	+ 50	+ 22	-5	+ 20	411
Guyana	428	+20	+ 86	-28	+ 1	-31	476
Haiti	225	+10	+ 16	-67	-2	+ 12	194
Jamaica	199	+ 3	+ 6	-11	-1	+ 7	204
Saint Lucia	361	+17	+ 41	+ 8	+ 0	+ 31	458

Saint Vincent and the Grenadines	158	+33	+ 7	+ 1	+ 0	+ 7	205
Suriname	508	+36	+ 111	+ 15	+ 3	-33	640
Trinidad and Tobago	220	+10	+ 40	+ 37	+ 0	-8	299
Bolivia	921	+ 3	-252	-67	-1	-19	585
Ecuador	822	+ 2	+ 29	-3	-7	-46	797
Peru	692	+ 2	-11	+ 17	-8	-17	674
Colombia	568	+ 2	-8	+ 19	-5	-36	539
Costa Rica	514	+13	-11	+ 32	-5	-26	517
El Salvador	329	+ 9	-22	-14	-3	-16	284
Guatemala	654	+13	-70	-39	+ 3	-31	530
Honduras	879	+ 6	+ 32	-111	+ 1	-47	761
Mexico	716	+ 6	-4	+ 58	-14	+ 14	777
Nicaragua	597	+11	+ 24	-69	+ 5	-27	540
Panama	493	+ 2	+ 75	+ 71	-5	-32	603
Venezuela	593	+12	-2	-37	-3	-37	526
Brazil	626	+ 3	+ 36	+ 26	-12	-31	648
Paraguay	716	+ 1	+ 33	-21	-4	-4	721
Bermuda	182	+21	+ 58	+ 88	-8	+125	467
Puerto Rico	152	+ 1	+ 27	+ 36	-2	+ 11	225
Virgin Islands	208	+ 7	+ 43	+ 72	+ 5	+ 61	395
North Africa and Middle East							
Algeria	185	+ 1	-1	+ 4	-2	+ 18	205
Bahrain	604	+ 1	+ 162	+ 178	-20	+116	1041
Egypt	637	+11	+ 144	+ 0	-18	+ 60	834

Iran	624	+ 7	-48	+ 40	-1	-2	621
Iraq	888	+ 8	+ 142	+ 21	+ 0	+ 73	1132
Jordan	718	+ 7	-93	-6	-13	+ 30	642
Kuwait	538	+ 0	+ 126	+ 195	-12	+ 55	903
Lebanon	653	+ 4	+ 74	+ 35	-12	-48	706
Libya	813	+14	+ 82	+ 4	+ 6	+123	1043
Morocco	651	+ 3	+ 42	-26	-8	+ 3	665
Palestine	853	+16	+ 85	-112	-17	-38	787
Oman	450	+ 0	+ 30	+ 101	+ 9	+ 26	617
Qatar	617	+ 1	+ 176	+ 330	-17	+ 71	1179
Saudi Arabia	245	+ 0	+ 11	+ 70	+ 1	+ 28	356
Syria	145	+ 6	-24	-21	-1	+ 5	110
Tunisia	844	+ 2	+ 129	+ 4	-7	+ 45	1016
Turkey	539	+14	+ 4	+ 71	-9	-13	606
United Arab Emirates	290	+ 1	+ 39	+ 107	-3	+ 28	462
Yemen	349	+ 4	-20	-98	+ 1	+ 6	242
Afghanistan	988	+ 2	-255	-225	+ 8	+ 15	533
Sudan	378	+ 5	-81	-59	+ 8	+ 4	255
South Asia							
Bangladesh	728	+ 2	+ 143	-122	-12	-49	690
India	748	+ 2	+ 53	-52	-5	-40	706
Nepal	893	+ 7	+ 28	-193	-4	-66	664
Pakistan	884	+ 5	+ 21	-116	-4	+ 7	796
Southeast Asia, East Asia, and Oceania							
China	1	+ 0	+ 0	+ 0	+ 0	+ 0	1

Taiwan (province of China)	5	+ 0	+ 1	+ 2	+ 0	+ 0	7
Cambodia	222	+16	+ 40	-37	+ 3	-29	215
Indonesia	517	+ 2	+ 54	+ 6	-4	-59	516
Malaysia	371	+10	+ 66	+ 62	-5	-69	436
Maldives	397	+ 5	-52	+ 30	-13	+200	567
Myanmar	304	+ 6	+ 34	-28	+ 4	-41	279
Philippines	340	+10	+ 55	-16	-4	-35	351
Sri Lanka	167	+ 3	+ 21	+ 3	-1	-12	182
Thailand	136	+ 8	+ 19	+ 11	+ 0	-22	152
Timor-Leste	264	+ 1	-6	-34	+ 2	-15	212
Vietnam	71	+ 3	+ 11	-7	+ 0	-10	67
Fiji	455	+11	+ 102	-23	-2	+254	797
Papua New Guinea	163	+19	-5	-32	+ 10	+ 11	166
Mauritius	67	+ 6	-3	+ 9	-1	+ 11	89
Seychelles	458	+15	+ 74	+ 101	+ 0	+159	806
Guam	482	+31	+ 91	+ 177	-8	+141	913
Northern Mariana Islands	54	+ 0	+ 10	+ 12	+ 0	+ 15	91
Sub-Saharan Africa							
Angola	427	+13	+ 35	-44	-3	-20	409
Central African Republic	451	+ 0	-103	-138	+ 6	-31	184
Congo (Brazzaville)	347	+21	-21	-42	+ 1	-34	272

DR Congo	341	+ 0	-75	-97	+ 3	-26	146
Equatorial Guinea	372	+ 8	-44	+ 44	+ 16	-39	356
Gabon	275	+13	-4	+ 18	+ 3	-28	277
Burundi	144	+ 4	-33	-45	+ 1	-12	58
Djibouti	460	+13	+ 31	-82	-3	-6	413
Eritrea	172	+ 1	-16	-47	+ 4	+ 0	115
Ethiopia	422	+ 7	-104	-95	+ 7	-17	219
Kenya	774	+ 4	-94	-131	+ 4	-66	491
Madagascar	599	+ 1	-11	-179	+ 11	+ 28	449
Malawi	696	+ 1	-111	-195	+ 9	-70	329
Mozambique	400	+ 1	+ 26	-127	+ 6	-22	285
Rwanda	372	+ 3	-90	-75	+ 3	-37	175
Somalia	682	+21	+ 30	-392	+ 19	+ 40	399
Uganda	466	+ 2	-112	-96	+ 6	-49	217
Zambia	477	+ 1	-121	-67	+ 4	-43	251
Botswana	793	+ 4	-246	+ 42	+ 27	+ 12	633
Lesotho	789	+ 3	-211	-136	+ 18	+ 0	463
Namibia	922	+ 3	-112	-8	+ 0	+ 44	849
South Africa	811	+ 4	-33	+ 13	-13	+ 7	789
Zimbabwe	690	+ 3	-169	-144	+ 6	-53	333
Benin	168	+ 3	+ 16	-40	+ 1	-19	130
Burkina Faso	385	+11	-97	-87	+ 6	-21	197
Cameroon	348	+12	-9	-61	+ 1	-32	259
Cape Verde	586	+ 4	-12	-48	+ 1	+130	662
Chad	239	+ 0	-63	-54	+ 8	+ 6	136

Côte d'Ivoire	358	+ 5	+ 15	-53	+ 2	-39	287
The Gambia	566	+ 1	+ 104	-159	-3	-58	452
Ghana	295	+ 1	+ 14	-43	+ 0	-38	230
Guinea	434	+ 1	-3	-107	+ 3	-41	287
Guinea-Bissau	437	+ 3	+ 80	-132	+ 4	-44	348
Liberia	327	+ 0	+ 23	-112	+ 2	-28	212
Mali	392	+ 3	-63	-98	+ 3	+ 18	254
Mauritania	482	+ 4	+ 74	-101	+ 3	+ 68	529
Niger	228	+ 1	-60	-69	+ 7	+ 18	125
Nigeria	424	+ 3	-14	-49	-1	-36	328
São Tomé and Príncipe	480	+11	-137	-83	+ 0	+ 89	359
Senegal	630	+ 1	+ 123	-144	+ 5	-25	590
Sierra Leone	186	+ 0	+ 18	-56	+ 1	-18	131
Togo	304	+ 2	+ 25	-82	+ 1	-37	211
South Sudan	312	+ 1	-89	-11	+ 27	-32	208

The first column represents the raw infections per capita, and each subsequent column represents the proportion of adjusted cumulative infections per capita that can be accounted for by seasonality, altitude, GDP per capita, population density, and a proxy for pre-exposure to beta coronavirus; the last column represents the adjusted infections per capita. The infections per capita metrics are color-coded based on their severity relative to all other countries, with red representing higher cumulative infections per capita and green representing lower cumulative infections per capita (raw and adjusted).

FIGURE 1B: DECOMPOSITION OF THE DIFERENCE BETWEEN IFR AND STANDARDISED IFR

		Marginal effect of standardizing to the global mean									
Country	Raw IFR per 1000 infections	Age pattern	Air pollution	BMI	Cancer prevalence	COPD prevalence	GDP per capita	Population density	Previous betacoronavirus exposure	Smoking prevalence	Adjusted IFR per 1000 infections
Central Europe, Eastern Europe, and Central Asia											
Armenia	4.42	-1.04	+ 0.06	-0.29	+ 0.20	-0.02	-0.07	+ 0.14	-0.19	-0.03	3.18
Azerbaijan	3.57	+ 1.12	-0.02	-0.39	+ 0.18	-0.02	+ 0.20	-0.04	-0.03	-0.02	4.54
Georgia	3.42	-1.35	+ 0.00	-0.20	+ 0.09	-0.01	-0.03	+ 0.03	-0.13	-0.02	1.79
Kazakhstan	2.95	+ 0.66	-0.07	-0.47	+ 0.16	-0.04	+ 0.39	-0.19	+ 0.28	-0.02	3.64
Kyrgyzstan	2.76	+ 1.61	-0.01	+ 0.06	+ 0.19	-0.04	-0.67	-0.12	+ 0.02	-0.02	3.77
Mongolia	0.96	+ 0.79	+ 0.04	+ 0.01	+ 0.06	+ 0.02	+ 0.02	+ 0.02	+ 0.15	-0.02	2.06
Tajikistan	1.19	+ 1.59	+ 0.06	+ 0.30	+ 0.08	+ 0.01	-0.44	-0.04	-0.01	+ 0.02	2.77
Uzbekistan	2.39	+ 2.51	+ 0.03	-0.18	+ 0.16	+ 0.03	-0.24	-0.09	+ 0.13	+ 0.02	4.76
Albania	4.49	-1.60	-0.04	-0.19	+ 0.36	+ 0.03	+ 0.09	+ 0.11	-0.18	-0.04	3.03
Bosnia and Herzegovina	5.43	-2.23	+ 0.04	-0.23	+ 0.39	-0.01	+ 0.07	-0.40	-0.22	-0.05	2.79
Bulgaria	8.47	-4.53	-0.04	-0.63	+ 0.62	-0.05	+ 0.63	-0.16	-0.37	-0.08	3.85
Croatia	5.84	-3.25	-0.05	-0.44	+ 0.63	-0.04	+ 0.60	-0.07	-0.24	-0.06	2.93
Czech Republic	4.78	-2.59	-0.06	-0.45	+ 0.41	-0.03	+ 0.76	+ 0.02	-0.16	-0.04	2.65
Hungary	7.00	-3.74	-0.08	-0.71	+ 0.54	-0.09	+ 0.87	+ 0.08	-0.30	-0.06	3.52
North Macedonia	6.52	-1.67	+ 0.07	-0.48	+ 0.54	+ 0.01	+ 0.24	-0.32	-0.30	-0.08	4.53
Montenegro	4.54	-1.50	-0.02	-0.40	+ 0.37	+ 0.05	+ 0.31	-0.36	-0.18	-0.05	2.76
Poland	8.08	-3.62	-0.02	-0.71	-0.57	-0.01	+ 0.99	+ 0.06	-0.20	-0.05	3.95
Romania	6.15	-3.33	-0.09	-0.39	+ 0.66	-0.02	+ 0.66	+ 0.15	-0.23	-0.04	3.51
Serbia	4.09	-1.78	+ 0.01	-0.37	+ 0.44	-0.03	+ 0.15	+ 0.01	-0.17	-0.04	2.31
Slovakia	13.89	-6.01	-0.13	-1.17	+ 1.37	+ 0.03	+ 2.16	-0.11	-0.62	-0.10	9.31
Slovenia	9.32	-5.42	-0.11	-0.84	+ 0.70	+ 0.01	+ 1.36	-0.05	-0.40	-0.05	4.53
Belarus	9.03	-3.83	-0.06	-0.54	+ 0.94	+ 0.03	+ 0.11	+ 0.19	-0.12	-0.10	5.65
Estonia	8.66	-5.10	-0.36	-0.81	+ 0.90	+ 0.08	+ 1.16	+ 0.26	+ 0.08	-0.06	4.79
Latvia	8.95	-5.27	-0.16	-0.78	+ 0.80	+ 0.09	+ 0.96	+ 0.05	-0.08	-0.08	4.49
Lithuania	8.96	-5.30	-0.20	-0.67	+ 0.95	+ 0.06	+ 1.18	-0.12	-0.14	-0.07	4.65
Moldova	4.05	-1.32	-0.04	-0.31	+ 0.37	+ 0.00	-0.35	-0.17	-0.11	-0.02	2.10
Russia	5.17	-2.18	-0.07	-0.59	+ 0.63	+ 0.02	+ 0.58	+ 0.10	+ 0.45	-0.05	4.06
Ukraine	4.50	-1.93	-0.02	-0.28	+ 0.47	+ 0.01	-0.16	+ 0.05	-0.05	-0.04	2.54

High-income											
Brunei	2.66	+ 2.38	-0.29	+ 0.57	+ 0.87	-0.05	+ 1.34	-0.01	-0.43	+ 0.01	7.04
Japan	11.87	-11.70	-0.30	+ 1.93	+ 2.13	+ 0.13	+ 2.35	+ 0.58	+ 0.12	-0.06	7.05
South Korea	2.88	-1.61	+ 0.01	+ 0.41	+ 0.59	+ 0.00	+ 0.67	+ 0.21	+ 0.08	-0.02	3.24
Singapore	0.49	-0.18	+ 0.00	+ 0.06	+ 0.11	+ 0.01	+ 0.20	+ 0.05	-0.06	+ 0.00	0.68
Australia	6.06	-2.87	-0.22	-0.91	-0.10	-0.07	+ 1.28	+ 0.29	+ 0.71	+ 0.00	4.18
New Zealand	4.99	-2.50	-0.25	-0.70	-0.06	-0.07	+ 0.90	+ 0.22	+ 1.09	-0.01	3.61
Andorra	6.28	-3.12	-0.15	-0.36	+ 0.23	-0.08	+ 1.74	+ 0.20	-0.30	-0.04	4.41
Austria	8.84	-5.44	-0.19	-0.22	+ 1.11	-0.10	+ 1.84	+ 0.04	-0.36	-0.09	5.44
Belgium	9.88	-5.81	-0.19	-0.14	+ 0.32	-0.16	+ 1.88	+ 0.15	-0.26	-0.04	5.61
Cyprus	3.21	-1.05	-0.04	+ 0.10	-0.04	-0.03	+ 0.56	+ 0.12	-0.10	-0.03	2.71
Denmark	9.72	-5.72	-0.29	+ 0.00	+ 0.30	-0.19	+ 2.07	+ 0.20	+ 0.16	-0.04	6.21
Finland	9.12	-5.89	-0.42	-0.30	+ 0.36	-0.02	+ 1.65	-0.16	+ 0.54	-0.03	4.85
France	7.00	-4.30	-0.16	+ 0.03	+ 0.21	+ 0.01	+ 1.26	+ 0.10	-0.26	-0.06	3.83
Germany	12.62	-8.24	-0.27	-0.57	+ 0.59	-0.15	+ 2.50	+ 0.24	-0.30	-0.09	6.34
Greece	11.24	-7.17	-0.12	-0.38	+ 0.28	-0.08	+ 1.24	+ 0.29	-0.35	-0.11	4.84
Iceland	1.61	-0.78	-0.08	-0.12	+ 0.02	-0.02	+ 0.39	+ 0.02	+ 0.38	+ 0.00	1.41
Ireland	6.94	-2.72	-0.29	-0.45	+ 0.26	-0.12	+ 2.07	+ 0.17	+ 0.04	-0.04	5.87
Israel	3.50	-0.73	-0.03	-0.13	+ 0.10	-0.01	+ 0.69	+ 0.22	-0.07	-0.01	3.52
Italy	11.76	-8.41	-0.13	+ 0.07	+ 0.69	-0.03	+ 1.89	+ 0.50	-0.41	-0.06	5.88
Luxembourg	7.00	-3.35	-0.23	-0.01	+ 0.26	-0.10	+ 2.29	+ 0.10	-0.23	-0.05	5.68
Malta	8.37	-5.18	-0.14	-0.34	+ 0.02	-0.03	+ 1.46	+ 0.45	+ 0.31	-0.04	4.87
Netherlands	9.47	-5.55	-0.22	-0.22	+ 0.36	-0.15	+ 2.11	+ 0.33	-0.13	-0.05	5.95
Norway	1.75	-1.01	-0.08	-0.04	+ 0.18	-0.03	+ 0.51	+ 0.02	+ 0.12	+ 0.00	1.42
Portugal	16.56	-10.20	-0.54	-0.37	+ 0.01	-0.10	+ 2.11	+ 0.42	-0.57	-0.06	7.26
Spain	13.99	-8.44	-0.39	-0.60	+ 0.38	-0.13	+ 2.23	+ 0.54	-0.45	-0.11	7.02
Sweden	8.11	-5.09	-0.38	-0.21	+ 0.37	-0.09	+ 1.72	+ 0.21	+ 0.33	+ 0.02	5.00
Switzerland	8.94	-5.48	-0.27	+ 0.14	+ 0.28	-0.05	+ 2.18	+ 0.25	-0.38	-0.05	5.56

UK	10.82	-5.60	-0.29	-0.87	-0.05	-0.17	+ 1.96	+ 0.58	-0.02	-0.05	6.31
Argentina	4.37	-0.72	-0.10	-0.31	+ 0.29	-0.05	+ 0.32	+ 0.21	+ 0.34	-0.03	4.31
Chile	6.22	-1.59	-0.03	-0.80	+ 0.42	-0.01	+ 0.79	+ 0.29	+ 0.76	-0.08	5.98
Uruguay	5.97	-2.54	-0.20	-0.39	+ 0.36	-0.07	+ 0.55	+ 0.34	+ 0.26	-0.06	4.23
Canada	7.17	-3.90	-0.32	-0.88	-0.04	-0.05	+ 1.43	+ 0.32	+ 0.78	+ 0.00	4.51
USA	7.48	-3.33	-0.30	-1.46	-0.16	-0.11	+ 1.71	+ 0.20	+ 0.52	-0.01	4.55
Latin America and Caribbean											
Antigua and Barbuda	4.63	-0.28	-0.04	-0.43	-0.10	+ 0.09	+ 0.63	-0.12	+ 0.25	+ 0.05	4.67
The Bahamas	5.37	+ 0.36	-0.07	-0.93	-0.14	+ 0.10	+ 0.96	+ 0.26	+ 0.78	+ 0.06	6.74
Barbados	5.62	-2.24	+ 0.00	-0.77	-0.06	+ 0.09	+ 0.28	+ 0.15	+ 0.39	+ 0.05	3.51
Belize	4.33	+ 2.22	+ 0.00	-0.82	-0.18	+ 0.02	-0.25	-0.78	-0.11	+ 0.02	4.45
Cuba	4.98	-1.89	-0.02	-0.51	-0.08	-0.03	-0.17	+ 0.02	+ 0.05	-0.03	2.32
Dominican Republic	3.47	+ 0.91	-0.09	-0.44	-0.15	+ 0.05	+ 0.23	+ 0.18	+ 0.12	+ 0.03	4.31
Guyana	4.59	+ 1.78	+ 0.00	-0.44	-0.19	+ 0.07	-0.30	-0.03	-0.20	+ 0.03	5.30
Haiti	3.72	+ 3.88	-0.08	+ 1.04	-0.23	+ 0.02	-1.76	+ 0.13	+ 0.18	+ 0.10	6.98
Jamaica	6.13	-0.41	-0.12	-0.59	-0.13	+ 0.02	-0.29	+ 0.09	+ 0.12	+ 0.00	4.80
Saint Lucia	4.93	-0.74	+ 0.00	-0.52	-0.12	+ 0.01	+ 0.09	-0.01	+ 0.20	+ 0.03	3.86
Saint Vincent and the Grenadines	4.33	-0.43	-0.01	-0.45	-0.11	+ 0.07	+ 0.03	+ 0.03	+ 0.08	-0.01	3.54
Suriname	4.66	+ 0.15	+ 0.02	-0.59	-0.18	+ 0.04	+ 0.11	-0.06	-0.15	-0.01	3.98
Trinidad and Tobago	7.67	-1.64	+ 0.01	-1.14	-0.22	+ 0.11	+ 0.97	+ 0.04	-0.12	+ 0.00	5.68
Bolivia	8.74	+ 4.49	-0.03	+ 0.13	-0.17	+ 0.03	-0.95	+ 0.05	-0.16	+ 0.12	12.26
Ecuador	5.92	+ 1.45	-0.12	-1.02	+ 0.05	+ 0.06	-0.02	+ 0.16	-0.20	+ 0.05	6.33
Peru	9.59	+ 0.85	+ 0.04	-0.72	-0.12	+ 0.15	+ 0.24	+ 0.36	-0.15	+ 0.12	10.36
Colombia	5.16	-0.45	-0.07	-0.25	-0.08	-0.03	+ 0.17	+ 0.15	-0.18	+ 0.02	4.43
Costa Rica	2.72	-0.15	-0.04	-0.29	-0.02	+ 0.00	+ 0.16	+ 0.07	-0.08	+ 0.00	2.37
El Salvador	5.11	+ 0.26	+ 0.01	-0.44	-0.09	+ 0.03	-0.23	+ 0.14	-0.15	+ 0.06	4.70
Guatemala	2.48	+ 1.80	+ 0.00	+ 0.10	-0.08	+ 0.05	-0.22	-0.05	-0.10	+ 0.02	4.01

Honduras	3.94	+ 3.03	-0.02	+ 0.12	-0.12	-0.02	-0.69	-0.02	-0.17	+ 0.01	6.06
Mexico	5.78	+ 0.85	-0.03	-0.94	+ 0.09	-0.02	+ 0.48	+ 0.36	+ 0.07	+ 0.02	6.65
Nicaragua	3.18	+ 1.88	-0.04	-0.09	-0.07	+ 0.02	-0.46	-0.10	-0.11	+ 0.02	4.23
Panama	3.98	+ 0.11	-0.13	-0.12	-0.07	+ 0.03	+ 0.54	+ 0.12	-0.14	+ 0.05	4.38
Venezuela	5.70	+ 0.13	-0.07	-0.34	-0.06	+ 0.00	-0.35	+ 0.09	-0.21	+ 0.01	4.91
Brazil	4.57	-0.17	-0.11	-0.07	-0.39	-0.04	+ 0.18	+ 0.26	-0.12	+ 0.04	4.15
Paraguay	3.66	+ 1.15	-0.12	-0.10	-0.33	+ 0.02	-0.11	+ 0.08	-0.01	+ 0.02	4.25
Bermuda	7.69	-5.01	-0.19	-1.50	-0.08	+ 0.09	+ 1.96	+ 0.53	+ 1.67	+ 0.04	5.20
Puerto Rico	7.88	-4.08	-0.24	-1.69	-0.13	-0.01	+ 1.09	+ 0.19	+ 0.19	+ 0.02	3.22
Virgin Islands	9.42	-3.94	-0.26	-2.21	-0.14	+ 0.09	+ 1.88	-0.38	+ 0.93	+ 0.12	5.53
North Africa and Middle East											
Algeria	3.93	+ 1.70	+ 0.12	-0.49	+ 0.35	+ 0.02	+ 0.11	+ 0.18	+ 0.28	-0.02	6.18
Bahrain	3.51	+ 2.30	+ 0.26	-1.26	+ 0.38	+ 0.00	+ 1.15	+ 0.40	+ 0.44	+ 0.01	7.19
Egypt	3.23	+ 2.88	+ 0.28	-0.93	+ 0.33	-0.04	+ 0.00	+ 0.35	+ 0.23	-0.02	6.30
Iran	3.44	+ 0.89	+ 0.09	-0.39	+ 0.23	+ 0.00	+ 0.25	+ 0.02	-0.01	+ 0.01	4.53
Iraq	2.65	+ 3.07	+ 0.19	-0.53	+ 0.30	+ 0.09	+ 0.09	+ 0.00	+ 0.18	-0.01	6.03
Jordan	2.05	+ 2.04	+ 0.05	-0.59	-0.01	+ 0.02	-0.03	+ 0.17	+ 0.08	-0.01	3.77
Kuwait	1.28	+ 1.04	+ 0.08	-0.58	+ 0.15	+ 0.04	+ 0.54	+ 0.10	+ 0.09	-0.01	2.73
Lebanon	6.11	+ 0.21	+ 0.08	-0.99	+ 0.53	-0.05	+ 0.32	+ 0.34	-0.25	-0.07	6.22
Libya	2.72	+ 1.15	+ 0.12	-0.55	+ 0.23	-0.02	+ 0.01	-0.07	+ 0.26	+ 0.00	3.85
Morocco	4.14	+ 1.33	+ 0.08	-0.38	+ 0.33	+ 0.01	-0.19	+ 0.17	+ 0.01	+ 0.03	5.53
Palestine	1.96	+ 2.71	+ 0.05	-0.18	+ 0.23	+ 0.03	-0.44	+ 0.21	-0.09	-0.02	4.45
Oman	3.70	+ 6.69	+ 0.21	-1.15	+ 0.51	+ 0.10	+ 1.38	-0.40	+ 0.21	+ 0.06	11.32
Qatar	0.61	+ 1.27	+ 0.08	-0.44	+ 0.18	+ 0.01	+ 0.52	+ 0.08	+ 0.07	+ 0.01	2.38
Saudi Arabia	2.94	+ 3.83	+ 0.30	-1.19	+ 0.37	+ 0.00	+ 1.20	-0.06	+ 0.29	+ 0.04	7.72
Syria	5.66	+ 2.05	+ 0.19	-0.60	+ 0.44	+ 0.00	-1.06	+ 0.10	+ 0.15	-0.03	6.89
Tunisia	4.75	-0.02	+ 0.11	-0.56	+ 0.34	+ 0.00	+ 0.02	+ 0.12	+ 0.14	-0.02	4.87
Turkey	3.03	-0.09	+ 0.09	-0.51	+ 0.33	-0.05	+ 0.39	+ 0.16	-0.04	-0.03	3.29
United Arab Emirates	3.20	+ 4.03	+ 0.14	-1.64	+ 0.40	-0.06	+ 1.58	+ 0.14	+ 0.24	+ 0.05	8.08
Yemen	2.65	+ 4.58	+ 0.17	+ 0.92	+ 0.32	+ 0.00	-1.68	-0.07	+ 0.06	-0.01	6.95
Afghanistan	3.20	+ 7.95	+ 0.28	+ 0.98	+ 0.46	-0.01	-2.18	-0.22	+ 0.08	+ 0.04	10.57

Sudan	2.24	+ 3.02	+ 0.14	-0.16	+ 0.23	+ 0.01	-0.66	-0.29	+ 0.03	+ 0.03	4.58
South Asia											
Bangladesh	1.90	+ 0.67	+ 0.09	+ 0.56	-0.43	-0.03	-0.37	+ 0.11	-0.09	-0.01	2.41
India	2.69	+ 1.12	+ 0.20	+ 0.84	-0.51	-0.05	-0.24	+ 0.07	-0.11	+ 0.01	4.01
Nepal	3.23	+ 1.67	+ 0.22	+ 0.54	-0.71	-0.06	-0.90	+ 0.06	-0.18	-0.02	3.85
Pakistan	2.25	+ 3.04	+ 0.15	+ 0.45	-0.60	-0.03	-0.50	+ 0.06	+ 0.02	+ 0.02	4.85
Southeast Asia, East Asia, and Oceania											
China	4.83	-1.28	+ 0.20	+ 0.38	-0.23	-0.02	+ 0.28	+ 0.12	+ 0.09	-0.03	4.33
Taiwan (province of China)	6.83	-3.39	+ 0.00	+ 0.28	-0.13	+ 0.13	+ 1.62	+ 0.43	-0.18	-0.02	5.57
Cambodia	3.62	+ 2.22	+ 0.02	+ 1.31	-0.34	-0.01	-0.78	-0.21	-0.35	-0.03	5.44
Indonesia	3.58	+ 1.49	-0.06	+ 0.64	-0.16	-0.02	+ 0.05	+ 0.10	-0.29	-0.06	5.27
Malaysia	3.78	+ 1.28	-0.07	+ 0.16	-0.27	+ 0.00	+ 0.69	+ 0.17	-0.45	-0.01	5.27
Maldives	1.62	+ 1.44	-0.13	+ 0.32	-0.19	-0.04	+ 0.17	+ 0.23	+ 0.66	-0.02	4.06
Myanmar	5.39	+ 1.84	+ 0.12	+ 1.34	-0.44	-0.12	-0.58	-0.25	-0.50	-0.04	6.75
Philippines	2.00	+ 1.42	-0.03	+ 0.54	-0.12	-0.01	-0.12	+ 0.11	-0.16	-0.02	3.60
Sri Lanka	4.24	-0.24	-0.15	+ 0.84	-0.30	-0.02	+ 0.08	+ 0.08	-0.17	+ 0.01	4.38
Thailand	4.90	-1.46	+ 0.02	+ 0.19	-0.26	+ 0.00	+ 0.31	-0.02	-0.37	-0.02	3.30
Timor-Leste	2.46	+ 2.39	-0.03	+ 1.19	-0.27	-0.02	-0.54	-0.10	-0.13	-0.04	4.90
Vietnam	6.68	+ 1.05	+ 0.09	+ 2.17	-0.47	-0.08	-0.75	+ 0.16	-0.64	-0.06	8.15
Fiji	4.62	+ 2.26	-0.18	-0.67	-0.56	+ 0.19	-0.21	+ 0.04	+ 1.40	-0.07	6.82
Papua New Guinea	2.03	+ 2.65	-0.08	+ 0.34	-0.30	-0.04	-0.57	-0.57	+ 0.11	-0.04	3.54
Mauritius	2.81	-0.69	-0.05	+ 0.04	-0.17	+ 0.00	+ 0.30	+ 0.13	+ 0.23	-0.02	2.59

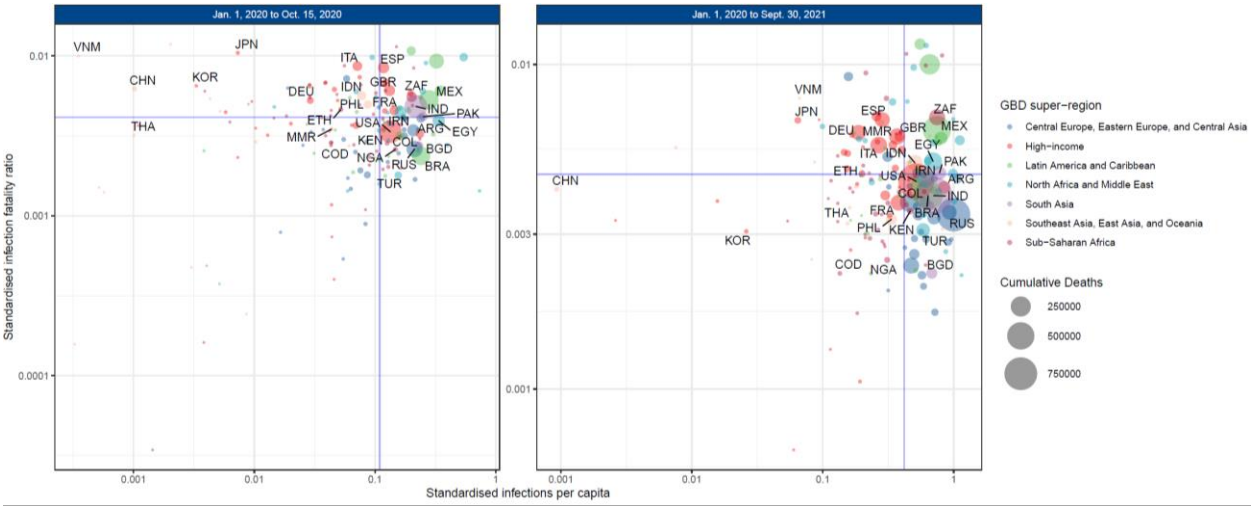
Seychelles	2.73	+ 0.05	-0.01	-0.09	-0.16	-0.01	+ 0.50	+ 0.00	+ 0.47	-0.02	3.46
Guam	3.32	-0.18	-0.10	-0.83	-0.32	+ 0.07	+ 0.88	+ 0.13	+ 0.41	-0.03	3.34
Northern Mariana Islands	5.32	-0.10	-0.19	-1.03	-0.39	+ 0.09	+ 0.87	-0.07	+ 0.64	-0.06	5.08
Sub-Saharan Africa											
Angola	1.86	+ 4.41	+ 0.06	+ 0.88	-0.27	+ 0.02	-0.44	+ 0.09	-0.12	+ 0.03	6.53
Central African Republic	1.82	+ 3.42	+ 0.14	+ 0.98	-0.22	+ 0.01	-1.55	-0.19	-0.20	+ 0.04	4.25
Congo (Brazzaville)	1.49	+ 1.96	+ 0.08	+ 0.27	-0.15	+ 0.00	-0.32	-0.02	-0.15	+ 0.02	3.17
DR Congo	1.06	+ 1.84	+ 0.05	+ 0.50	-0.12	+ 0.00	-0.79	-0.08	-0.12	+ 0.04	2.37
Equatorial Guinea	1.87	+ 4.27	+ 0.15	+ 0.15	-0.25	+ 0.01	+ 0.47	-0.55	-0.25	+ 0.04	5.91
Gabon	2.59	+ 2.34	+ 0.11	-0.17	-0.22	+ 0.02	+ 0.23	-0.12	-0.22	+ 0.02	4.59
Burundi	1.62	+ 2.96	+ 0.06	+ 0.83	-0.41	+ 0.01	-1.35	-0.10	-0.21	+ 0.03	3.45
Djibouti	2.97	+ 4.01	+ 0.15	+ 0.93	-0.69	+ 0.05	-0.92	+ 0.11	-0.04	-0.02	6.55
Eritrea	1.46	+ 2.87	+ 0.10	+ 1.00	-0.41	+ 0.01	-0.95	-0.24	+ 0.00	+ 0.05	3.90
Ethiopia	1.87	+ 3.48	+ 0.08	+ 1.13	-0.47	+ 0.06	-1.08	-0.22	-0.11	+ 0.09	4.82
Kenya	1.88	+ 2.79	+ 0.03	+ 0.45	-0.40	+ 0.01	-0.64	-0.06	-0.19	+ 0.03	3.90
Madagascar	1.55	+ 2.79	+ 0.00	+ 0.84	-0.41	-0.01	-0.97	-0.19	+ 0.09	+ 0.01	3.70
Malawi	2.20	+ 3.43	+ 0.01	+ 0.53	-0.48	+ 0.03	-1.35	-0.18	-0.28	+ 0.03	3.94
Mozambique	3.66	+ 6.83	-0.02	+ 1.37	-0.91	+ 0.05	-2.40	-0.35	-0.23	+ 0.03	8.03
Rwanda	2.44	+ 3.17	+ 0.10	+ 0.68	-0.51	+ 0.01	-1.05	-0.12	-0.30	+ 0.01	4.42
Somalia	2.03	+ 4.43	+ 0.06	+ 1.09	-0.54	+ 0.03	-2.72	-0.38	+ 0.15	+ 0.03	4.18
Uganda	2.02	+ 4.22	+ 0.13	+ 0.80	-0.52	+ 0.03	-1.13	-0.21	-0.33	+ 0.04	5.07

Zambia	4.67	+ 8.98	+ 0.06	+ 1.30	-1.18	+ 0.05	-1.61	-0.28	-0.60	-0.01	11.39
Botswana	4.68	+ 4.77	+ 0.01	+ 0.16	+ 0.42	-0.02	+ 0.41	-0.84	+ 0.07	-0.03	9.62
Lesotho	6.94	+ 6.15	+ 0.08	+ 0.37	+ 0.51	-0.09	-2.04	-0.81	+ 0.00	-0.03	11.07
Namibia	4.55	+ 4.73	+ 0.05	+ 1.02	+ 0.43	-0.02	-0.06	-0.01	+ 0.22	-0.01	10.89
South Africa	5.15	+ 2.07	+ 0.03	-0.64	+ 0.39	-0.02	+ 0.10	+ 0.31	+ 0.03	-0.02	7.40
Zimbabwe	3.96	+ 5.67	-0.01	+ 0.87	+ 0.36	+ 0.00	-1.88	-0.22	-0.40	-0.02	8.33
Benin	1.77	+ 3.06	+ 0.07	+ 0.27	-0.20	+ 0.00	-0.80	-0.09	-0.22	+ 0.05	3.91
Burkina Faso	0.78	+ 1.33	+ 0.04	+ 0.21	-0.09	+ 0.01	-0.41	-0.08	-0.06	+ 0.01	1.74
Cameroon	1.66	+ 2.71	+ 0.14	+ 0.03	-0.18	-0.01	-0.56	-0.04	-0.17	+ 0.04	3.62
Cape Verde	1.61	+ 0.65	+ 0.04	+ 0.15	-0.11	+ 0.02	-0.15	-0.01	+ 0.25	+ 0.03	2.46
Chad	1.66	+ 3.86	+ 0.16	+ 1.01	-0.23	+ 0.02	-1.04	-0.49	+ 0.07	+ 0.02	5.04
Côte d'Ivoire	1.26	+ 2.16	+ 0.02	+ 0.22	-0.15	+ 0.01	-0.37	-0.04	-0.16	+ 0.02	2.98
The Gambia	2.34	+ 3.42	+ 0.07	+ 0.50	-0.25	+ 0.00	-1.17	+ 0.07	-0.25	+ 0.03	4.77
Ghana	1.61	+ 1.90	+ 0.05	+ 0.20	-0.15	+ 0.01	-0.39	-0.01	-0.20	+ 0.05	3.06
Guinea	1.75	+ 2.55	+ 0.02	+ 0.57	-0.17	+ 0.00	-0.85	-0.08	-0.19	+ 0.01	3.60
Guinea-Bissau	2.37	+ 4.54	+ 0.06	+ 0.89	-0.28	+ 0.00	-1.46	-0.13	-0.28	+ 0.08	5.78
Liberia	2.03	+ 2.66	-0.03	+ 0.13	-0.19	+ 0.02	-1.21	-0.06	-0.17	+ 0.05	3.24
Mali	1.72	+ 3.26	+ 0.07	+ 0.67	-0.21	-0.01	-1.01	-0.08	+ 0.11	+ 0.02	4.53
Mauritania	2.47	+ 2.74	+ 0.12	+ 0.07	-0.23	+ 0.02	-0.72	-0.06	+ 0.28	-0.03	4.64
Niger	1.41	+ 3.47	+ 0.18	+ 0.81	-0.20	+ 0.02	-1.24	-0.37	+ 0.18	+ 0.03	4.29
Nigeria	0.96	+ 1.79	+ 0.09	+ 0.26	-0.09	+ 0.02	-0.24	+ 0.01	-0.11	+ 0.05	2.74

São Tomé and Príncipe	1.44	+ 1.72	+ 0.02	+ 0.12	-0.14	-0.03	-0.45	+ 0.00	+ 0.27	+ 0.06	3.03
Senegal	2.14	+ 2.64	+ 0.08	+ 0.45	-0.21	+ 0.01	-0.77	-0.08	-0.08	+ 0.03	4.22
Sierra Leone	1.75	+ 2.53	+ 0.00	+ 0.53	-0.18	+ 0.01	-0.98	-0.03	-0.19	+ 0.00	3.43
Togo	1.53	+ 2.17	+ 0.05	+ 0.43	-0.16	+ 0.00	-0.78	-0.02	-0.20	+ 0.03	3.05
South Sudan	1.53	+ 2.37	+ 0.07	+ 0.38	-0.36	+ 0.02	-0.10	-0.77	-0.17	+ 0.02	2.99

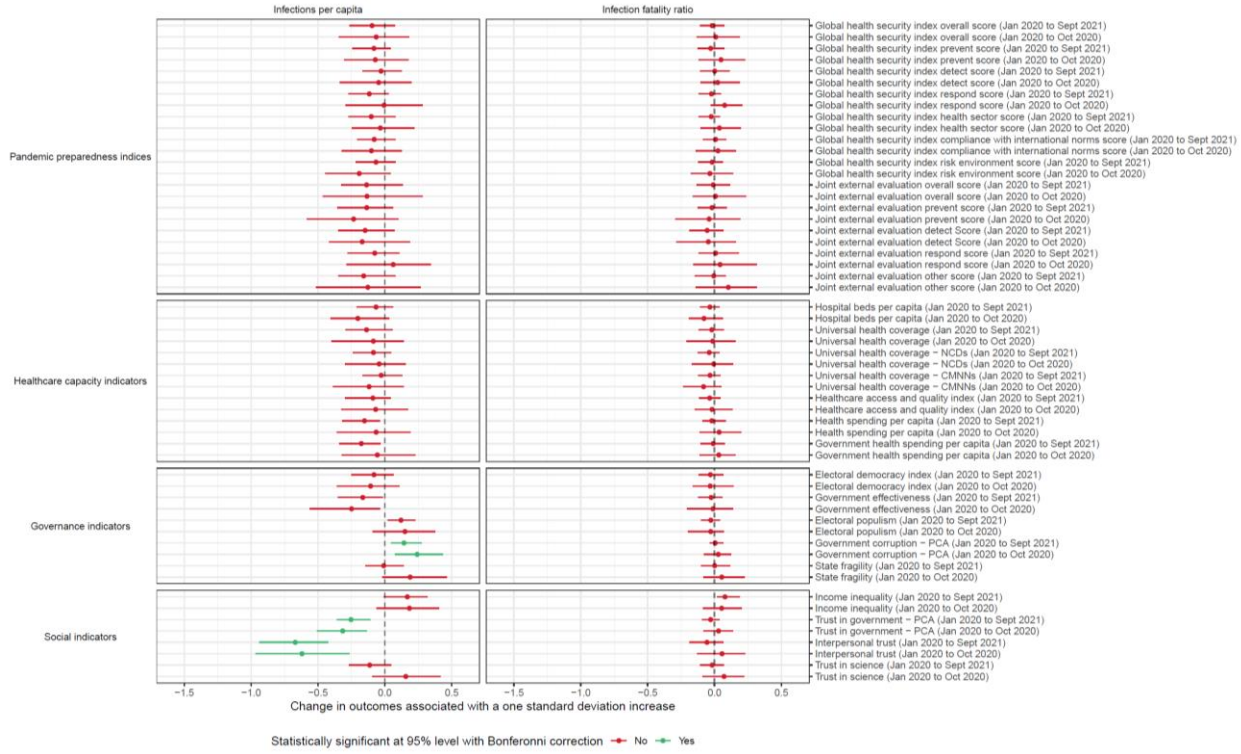
The first column represents the raw IFR, and each subsequent column represents the proportion of IFR that can be accounted for by age structure, air pollution, BMI, cancer prevalence, COPD prevalence, GDP per capita, population density, a proxy for pre-exposure to beta coronavirus, and smoking prevalence; the last column represents the adjusted IFR. The IFR metrics are color-coded based on their severity relative to all other countries, with red representing higher IFR and green representing IFR (raw and adjusted). BMI=body-mass index. COPD=chronic obstructive pulmonary disease. IFR=infection-fatality ratio.

FIGURE 2: STANDARDIZED INFECTIONS PER CAPITA AND STANDARDIZED INFECTION-FATALITY RATIOS



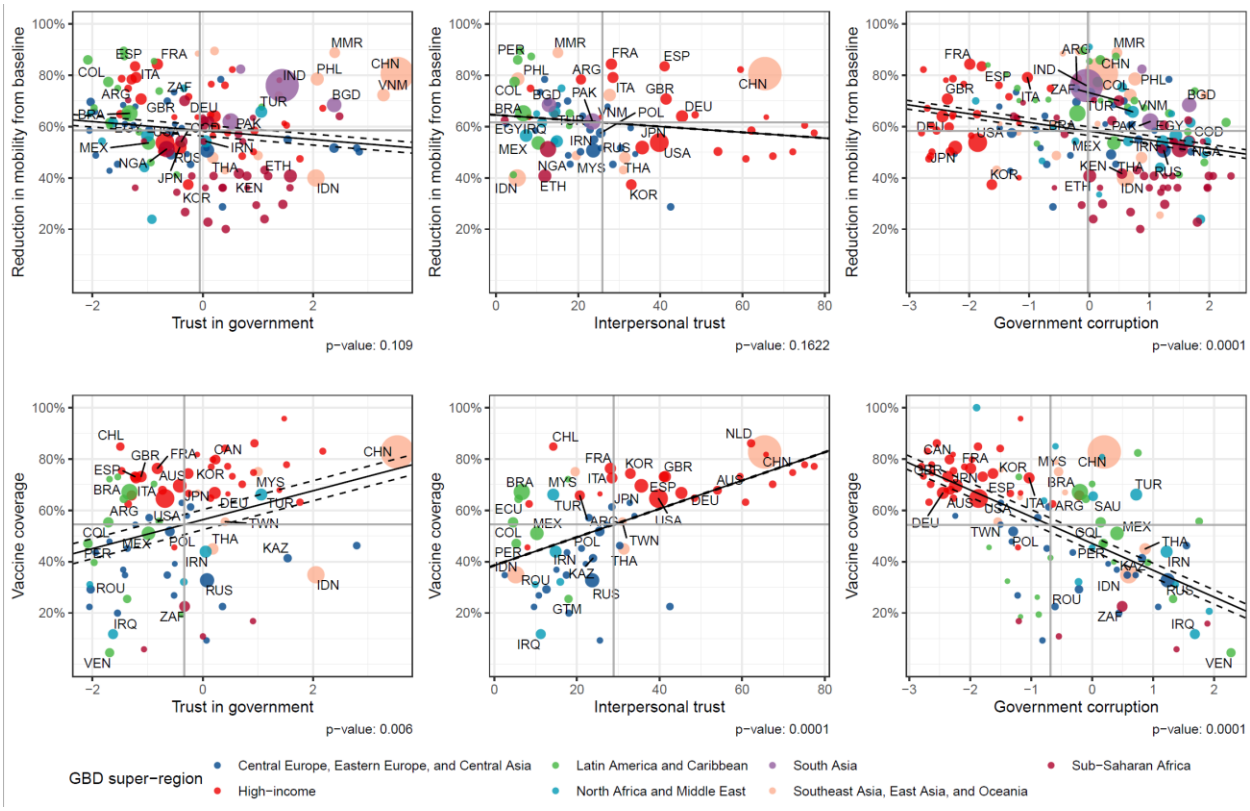
The graph on the left shows the relationship between adjusted infections per capita and adjusted infection-fatality ratios from January 1, 2020, to September 30, 2021. The graph on the right shows the relationship between adjusted infections per capita and adjusted infection-fatality ratios from January 1, 2020, to October 15, 2020. The size of each circle represents the magnitude of cumulative deaths. GBD=Global Burden of Diseases, Injuries, and Risk Factors Study. IFR=infection-fatality ratio. ARG=Argentina, BGD=Bangladesh, BRA=Brazil, CHN=China, COD=Democratic Republic of the Congo, COL=Colombia, DEU=Germany, EGY=Egypt, ESP=Spain, ETH=Ethiopia, FRA=France, GBR=United Kingdom, IDN=Indonesia, IND=India, IRN=Iran, ITA=Italy, JPN=Japan, KEN=Kenya, KOR=South Korea, MEX=Mexico, MMR=Myanmar, NGA=Nigeria, PAK=Pakistan, PHL=Philippines, RUS=Russian Federation, THA=Thailand, TUR=Turkey, USA=United States of America, VNM=Vietnam, ZAF=South Africa.

FIGURE 3: ASSOCIATIONS BETWEEN KEY PREPAREDNESS, CAPACITY, GOVERNANCE, AND SOCIAL INDICATORS AND INFECTION RATES AND IFR



The graph on the left shows estimated associations between indicators of key contextual factors (pandemic preparedness indices; health-care capacity indicators; governance indicators; and social indicators) and infections per capita. The graph on the right shows estimated associations between key contextual factors and the infection-fatality ratio. Red indicates the association is not significant while green indicates the association is significant at a 95% confidence interval with a Bonferroni correction.

FIGURE 4: ASSOCIATION BETWEEN TRUST AND GOVERNMENT CORRUPTION, AND VACCINE COVERAGE AND CHANGE IN MOBILITY



The size of each circle represents total population. The solid line represents the fit of the linear regression for the two variables, while dotted lines represent the 95% confidence interval.

Role of the funding source

Funding was provided by the Bill & Melinda Gates Foundation, Bloomberg Philanthropies, J. Stanton, T. Gillespie, and J. and E. Nordstrom. The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. Members of the core research team for this topic area had full access to the underlying data used to generate estimates presented in this paper. All other authors had access, and reviewed, estimates as part of the research evaluation process, which includes additional stages of formal review.

SUPPLEMENTAL INFORMATION FOR CHAPTER 2

This appendix provides further methodological and supplementary results for "**Pandemic preparedness and COVID-19: an exploratory analysis of infection and fatality rates and contextual factors associated with preparedness in 177 countries, from January 1, 2020, to September 30, 2021**."

GATHER Table

Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Summary. Main Text: Introduction, Methods (Overview).
2	List the funding sources for the work.	Summary. Main Text: Acknowledgements and declarations.
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Main Text: Methods. Supplementary Appendix, Section 3.
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Main Text: Methods.
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Supplementary Appendix: Section 2.0, Table 2. Main characteristics of data, metadata, and/or NIDs

		available through: http://ghdx.healthdata.org/ (upon publication)
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Main text: Limitations section. Supplementary appendix (biases for input data in each modelling step identified in each section)
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	N/A
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Available through: http://ghdx.healthdata.org/ (upon publication)
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Main text: Methods
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Main text: Methods
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Supplementary Appendix: Section 3
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Supplementary Appendix: Sections 3.0 & 4.0

13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main Text: Methods; Supplementary Appendix
14	State how analytic or statistical source code used to generate estimates can be accessed.	Available through: http://ghdx.healthdata.org/ (upon publication)
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Available through: http://ghdx.healthdata.org/ (upon publication)
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Available through: http://ghdx.healthdata.org/ (upon publication)
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Main Text: Discussion
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Main Text: Limitations

Covariate name, spatiotemporal coverage, data source, notes, assessment of missingness, and summary statistics

Short name	Covariate name	Temporal coverage	Spatial coverage	Data source	Notes	N (%) missing	Median (IQR)	Range
Pneumonia RR	Relative risk of death from pneumonia divided by the average risk of death from pneumonia	2013-2019	National and subnational	Modelling COVID-19 scenarios for the United States[43]	Varies weekly	0 (0%)	0.93 (0.91 – 0.95)	0.76 – 1.22
Age	Age structure of the population (5-year age bins)	2020	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	-	-
Altitude	% of population living below 100 m	2015	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	30.4 (1.5 – 63.9)	0.0 – 100.0
Population density	% of population living above 1000 people/km^2	2020	National and subnational	Modelling COVID-19 scenarios for the United States[43]		0 (0%)	51.9 (36.2 – 69.6)	0.0 – 100.0
Air pollution	$PM_{2.5}$ air pollution concentration (mg/m^3)	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	18.5 (10.2 – 34.2)	3.5 - 217.5
Smoking prevalence	Age-standardized tobacco smoking prevalence	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	0.17 (0.12 – 0.22)	0.04 - 0.44
GDP	Gross domestic product per capita	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	15,722.8 (7345.9 – 39772.2)	131.8 – 102,793.9

BMI	Population-adjusted body-mass index	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	26.5 (24.5 – 28.2)	20.5 – 30.8
UHC	Universal health coverage	2019	Nationals	Global Burden of Disease Study 2019[62], Measuring Universal Health Coverage[66]	Included 2 subcomponents – communicable and non-communicable, maternal, and neonatal	0 (0%)	61.2 (49.6 – 72.7)	22.3 – 96.3
Mobility	Largest % change from a January 2020 baseline	2020-2021	National and subnational	Modelling COVID-19 scenarios for the United States[43]		0 (0%)	61.3 (51.2 – 72.9)	20.0 – 93.2
Mandates	Mean fraction of mandates on over period	2020-2021	National and subnational	Modelling COVID-19 scenarios for the United States[43]	Locations measured at the subnational level had a mandate in place if 2/3 of locations or more had it in place on a given date	1/361 (0.3%)	44.0 (33.3 – 49.5)	0.0 – 85.5
Testing	Mean testing per capita over the time period	2020-2021	National and subnational	Modeling COVID-19 scenarios for the United States[43]		0 (0%)	71.4 / 100,000 (21.5 / 100,000 – 200.7 / 100,000)	0.3 / 100,000 – 1713.3 / 100,000
Vaccine coverage	Maximum vaccine coverage over the time period	2021	National and subnational	Modeling COVID-19 scenarios for		0 (0%)	50.9 (27.4 – 65.0)	0.0 – 94.3

				the United States[43]				
COPD	Age-standardized COPD prevalence	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	2.3 (2.0 - 3.2)	0.7-4.4
Cancer	Age-standardized cancer prevalence	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	5.6 (4.3-8.1)	2.1 – 20.8
Interpersonal trust	Trust in other people	2017-2021	National only	WORLD VALUES SURVEY WAVE 7[75]	Trust coded as those who answered "most people can be trusted" on Q57	102/177 (57.6%)	20.7 (11.9 – 32.9)	2.1 – 77.4
Trust in science	Trust in science	2018	National only	Wellcome Global Monitor Survey[76]	Those that answered "A lot" to trusting science	40/177 (22.6%)	29.8 (23.0 – 39.4)	6.7 – 76.0
Trust in government - WVS	Trust in one's government	2017-2021	National only	WORLD VALUES SURVEY WAVE 7[75]	Coded as "A great deal" or "Quite a lot" on Q71 asking about confidence in government	102/177 (57.6%)	40.1 (37.3 – 51.7)	0.0 – 95.2
Trust in government - Gallup	Trust in one's government		National only	Gallup World Poll[73]		46/177 (26%)	53.7 (39.1 – 68.9)	15.7 – 99.3
Governmental Corruption - CPI	Perceived governmental corruption	2020	National only	Transparency International[68]		10/177 (5.6%)	40.0 (29.0 – 56.5)	12.0 – 88.0

JEE	Joint External Evaluation Components and Prevent Epidemics' Preparedness overall score	2016-2021	National only	WHO and Prevent Epidemics[65]	Only places that have completed a JEE; overall score is a summary variable of JEE components created by Prevent Epidemics	89/177 (50.3%)	Overall score: 50.0 (38.0 - 69.3)	Overall score: 26.0 – 93.0
GHSI	Global Health Security Index components and overall score	2019	National only	Global Health Security Index 2019[6]	Weighted average of the other components	7/177 (4.0%)	Overall score: 39.3 (31.9-51.6)	Overall score: 16.2 – 83.5
GINI	Gini Index		National only	SWIID v8.2[77] & Bosancinau[31]		27/177 (15.3%)	38.38 (33.10 – 44.05)	23.68 – 65.11
HAQ Index	Healthcare Access and Quality Index	2019	National only	Global Burden of Disease Study 2019[62]		0 (0%)	63.3 (42.4 - 79.5)	12.8 – 96.8
Electoral populism	Populism-based campaign run		National only	Populism in Power[74] & Bosancinau[31]	Whether a democratically elected head of government ran a populist campaign	0 (0%)	0 (0 – 0)	0 -1
Government effectiveness			National only	World Bank Indicators[71] & Bosancinau[31]	Perceived quality of public services, its provision and providers	1/177 (0.6%)	-0.09 (-0.66 – 0.57)	-2.45 – 2.23

State fragility	State Fragility Index		National only	State Fragility Index[72] & Bosancinau[31]	Incapacity to provide essential public goods and services and cope with shocks	19/177 (10.7%)	7.0 (3.0 – 12.0)	0 .0 – 24.0
Index of federalism		2017	National only	Database of Political Institutions[78]	Extent to which power and decision-making processes are decentralised	54/177 (30.5%)	-0.07 (-0.59 – 0.68)	-1.03 – 1.51
Bureaucracy corruption	Public sector corruption		National only	Varieties of Democracy Institute, Version 10[69,70]	Pervasiveness of bureaucratic corruption in the public sector	13/177 (7.3%)	0.48 (0.19 – 0.72)	0 – 0.97
EDI	Electoral Democracy Index	2020	National only	Varieties of Democracy Institute, Version 11[73,74]	Aggregate indicator combining free and fair elections, free association, freedom of expression, and access to alternative information, suffrage, and elected officials	13/177 (7.3%)	0.32 (0.05 – 0.63)	0.00 – 0.86
Beds per capita	Number of hospital beds per capita before start of the pandemic	2019	National and subnational	Global Burden of Disease Study 2019[62]		0 (0%)	206.0 / 100,000 (102.7 / 100,000	18.4 / 100,000– 1185.9 / 100,000

							– 328.3 / 100,000)	
Health spending per capita	Total health expenditure per capita	2020	National only	Global Burden of Disease Health Financing Collaborator Network[67]	Mean value	0 (0%)	538.1 (87.1 – 1744.7)	5.0 – 6869.6
Government health spending per capita	Government health spending per capita	2020	National only	Global Burden of Disease Health Financing Collaborator Network[67]	Mean value	0 (0%)	932.7 (252.2-2518.3)	23.5 – 12131.9
Bats	Average number of beta-coronavirus host bat species in a given location	2021 Bats & Ranges	National only	IUCN[63] & Verena Consortium[64]	See section 3.1 below	0 (0%)	11.5 (4.2 -16.6)	0.0 – 42.0

Analysis of multicollinearity between stage 1 variables

Covariates	Variance inflation factors	
	Cumulative infections per capita	IFR

GDP per capita	1.280	2.860
% of population living above 1000 people/km^2	1.242	1.181
Average number of beta-coronavirus host bat species	1.105	1.299
% of population living below 100 m	1.245	-
BMI	-	2.432
Smoking prevalence	-	1.486
$PM_{2.5}$ air pollution concentration (mg/m^3)	-	1.455
COPD prevalence	-	1.703
Cancer prevalence	-	1.215

Correlation between stage 1 variables

	GDP per capita	% of population living above 1000 people/km^2	% of population living below 100 m	Average number of beta-coronavirus host bat species	BMI	$PM_{2.5}$ air pollution concentration (mg/m^3)	Smoking prevalence	COPD prevalence	Cancer prevalence
GDP per capita	1	0.343	0.135	-0.380	0.709	-0.594	0.417	0.336	0.449
% of population living above 1000 people/km^2	0.343	1	0.231	-0.122	0.287	-0.205	0.054	0.095	0.224

% of population living below 100 m	0.135	0.231	1	-0.063	-	-	-	-	-
Average number of beta-coronavirus host bat species	-0.380	-0.122	-0.063	1	-0.526	0.345	-0.077	-0.102	-0.087
BMI	0.709	0.287	-	-0.526	1	-0.584	0.193	0.117	0.446
$PM_{2.5}$ air pollution concentration (mg/m^3)	-0.594	-0.205	-	0.345	-0.584	1	-0.198	-0.304	-0.268
Smoking prevalence	0.417	0.054	-	-0.077	0.193	-0.198	1	0.224	0.420
COPD prevalence	0.336	0.095	-	-0.102	0.117	-0.304	0.224	1	-0.166
Cancer prevalence	0.449	0.224	-	-0.087	0.446	-0.268	0.420	-0.166	1

Results of stage 1 multivariate regressions, January 1, 2020 – September 30, 2021

Covariates	Beta estimate (uncertainty interval)	
	Cumulative infections per capita	IFR
GDP per capita	-0.17 (-0.28 - -0.05)	-0.17 (-0.28 - -0.05)
% of population living above 1000 people/km^2	0.05 (-0.10 – 0.19)	-0.03 (-0.16-0.06)
Average number of beta-coronavirus host bat species	0.08 (-0.04 – 0.23)	0.07 (-0.01-0.18)

% of population living below 100 m	-0.15 (-0.25 - -0.06)	-
BMI	-	1.74 (0.65-3.2)
Smoking prevalence	-	0.01 (-0.16-0.19)
$PM_{2.5}$ air pollution concentration (mg/m^3)	-	-0.03 (-0.16-0.06)
COPD prevalence	-	0.04 (-0.16-0.27)
Cancer prevalence	-	-0.16 (-0.4-0.01)

Results of stage 2 bivariate regressions, January 1, 2020 – September 30, 2021

Covariates	Beta estimate (uncertainty interval)	
	Cumulative infections per capita	IFR
Hospital beds per capita	-0.07 (-0.21 - 0.06)	-0.03 (-0.11 - 0.04)
Government health spending per capita	-0.17 (-0.34 - 0)	-0.01 (-0.10 - 0.08)
Healthcare Access and Quality Index	-0.09 (-0.28 - 0.05)	-0.04 (-0.11 - 0.05)
Health spending per capita	-0.16 (-0.32 - -0.02)	-0.02 (-0.09 - 0.08)
Universal health coverage - CMNNs	-0.03 (-0.16 - 0.13)	0.00 (-0.07 - 0.09)
Electoral populism	0.12 (0.02 - 0.22)	-0.03 (-0.12 - 0.05)
Global health security index overall score	-0.10 (-0.26 - 0.07)	-0.03 (-0.10 - 0.04)
Global health security index prevent score	-0.08 (-0.24 - 0.04)	0.01 (-0.08 - 0.12)
Global health security index detect score	-0.03 (-0.17 - 0.12)	-0.02 (-0.11 - 0.07)
Global health security index respond score	-0.12 (-0.28 - 0.03)	-0.03 (-0.13 - 0.08)

Global health security index health sector score	-0.11 (-0.27 - 0.07)	0.00 (-0.11 - 0.11)
Global health security index compliance with international norms score	-0.08 (-0.2 - 0.08)	-0.02 (-0.12 - 0.05)
Global health security index risk environment score	-0.06 (-0.22 - 0.08)	-0.02 (-0.12 - 0.04)
Income inequality	0.17 (0.00 - 0.31)	0.01 (-0.09 - 0.09)
Government effectiveness	-0.16 (-0.34 - -0.01)	-0.02 (-0.12 - 0.06)
Government corruption - PCA	0.14 (0.05 - 0.27)	0.08 (0.02 - 0.19)
Trust in government - PCA	-0.25 (-0.36 - -0.11)	-0.03 (-0.12 - 0.06)
Interpersonal trust	-0.67 (-0.94 - -0.42)	0.01 (-0.03 - 0.07)
Joint external evaluation overall score	-0.15 (-0.35 - 0.07)	-0.02 (-0.17 - 0.08)
Joint external evaluation prevent score	-0.16 (-0.35 - 0.08)	0.00 (-0.07 - 0.06)
Joint external evaluation detect Score	-0.14 (-0.33 - 0.14)	-0.03 (-0.09 - 0.04)
Joint external evaluation respond score	-0.14 (-0.35 - 0.06)	-0.06 (-0.19 - 0.07)
Joint external evaluation other score	-0.08 (-0.28 - 0.11)	-0.05 (-0.19 - 0.07)
Universal health coverage - NCDs	-0.08 (-0.24 - 0.05)	-0.01 (-0.15 - 0.09)
State fragility	-0.01 (-0.15 - 0.14)	-0.01 (-0.13 - 0.12)
Trust in science	-0.11 (-0.27 - 0.05)	-0.02 (-0.12 - 0.09)
Universal health coverage	-0.14 (-0.29 - 0.07)	0.01 (-0.12 - 0.18)
Electoral democracy index	-0.08 (-0.25 - 0.07)	0.02 (-0.07 - 0.11)

Results of stage 1 multivariate regressions, January 1, 2020 – October 15, 2020

Covariates	Beta estimate (uncertainty interval)

	Cumulative infections per capita	IFR
GDP per capita	-0.21 (-0.39 - -0.09)	-0.19 (-0.31 - 0.01)
% of population living above 1000 people/km^2	0.10 (-0.13 – 0.35)	-0.04 (-0.17 - 0.08)
Average number of beta-coronavirus host bat species	0.01 (-0.19 – 0.22)	0.04 (-0.09 - 0.14)
% of population living below 100 m	-0.24 (-0.37 - -0.09)	-
BMI	-	3.36 (1.72 - 4.88)
Smoking prevalence	-	-0.38 (-0.64 - -0.11)
$PM_{2.5}$ air pollution concentration (mg/m^3)	-	-0.20 (-0.39 - 0.03)
COPD prevalence	-	0.51 (0.19 - 0.78)
Cancer prevalence	-	-0.13 (-0.42 - 0.1)

Results of stage 2 bivariate regressions, January 1, 2020 – October 15, 2020

Covariates	Beta estimate (uncertainty interval)	
	Cumulative infections per capita	IFR
Hospital beds per capita	-0.21 (-0.41 - 0.02)	-0.03 (-0.11 - 0.04)
Government health spending per capita	-0.05 (-0.28 - 0.17)	-0.01 (-0.1 - 0.08)
Healthcare Access and Quality Index	-0.07 (-0.31 - 0.19)	-0.04 (-0.11 - 0.05)
Health spending per capita	-0.09 (-0.36 - 0.14)	-0.02 (-0.09 - 0.08)

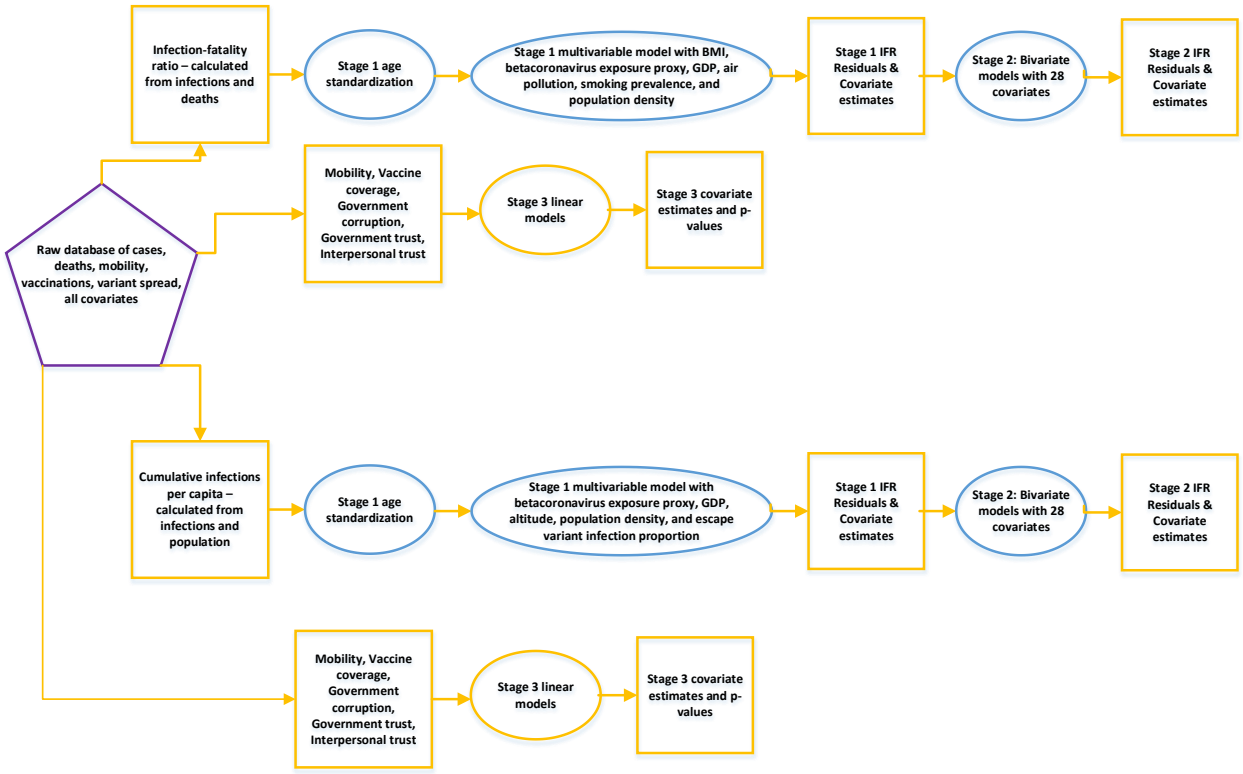
Universal health coverage - CMNNs	-0.12 (-0.38 - 0.13)	0.00 (-0.07 - 0.09)
Electoral populism	0.15 (-0.09 - 0.37)	-0.03 (-0.12 - 0.05)
Global health security index overall score	-0.06 (-0.34 - 0.18)	-0.03 (-0.10 - 0.04)
Global health security index prevent score	-0.07 (-0.30 - 0.18)	0.01 (-0.08 - 0.12)
Global health security index detect score	-0.04 (-0.33 - 0.20)	-0.02 (-0.11 - 0.07)
Global health security index respond score	-0.01 (-0.28 - 0.27)	-0.03 (-0.13 - 0.08)
Global health security index health sector score	-0.04 (-0.25 - 0.22)	0.00 (-0.11 - 0.11)
Global health security index compliance with international norms score	-0.10 (-0.32 - 0.12)	-0.02 (-0.12 - 0.05)
Global health security index risk environment score	-0.20 (-0.44 - 0.04)	-0.02 (-0.12 - 0.04)
Income inequality	0.19 (-0.05 - 0.40)	0.01 (-0.09 - 0.09)
Government effectiveness	-0.24 (-0.55 - -0.05)	-0.02 (-0.12 - 0.06)
Government corruption - PCA	0.24 (0.07 - 0.43)	0.08 (0.02 - 0.19)
Trust in government - PCA	-0.31 (-0.51 - -0.13)	-0.03 (-0.12 - 0.06)
Interpersonal trust	-0.62 (-0.97 - -0.26)	0.01 (-0.03 - 0.07)
Joint external evaluation overall score	-0.17 (-0.42 - 0.19)	-0.02 (-0.17 - 0.08)
Joint external evaluation prevent score	-0.13 (-0.52 - 0.27)	0.00 (-0.07 - 0.06)
Joint external evaluation detect Score	-0.13 (-0.46 - 0.28)	-0.03 (-0.09 - 0.04)
Joint external evaluation respond score	-0.23 (-0.58 - 0.1)	-0.06 (-0.19 - 0.07)
Joint external evaluation other score	0.06 (-0.29 - 0.34)	-0.05 (-0.19 - 0.07)
Universal health coverage - NCDs	-0.04 (-0.30 - 0.16)	-0.01 (-0.15 - 0.09)
State fragility	0.19 (-0.02 - 0.47)	-0.01 (-0.13 - 0.12)

Trust in science	0.16 (-0.08 - 0.43)	-0.02 (-0.12 - 0.09)
Universal health coverage	-0.10 (-0.41 - 0.13)	0.01 (-0.12 - 0.18)
Electoral democracy index	-0.11 (-0.36 - 0.11)	0.02 (-0.07 - 0.11)

Additional methods

For our final analysis, we included all variables that we had access to, there was previous literature connecting, and there was theoretical perspective on how they could be included. In general, we opted for an inclusive modelling strategy and included rather than excluded variables in this exploratory analysis. A diagram of our analytic pathway follows.

Modelling pathway for Stages 1-3 for IFR and infections



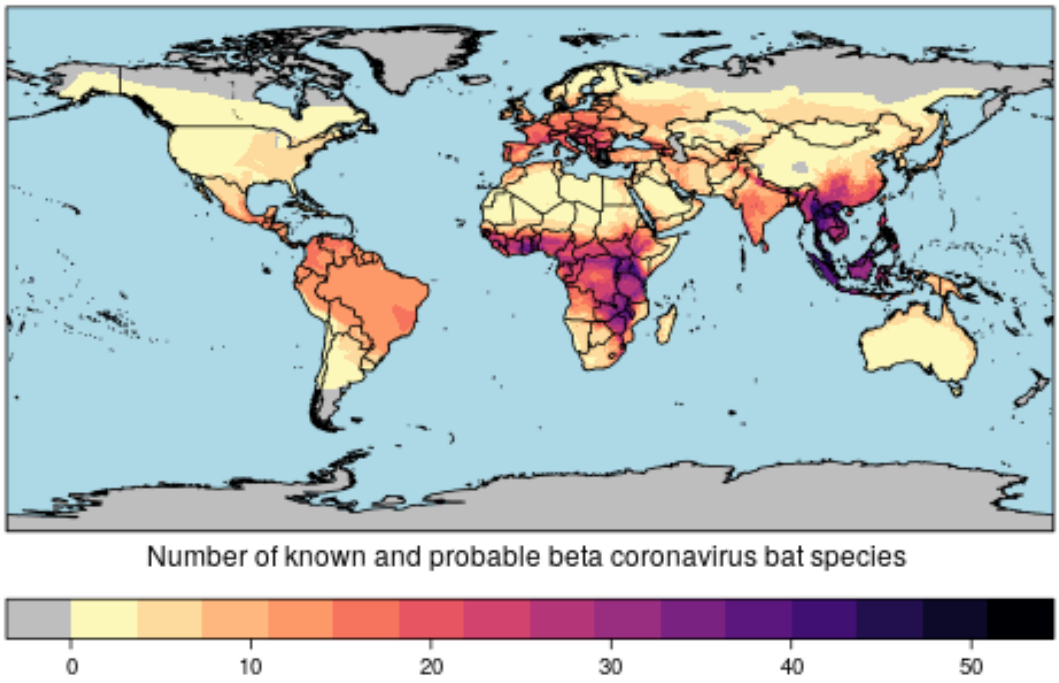
Proxy for previous exposure to beta coronaviruses

Literature suggests that possible previous exposure to SARS, MERS, or other beta coronaviruses may provide cross-immunity to SARS-CoV2.[79–81] In order to capture previous exposure to other beta coronaviruses, we obtained a list of possible bat hosts of beta coronaviruses produced by authors at the Verena Consortium.[64] These authors used an ensemble model of seven other statistical models (network- and trait-based models) to predict possible bat beta coronavirus hosts in addition to known bat hosts. This list of 300+ species was then compared against known species ranges, determined by experts, using the IUCN Red List of Threatened Species.[63] Of the 448 known and probable species extracted from the publication by Becker et al,[64] 441 were able to be retrieved from the IUCN red list, allowing for possible changes in species naming convention.

Following the extraction of a geographical range for each species, each range was converted to a 1-km by 1-km raster in R using the raster package. Ranges were then layered one on top of the other, interpolated to a 5-km by 5-km grid cell range for processing times using the average of all cells in that grid. All ranges

were then summed together to get the estimated number of bat species per grid cell, as seen in Figure 1 below.

Number of known and probable beta coronavirus bat species per grid cell



The number of species per grid cell were then averaged over the first and second administrative region in agreement with our COVID-19 units of analysis. Number of bat species per location ranged from 0 to 42, with a median exposure of 11.5 (IQR: 4.2–16.6).

PCA analysis for trust in government and corruption

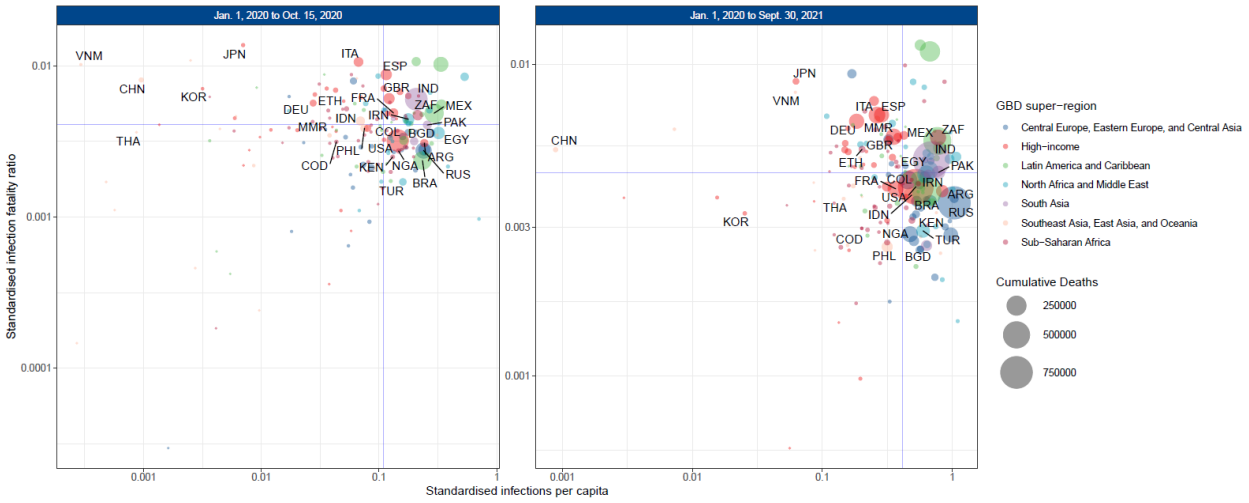
We used principal component analysis (PCA) to create summary metrics that combine information about trust in government and/or corruption. The input variables were governmental corruption, bureaucracy corruption, trust in government (WVS), and trust in government (Gallup). The first summary metric combined the two trust covariates, and the second combined the two corruption covariates. Using centered and scaled versions of the covariates, the summary metrics consist of the first principal component from each PCA analysis. The first component (of four) explained 92.6% of the variation for the trust variable and 94.4% of the corruption variable. PCA requires that all variables have complete data, but some of the variables had missing data. We used the imputePCA function from the missMDA R package to impute missing values, but only used observations that had at least one of the two original observations. The package implements the iterative PCA method described in Josse and Husson (2010).[42] To propagate uncertainty from the imputation process, we created 100 datasets with random realisations of the imputation.

Sensitivity analyses

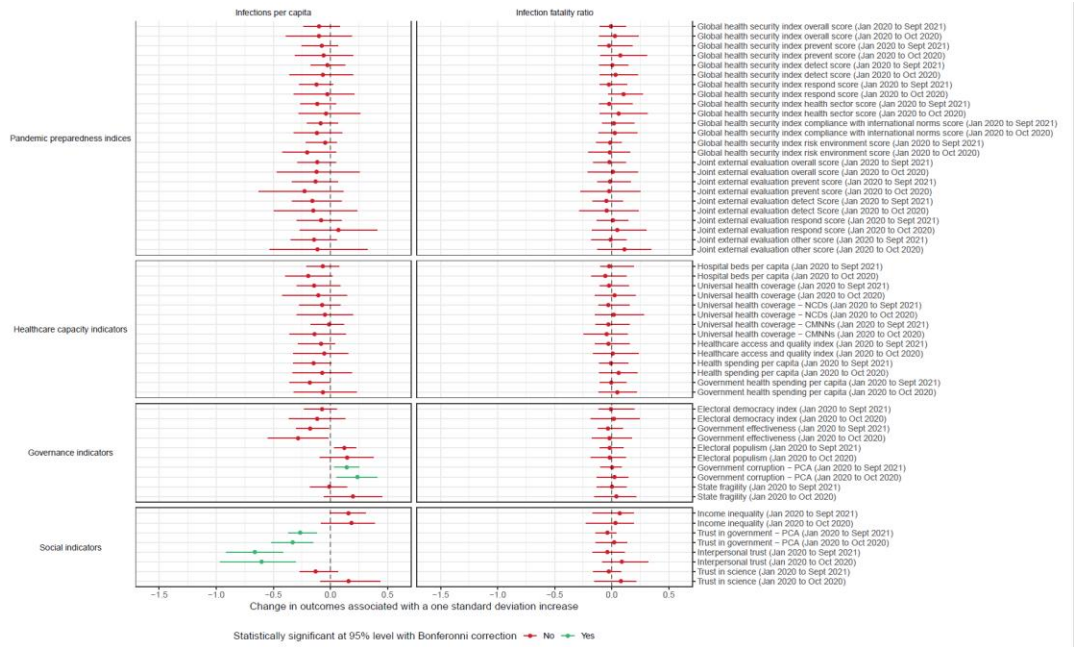
Using a correction of 1% of median for log transformations

Infections vs. IFR

Figure 2: Standardised infections per capita and standardised infection fatality ratios



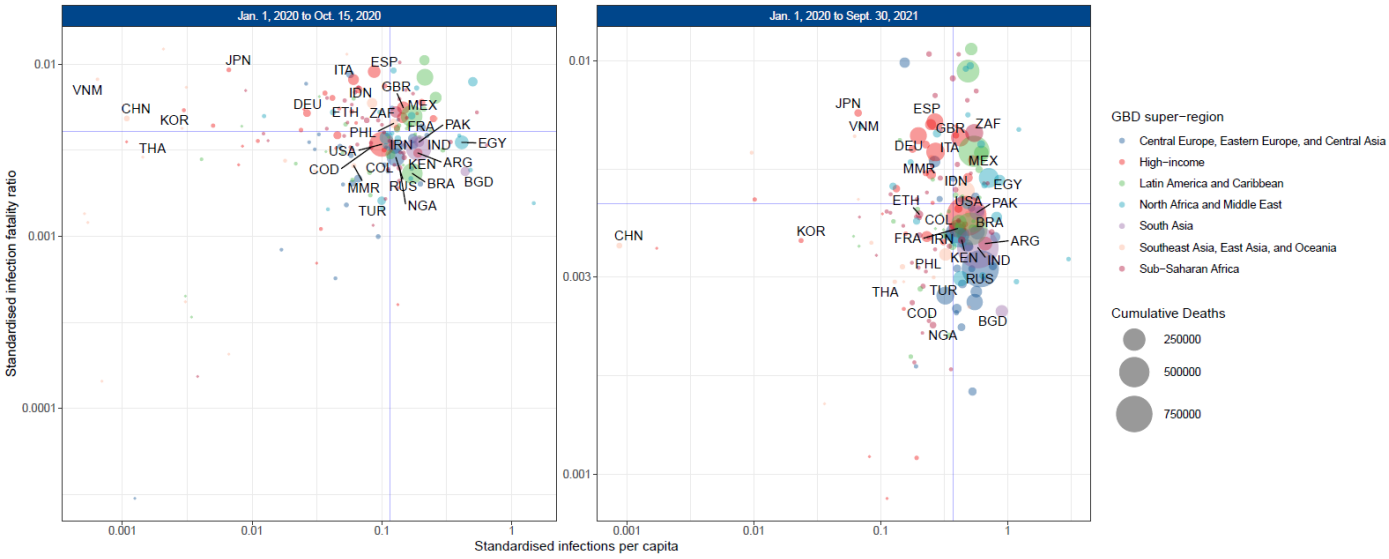
Bivariate results



Using centered and scaled variables

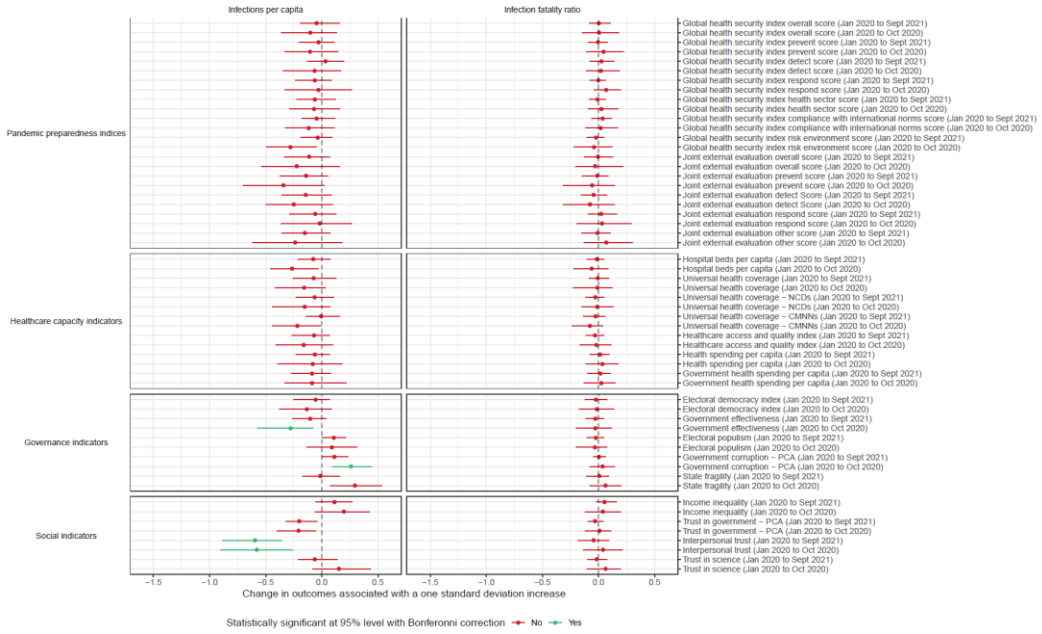
Infections vs. IFR

Figure 2: Standardised infections per capita and standardised infection fatality ratios



Bivariate results

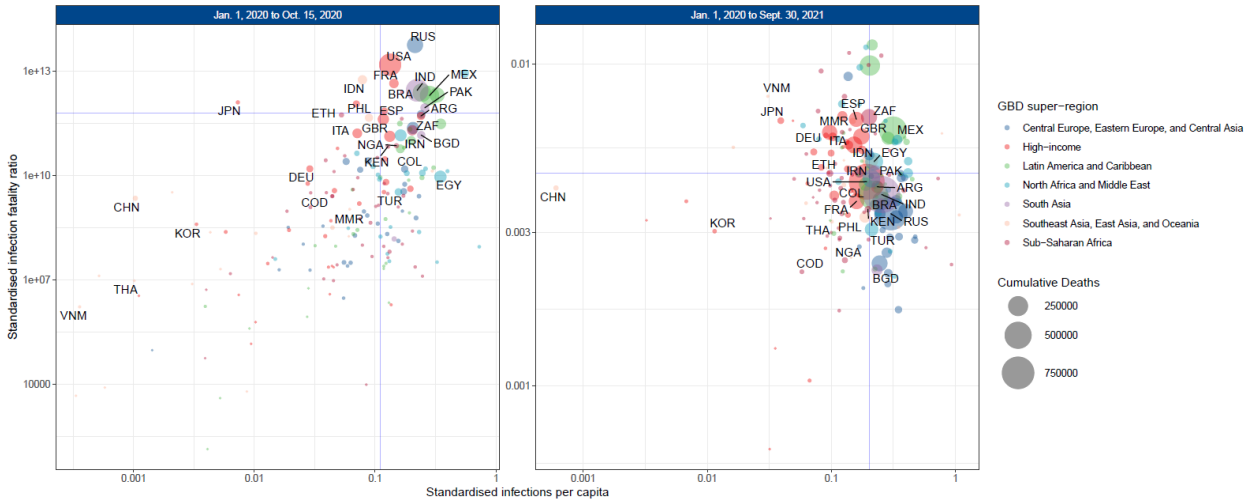
Figure 3: Associations between key preparedness, capacity, governance, and social indicators and infections and infection fatality ratio



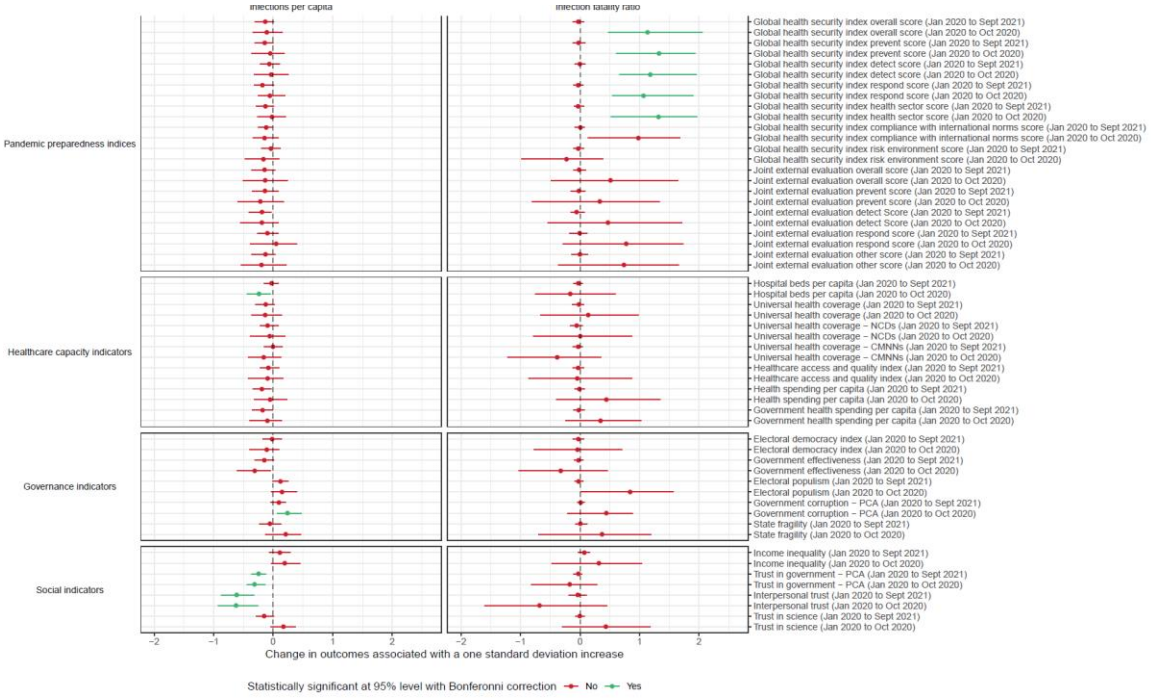
Including variant spread in stage 1

Infections vs. IFR

Figure 2: Standardised infections per capita and standardised infection fatality ratios

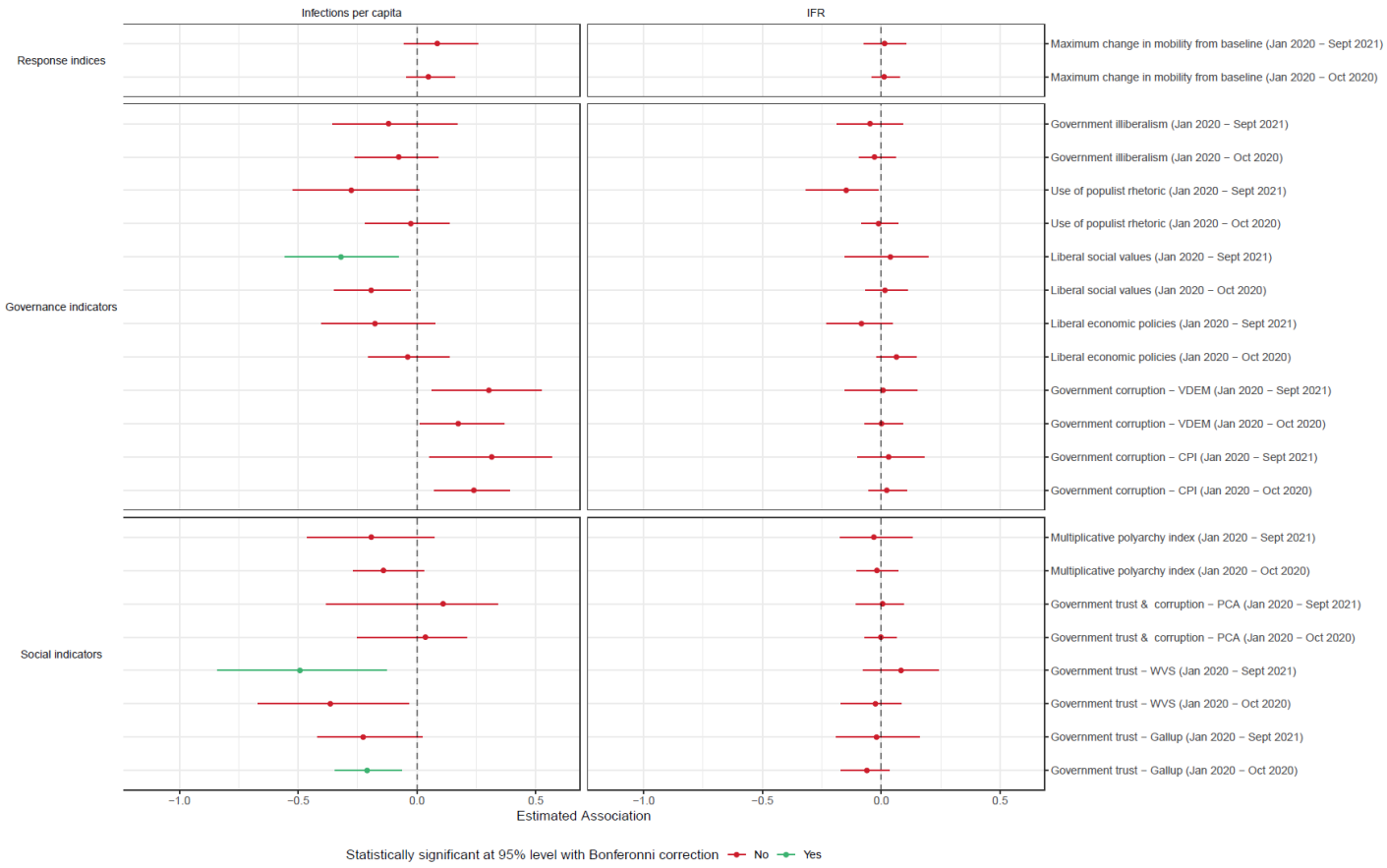


Bivariate results

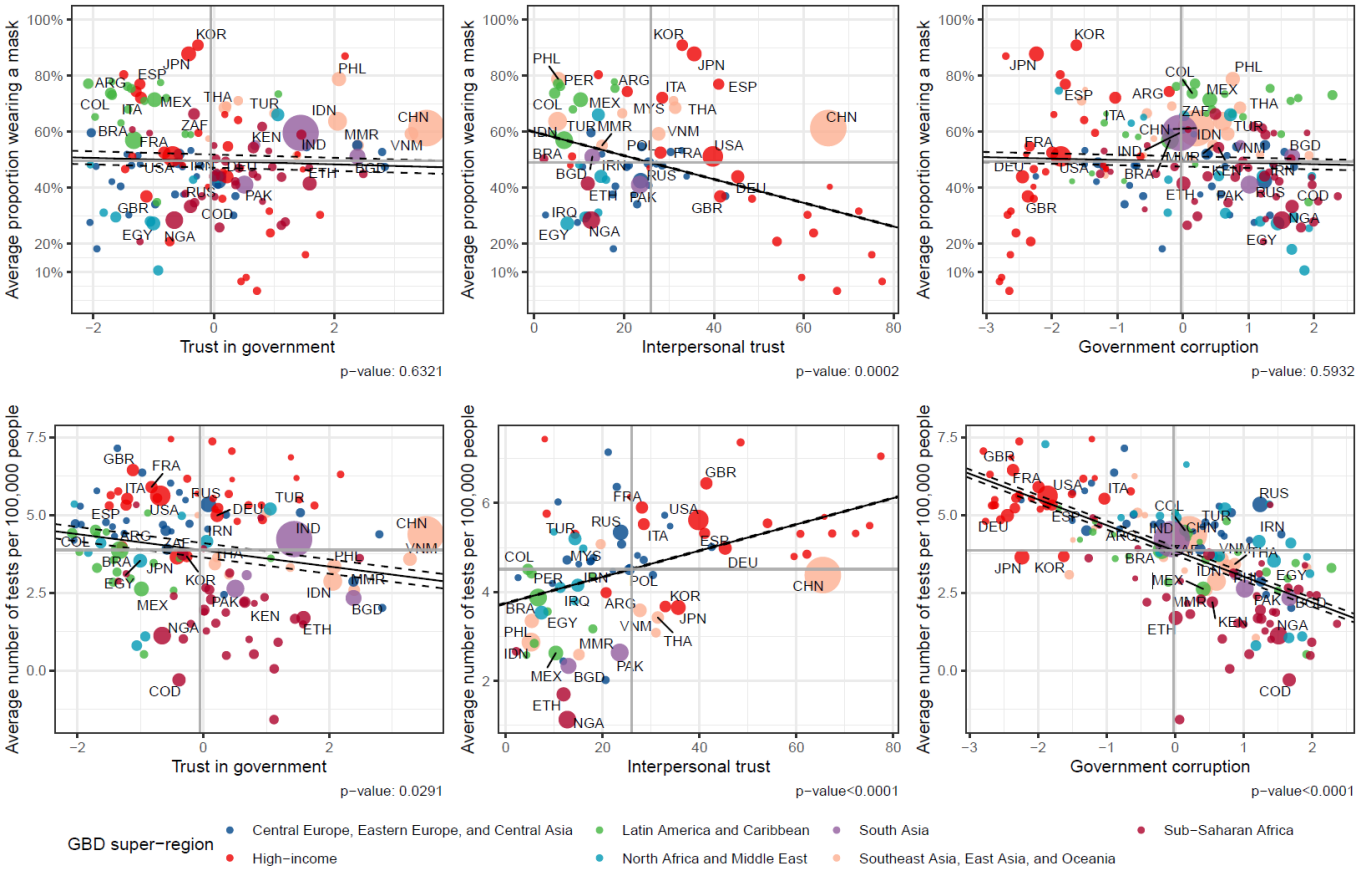


Supplemental results

Additional bivariate analyses

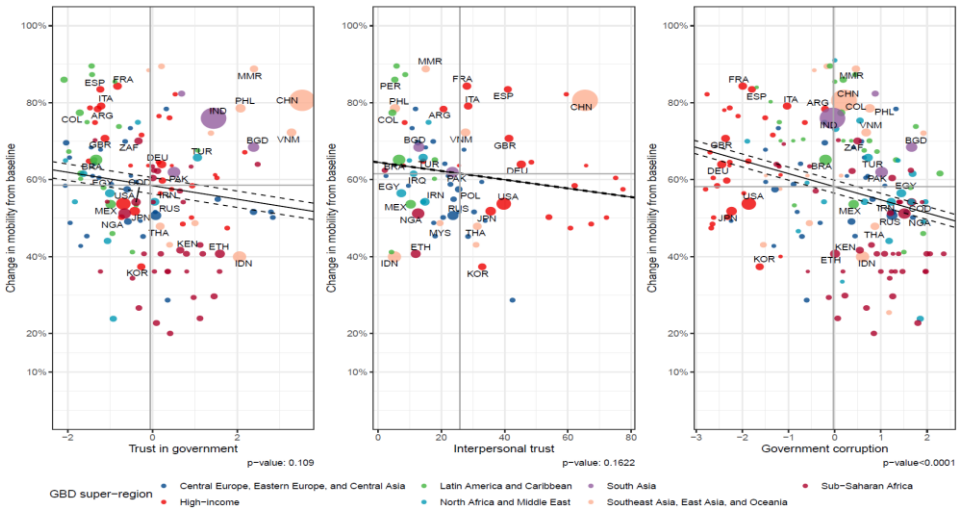

Infections per capita
IFR
Response indices
Governance indicators
Social indicators
Maximum change in mobility from baseline (Jan 2020 – Sept 2021)
Maximum change in mobility from baseline (Jan 2020 – Oct 2020)
Government illiberalism (Jan 2020 – Sept 2021)
Government illiberalism (Jan 2020 – Oct 2020)
Use of populist rhetoric (Jan 2020 – Sept 2021)
Use of populist rhetoric (Jan 2020 – Oct 2020)
Liberal social values (Jan 2020 – Sept 2021)
Liberal social values (Jan 2020 – Oct 2020)
Liberal economic policies (Jan 2020 – Sept 2021)
Liberal economic policies (Jan 2020 – Oct 2020)
Government corruption – VDEM (Jan 2020 – Sept 2021)
Government corruption – VDEM (Jan 2020 – Oct 2020)
Government corruption – CPI (Jan 2020 – Sept 2021)
Government corruption – CPI (Jan 2020 – Oct 2020)
Multiplicative polyarchy index (Jan 2020 – Sept 2021)
Multiplicative polyarchy index (Jan 2020 – Oct 2020)
Government trust & corruption – PCA (Jan 2020 – Sept 2021)
Government trust & corruption – PCA (Jan 2020 – Oct 2020)
Government trust – WVS (Jan 2020 – Sept 2021)
Government trust – WVS (Jan 2020 – Oct 2020)
Government trust – Gallup (Jan 2020 – Sept 2021)
Government trust – Gallup (Jan 2020 – Oct 2020)
−1.0
−0.5
0.0
0.5
Estimated Association
Statistically significant at 95% level with Bonferonni correction
No
Yes

Additional intermediate pathway analyses looking at testing and mask use



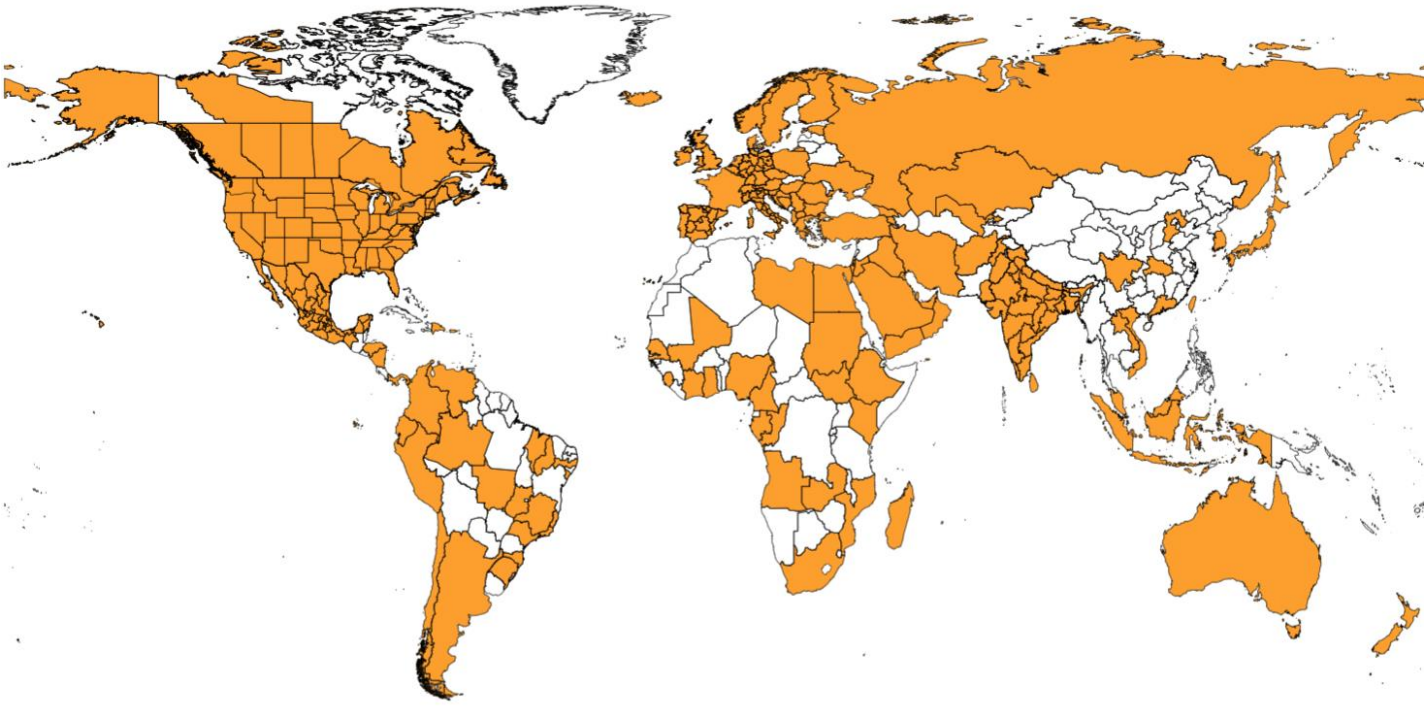
Additional analyses for the first phase of the pandemic (pre-variants and vaccines, January 1, 2020 – October 15, 2020)

Intermediate mobility pathways



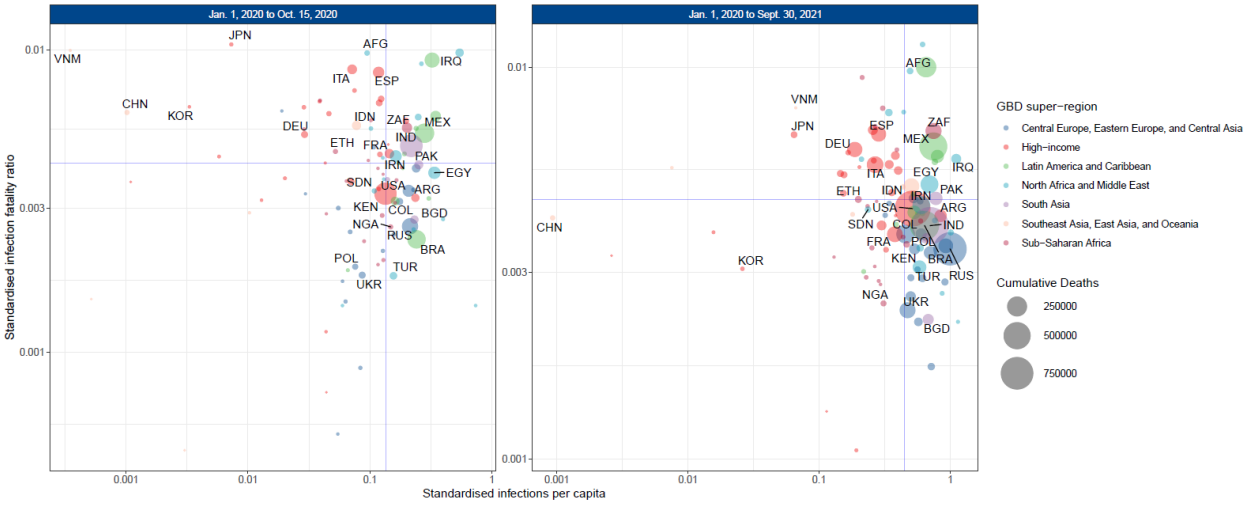
Analyses for seroprevalence study locations (n=303 nationals and subnationals, n=101 nationals only)

Seroprevalence study locations

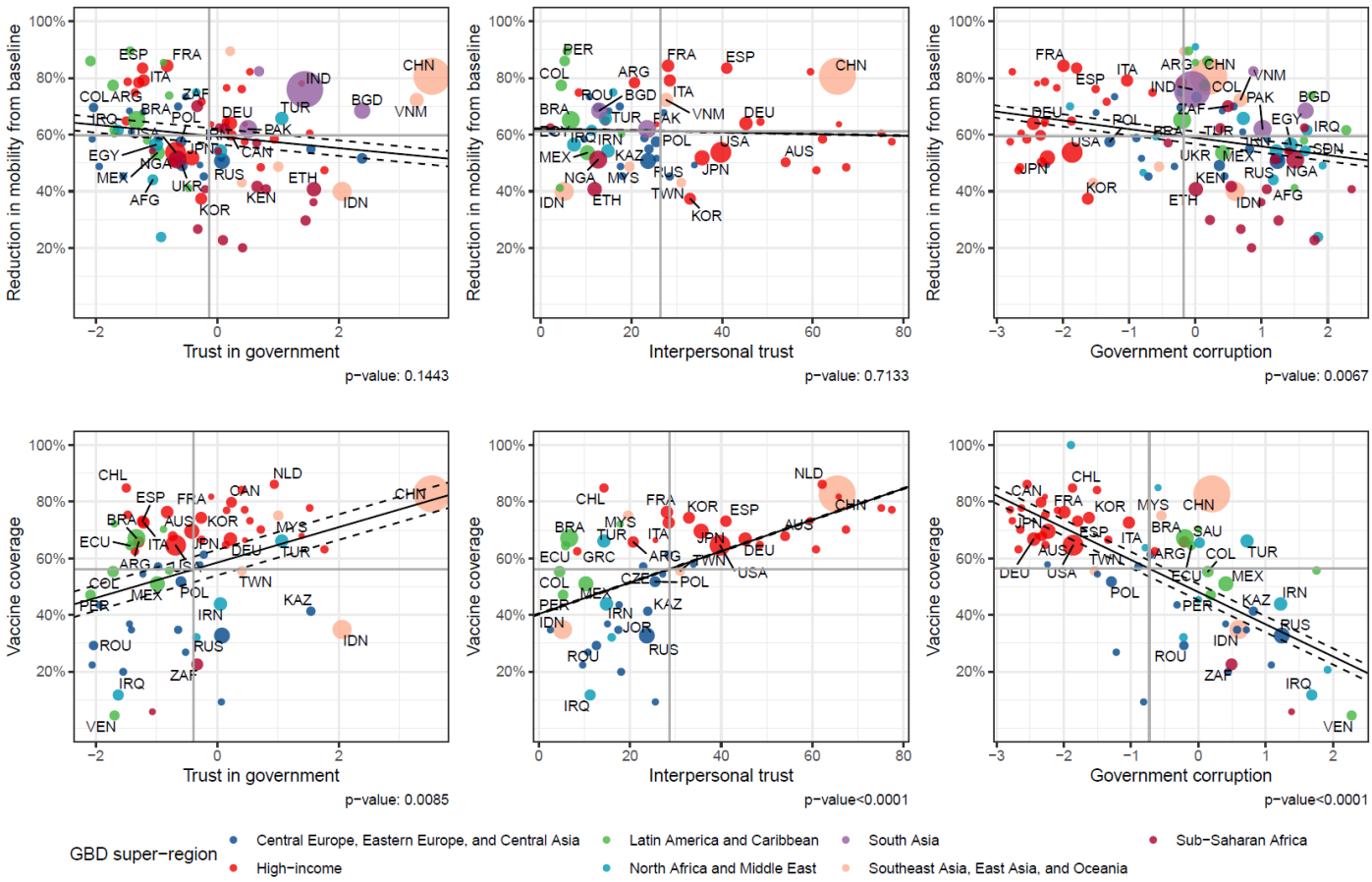


Infections vs. IFR

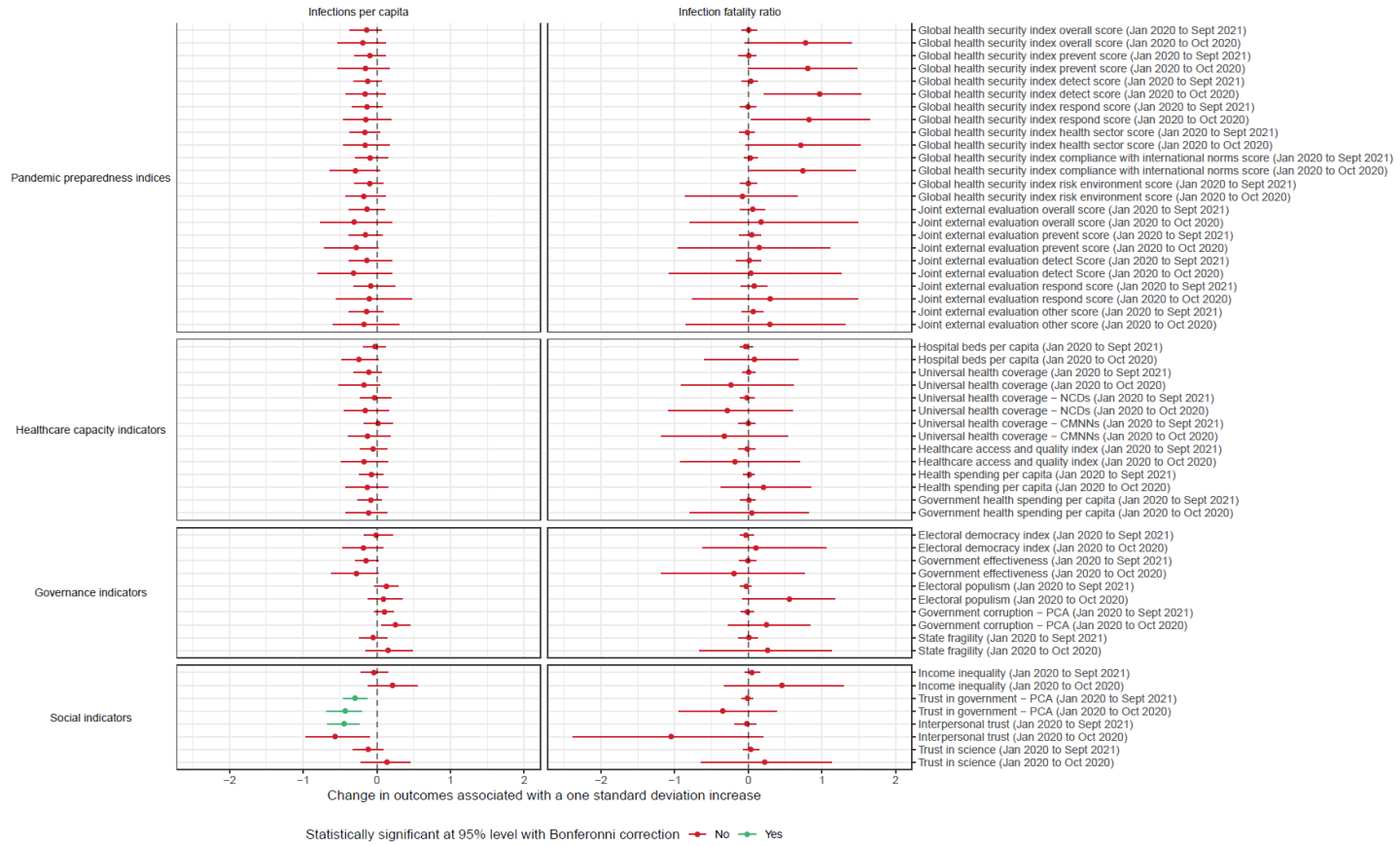
Figure 2: Standardised infections per capita and standardised infection fatality ratios



Intermediate pathways, vaccine coverage, and mobility change, January 1, 2020 – September 30, 2021



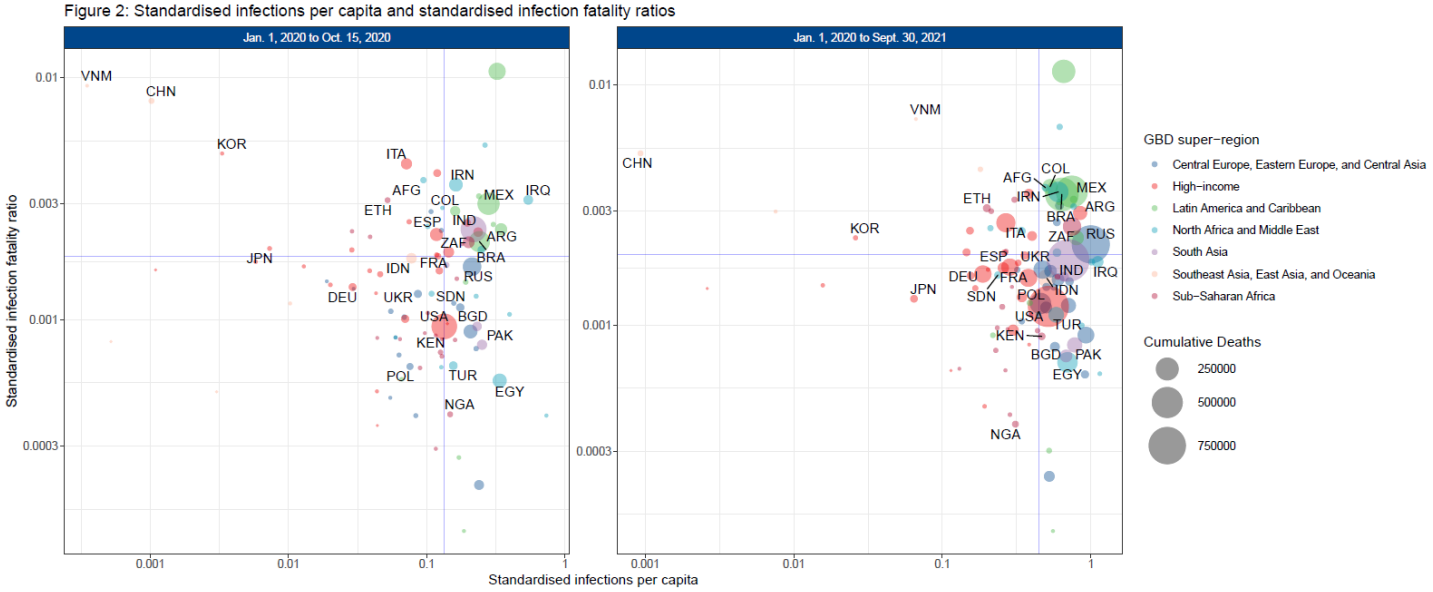
Bivariate results



Analyses using only reported COVID deaths

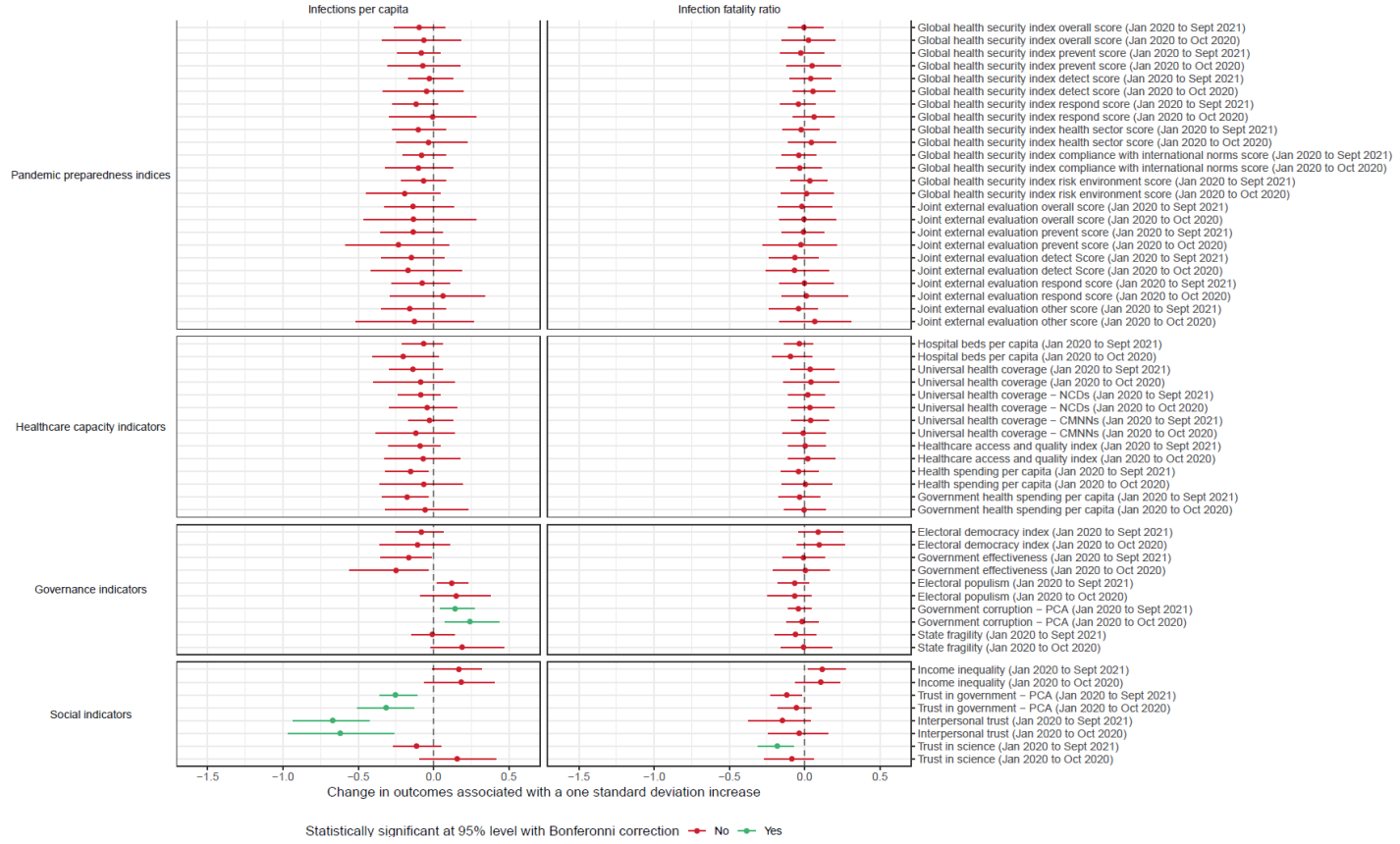
Infections vs. IFR

Figure 2: Standardised infections per capita and standardised infection fatality ratios



Bivariate plots

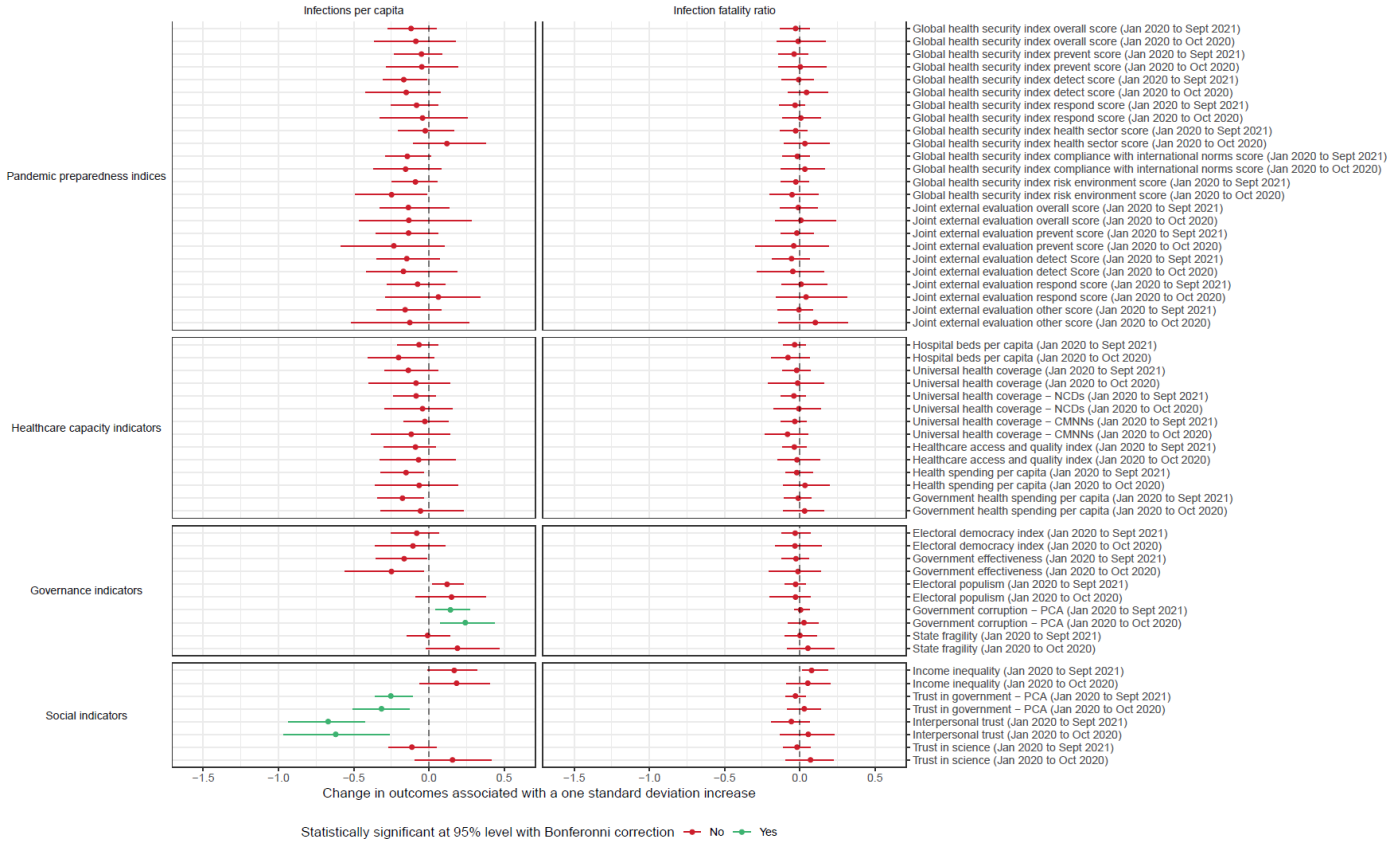
Figure 3: Associations between key preparedness, capacity, governance, and social indicators and infections and infection fatality ratio



Scatter of raw data versus adjusted for stage 1 variables – IFR and cumulative infections

Using 2021 Global Health Security Index metrics in lieu of 2019 metrics, bivariate results

Figure 3: Associations between key preparedness, capacity, governance, and social indicators and infections and infection fatality ratio



CHAPTER 3: AN EXPLORATORY ANALYSIS OF IMPROVED COVID-19 OUTCOMES IN SUBNATIONAL LOCATIONS ACROSS TWO COUNTRIES: THE UNITED STATES AND BRAZIL, JANUARY 2020 THROUGH MAY 2022.

SUMMARY

Background

Brazil and the United States were among the countries with the highest reported death tolls throughout the COVID-19 pandemic despite having relatively high pre-pandemic preparedness scores. Recent investigations into cross-country variations in COVID-19 outcomes have revealed the importance of trust, but little evidence exists of drivers of within-country variability. Understanding drivers of differential COVID-19 outcomes in these two countries is imperative to target policies and actions for improved preparedness in advance of future threats and will provide insights into relationships in outcomes both nationally and subnationally.

Methods

For all states and territories in Brazil (n=27) and the United States (n=51), daily SARS-CoV-2 infections and COVID-19 death rates were extracted from the estimates developed by the Institute for Health Metrics and Evaluation. Infection fatality ratios (IFRs) were calculated from estimated infections and cumulative deaths through May 31, 2022. Infections were standardized for key demographics and socioeconomic factors including daily seasonality, daily variant prevalence, gross domestic product (GDP) per capita, population density, proportion of the population living below 100m, and a proxy for pre-exposure to other betacoronaviruses. For IFR, we standardized for age structure via indirect age standardization, mean body mass index (BMI), mean air pollution levels, age-standardized prevalence of chronic obstructive pulmonary disease (COPD) and cancer, mean smoking prevalence, the proxy for pre-exposure to other betacoronaviruses, and GDP per capita. Standardized infections and IFRs were then modeled against 20 social, governmental, health care, and preparedness indicators, including modeled subnational global health security index scores and its sub-components.

Findings

COVID-19 deaths and infections were heterogenous both across the two countries and within for each Brazil and the United States, showing strong regional patterns. After adjusting for key demographic and socioeconomic indicators, both infections and IFRs were higher among Brazilian states than American states; for infections in Brazil in particular, regional patterns remained, with the north showing higher infection rates than the south. Our investigation into political, preparedness, social, and governmental indicators revealed no correlates with either the United States or Brazil, despite national significance. Only number of pre-pandemic hospital beds per capita was a significant predictor of SARS-CoV-2 infections in the United States, and only in the early era through October 2020. Our research additionally suggested several other indicators as possibly correlative with fewer SARS-CoV-2 infections, including the percentage of the population within 2 hours of a hospital in Brazil, GHSI environment score and Universal Health Coverage, and maximum mobility reduction in the United States, and percentage of mandates in place in both locations. Neither governmental trust nor interpersonal trust was predictive of COVID-19 outcomes across both locations and both time periods studied.

Interpretation

After controlling for non-policy amenable factors, differences between the two countries studied were starker than those within each country. Trust in the government and in other people, which was a strong predictor of national COVID-19 infection rates, was not a significant driver of within-country deaths or

infections. We again identified that preparedness indicators were not predictive of improved COVID-19 outcomes. Despite these findings, we note that limited data were available for our subnational locations and call for subnational studies of trust, preparedness, and health care to improve our understanding of local contexts.

INTRODUCTION

COVID-19 is not only considered one of the most catastrophic pandemics to date with millions of lives lost,[24] hundreds of millions of persons infected,[9] and trillions of dollars spent,[82] it has also been considered an epidemiologic mystery,[23] wherein those countries with the highest SARS-CoV-2 infections have largely been middle- and high-income countries where health care systems often function in higher capacities, rather than in low-income countries, as is the profile for most infectious diseases. As the world begins to shift the focus away from COVID-19 pandemic mitigation strategies and onto future threats, researchers are analysing what we have learned from COVID-19 preparedness and response that can be applied to new and re-emerging pathogens.[83–85]

Several studies have examined the relationship between country preparedness and COVID-19 and have highlighted that existing preparedness metrics - including the Joint External Evaluation (JEE) and the Global Health Security Index (GHSI) - are not predictive of COVID-19 outcomes, particularly when controlling for age-pattern, density, and comorbidities, among other factors.[26,29,86] In contrast, obesity,[87,88] age-pattern,[89,90] sex,[89] comorbidities,[91–94] and environmental covariates[95,96] have all been found to be related to COVID-19 outcomes, including mortality. A surprising finding that has been observed over a multitude of studies is that trust – in one's government and in one's peers – is an incredibly important driver of COVID-19 outcomes: those countries with lower trust largely had poorer COVID-19 outcomes – infections, mortality, or health behaviours – than countries with higher levels of trust.[52,86,97]

However, despite the recent surge of research investigating drivers of COVID-19 outcomes at the national level, less evidence exists digging into subnational variation in COVID-19 outcomes. Moreover, these analyses often are not comparative across multiple countries, [96–102] or consider only one aspect of variability such as political votership[104,105] or gender / racial disparities.[103,106] A recent analysis comprehensively investigated standardized COVID-19 outcomes within the United States, finding that poverty rate, lower access to quality healthcare, fewer health care workers, increases in percentage of the population without health insurance, lower interpersonal trust, and lower educational attainment were all associated with states with higher mortality rates, while poverty rate, lower access to quality healthcare, lower interpersonal trust, lower educational attainment, and lower use of social distancing policies, including mask use, were associated with states with higher infection rates.[107] However, this analysis was not extended to other countries. To our knowledge, this manuscript is the first analysis that compares subnational variation in COVID-19 across two different contexts, adjusting for underlying differences in sociodemographics of the populations.

In this analysis, we compare and contrast the drivers of state-level COVID-19 in each Brazil and the United States. These two countries were chosen as they had among the highest reported COVID-19 deaths throughout the pandemic,[108] noted clear disparities in health care access and quality,[109] income,[110] COVID-19 infections and deaths within each country,[98,111–113] (Figure 1) and had populist leaders and politicization of the pandemic in early 2020.[114,115] This analysis builds on previous work conducted by the authors looking at cross-country outcomes[86] and uses results from the Institute for Health Metrics and Evaluation (IHME) on estimated SARS-CoV-2 infections and deaths adjusted for underreporting (via excess mortality analyses).[108,111] In addition we include several modeled covariates of interest from IHME as well

as external sources to adjust for comorbidities, underlying population demographics, age-structure of the population, and unequal variant spread and seasonality, among other factors. At present, most pandemic preparedness planning is done at the national level, but the COVID-19 pandemic has demonstrated that marked heterogeneities exist within each country. Understanding drivers of such heterogeneities is important to quantify populations at risk for various pathogens of pandemic potential; this analysis aims to understand possible drivers of these heterogeneities in the context of the COVID-19 pandemic for two key countries.

METHODS

Overview

In this analysis, we focused again on cumulative infections per capita and infection fatality ratios (IFRs) to most closely match our national-level analyses. Both estimates were calculated using outputs from IHME's COVID-19 research[33,108,111] and were restricted to the period of January 1, 2020 through May 31, 2022, as well as a secondary focus on a pre-vaccine and pre-variant era from January 1, 2020 through October 15, 2020. We again took a two-stage approach to these analyses wherein at the first stage we standardized infection rates and IFRs to key underlying drivers of COVID-19 outcomes. This first included a daily standardization to a global level for seasonality and mean prevalence of variants of concern (namely Delta and Omicron) for infections, followed by cross-sectional standardizations for age-structure for IFR, and lastly comorbidities, population density and demographics, environmental features, and previous coronavirus exposure risk for both infections and IFR. In the second stage, we used these standardized outputs modeled against a suite of preparedness, health care, sociopolitical, and governance indicators. We sought to include all covariates studied in the cross-country analysis, where possible, and included additional subnationally relevant covariates of interest. All models constructed were log-log models and were evaluated separately for Brazil and the United States. All analyses were conducted using R version 4.0.3.

This study complies with the Guidelines for Accurate and Transparent Health Estimates Reporting (GATHER) recommendations (appendix section 2.1).

COVID-19 infection and mortality estimates

Daily estimated infections and deaths were extracted from the IHME COVID-19 database for the two periods of interest: January 1, 2020 through May 31, 2022 and January 1, 2020 through October 15, 2020 for all American and Brazilian first subnational units, representing 76 states and 2 federal districts combined. Estimation of infections and adjusted deaths for underreporting have both been described in depth elsewhere.[33,86,108,111] In brief, SARS-CoV-2 infections were estimated from the number of deaths, hospitalizations, and reported cases per location, pulled from the from the Johns Hopkins University Center for Systems Science and Engineering COVID-19 database[8] with internal adjustments for reporting lags and missing data; IFR, infection-hospitalization ratios, and infection-detection ratios were then estimated for each location, and infections were derived from the triangulation of these three metrics and adjusted against seroprevalence data adjusted for testing capacity and reporting, where available. Cumulative infections were calculated by summing up the daily infections per location and were represented in per-capita space by dividing by 2019 population estimates.

Deaths adjusted for underreporting were first obtained from the Johns Hopkins University Center for Systems Science and Engineering COVID-19 database[8], supplemented with data from ministries and departments of health, and the ratio of excess deaths due to COVID-19 versus reported deaths was then calculated for each location using spatial correlations and additional data. The IFR was then calculated by first applying a nine-day lag to the infections to account for the estimated average time between infection

and subsequent death, and subsequently dividing the cumulative deaths over the cumulative infections. Underlying data and model uncertainty were quantified and propagated at each stage of this analysis for both infections and IFR.

Variable selection, acquisition, and estimation

In the first stage of analysis, variables were selected to adjust for epidemiologic, sociodemographic, comorbid, or environmental factors believed to be associated with COVID-19 infections or IFR. We chose to use the same variables for this analysis as were used from the national analysis[86], with the exception of adding daily prevalence of variants of concern for infections at the same time as adjustments for seasonality were made in order to control for differential infectivity and fatality patterns of different variants. For cumulative infections, we adjusted first for seasonality, variant prevalence, Gross Domestic Product (GDP) per capita, altitude, population density, and a proxy for previous exposure to betacoronavirus bat host species. Prevalence of the variants of concern was calculated using genetic sequences of variants from the GISAID initiative[116] with models of invasion date and rate of invasion used in geospatial forecasting models for several variants of concern, including Delta and Omicron; more details are available elsewhere.[117] These data were modeled daily for each location; to use in this cross sectional analysis, we estimated the average prevalence of infections caused by Omicron variant and Delta variant separately over each of the two time periods. To produce the proxy of previous betacoronavirus exposure, we first obtained a list of possible bat hosts produced by authors at the Verena Consortium using ensemble modeling.[64] We next extracted the estimated species range of each bat using the expert-compiled IUCN Red List of Threatened Species.[63] Each of these ranges was next converted to a raster, and ranges for reach bat were stacked one on top of the other to get the total sum of betacoronavirus probable bats in a given grid-cell. Lastly, we then averaged the number of species over all first administrative units to get the average number of bat species per state or federal district in Brazil and the United States; further details are available in the appendix (section 4.1).

For IFR we included an indirect age standardization, age-standardized prevalence of cancer, age-standardized prevalence of chronic obstructive pulmonary disease (COPD), population density, GDP per capita, average Body Mass Index (BMI), smoking prevalence, and a proxy for previous exposure to betacoronavirus bat host species. These variables were considered our 'stage 1' variables as they are largely factors that aren't policy amenable, such as underlying comorbidities like age-standardized cancer and COPD prevalence, population GDP, population density, variant spread, or seasonality. Additional factors were included that are more distally policy amenable, such as average BMI, mean smoking prevalence, or air pollution, but are not immediately actionable.

In the second stage, we used the stage 2 variables from the national analysis as a framework for inclusion in this analysis.[86] Table 1 demonstrates the variables considered from the national analysis, their provenance and availability for each Brazil and the United States, and any additional notes, especially where national data were not relevant or not included. This table also documents any additional variables considered for the subnational analysis. Additional methods for creating these variables, where indicated, are available in the appendix (section 4). For some of the national stage 2 variables, corresponding variables were not available at the subnational level, so proxies or composite measures were used.

The first among these were the preparedness indicators. For the national analysis, Joint External Evaluation (JEE) and Global Health Security Index (GHSI) scores were available for most of our countries of interest and included sub-sectional scores (e.g. Prevent score, Detect score, and Respond score, among others). These metrics do not exist subnationally for either Brazil or the United States. We therefore examined the documentation for creating the existing national-level GHSI sub-section scores[118] to identify which variables were used in developing the section scores, and identified which we had available at the

national and subnational level. Further information on exact variable and sub-section matching is available in Table 1 and in the appendix (section 4.2). Once we had a set of variables to map to the sub-sections, we first created national-only models to estimate the correlation between these proxies and the sub-section score, and then used the model estimates to obtain a predicted score per subnational location using subnational data; one score for each sub-section was developed. Unfortunately, for several sub-sections (Detect, Respond, and Adherence to International Norms) there was not data available comprehensively (Detect and Respond) or the section was not applicable at the subnational level (International Norms), so these scores could not be estimated. Using the three subsection scores we did estimate per location, we created a model of the three sub-sections against the overall score again at the national-level only, and then predicted out subnational-level overall scores. The second proxy was the creation of a variable looking at the percentage of the population living within two hours of a health facility. Travel times to the nearest health facility were created by Weiss et al.[119] and generated globally. We converted this geospatial estimate to a state-level aggregate by re-sampling to 5x5km for computational efficiency and to match grid-cell population estimates. We then created a binary variable per grid-cell as to whether that grid-cell was within 2 hours travel time of a health facility. This binary variable (1 if within 2 hours, 0 otherwise) was multiplied by the per grid-cell population and then ultimately summed this at the state-level. Lastly, we then divided the total weighted population within 2 hours of a health facility per state by the total population per state to get the estimated percent of the population within 2 hours of healthcare. For our third and final proxy, instead of using a metric of whether a country had run a populist campaign (as was used in the national analysis), we instead looked at the percentage of the population who voted for the populist leader in recent elections: Donald Trump in the United States in 2016 and Jair Bolsonaro in Brazil in 2018.

Stage 1: Standardizing infection rates and IFRs

We considered a two-stage analysis to first standardize those control covariates not directly related to the question of interest regarding COVID-19 outcomes, and then to regress the covariates of interest against globally-standardized data. In stage 1, for infections, we first regressed the daily infections versus daily estimates of relative risk of pneumonia mortality (a proxy for seasonality), prevalence of the Delta variant, and prevalence of the Omicron variant, and then predicted out each covariate to a 'global' mean level, wherein the mean levels were obtained over-time from all American and Brazilian subnational locations. Following this time-varying standardization, infections and deaths were summarized over the two periods, as described above. We then constructed multivariable regression analyses to control for time-invariant measures. For seasonal- and variant-adjusted cumulative infections, this model included GDP per capita, the previously described proxy for previous exposure to betacoronavirus bat host species, population density, and the fraction of the population living below 100 meters in altitude. For IFR, we first adjusted for the age structure of the location using indirect age standardization methods. Using age-adjusted IFR, we then again constructed a multivariable model including GDP per capita, the previously described proxy for previous exposure to betacoronavirus bat host species, population density, mean body mass index (BMI), age-standardized COPD and cancer prevalences, air pollution, and average smoking prevalence. All models in stage 1 were log-log linear models.

Stage 2: Exploring health care, governance, and social associations with standardized COVID-19 outcomes

In stage 2, we constructed a series of bivariate models using the standardized infections and IFR from stage 1 for all Brazilian and American states as the dependent variable, and the available 20 primary interest variables in Table 1 as the independent variables. All of the stage 2 variables were centered and scaled for ease of comparison and interpretability. All models again were linear log-log models. To account for running tests for multiple hypotheses, we used an adjusted p-value using a Bonferroni

correction for each primary stage 2 analysis (n=20) and an alpha of 0.05, yielding an adjusted p-value threshold of 0.0025.

Capturing model and data uncertainty

We constructed 100 independent replications of each stage 1 and stage 2 models, using individual death and infection draws produced by the IHME modeling framework, in order to account for uncertainty in the model. For each of the regressions, we used a multivariate normal distribution and the estimated variance-covariance matrix to get an estimate of the beta coefficients, and used the residuals from stage 1 for use in stage 2. We report the mean estimate across the 100 draws and present the uncertainty interval as the 2.5^{th} percentile and 97.5^{th} percentile across all 100 draws.

RESULTS

The overall unadjusted infection rate in the United States was 79.8 infections per 1,000 population between January 1, 2020 and October 15, 2020 and 1,059.9 infections per 1,000 population from January 1, 2020 to May 31, 2022; in Brazil it was 210.4 and 1,282.4 infections per 1,000 population, respectively. Unadjusted IFRs were 104.7 deaths per 10,000 infections from January 1, 2020 to October 15, 2020 and 36.7 deaths per 10,000 infections between January 1, 2020 and May 31, 2022 in the United States and 40.8 deaths per 10,000 infections through October 15, 2020 and 28.1 deaths per 10,000 infections through May 31, 2022 in Brazil. Figure 1 demonstrates the rates of unadjusted infections and IFR through May 31, 2022 in Brazil and in the United States. We can observe that the overall unadjusted infection rates in Brazil were on average much higher than those in the United States, but both countries had high heterogeneity and observable regional patterns, with northern Brazil and south and Midwest United States having higher relative infection rates compared to the south of Brazil and northeast and west coasts of the United States. In contrast, we see much higher levels of IFRs in the United States than in Brazil for the same time period, this time observing higher IFRs all along the eastern coast of the United States.

In our adjustment for sociodemographic and other background and control characteristics of our study sample, we observed that there were no significant variables associated with IFR in either American or Brazilian states in the full time period (Table 2a). In contrast, for infections, the percent of the population living below 100m altitude and the mean GDP per capita both had significant inverse associations for the United States and the percent of the population living at a density greater than 1,000 people per square kilometre and average number of betacoronavirus bats were both significantly and positively correlated with infections for the full time period in the US. In Brazil, only the number of betacoronavirus bats was a significant variable in the model for infections, displaying a positive correlation between the average number of bats and the number of infections per capita in the full time period. In the early era (Table 2b), we observed that the percent of the population living at a density greater than 1,000 people per square kilometre was significantly and negatively associated with IFR in the United States while age-standardized cancer prevalence and average number of betacoronavirus bats were significantly and positively associated with IFR; in Brazil, again no covariate was significant. For infections, in the United States, we observe the same significance and relationships for all covariates as the full-era model with the exception of altitude, which is not significant in this earlier and shorter era. Similarly, in Brazil, we again only see the significant positive correlation between infections and the proxy for previous coronavirus exposure via bats.

After adjusting for our control and sociodemographic variables, we can first see in Figure 2 that the areas of highest infections in the United States have shifted from the south and Midwest to the west coast and mountain regions. In contrast, adjusted IFR remains highest in the south still. In Brazil, after adjustment we see the pattern of higher infection rates in the north even more clearly than before, while IFRs remain

heterogeneous throughout the country. Most striking in the adjusted plots is that after adjustment, IFRs for Brazil become much higher than those in the United States.

This effect is visible again in Figure 3. Additionally, we observe in the early era of the pandemic, in general Brazilian states had relatively higher infections but lower IFR than American states, though there is a fair amount of overlap, particularly around those states that had average levels of both infections and IFR. In contrast, American states had relatively high IFRs in this era, but surprisingly lower infections. In the full era, however, there was a much clearer separation between the American and Brazilian states, with the former having lower relative levels of both infections and deaths than the latter. There is again some mixing around those with more average levels of both infections and IFR, but largely we see that Brazilian states exhibited both higher infections and higher IFR in the full era. Notably, American states seemed to experience a wider range of IFRs across both eras.

Figure 4 displays the relationship between our COVID-19 outcomes – infections per capita and IFR – and our policy and social variables after adjusting for our stage 1 covariates. Much like the study at the national level,[86] there were no covariates correlated with differing COVID-19 IFR levels after controlling for underlying differences; this was consistent whether or not we controlled for multiple hypothesis testing. In the first analysis not controlling for multiple hypotheses, for Brazil infections, increasing percent of the population within 2 hours of a hospital was associated with significantly reduced cumulative infection rates for both time periods. In addition, increasing percentage of mandates applied per day, on average, was associated with a significant decrease in infection rates, but only in the early era. None of these associations remained statistically significant with the Bonferroni correction. In the United States for infections in the early era, increasing GHSI risk environment score, increasing Universal Health Coverage, increasing percentage of mandates applied per day, on average, and increasing the maximum reduction in mobility were all associated with significantly decreased cumulative infection rates when considering a significance level of 0.05. In contrast, increases in baseline under-5 mortality in the early era and the baseline number of hospital beds per capita in the early era were both associated with significant increases in infections. In the model controlling for multiple comparisons, only the number of hospital beds per capita remained significant, and in the early era alone.

Discussion

This analysis is the first to attempt to explain differences in subnational drivers of COVID-19 outcomes across two similar but distinct contexts. We have several main conclusions from this work.

First, this analysis largely replicates the findings of the national-level analysis finding that pandemic preparedness indicators were not predictive of COVID-19 outcome successes. While not significant with our Bonferroni correction, our finding of marginal significance of the modelled GHSI environment risk score and health care access and coverage covariates provide an avenue for exploration to understand whether particular sections of the GHSI or JEE have significance in predicting improved COVID-19 outcomes, such as mandate adherence or vaccine uptake. Future research is needed to understand which elements were most useful at understanding COVID-19 heterogeneities both nationally and subnationally. Similarly, we also largely replicate our results for IFR from the cross-country paper, finding no significant relationships with any of the 20 covariates examined and IFR; this is consistent for both the United States and Brazil. In our cross-country analysis, we concluded that age profile was the largest individual driver of differential mortality, and thus, once age distribution was corrected for (in addition to other key demographics), no factors remained significant.[86] While age of a population is not policy amenable, established policy recommendations with targeted, age-appropriate communication as well as prioritized therapeutics and vaccination distribution are essential to minimize the risk amongst at-risk age groups for future threats. It is important to consider that not all pathogens of interest will present as COVID-19 did;

Zika, for example, is a larger risk for neonates and pregnant women. Preparedness plans should consider a vast array of pathogens of pandemic potential and consider targeted response activities appropriate for the given risk profile. For infections, when correcting for multiple hypotheses, only the number of hospital beds per capita was a significant predictor of infections, with more beds per capita being associated with higher infections in the United States, and only in the early era of the pandemic. Many studies have found an inverse relationship between mortality and per capita hospital beds, to our knowledge this is the first study finding a positive association between infections and baseline hospital bed capacity, and as such the mechanism behind this relationship remains inconclusive. We hypothesize that a greater number of baseline beds per capita reflects higher health investment, which often correlates with not only higher health sector preparedness and health care accessibility, but also with density, which ultimately align with higher infection rates (plots of CDC funding by state in FY2020[120,121] versus these covariates can be found in appendix 3.2). However, without conclusive evidence, more research is needed to better understand the relationship between per capita hospital preparedness, health investment, and infection rates.

Second, in contrast to the cross-country paper, neither governmental nor interpersonal trust was significant for either Brazil or the United States for reducing infection rates after standardization; previous research found both interpersonal trust and governmental trust to be strongly tied to lower infections at a national level, consistently for both the early era (through October 15, 2020) as well as the full era (September 30, 2021).[86] Given that behavioural changes required to mitigate spread in a pandemic (such as mask wearing or vaccination acceptance) require trust in those communicating the risk profile, building trust in one's community as well as those in positions of governmental power now is essential to effective communication for future threats. This study suggests that at a local level, federal governmental trust is not as relevant for infection-reduction behaviours. More surprising was that interpersonal trust was also not significant – our prior hypotheses were that community trust was even more important at a subnational level than at a national level. It is critical to note that the estimated levels of both governmental and interpersonal trust at the state level were much less variable than those in the cross-country analysis. Whether these differences really are much starker at a national scale and therefore have much less bearing at a subnational level, or whether current estimates and county-level aggregations mask true variability remains unknown. Future research should consider the impact of trust in local (rather than national) government and its influence on COVID-19 outcomes, and to further dissect the reasons why these variabilities were so much less notable in the subnational analysis. It is important to note that both the interpersonal and governmental trust variables were vulnerable to small sample sizes, as the responses were calculated from sub-national location information provided on the World Values Surveys nationally representative samples. As such, many smaller locations have wide confidence intervals, as the study was not designed to be subnationally representative. In addition, those smaller locations had estimates based on only a small handful of responses, leading to a higher possibility of bias. Similarly, our supplemental interpersonal and governmental trust covariates in the United States were generated from the Harvard Cooperative Election Study group modules that included questions on federal trust and / or trust in other people, a small subset of all included modules.[122–125] With subnationally representative surveys, we may have indeed found a significant correlation between trust and COVID-19 outcomes, and thus call for much needed research on trust at the subnational level to better understand how governmental and interpersonal trust influence behaviours and risk reduction for future threats.

Third, pre-pandemic state-level GDP and population density were both consistently significantly related to infections in both the early and full era in the United States. This finding is similar to recent US-centric research which suggests that the poverty rate was associated with higher infections and deaths throughout the pandemic.[107] One mechanism by which we hypothesize this may impact infections is that states with higher poverty rates (and lower GDP) may have higher percentages of frontline, non-

healthcare essential workers, which could increase COVID-19 exposure due to extended face-to-face interactions.[126] Similarly, states with higher percentages of populations living at higher densities would have faced similar burdens of increased pathogen exposure, confirming the finding that those locations with higher density had higher infections. While efforts were taken in some states to limit the exposure to SARS-CoV-2 by frontline workers, other states implemented few mandates, if any.[127] In many cases, implemented efforts were abandoned too soon; importantly, this easement was found to be political in nature, with those states with republican governors easing social distancing mandates a week earlier on average, all else being equal.[104] As we prepare for future pandemics, plans for protecting those frontline and essential workers is of the utmost importance to protect their health and wellbeing and maintain a high level of functioning in society, regardless of political affiliation. Density had an inverse relationship with IFR in the United States in the early era, with lower density resulting in higher IFR. This finding is consistent with other research[128] that suggests that COVID-19 mortality was lower where infrastructure was most established and care was easiest to access – mostly in highly dense cities – particularly in the earliest days of the pandemic. Similarly, our second stage analysis after standardization suggested that in Brazil, increases in the percent of the population within two hours of a health facility was also significantly related to lower infections while in the United States, the percentage of the population with universal health coverage (UHC – defined as access to all necessary physical and mental health care in a timely fashion without undue financial strain for all persons[66]) was associated with infections, such that increasing levels of UHC was associated with lower infections. Combined, these results suggest that those with higher access to affordable, timely, and necessary care had more timely responses to case notifications, preventing subsequent transmission. In planning for future threats, local governments should consider how density and urbanicity influence disease transmission and response, setting up strategies to reduce subsequent transmission following initial infection in high density locations, and ensuring those in more rural areas have timely and high-quality access to care either through improved transportation, mobile clinics, or the development of new infrastructure.

Fourth, in contrast to the findings for the cross-country analysis, BMI was not significant at all in the stage 1 model (Table 2 a and b). We do observe much wider variability in average BMI across countries (range 20.86 – 30.80) versus within the United States and Brazil (range: 25.36 – 29.98, supplemental figure 3.3).[86] This suggests that while BMI might be higher on average in the United States and Brazil, it was not a main factor in disparate COVID-19 mortality throughout the pandemic. While this research suggests that small disparities in BMI did not influence IFR, the national research suggests that increasing BMI is significantly related to higher IFR and should still be considered for policy changes including subsidies to healthier food options or sugar-sweetened beverage taxes to help improve not only COVID-19 outcomes, but other morbidities and mortalities across the globe.[86] For our stage 1 analysis, the only variable significantly related to infections for Brazil in both the early era and the full era was the proxy for the number of betacoronavirus bats per location; IFR had no significant relationships. The number of betacoronavirus bats was also a significant predictor of infections in the United States for both eras. Additionally, number of betacoronavirus bats was a significant correlate of IFR in the United States in the early era. A recent study of pre-existing betacoronavirus antibodies in humans and SARS-CoV-2 immunity by Lin et al.[129] has suggested that that higher magnitudes of pre-existing betacoronaviruses antibodies can inhibit SARS-CoV-2 immunity, resulting in greater disease severity. We therefore hypothesize that previous exposure to betacoronavirus bats may lead to higher baseline levels of these antibodies, resulting in more severe COVID-19 presentations and death, increasing the IFR in those locations. Further research is needed to understand how exposure to these bats may influence baseline betacoronavirus levels, but an understanding the geographic range of these bats is beneficial for recognizing how they interact with humans and creating targeted mitigation strategies. However, given that this covariate has high spatial heterogeneity, while it's possible that this is truly capturing previous exposure to betacoronaviruses, it's

also possible this variable is capturing other, unmeasured heterogeneity, and warrants further exploration, particularly as the relationship between higher levels of betacoronavirus bats and higher infections is not well understood. In addition, broader research understanding how previous infection impacts disease presentation, whether for the better, like pandemic influenza immunity[130], or for worse, like Dengue haemorrhagic fever[131,132], is critical for triaging therapies and other responses for the subsequent pandemics of the future. In the United States, higher percentages of the population living below 500 meters was found to be significantly related to lower infections. Previous research has observed that the occurrence of respiratory illnesses is greater at higher altitudes; the mechanism by which this has been hypothesized to occur is either through behavioural changes, like spending more time indoors, or climatic factors, like relative humidity.[38–40,86] While altitude is not policy amenable as a risk factor, an understanding of the increased risk related to higher altitudes is important to consider for future pandemic preparedness efforts. Additionally, climate change is poised to alter not only how we interact with wildlife and other pathogen hosts, but it will undoubtedly influence our behaviours, driving or limiting onward transmission.[133] Acknowledging these changing profiles of spillover risk as well as amplification and transmission potential are essential for future pandemic preparedness plans to consider how threats may present in the future. Lastly, higher cancer prevalence was found to be significantly associated with higher IFR in the United States in the early era. This is consistent with other studies which demonstrate that mortality amongst those with comorbid cancer was much higher than in the general population.[134–137] Combined with the findings that treatments and screenings were delayed, sometimes substantially, during the early months of COVID-19 either due to reluctance to seek care or health system disruptions, immunocompromised individuals faced a double disease burden of higher COVID-19 mortality and worsened cancer outcomes.[135,138–140] Strong mitigation tactics to prevent disease transmission among at-risk populations, prioritized therapeutics and vaccine delivery, and support for routine health system functioning are essential efforts to research now to hopefully to reduce the multiplicative burden of disease among the most at-risk populations in future threats.

Last, while the raw IFR and infections suggest that the United States had much higher IFR levels than Brazil in both the early era (104.7 deaths per 10,000 infections in the US versus 40.8 deaths per 10,000 infections in Brazil) and the full time period (36.7 deaths per 10,000 infections in the US and 28.1 deaths per 10,000 infections in Brazil), we can see in figures 2 and 3 that after adjusting for the sociodemographic characteristics in stage 1, Brazilian states had, on average, higher IFRs than the United States for the full period. Similarly, figure 3 suggests that while infections and IFR were relatively heterogeneous for both countries in the early era, by the full time period, the United States had lower levels of both infections and IFR than Brazil, after standardization. While our paper did not find any correlations with trust in other people to explain within-country differences in COVID-19 outcomes, higher interpersonal was trust significantly related to decreased infection incidence in the cross-country study.[86] Given that Americans report much higher interpersonal trust (approximately 40%) versus Brazilians (approximately 7%), this may explain some of the spread between Brazilian and American infection rates.[75] Similarly, we know that high access to quality health care is related to improved health care outcomes.[141] While the Healthcare Access and Quality Index (HAQI) was not related to within-country differences in COVID-19 IFR, the United States and Brazil have widely different HAQI values (82% in the US versus 53% in Brazil) [141], which may explain the dispersion. Unlike interpersonal trust, this was not a significant finding in the cross-country analysis but does warrant further exploration.

Limitations

There are several limitations to this analysis. First, this analysis is meant to compliment the national analysis and is therefore also cross-sectional in nature. Because of this, we cannot any attribute temporality or causality to these analyses. This is particularly important to note for the mandate and

mobility findings: it is difficult to disentangle whether the mandate application preceded the mobility reduction, or vice versa, or whether they were uncorrelated altogether. Formal causal and time series models are necessary to better investigate these drivers and their impact on COVID-19 outcomes. Second, this is an ecological analysis and is therefore not meant to be diagnostic of the causes of COVID-19 variation. Third, despite our efforts to include uncertainty by propagating model uncertainty from the earliest stages using 100 bootstraps of our data, many of the explanatory variables do not include uncertainty and thus are likely underestimates of the true uncertainty in the data. Fourth, this analysis includes subnational locations across just two key countries. Expanded analyses may find differential patterns in outcomes than those identified here. Finally, the sources used in this manuscript are highly variable and of varying quality and should be interpreted in light of the quality of evidence. Important to this paper in particular, subnational data were often not available where national data exist, so were either modelled using other sources or were omitted altogether, as we describe in Table 1. This introduces another layer of variability and bias into the model and such variables should be interpreted with caution. Where data were modelled, such as for the trust variables and the GHSI variables, the models were built on a small subset of survey and previously modelled data, resulting in wide confidence intervals, and smaller states may be subject to bias from a very small number of respondents. Additional efforts to conduct surveys and research of local pandemic preparedness and governmental, interpersonal, and scientific trust would be a great benefit both to future analyses of COVID-19 outcomes, but also for understanding drivers in state-level differences more broadly.

Conclusions

This is the first paper to our knowledge to address subnational variability in COVID-19 outcomes across two similar contexts with high political polarization and high burdens of COVID-19 morbidity and mortality. Despite heterogeneity across both Brazil and the United States, we observed stronger heterogeneity between the two countries than within after controlling for non-policy amenable factors. Trust in the government and in other people, which were strong predictors of cross-country COVID-19 infection rates, were not significant drivers of within-country deaths or infections, though additional research is needed to provide more robust estimates of state level trust in both the United States and Brazil. As the estimated levels of governmental and interpersonal trust were much more variable between countries, we emphasize the importance of dissecting measurement error and bias from true homogeneity in future research. Importantly, focusing not only on trust as a static measure but as a dynamic one that changes in response to political and environmental threats is essential to understanding patterns and shifts in attitudes, ultimately impacting mandate adherence and credence in the communication of elected officials. Existing pandemic preparedness measures again failed to account for heterogeneities in COVID-19 outcomes, though certain elements including health care coverage and access were marginally significant, suggesting avenues to explore particularly with regards to vaccine delivery and mandate adherence.

Much of pandemic preparedness planning is done at the national level. While national policies aimed at improving chronic risk factors like obesity and smoking and comorbidities like diabetes and COPD will undoubtedly improve health subnationally, this research demonstrates that heterogeneities within each country will persist, even though standardization can minimize these when compared to national differences. Considerations into heterogeneous risk profiles within a country, such as health care coverage and health facility access, will help to prioritize limited resources to more vulnerable and harder to reach populations. We additionally acknowledge the importance of trust in pandemic preparedness and response, with higher trust in government officials or other people likely leading to higher vaccine uptake and mandate adherence. With limited trust data available subnationally, the necessity of further research into measures of local trust cannot be understated. This current analysis was limited to two

countries heavily burdened by COVID-19; expanding this research to all subnational locations globally can help inform these relationships at a more global scale. Additionally, focusing efforts even more locally, such as the county level, may help identify additional drivers of subnational heterogeneities in COVID-19 outcomes.

List of Tables and Figures

TABLE 1: STAGE 1 AND STAGE 2 COVARIATES USED IN NATIONAL ANALYSIS AND AVAILABILITY AND PROVENANCE AT THE SUBNATIONAL LEVEL IN BRAZIL AND THE UNITED STATES

Short Name	Covariate Name	Available for US States?	Data Source	Available for Brazil states?	Data Source	Notes
Stage 1						
Pneumonia RR	Relative risk of death from pneumonia divided by the average risk of death from pneumonia	Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	
Age	Age structure of the population (5 year age bins)	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Altitude	% of population living below 100m	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Population Density	% of population living above 1,000 people / km^2	Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	
Air Pollution	PM 2.5 air pollution concentration (mg/m^3)	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Bats	Average number of Beta-Coronavirus host bat species in a given location	Y	IUCN[63] & Verena Consortium[64]	Y	IUCN[63] & Verena Consortium[64]	See additional methods in appendix 4.1

Smoking Prevalence	Age-standardized tobacco smoking prevalence	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
GDP	Gross Domestic Product per Capita	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
COPD	Age-standardized COPD prevalence	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Cancer	Age-standardized cancer prevalence	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
BMI	Population-adjusted body mass index	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Stage 1 - new inclusions						
Variant prevalence	Prevalence of variants of concern Delta and Omicron	Y	Forecasting the trajectory of the COVID-19 pandemic into 2023 under plausible variant and intervention scenarios: a global modelling study[117]	Y	Forecasting the trajectory of the COVID-19 pandemic into 2023 under plausible variant and intervention scenarios: a global modelling study[117]	
Stage 2 - considered from national analysis						
UHC	Universal Health Coverage	Y	Global Burden of Disease Study 2019[62], Measuring Universal Health Coverage[66]	Y	Global Burden of Disease Study 2019[62], Measuring Universal Health Coverage[66]	
Mobility	Largest % change from a January 2020 baseline	Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	

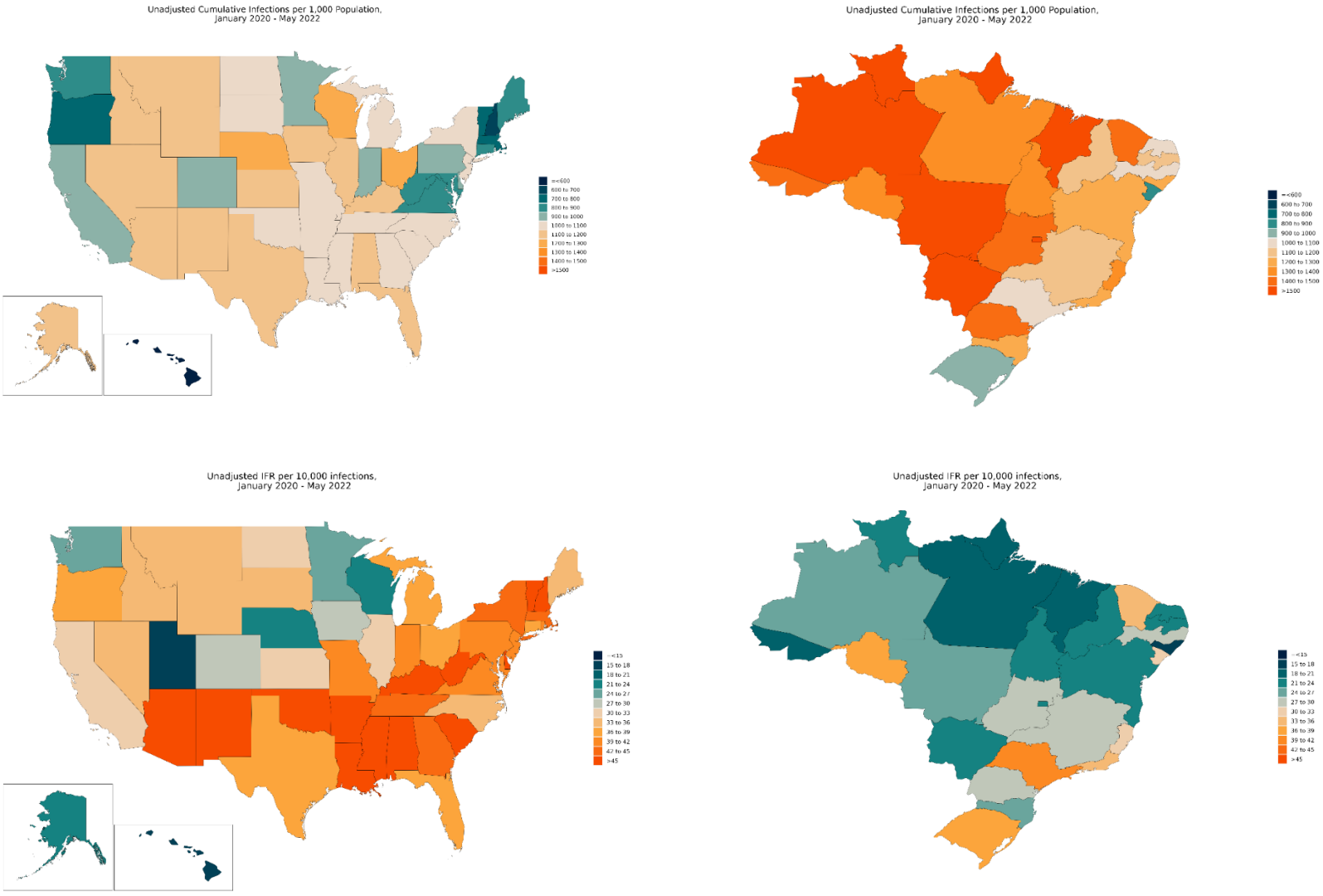
Mandates	Mean Fraction of mandates on over period	Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	
Testing	Mean Testing Per Capita over the time period	Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	
Vaccine Coverage	Maximum at least one dose vaccine coverage over the time period	Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	Only relevant for January 2020 - May 2022
Interpersonal Trust	Trust in Other People	Y	Main analysis: World values survey wave 7[75] Sensitivity analysis: Harvard Cooperative Election Study, group modules[122–125,142,143]	Y	World values survey wave 7[75]	See additional methods in appendix 4.3 & 4.4
Trust in Science	Trust in Science	Y	Sensitivity analysis: Harvard Cooperative Election Study, group modules[142,144,145]	N	Not available at Brazilian subnational level	See additional methods in appendix 4.4
Trust in government	Trust in one's government	Y	Main analysis: World values survey wave 7[75] Sensitivity analysis: Harvard Cooperative Election Study, group modules[122,143,146–151]	Y	World values survey wave 7[75]	See additional methods in appendix 4.3 & 4.4

Government Corruption	Perceived governmental corruption	N		N		
Preparedness	OVERALL	Y	Modeled estimate	Y	Modeled estimate	See methods section and appendix 4.2 for construction
	PREVENT	Y	Measles containing vaccine coverage[62], DTP3 vaccine coverage[62]	Y	Measles containing vaccine coverage[62], DTP3 vaccine coverage[62]	Based on: 1) Component 1.6: Immunization
	DETECT	N	Not available at subnational level	N	Not available at subnational level	
	RESPONSE	N	Not available at subnational level	N	Not available at subnational level	
	HEALTH	Y	Number of beds at baseline per capita, Number of ICU beds at baseline per capita, Number of doctors per capita, Number of nurses and midwives per capita[62] Global maps of travel time to healthcare facilities[119]	Y	Number of beds at baseline per capita, Number of ICU beds at baseline per capita, Number of doctors per capita, Number of nurses and midwives per capita[62] Global maps of travel time to healthcare facilities[119]	Based on: 1) Component 4.1: Health capacity in clinics, hospitals, and community care 2) Component 4.4: Healthcare access

	NORMS	N	Not relevant at subnational level	N	Not relevant at subnational level	
	RISK	Y	Percent residence: urban[62] Healthcare Access and Quality Index[62,141] Improved sanitation access[62,152] Improved water access[62,152]	Y	Percent residence: urban[62] Healthcare Access and Quality Index[62,141] Improved sanitation access[62,152] Improved water access[62,152]	Based on: 1) Component 6.4: Environmental Risks 2) Component 6.5: Public health vulnerabilities
Gini Index	Income Inequality	Y	GINI Index[153,154]	Y	GINI Index[155]	
HAQI	Healthcare Access and Quality Index	Y	Global Burden of Disease Study 2019[62], Healthcare Access and Quality Index[141]	Y	Global Burden of Disease Study 2019[62], Healthcare Access and Quality Index[141]	
Electoral Populism	% voted for populist leader in prior presidential election (Trump / Bolsonaro)	Y	Percent Trump vote by state in 2016[104]	Y	Percent Bolsonaro vote by state in 2018[156,157]	
State Fragility	State Fragility Index	N	Not relevant at subnational level	N	Not relevant at subnational level	
Index of Federalism	Index of Federalism in a location	N	Not relevant at subnational level	N	Not relevant at subnational level	
EDI	Electoral Democracy Index	N	Not relevant at subnational level	N	Not relevant at subnational level	
Government Effectiveness	Effectiveness of government services	N	Not available at subnational level	N	Not available at subnational level	

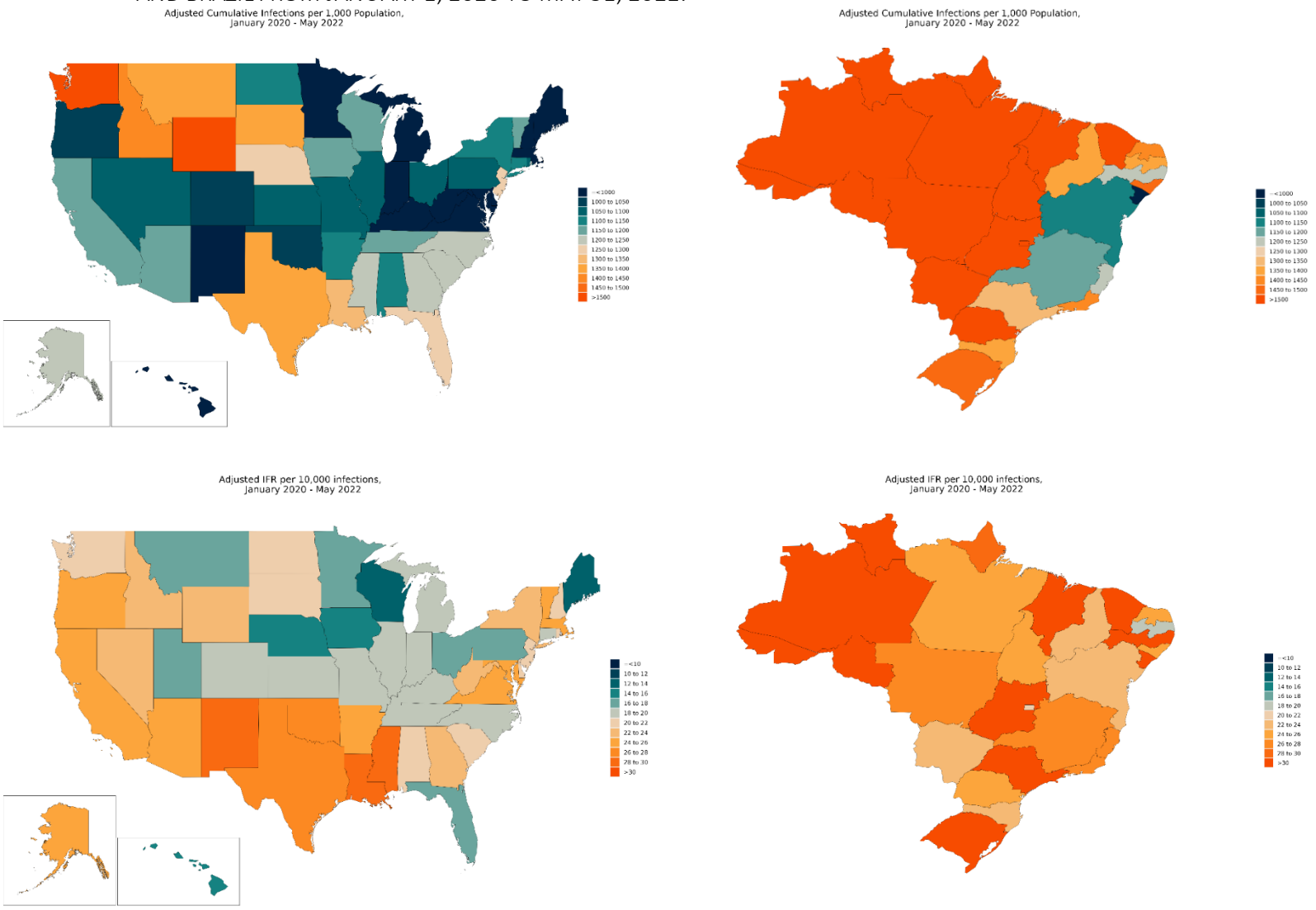
Beds per Capita	Number of hospital beds per capita before start of the pandemic	Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Health spending per capita	Total Health Expenditure Per Capita	N	Not available at subnational level	N	Not available at subnational level	
Government health spending per capita	Government Health Spending Per Capita	N	Not available at subnational level	N	Not available at subnational level	
Stage 2 - new variables						
Sociodemographic Index		Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Vaccine hesitancy		Y	Modeling COVID-19 scenarios for the United States[43]	Y	Modeling COVID-19 scenarios for the United States[43]	
Under 5 mortality		Y	Global Burden of Disease Study 2019[62]	Y	Global Burden of Disease Study 2019[62]	
Health care accessibility	% of grid cells within 2 hours of health facility	Y	Global maps of travel time to healthcare facilities[119]	Y	Global maps of travel time to healthcare facilities[119]	See methods section and appendix 4.5 for details

FIGURE 1: UNADJUSTED INFECTIONS PER 1,000 POPULATION AND IFR PER 10,000 INFECTIONS FOR THE USA AND BRAZIL FROM JANUARY 1, 2020 TO MAY 31, 2022.



A) Unadjusted infections per 1,000 population in the United States, January 1, 2020 through May 31, 2022; B) Unadjusted infections per 1,000 population in Brazil, January 1, 2020 through May 31, 2022; C) Unadjusted IFR per 10,000 infections in the United States, January 1, 2020 through May 31, 2022; D) Unadjusted IFR per 10,000 infections in Brazil, January 1, 2020 through May 31, 2022.

FIGURE 2: ADJUSTED INFECTIONS PER 1,000 POPULATION AND IFR PER 10,000 INFECTIONS FOR THE USA AND BRAZIL FROM JANUARY 1, 2020 TO MAY 31, 2022.



A) Adjusted infections per 1,000 population in the United States, January 1, 2020 through May 31, 2022; B) Adjusted infections per 1,000 population in Brazil, January 1, 2020 through May 31, 2022; C) Adjusted IFR per 10,000 infections in the United States, January 1, 2020 through May 31, 2022; D) Adjusted IFR per 10,000 infections in Brazil, January 1, 2020 through May 31, 2022.

TABLE 2A: BETA ESTIMATES OF STAGE 1 RESULTS BRAZIL VS US, JANUARY 1 2020 – MAY 31, 2022

	Infections		IFR	
	Brazil	**US**	**Brazil**	**US**
Altitude	0.0116 (-0.1309 - 0.1588)	*-0.0851 (-0.1452 - -0.0293)*	-	-
GDP	-0.0025 (-0.3789 - 0.3404)	*-0.7136 (-1.0391 - -0.3734)*	-0.0817 (-0.4224 - 0.3949)	-0.0856 (-0.6398 - 0.4815)
Population Density	-0.2637 (-0.8336 - 0.2643)	*0.0759 (0.0148 - 0.1345)*	-0.1703 (-0.9135 - 0.4106)	-0.0753 (-0.1927 - 0.0377)
Coronavirus Bat Proxy	*1.0968 (0.0551 - 2.1969)*	*0.1634 (0.0222 - 0.2887)*	0.4279 (-0.9885 - 1.7476)	0.1509 (-0.1198 - 0.3795)
BMI	-	-	0.2954 (-0.5267 - 0.9763)	-0.1479 (-0.6121 - 0.3972)
Air pollution	-	-	-0.0307 (-0.1778 - 0.1301)	0.1424 (-0.1037 - 0.3726)
Cancer prevalence	-	-	-0.7447 (-1.737 - 0.1145)	0.4029 (-0.5677 - 1.144)
COPD prevalence	-	-	0.0345 (-1.1587 - 1.1797)	0.5125 (-0.4756 - 1.2966)
Smoking prevalence	-	-	0.0377 (-0.3278 - 0.4495)	0.0866 (-0.1966 - 0.3242)

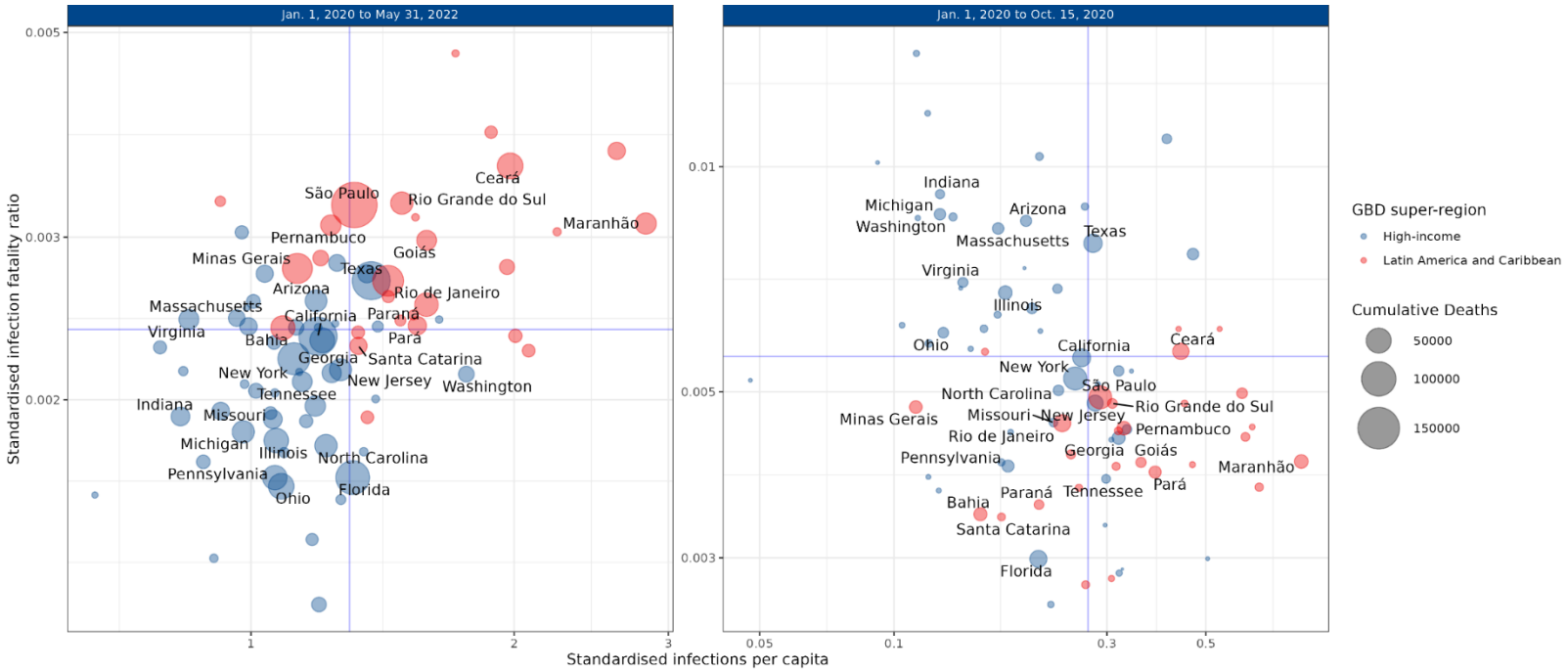
Italicized entries are significant at the alpha = 0.05 level.

TABLE 2B: BETA ESTIMATES OF STAGE 1 RESULTS BRAZIL VS US, JANUARY 1 2020 – OCTOBER 15, 2020

	Infections		IFR	
	Brazil	**US**	**Brazil**	**US**
Altitude	0.1678 (-0.0792 - 0.507)	-0.0876 (-0.2309 - 0.061)	-	-
GDP	-0.1818 (-0.713 - 0.3389)	*-1.6775 (-2.6998 - -0.5984)*	-0.3205 (-0.8314 - 0.0857)	0.4549 (-0.4456 - 1.2485)
Population Density	-0.2498 (-1.293 - 0.7486)	*0.3134 (0.132 - 0.4984)*	0.2207 (-0.3443 - 0.8317)	*-0.2336 (-0.3999 - -0.0557)*
Coronavirus Bat Proxy	*3.8396 (2.1703 - 5.7513)*	*0.5044 (0.1232 - 0.8885)*	-0.8472 (-1.9359 - 0.7446)	*0.4287 (0.0957 - 0.9771)*
BMI	-	-	0.3544 (-0.1946 - 0.9653)	-0.2411 (-1.3026 - 1.0298)
Air pollution	-	-	-0.0095 (-0.1862 - 0.1303)	0.017 (-0.3697 - 0.3679)
Cancer prevalence	-	-	-0.566 (-1.3511 - 0.1675)	*2.92 (1.0898 - 4.2476)*
COPD prevalence	-	-	0.2992 (-0.8623 - 1.6128)	-0.6218 (-2.3484 - 0.6422)
Smoking prevalence	-	-	-0.1586 (-0.48 - 0.2243)	-0.084 (-0.4858 - 0.3736)

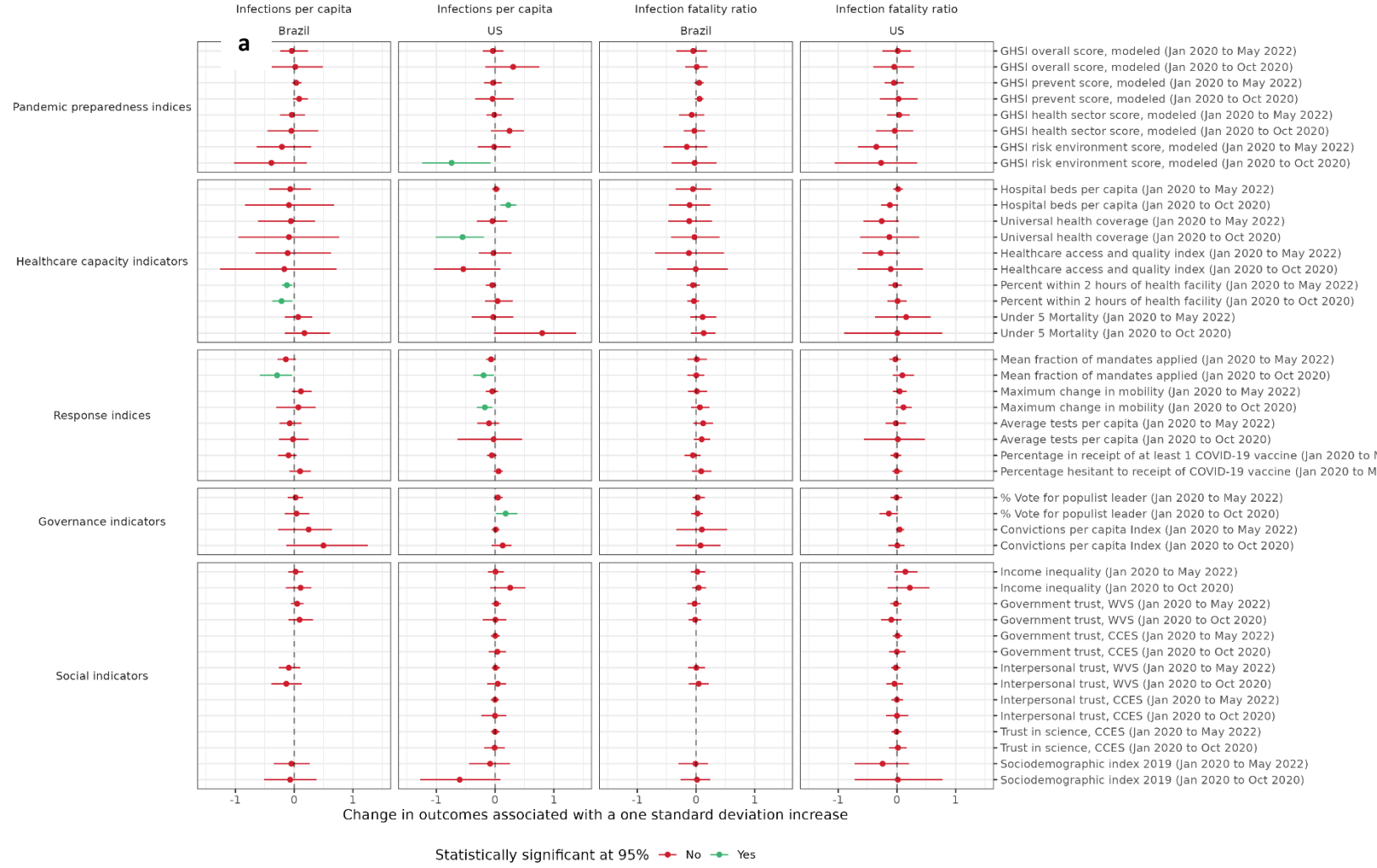
Italicized entries are significant at the alpha = 0.05 level.

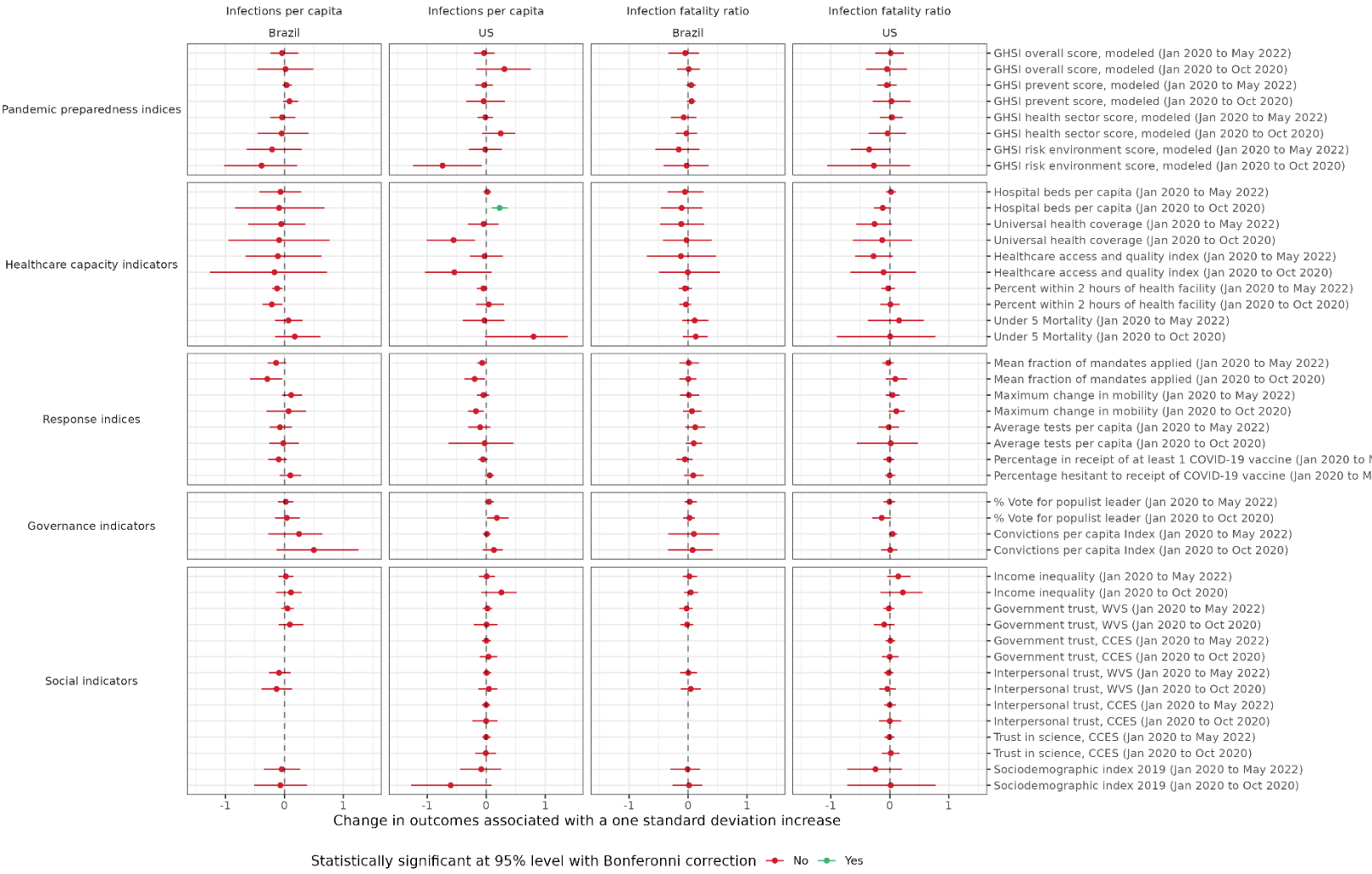
FIGURE 3: STANDARDIZED INFECTIONS PER CAPITA AND STANDARDIZED INFECTION-FATALITY RATIOS



The graph on the left shows the relationship between adjusted infections per capita and adjusted infection-fatality ratios from January 1, 2020, to May 31, 2022. The graph on the right shows the relationship between adjusted infections per capita and adjusted infection-fatality ratios from January 1, 2020, to October 15, 2020. The size of each circle represents the magnitude of cumulative deaths.

FIGURE 4: ASSOCIATIONS BETWEEN KEY PREPAREDNESS, CAPACITY, GOVERNANCE, RESPONSE, AND SOCIAL INDICATORS AND INFECTION RATES AND IFR WITHOUT MULTIPLE HYPOTHESIS CORRECTION (A) AND WITH BONFERRONI CORRECTION (B)





For each figure, the two graphs on the left show estimated associations between indicators of key contextual factors (pandemic preparedness indices; health-care capacity indicators; governance indicators; response indices; and social indicators) and infections per capita for each Brazil and the United States. The two graphs on the right show estimated associations between key contextual factors and the infection-fatality ratio for each Brazil and the United States. Red indicates the association is not significant while green indicates the association is significant at a 95% confidence interval both without (a) and with (b) a Bonferroni correction.

SUPPLEMENTAL INFORMATION FOR CHAPTER 3

This appendix provides further methodological and supplementary results for "An exploratory analysis of improved COVID-19 outcomes in subnational locations across two countries: the United States and Brazil, January 2020 through May 2022."

Section 1: Abbreviations

BMI: body-mass index

COVID-19: coronavirus disease 2019

JEE: Joint External Evaluation

GBD: Global Burden of Diseases, Injuries, and Risk Factors Study

GHS Index: Global Health Security Index

HAQ Index: Healthcare Access and Quality Index

IFR: infection-fatality ratio

IHR: infection-hospitalisation ratio

IDR: infection-detection ratio

IHME: Institute for Health Metrics and Evaluation

PCA: principal component analysis

SARS-CoV2: severe acute respiratory syndrome coronavirus 2
WHO: World Health Organization

UHC effective coverage index: universal health coverage effective coverage index

UI: uncertainty interval

Section 2: Additional tables

2.1 Table 1: GATHER

Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Summary. Main Text: Introduction, Methods (Overview).
2	List the funding sources for the work.	Summary. Main Text: Acknowledgements and declarations.
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Main Text: Methods. Supplementary Appendix, Section 4
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Main Text: Methods.
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Main text: Table 1. Main characteristics of data, metadata, and/or NIDs available through: http://ghdx.healthdata.org

		/ (upon publication)
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Main text: Limitations section.
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	N/A
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Available through: http://ghdx.healthdata.org / (upon publication)
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Main text: Methods
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing, data adjustments and weighting of data sources, and mathematical or statistical model(s).	Main text: Methods
11	Describe how candidate models were evaluated and how the final model(s) were selected.	N/A
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	N/A
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main Text: Methods
14	State how analytic or statistical source code used to generate estimates can be accessed.	Available through: http://ghdx.healthdata.org / (upon publication)
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Available through: http://ghdx.healthdata.org / (upon publication)

16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Available through: http://ghdx.healthdata.org/ (upon publication)
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Main Text: Discussion
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Main Text: Limitations

Section 3: Additional figures

Section 3.1 Maps of unadjusted and adjusted infections and IFR for Brazil and United States, January 1, 2020 through October 15, 2020

Figure 3.1.1 Unadjusted infections per 1,000 population

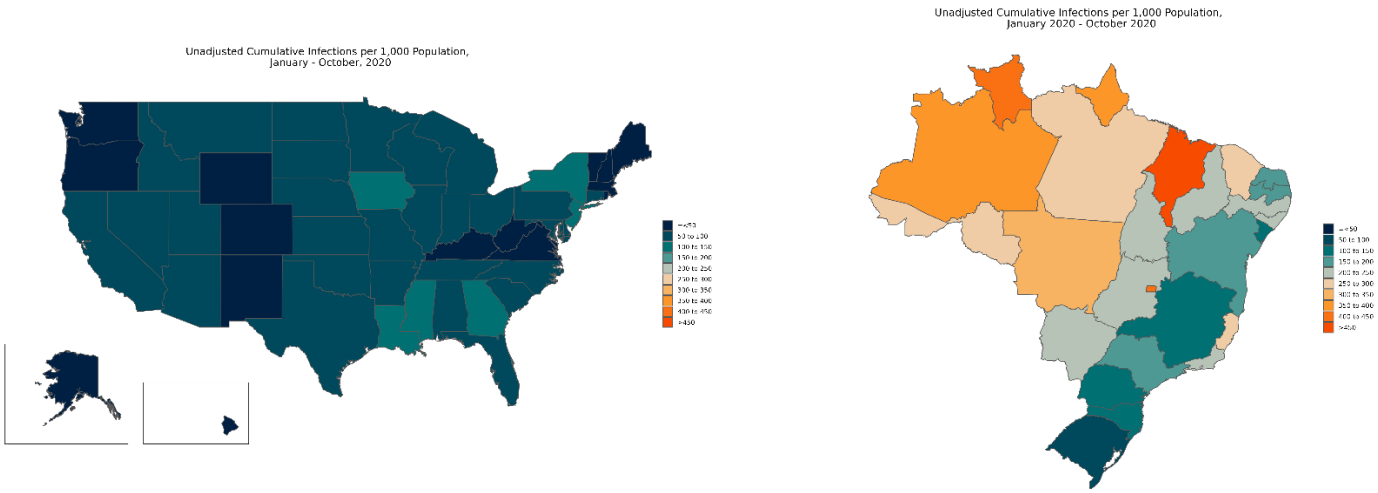
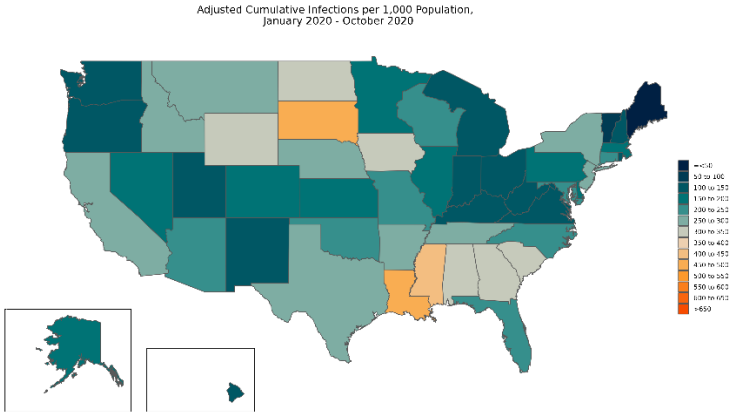


Figure 3.1.2 Adjusted infections per 1,000 population



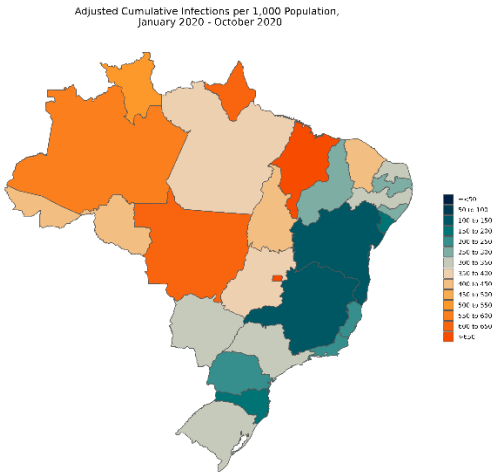
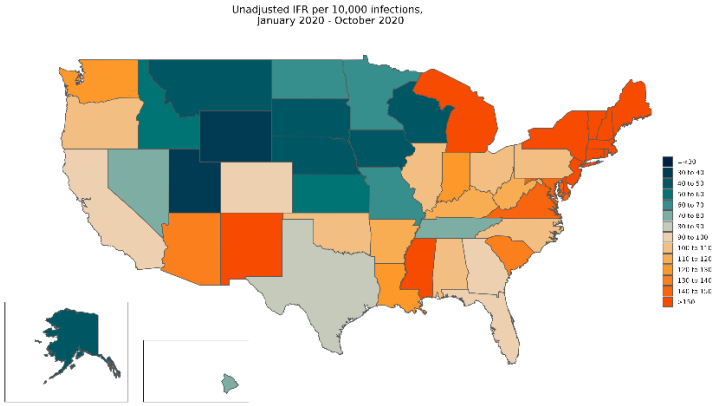


Figure 3.1.3 Unadjusted IFR per 10,000 infections



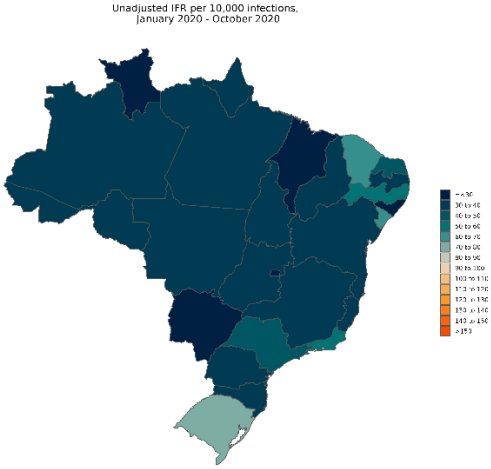
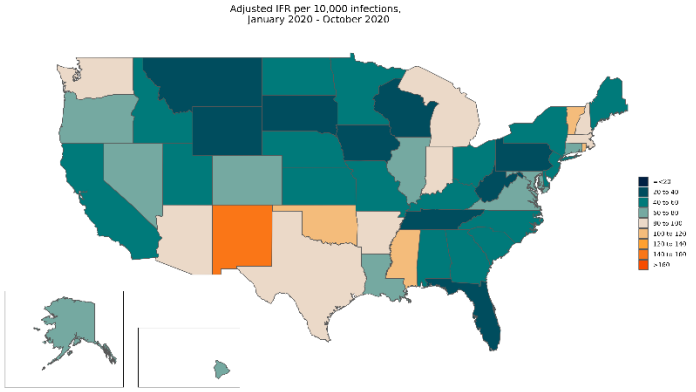
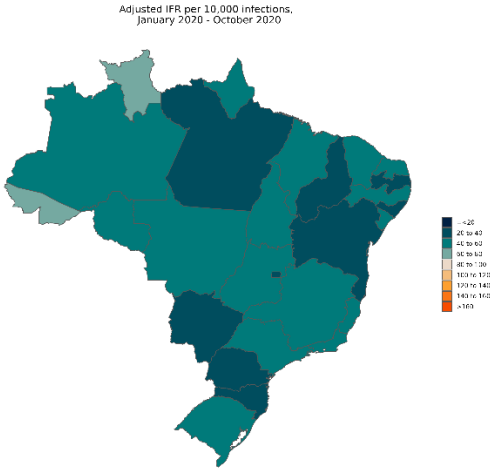


Figure 3.1.4 Adjusted IFR per 10,000 infections





Section 3.2 Correlations between CDC FY2020 funding and health sector preparedness score, Healthcare Access and Quality Index (HAQI), health care accessibility, and density

Figure 3.2.1 CDC FY2020 state level spending versus modeled GHSI Health Sector Score (see section 4.2)

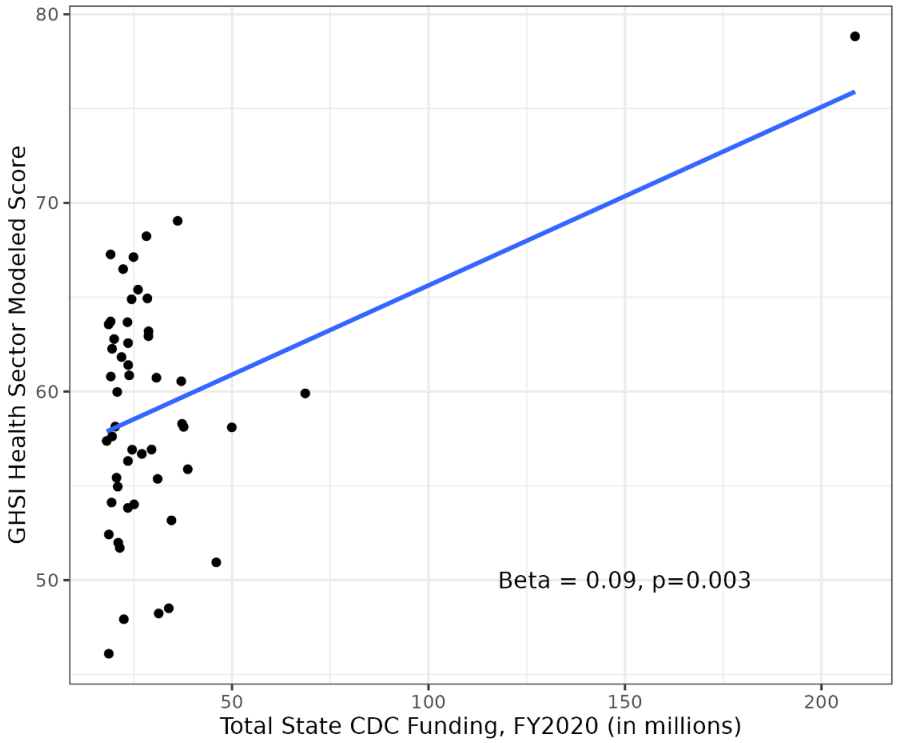


Figure 3.2.2 CDC FY2020 state level spending versus percentage of the population living at a density greater than 1000 people per km

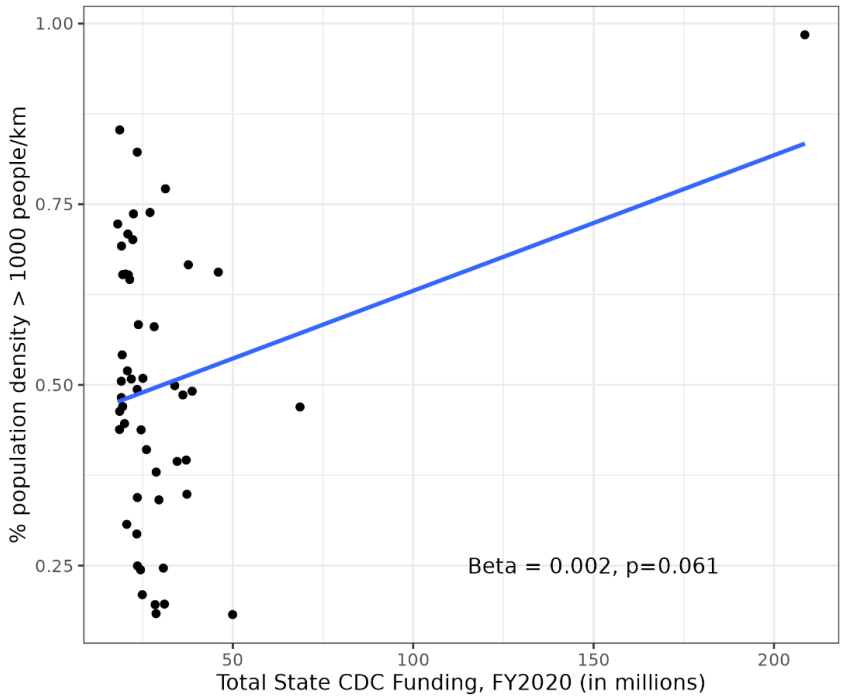


Figure 3.2.3 CDC FY2020 state level spending versus % of the population within 2 hours of a health facility

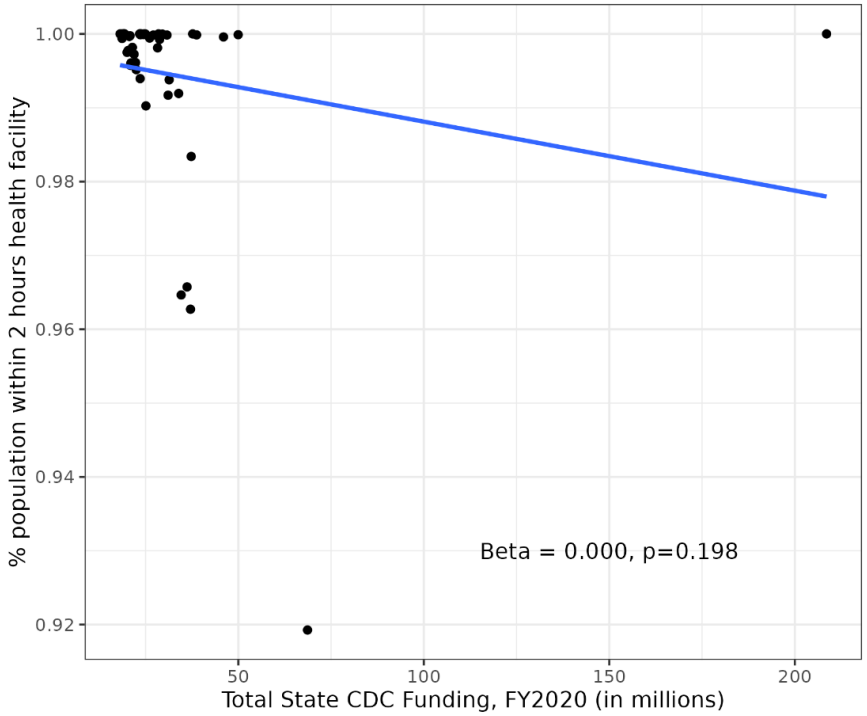


Figure 3.2.4 CDC FY2020 state level spending versus mean HAQI score

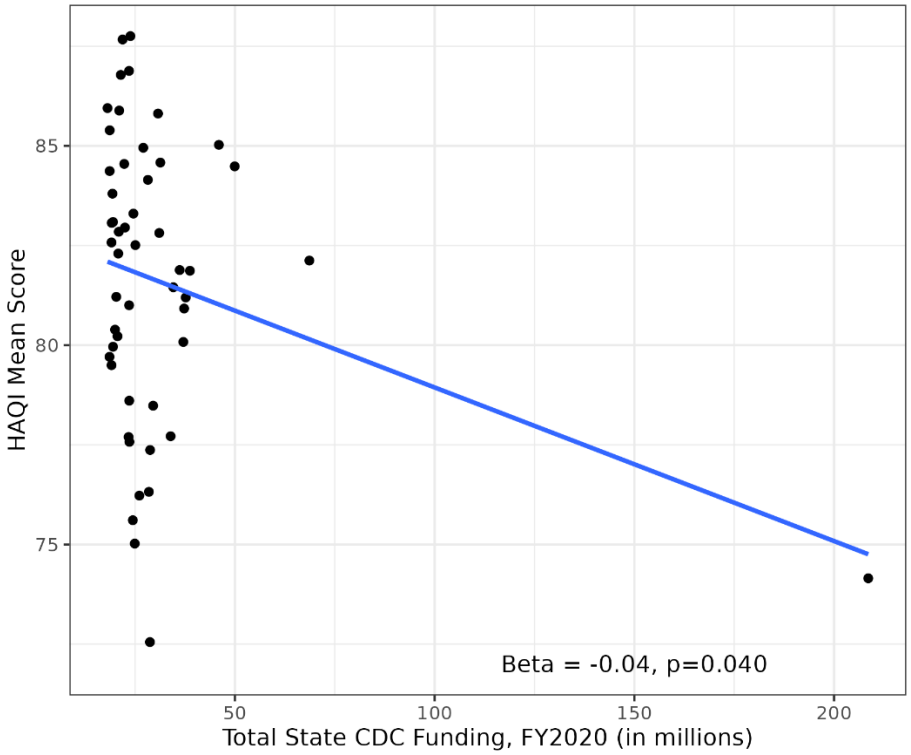
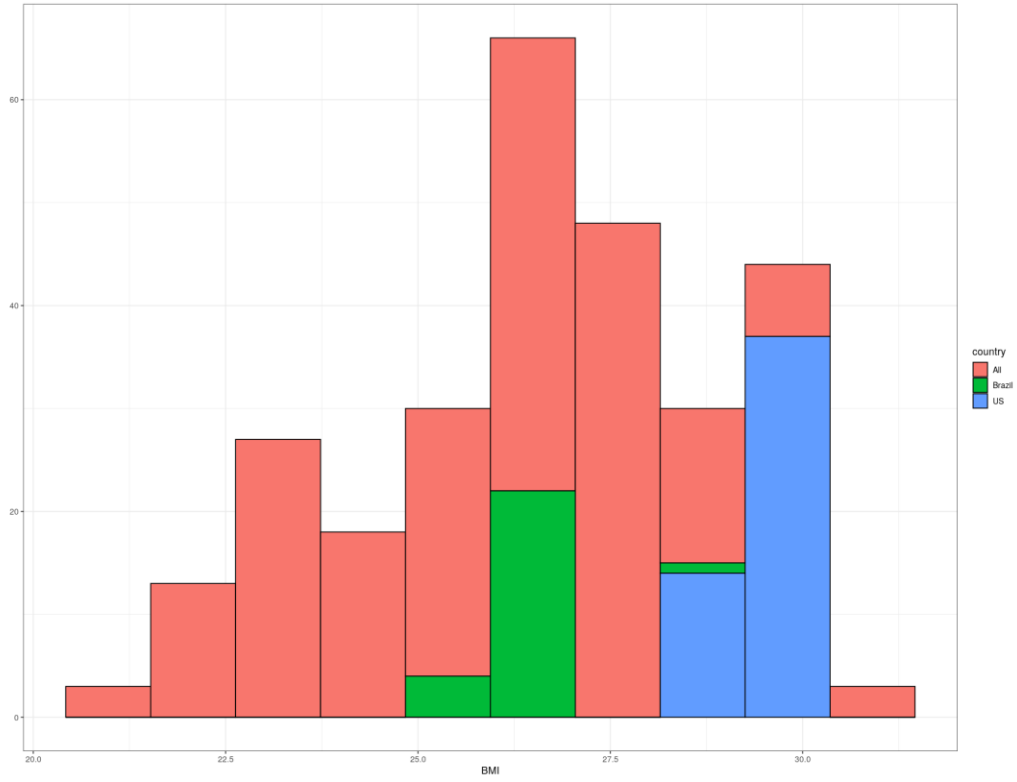


Figure 3.3 Histogram of BMI for all countries (pink) versus Brazil (green) and US (blue) only



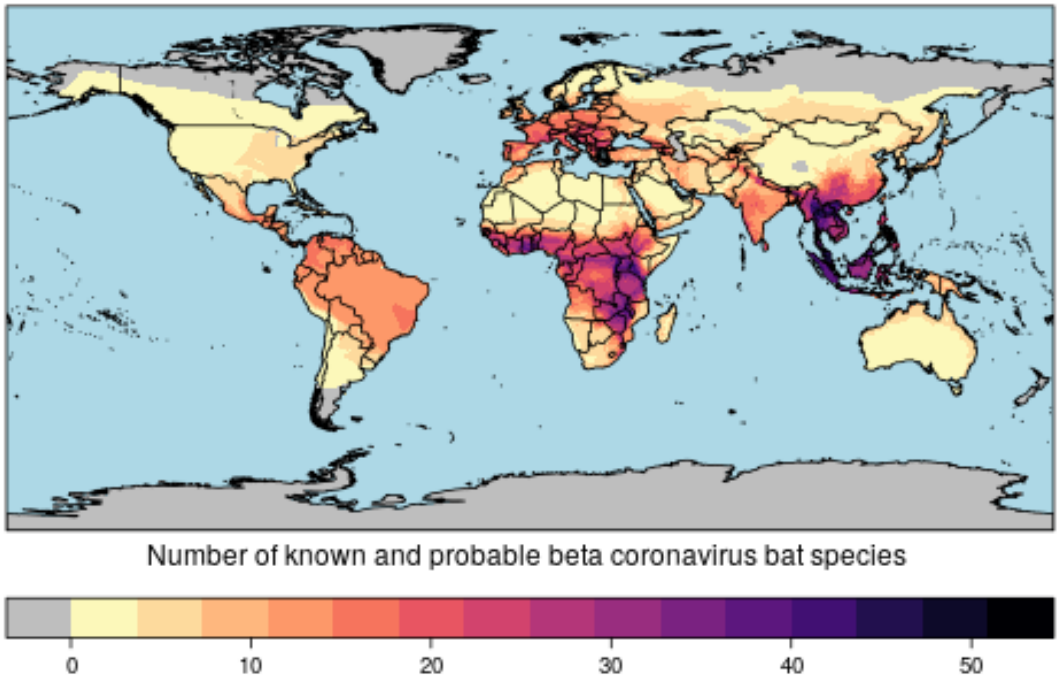
Section 4: Additional methods

Section 4.1 Proxy for previous exposure to beta coronaviruses

Literature suggests that possible previous exposure to SARS, MERS, or other beta coronaviruses may provide cross-immunity to SARS-CoV2.[79–81] In order to capture previous exposure to other beta coronaviruses, we obtained a list of possible bat hosts of beta coronaviruses produced by authors at the Verena Consortium.[64] These authors used an ensemble model of seven other statistical models (network- and trait-based models) to predict possible bat beta coronavirus hosts in addition to known bat hosts. This list of 300+ species was then compared against known species ranges, determined by experts, using the IUCN Red List of Threatened Species.[63] Of the 448 known and probable species extracted from the publication by Becker et al, [64] 441 were able to be retrieved from the IUCN red list, allowing for possible changes in species naming convention.

Following the extraction of a geographical range for each species, each range was converted to a 1-km by 1-km raster in R using the raster package. Ranges were then layered one on top of the other, interpolated to a 5-km by 5-km grid cell range for processing times using the average of all cells in that grid. All ranges were then summed together to get the estimated number of bat species per grid cell, as seen in Figure 1 below.

Figure 4.1.1: Number of known and probable beta coronavirus bat species per grid cell



The number of species per grid cell were then averaged over the first and second administrative region in agreement with our COVID-19 units of analysis.

Section 4.2 Mapping GHSI components to variables and estimating subnational preparedness

We identified data available for both Brazil and the United States for three of the six GHSI categories: Prevent, Health Systems and Risks. Each of the three categories is built from multiple sub-sections with specific indicators, all outlined in the 2021 GHSI methodology.[6] Each of the sub-sections used and the indicator are outlined in Table 4.2.1 below.

Table 4.2.1: GHSI Components mapped to subnational data, Brazil and United States

Category	GHSI Subsection	Indicator
PREVENT	Based on Component 1.6: Immunization	Measles vaccine coverage DTP3 vaccine coverage
HEALTH SYSTEM	Based on: Component 4.1: Health capacity in clinics, hospitals, and community care centers. & Component 4.4: Healthcare access	Number of beds at baseline per capita Number of ICU beds at baseline per capita Number of Doctors per capita at baseline Number of nurses and midwives per capita at baseline Average travel time to health facilities
RISK ENVIRONMENT	Based on: Component 6.4: Environmental Risks & Component 6.5: Public Health Vulnerabilities	Percent population with urban residence Healthcare Access and Quality Index (HAQI) score Percent population with Improved Sanitation Access Percent population with Improved Water Access

For the Prevent category, we obtained the estimates of 2019 measles containing vaccine coverage and 2019 Diphtheria-Tetanus-Pertussis (DTP3) for all GHSI locations. We extracted 2019 Bacille Calmette-Guérin (BCG) coverage as well, though BCG was highly correlated with MCV and DTP3 and omitted from further analyses. We modeled the national estimates for GHSI Category 1 linearly against MCV and DTP3. Using the estimated coefficients for each MCV (27.276) and DTP3 (8.233) we then predicted out a GHSI Prevent Score for each subnational location using each subnational location's MCV and DTP3 scores.

For the Health System category, we used estimates of hospital beds, ICU beds, Doctors, and Nurses and Midwives from 2019 and divided them by 2019 population to get per-capita estimates. We used the motorized travel time to health care facilities 2020 layer produced by Weiss et al.[119] and summarized the mean travel times per national and subnational location. Notably, Greenland was excluded from the national analyses as its travel times were a strong outlier (mean travel time in Greenland was over 7000 minutes, while the global mean was 207 minutes). We again constructed a linear model and used the coefficients for hospital beds (-775.70), ICU beds (10980.00), nurse and midwives (0.142), doctors (0.141), and travel time to health facilities (-0.002) along with subnational data to estimate one Health System score for each Brazilian and American subnational location.

For the Risk Environment category, we used the 2019 estimates of the percent of the population in urban residence, the mean HAQI score, the percent of the population with access to improved sanitation, and the percent with access to improved water in our linear model. The coefficients estimated at the national level were -2.383 for percentage in urban residence, 5.516 for the percentage with access to improved sanitation, 15.406 for the percentage with access to improved water, and 0.462 for HAQI mean.

Lastly, to get one overall estimate of preparedness, we used our three modeled national category scores to get a predicted overall GHSI score from just these three categories. The coefficients estimated at the national level were 0.303 for Prevent, 0.333 for Health Sector, and 0.187 for Risk Environment. These coefficients were used to estimate one overall GHSI score at the subnational level in Brazil and the United States. Table 4.2.2 below notes the three category scores and estimated overall GHSI score by subnational location.

Table 4.2.2: Estimated Prevent, Health Sector, Risk Environment and Overall GHSI score by subnational location.

Location	Prevent Score	Health Sector Score	Risk Environment Score	Predicted Overall Score
Alabama	34.41	67.13	67.35	54.81
Alaska	31.86	59.90	70.55	52.22
Arizona	34.19	54.96	70.14	51.20
Arkansas	34.11	64.89	67.72	54.04
California	34.10	52.42	71.09	50.51
Colorado	33.05	66.49	71.02	54.87
Connecticut	34.95	53.83	72.19	51.44
Delaware	34.09	55.88	70.01	51.46
District of Columbia	34.00	78.83	65.48	58.23
Florida	33.46	62.26	70.21	53.43
Georgia	34.29	56.92	68.51	51.59
Hawaii	32.81	48.23	71.30	48.76
Idaho	33.75	54.01	70.52	50.82

Illinois	34.85	60.79	70.25	53.37
Indiana	33.31	63.55	69.16	53.62
Iowa	34.56	56.92	71.11	52.15
Kansas	32.94	59.98	70.24	52.52
Kentucky	34.64	62.57	68.88	53.64
Louisiana	33.64	63.19	68.17	53.41
Maine	34.17	55.37	71.30	51.55
Maryland	34.31	58.13	69.49	52.17
Massachusetts	35.20	60.86	72.45	53.91
Michigan	33.94	57.62	69.16	51.83
Minnesota	34.67	61.83	72.73	54.12
Mississippi	32.78	62.93	66.39	52.74
Missouri	32.56	62.78	69.46	53.19
Montana	33.64	58.29	70.22	52.16
Nebraska	34.29	68.23	71.18	55.86
Nevada	32.01	56.31	69.17	50.81
New Hampshire	34.96	60.73	72.40	53.78
New Jersey	34.14	57.38	71.37	52.22
New Mexico	33.45	48.51	68.27	48.48
New York	34.32	56.69	71.03	51.99
North Carolina	33.71	55.43	69.56	51.11
North Dakota	34.13	69.04	70.49	55.95
Ohio	33.66	67.27	68.94	54.92
Oklahoma	33.71	65.40	67.74	54.09
Oregon	33.73	51.99	71.74	50.37
Pennsylvania	34.18	63.71	70.38	54.16
Rhode Island	35.29	50.94	71.17	50.39
South Carolina	33.99	61.40	68.44	52.97
South Dakota	33.79	60.55	69.71	52.86
Tennessee	33.62	63.67	68.41	53.61

Texas	34.23	58.14	69.47	52.15
Utah	33.60	47.93	70.15	48.68
Vermont	34.06	58.10	72.17	52.59
Virginia	34.89	54.12	70.88	51.27
Washington	34.00	51.71	72.04	50.42
West Virginia	33.72	64.94	68.18	54.02
Wisconsin	34.47	46.10	71.36	48.56
Wyoming	33.33	53.17	70.48	50.41
Acre	32.69	27.04	51.82	38.02
Alagoas	34.86	29.74	50.83	39.40
Amazonas	36.42	28.69	53.22	39.97
Amapá	32.26	28.67	53.68	38.78
Bahia	28.69	31.92	53.04	38.66
Ceará	34.49	29.84	54.15	39.94
Distrito Federal	33.75	67.23	59.90	53.25
Espírito Santo	33.46	42.03	55.91	44.02
Goiás	33.63	37.82	55.13	42.52
Maranhão	32.01	27.71	49.36	37.58
Minas Gerais	31.61	39.02	57.02	42.66
Mato Grosso do Sul	30.19	37.36	54.81	41.26
Mato Grosso	36.41	38.00	55.15	43.43
Pará	27.31	26.71	51.64	36.25
Paraíba	29.08	31.71	54.72	39.03
Paraná	31.96	41.99	56.33	43.63
Pernambuco	32.39	36.46	52.69	41.24
Piaui	31.89	28.12	52.66	38.30
Rio de Janeiro	34.92	53.03	55.73	48.09
Rio Grande do Norte	33.23	35.08	55.95	41.64
Rondônia	34.71	34.09	52.10	41.04
Roraima	34.48	28.26	54.36	39.45

Rio Grande do Sul	34.22	40.91	58.50	44.36
Santa Catarina	35.10	36.10	58.74	43.07
Sergipe	34.68	32.77	53.64	40.88
São Paulo	30.06	45.04	58.10	44.40
Tocantins	34.80	32.05	53.38	40.62

Section 4.3 Modeling interpersonal trust and governmental trust from World Values Survey

We used national-level survey data from the World Values Survey Wave 7. These data were used at the national level in the national-level paper published in 2022.[75] Data were available at the state level in each Brazil and the United States, though were not powered to provide estimates at that level. For interpersonal trust, we used Q57 and coded all answers of 'Most people can be trusted' as 'trust', while answers of 'Need to be very careful' as 'no trust'. For government trust, we coded all answers of 'A great deal' and 'Quite a lot' as 'trust' when asked how much confidence the respondent has in the government (Q71), and 'Not very much' and 'None at all' as 'no trust'.

Population estimates for 2019 for each location were obtained, and we constructed weights of the population over number of respondents per location to get a population-weighed estimate. Then, using survey design methods in R and a simple random weighed sample, we estimated the mean trust for each state as well as the survey error. To get uncertainty estimates for each location, we then created 100 random samples from random normal distribution, using the estimated mean as the mean and the survey error as the standard error. The mean was used as our point estimate, while the 2.5th percentile and 97.5th percentile formed our confidence interval. In cases where the sample sizes were small, confidence intervals falling outside of the 0 to 1 range were recoded. Similarly, states with no error (Tocantins, Sergipe, Hawaii, North Dakota) and therefore no confidence intervals were recoded to have an interval from 0 to 1 to account for the small sample size.

Section 4.4 Modeling interpersonal trust, governmental trust, and trust in science in the United States from Harvard CCES

We used Harvard Cooperative Election Study (CCES) modules[158] asking questions on trust in the federal government, trust in scientists or the scientific community, and trust in other people to get estimates of trust in government, trust in science, and interpersonal trust at the state level in the United States alone. For government trust, we focused exclusively on 2018 modules as partisanship is heavily influential on trust in the government, whereas for science and interpersonal trust, we looked at all modules between 2016 and 2020. A comprehensive search of the different modules was conducted, identifying 15 modules from 2018 on government trust, 10 surveys on interpersonal trust, and 7 modules on trust in scientists.

Of the 15 government trust modules, we excluded questions that asked about presidential or congressional trust, modules that asked about trust in the government on a scale from 0 to 10 (or 0 to 100), and modules that did not provide an option of "Never" or "Almost Never" for the question for the federal government "How much of the time can you trust the following groups to do what is right?". Following these criteria, 8 modules remained, with one survey having both pre-election and post-election questionnaires, resulting in 9 module questionnaires of each 1000 participants. [122,143,146–151] Each survey question was first recoded into a binary variable of trust (1) versus no trust (0) in the federal government with answers of "Always", "Almost always", "Most of the time" and "About half of the time" coded as

trust while “Never”, “Almost never”, “Hardly ever” or “Some of the time”, were coded as no trust. These 9 binary questions were then combined into one single variable of trust versus no trust with 8619 respondents after removing non-respondents and those without survey weights. Using the survey weights (‘teamweight’) provided in each module, we then used the Survey package in R with a weighted simple random sample design to estimate the mean trust for each state as well as the survey error. To get uncertainty estimates for each location, we then created 500 random samples from random normal distribution, using the estimated mean as the mean and the survey error as the standard error. The mean was used as our point estimate, while the 2.5^{th} percentile and 97.5^{th} percentile formed our confidence interval. In cases where the sample sizes were small, confidence intervals falling outside of the 0 to 1 range were recoded. Similarly, states with no error (Alaska, Hawaii, North Dakota) and therefore no confidence intervals were recoded to have an interval from 0 to 1 to account for the small sample size.

We replicated these methods for both trust in scientists and trust in other people. For trust in scientists, we used three different modules, representing 3758 respondents.[142,144,145] These modules asked two variations of questions on trust in scientists; first, “How much confidence do you have in the scientific community?” and second, “How much of the time do you think you can trust each of the following to do what is right? – Scientists”. For the first question, responses of “No confidence” and “A little confidence” were coded as no trust, while “Moderate Confidence” and “A lot of confidence” were coded as trust. For the second question, responses of “Never”, “Almost Never”, “Only some of the time” and “Some of the time” were coded as no trust, while responses of “About half of the time”, “Most of the time”, “Almost always” and “Just about always” were coded as trust. For trust in other people, we used 6 modules representing 6484 observations.[122–125,142,143] Again, there were two different types of questions, each of which was coded into a binary trust / no trust variable: first, “Generally speaking would you say that most people can be trusted, or that you need to be very careful in dealing with others?” and second, “How much of the time can you trust the following groups to do what is right? -- People in general”. For the first question, “Most people can be trusted” was coded as trust, while “Need to be very careful” was coded as no trust; for the second, “Almost always” and Most of the time” were coded as trust, while “Some of the time” and “Almost never” were coded as no trust. Finally, for each iteration of the analysis, one draw from a uniform distribution from the confidence interval.

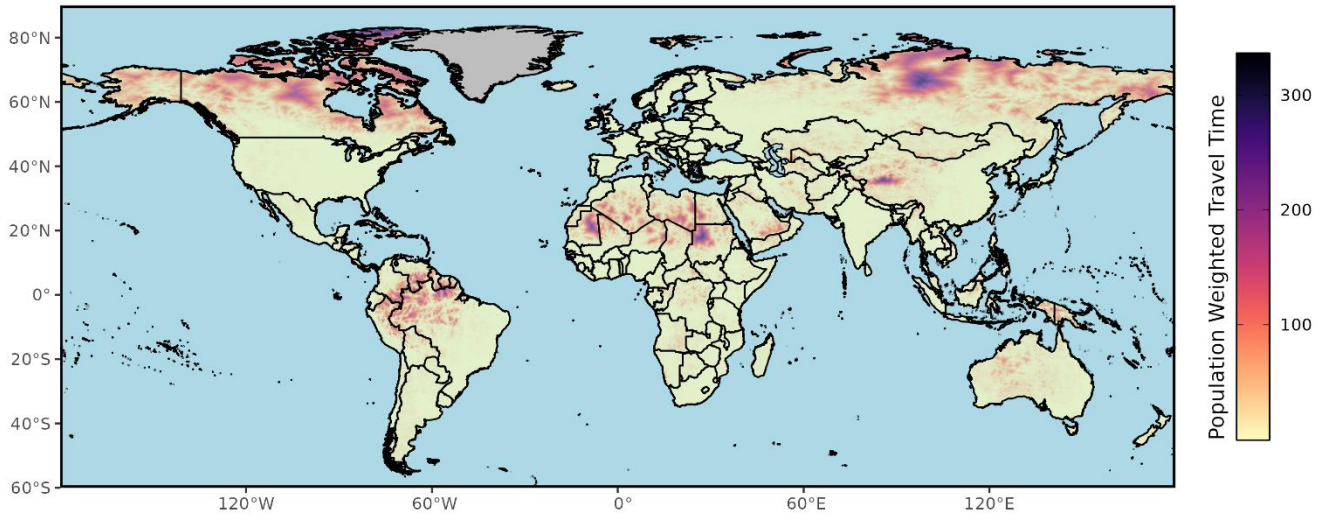
The point estimates and confidence intervals for each trust variable by state are shown in Table 4.4.1 below.

Table 4.4.1: Estimated trust variables and confidence intervals from CCES studies by state

State	Government Trust, Mean	Government Trust, Lower CI	Government Trust, Upper CI	Interpersonal Trust, Mean	Interpersonal Trust, Lower CI	Interpersonal Trust, Upper CI	Science Trust, Mean	Science Trust, Lower CI	Science Trust, Upper CI
Alabama	0.33	0.21	0.46	0.32	0.20	0.44	0.59	0.40	0.79
Alaska	0.19	0.00	0.42	0.33	0.00	0.66	1.00	0.00	1.00
Arizona	0.32	0.24	0.40	0.47	0.37	0.58	0.73	0.59	0.85
Arkansas	0.20	0.06	0.34	0.22	0.09	0.36	0.62	0.41	0.85
California	0.32	0.27	0.37	0.38	0.33	0.44	0.84	0.78	0.89
Colorado	0.25	0.16	0.33	0.41	0.28	0.53	0.57	0.34	0.82
Connecticut	0.27	0.16	0.37	0.44	0.29	0.60	0.69	0.51	0.85
Delaware	0.46	0.18	0.75	0.55	0.33	0.78	0.24	0.00	0.57
District of Columbia	0.53	0.35	0.73	0.38	0.18	0.61	0.85	0.62	1.00
Florida	0.33	0.29	0.38	0.40	0.34	0.46	0.71	0.64	0.80
Georgia	0.29	0.21	0.37	0.32	0.23	0.41	0.71	0.60	0.81
Hawaii	0.30	0.00	0.71	0.48	0.19	0.80	1.00	0.00	1.00
Idaho	0.27	0.11	0.43	0.49	0.29	0.68	0.75	0.58	0.92
Illinois	0.30	0.24	0.37	0.46	0.38	0.55	0.76	0.66	0.87
Indiana	0.33	0.25	0.40	0.42	0.33	0.51	0.78	0.69	0.87
Iowa	0.26	0.14	0.38	0.51	0.35	0.67	0.86	0.73	0.99
Kansas	0.22	0.08	0.35	0.44	0.28	0.58	0.81	0.63	0.99
Kentucky	0.33	0.24	0.41	0.31	0.19	0.41	0.66	0.51	0.81
Louisiana	0.37	0.24	0.48	0.39	0.23	0.55	0.69	0.48	0.87
Maine	0.32	0.16	0.47	0.52	0.34	0.69	0.87	0.72	1.00
Maryland	0.36	0.27	0.45	0.45	0.35	0.56	0.78	0.63	0.92
Massachusetts	0.25	0.17	0.34	0.48	0.37	0.60	0.92	0.87	0.97
Michigan	0.33	0.25	0.41	0.47	0.38	0.56	0.59	0.47	0.73
Minnesota	0.32	0.22	0.41	0.56	0.44	0.66	0.82	0.68	0.95
Mississippi	0.29	0.15	0.47	0.19	0.07	0.34	0.65	0.39	0.91
Missouri	0.28	0.21	0.35	0.38	0.28	0.48	0.64	0.52	0.75
Montana	0.15	0.04	0.26	0.51	0.27	0.76	0.82	0.63	1.00
Nebraska	0.23	0.08	0.36	0.29	0.10	0.46	0.80	0.62	0.96
Nevada	0.33	0.19	0.48	0.41	0.27	0.56	0.70	0.55	0.87
New Hampshire	0.25	0.05	0.46	0.56	0.35	0.79	0.74	0.50	0.96
New Jersey	0.30	0.22	0.38	0.37	0.28	0.45	0.74	0.62	0.85
New Mexico	0.16	0.04	0.30	0.38	0.21	0.56	0.93	0.83	1.00
New York	0.35	0.29	0.41	0.44	0.36	0.52	0.75	0.67	0.82
North Carolina	0.25	0.18	0.31	0.37	0.30	0.45	0.68	0.57	0.81
North Dakota	0.15	0.00	0.30	0.19	0.00	0.44	0.41	0.04	0.77
Ohio	0.26	0.21	0.32	0.37	0.29	0.45	0.68	0.60	0.77
Oklahoma	0.34	0.22	0.45	0.38	0.21	0.54	0.89	0.80	0.98
Oregon	0.29	0.18	0.39	0.48	0.36	0.61	0.86	0.75	0.97
Pennsylvania	0.26	0.21	0.32	0.39	0.32	0.46	0.71	0.62	0.79
Rhode Island	0.30	0.05	0.54	0.18	0.00	0.38	0.80	0.55	1.00
South Carolina	0.36	0.25	0.45	0.35	0.22	0.47	0.68	0.52	0.85
South Dakota	0.46	0.27	0.65	0.44	0.17	0.72	0.84	0.63	1.00
Tennessee	0.30	0.21	0.38	0.43	0.30	0.55	0.69	0.53	0.82
Texas	0.29	0.24	0.34	0.41	0.35	0.46	0.75	0.68	0.82
Utah	0.23	0.14	0.34	0.52	0.39	0.68	0.87	0.74	0.99
Vermont	0.26	0.00	0.51	0.37	0.04	0.67	1.00	0.00	1.00
Virginia	0.23	0.16	0.29	0.42	0.33	0.50	0.64	0.51	0.76
Washington	0.41	0.32	0.50	0.49	0.38	0.59	0.80	0.72	0.90
West Virginia	0.15	0.07	0.23	0.30	0.16	0.45	0.68	0.45	0.89
Wisconsin	0.25	0.18	0.33	0.45	0.36	0.54	0.78	0.67	0.89
Wyoming	0.30	0.07	0.54	0.57	0.22	0.94	1.00	0.00	1.00

Section 4.5 Modeling health care accessibility via the % of population within two hours of a hospital

Figure 4.5.1: Population-weighted access within two hours of a health facility



We wanted to measure the health facility accessibility of the populations living in our subnational units. To do so, we first used travel time from health facilities via motorized vehicles published by Weiss et. al. in 2020,[119] available at the 5 by 5-km grid cell level. We then calculated whether each grid cell was within two hours of a health facility (1) or not (0). In order to get the population-weighted travel time, we first resampled population estimates at a 1 by 1-km grid cell level from Worldpop[159] to a 5 x 5-km grid cell level to match the resolution of the travel time layer using bilinear interpolation. We multiplied each grid cell by the population per cell, so that only those locations with travel times under 2 hours would have a (population-weighted) value. We then summarized the sum of the grid cells over each unit of analysis (i.e. state) to get a population-weighted sum of those grid cells within two hours of a health facility. In order to get a percentage, we also needed a population-weighted denominator, so we took the sum of all grid cells within a unit of analysis; percentage within two hours of a health facility was calculated by dividing the sum of the population-weighted grid-cells within two hours of a health facility by the sum of all population-weighted grid cells. Lastly, Greenland was excluded from all analyses and mapping exercises, including use in the preparedness score mapping in section 4.2, as it was highly anomalous.

CHAPTER 4: CONSIDERING MEASLES CONTAINING VACCINE AS A PROXY FOR PANDEMIC PREPAREDNESS IN THE CONTEXT OF COVID-19: ARE WE TRULY MEASURING WHAT MATTERS?

SUMMARY

Background

COVID-19 is now considered one of the most catastrophic pandemics in history, though vaccines have proved to be one of the most useful tools in reducing mortality. Unfortunately, we have seen throughout the past three years that our response – particularly with regards to vaccine delivery – has been highly inequitable. Most pandemic preparedness metrics consider routine immunization a key indicator of preparedness for vaccine delivery; for the Joint External Evaluations, measles containing vaccine (MCV) one-dose coverage is considered this proxy. Previous research on COVID-19 cross-country differences has determined that pre-existing metrics of pandemic preparedness were not predictive of a country's success in staving off high infection and mortality rates. As such, we now wish to understand whether specific indices were beneficial in understanding specific aspects of the COVID-19 pandemic, such as vaccination. In doing so, researchers will be able to understand whether there are certain indicators that are more suited to tracking, funding, and capacity building than others.

Methods

We model one-dose 2019 MCV coverage against at least one dose COVID-19 vaccination, extracted from Our World in Data, between December 1, 2020 and December 1, 2022 for national and subnational locations separately. In each location, we consider the time to various thresholds of coverage (1%, 5%, and 10%) to understand the relationship between pre-pandemic immunization and speed of novel vaccine roll out, the maximum number of persons vaccinated in a single day (smoothed and averaged over a one-month period to adjust for noisy data) as a measure of speed of scale-up, and the maximum level of coverage achieved for at least one dose COVID-19 vaccination coverage; all models also controlled for pre-pandemic vaccine hesitancy (nationally) and percentage of the population over 65 years of age. Subnational models included a variable of the parent country. We considered two unique subsets of data – countries not meeting the target 90% routine MCV threshold and the first six months of COVID-19 vaccination – to understand nuanced patterns in vaccine delivery and additionally assess the performance of other measures of routine immunization.

Findings

Our research suggests that the level of pre-pandemic one-dose MCV coverage across 134 countries was successful in predicting the time to vaccine roll out at varying thresholds and the overall vaccination level achieved. In the subnational model, we found no significant relationships between routine immunization coverage and one-dose COVID-19 vaccine delivery, a relationship that persisted across all data subsets and additional indicators of routine immunization. In considering our additional data subsets, we find that the analysis focusing on the countries not reaching 90% routine MCV coverage mirrored the results of the full data series; in contrast, the analysis of the first six months only found a significant association between maximum coverage and MCV coverage. Considering other metrics of routine immunization revealed heterogeneous results, suggesting the need for additional research to understand the differences in routine MCV immunization versus polio, DTP3, or BCG immunization. Controlling for government trust suggested that MCV was a significant driver of maximum vaccination achieved.

Interpretation

While composite metrics of pandemic preparedness are not effective at predicting pandemic COVID-19 outcomes, specific, targeted indicators have stronger predictive validity than the composites. Specifically, this analysis demonstrates that measles vaccine coverage is an effective metric for quantifying immunization readiness at the national level via time to various thresholds and maximum coverage achieved, and can provide utility for considering equitable delivery of vaccines and therapies for future threats; in contrast, MCV coverage was not correlated with COVID-19 vaccination at all subnationally in this analysis. Future research should consider how other indices map with COVID-19 outcomes to better understand which metrics were tied to this pandemic, which ones may be useful in other pandemics impacting other populations at risk, and which may not be useful altogether.

INTRODUCTION

With over 12 billion estimated infections, 650 million reported cases, and 7 million reported deaths as of December 2022, COVID-19 is now considered one of the most catastrophic pandemics in history.[160] Although the battle with COVID-19 rages on, we have come far in our understanding of risks and drivers of infections and therapies to reduce mortality, the best among these being vaccinations.[161] With two years of vaccine delivery for COVID-19 behind us, we can now begin to understand what we as public health experts – globally and locally – can do differently to mitigate not only disease spread but subsequent morbidity and mortality. Unfortunately we have seen throughout the past three years that our response – particularly with regards to vaccine delivery – has been highly inequitable: in high income countries, an estimated 75-80% of all eligible persons were vaccinated within the first year, while in low income countries fewer than 10% of all eligible persons were estimated to have been vaccinated.[162]

Most pandemic preparedness metrics consider routine immunization a key indicator of preparedness for vaccine delivery. This indicator is meant to be a proxy of how readily a country can respond to a novel threat and is a composite proxy of reach of vaccination efforts, quality control and cold stage storage, and distribution ease.[5] For the Joint External Evaluation (JEE),[5] measles containing vaccine (MCV) one-dose coverage is considered the proxy for immunization readiness. Previous research on COVID-19 cross-country differences has determined that pre-existing metrics of pandemic preparedness – the Global Health Security Index (GHSI) and the JEE – were not predictive of a country's success in staving off high infection and mortality rates.[26,28,29,86] While research has begun to investigate how better to quantify preparedness as a whole,[163,164] it is important to understand whether specific indicators among the many combined within the composite pandemic preparedness scores were correlated with specific aspects of the COVID-19 pandemic. In doing so, researchers will be able to understand whether there are certain indicators that are more suited to tracking, funding, and capacity building than others. Moreover, taking a more focused approach to pandemic preparedness indicators will allow us to identify differential areas for prevention and response based on the type of pathogen: for COVID-19, a respiratory virus targeting older individuals with comorbidities, this may look like trying to isolate and vaccinate elderly persons first and encourage mask wearing, while for Zika virus, a vector-borne disease targeting pregnant women and neonates, bed net use, vaccination delivery during pregnancy, and early screening may be more relevant.

Understanding how MCV coverage correlates with national or subnational COVID-19 vaccination is essential for future preparedness efforts. Given that the goal of most JEE mapping exercises is to develop National Action Plans to improve country preparedness, understanding whether exercises to map and improve MCV coverage are influencing pandemic vaccination efforts are crucial for directing resources and capacity building efforts. Moreover, recent analyses have identified wide within-country heterogeneities in both COVID-19 outcomes and response efforts, many of which are not captured by national-level pandemic preparedness scores. In this analysis, we first aim to understand whether a

correlation exists between MCV and three different metrics considering the initially vaccinated COVID-19 time series: 1) time to different vaccine thresholds – indicative of speed of roll out; 2) and average of the top month of daily doses administered per 100 population – a proxy for the magnitude of scale up; and 3) the maximum level of vaccination achieved by December 2022 – suggestive of the maximum reach (Figure 1). Similarly, we want to understand how these patterns differ between national and subnational locations. Subsequently, we wish to understand whether there may be better proxies of vaccine readiness in which to invest to better quantify preparedness. Lastly, we consider a number of data subsets to understand nuanced patterns in routine and pandemic vaccine delivery.

METHODS

Overview

We consider two years of COVID-19 vaccine delivery data in this analysis, from December 1, 2020 through December 1, 2022. Data from Our World in Data,[165] and other governmental and regional sources, where relevant, were extracted, cleaned, and vetted for 167 countries and 165 subnational locations across 6 countries; all six countries were chosen for data availability of subnational COVID-19 vaccination data, MCV coverage data, and additional covariates. The time to various vaccination levels (1%, 5%, and 10% of the population) were calculated for each location using cumulative vaccinations, removing those locations with sparse data series or undocumented jumps from no vaccine doses to 5% or greater. We additionally looked at the daily vaccinations administered, and, using a seven-day moving average to smooth noisy data, obtained an average of the top 30 days of vaccine delivery – herein called maximum daily doses - as a proxy for speed of scale up. Lastly, we found the highest cumulative value of the initially vaccinated COVID-19 coverage for each location to estimate the maximum level of vaccination achieved. Each of these variables were then modelled against 2019 one-dose MCV coverage (Figure 2), controlling for the percentage of the population over 65 years of age to account for the influence of age structure on COVID-19 outcomes[86] and vaccine prioritization (appendix figures 3.1, 3.2), modelling subnational locations separately from national ones. For national locations, we also included a measure of pre-pandemic vaccine hesitancy to account for pre-existing behaviours influencing vaccine uptake beyond what can be quantified by MCV coverage (appendix figure 3.3);[166] missing country-level data restricted the sample size for this analysis to 134 national locations. Pre-pandemic vaccine hesitancy was not available for subnational locations. A sensitivity analysis looking at mid-pandemic vaccine hesitancy both nationally and subnationally is available in appendix section 5.2. For the subnational model, parent country was also included as a control to account for country-specific factors, including national pre-pandemic hesitancy.

We considered additional analyses looking only at the first six months of delivery, before boosters were available and prior to widespread distribution to children and teens in order to understand vaccine delivery in the earliest time period when the focus was on vaccinating those most at risk and adults, and before countries faced the decision of not vaccinating due to a high number of natural infections and the finding that COVID-19 vaccines were not altogether effective in limiting transmission.[167] Similarly, we considered an analysis looking only at those countries with MCV scores under 90% to understand patterns between MCV coverage and initial COVID-19 vaccination for those places target routine immunization coverage was not achieved as a means of focusing on those places where improvements may be most necessary. We then included alternate covariates in lieu of MCV coverage in our model, including three-dose Diphtheria-Tetanus-Pertussis (DTP3) vaccination coverage (Figure 3), three-dose poliovirus (polio) vaccine coverage (Figure 4), and at least one dose Bacille Calmette-Guérin (BCG) vaccination coverage where it is recommended for country-wide administration (Figure 5).[168] Lastly, for the national locations only, we considered a model including governmental trust (appendix figure 3.6) as

a control, and then as an interaction term with MCV; interpersonal trust, despite being highly correlated with improved COVID-19 outcomes,[86] was omitted from the main due to a high degree of missingness but is available in the appendix (sections 6.6 and 6.7). Models were replicated 100 times to capture uncertainty in the data and models.

Data sourcing and cleaning

Initial COVID-19 vaccination data were obtained primarily from the Our World in Data (OWiD) online repository through December 1, 2022 using the metric *people_vaccinated* to represent individuals with at least one COVID-19 vaccine dose.[165] For locations with subnational data, government location-specific data vaccinations were obtained at the subnational unit and were aggregated to the national level. For many European countries, European CDC data were used to supplement the OWiD data. For each location, the first date of vaccine delivery and last delivery date (on or before December 1, 2022) were recorded. Data cleaning like removing negative daily values, erroneous data spikes, and population caps were implemented on a case-by-case basis (see appendix section 4.2). National locations were excluded if erratic data could not be vetted or if coverage percentages jumped from no vaccination to 5% or greater at first dose; subnational locations were excluded if they were missing raw data (and therefore were modelled from the national data). Locations with unexplained late-term spikes were removed only for the maximum daily dose analysis; for the national analysis this was inclusive of Egypt and Lebanon. Ukraine was removed from all analyses due to unavailability of data following Russian invasion.

We obtained 2019 one-dose MCV coverage data nationally and subnationally from the Global Burden of Disease (GBD) study, including the estimated mean coverage and 95% uncertainty interval, and also extracted estimates of three-dose DTP3, at least one dose BCG, and three-dose polio vaccine coverage.[169] For each of the 100 replications, a point estimate of coverage from a uniform distribution using the 95% uncertainty bounds as the minimum and maximum was used in the model to capture the uncertainty in the coverage modelled estimate. Similarly, the age profile of a given location was obtained from GBD as well. Pre-pandemic vaccine hesitancy was averaged across three published modelled facets of vaccine hesitancy in December 2019: vaccine safety perceptions, vaccine importance perceptions, and vaccine effectiveness perceptions.[166] These data were available for 149 national locations. Mid-vaccine hesitancy - used in our sensitivity analyses - was extracted from IHME's COVID-19 forecasting models.[117]

Trust in the government was extracted for all national locations from the World Values Survey[75] and Gallup Global Surveys.[76,170] As in our cross-country analyses,[86] we then used a principal components analysis (PCA) to create one governmental trust metric combining information from both sources, each of which is incomplete on its own. While we imputed missing data, we only retained a government trust score for the locations that had data from at least one of the two original sources. Further details are available elsewhere.[86]

Models

Linear models were constructed for each outcome, looking at MCV and our additional indicators of interest. For subnational locations, only MCV, DTP3, BCG, and polio vaccination were investigated. BCG was only assessed where it was a current nationally recommended vaccine.[168] For national locations, we also looked at a model including government trust as a control, and then additionally as an interaction term with MCV. For each model, we replicated our analysis 100 times to capture model and variable uncertainty, drawing one coefficient from a multivariate normal distribution per simulation.

Time to threshold

In order to estimate the time to roll-out for COVID-19 vaccination, we estimated the time to various thresholds. For the time to a given percentage of the population vaccinated (1%, 5%, and 10%), the date the location first met or exceeded that percentage in cumulative space was recorded, and the number of days from December 1, 2020 was obtained. Each of these variables was log transformed due to highly right skewed data. Linear models were constructed modelling the log time to threshold against MCV coverage, controlling for the percentage of the population greater than 65 years and vaccine hesitancy, and, for subnational locations, the national parent location. To understand whether a different immunization metric performed better than MCV coverage, BCG (where relevant), DTP3, and polio coverage were modelled in lieu of MCV. Additionally, MCV was modelled controlling for governmental trust and as an interaction with governmental trust.

Maximum daily doses administered

In order to estimate a proxy for the maximum speed of scale of up vaccine distribution, we estimated the maximum people initially vaccinated per capita over the two-year time period using a seven-day moving average to smooth out noisy reporting. We then took the top month (30 days) of all smoothed daily values and averaged our data over that month to down weight any highly anomalous reporting days, and this average was then modelled against logit-transformed vaccine coverage (MCV, BCG, DTP3, polio) with and without including trust (as a covariate and as an interaction term) using linear models with 100 replications to capture model uncertainty.

Maximum overall coverage analysis

Lastly, to estimate the maximum level of vaccine coverage obtained per location, we extracted the maximum cumulative level of at least one dose COVID-19 vaccination, logit-transformed, by December 1, 2022 and subsequently modelled this against logit-transformed MCV vaccine coverage and the alternate metrics (BCG, DTP3, and polio vaccination, controlling for government trust, and interacting with government trust), as well as controlling for log-transformed vaccine hesitancy and percent of the population over 65 years of age. For subnational locations, we also controlled for parent location.

Uncertainty analysis

Each model was replicated 100 times to capture uncertainty in the vaccine coverage estimates, as well as in the governmental trust PCA variable, where applicable. For each model run, a point estimate was taken from a random uniform distribution with the lower 95% uncertainty interval of the coverage variable as the minimum, and the upper 95% uncertainty interval as the maximum. From the linear model, one coefficient draw was chosen from a multivariate random normal distribution. Uncertainty intervals and point estimates were obtained by taking the mean, 2.5th and 97.5th draws across all 100 iterations.

Sensitivity and supplemental analyses

We considered several sensitivity and supplemental analyses to validate our model assumptions and explore alternate parameterizations of our models and data. Sensitivity analyses included using different quantifications of maximum doses administered per day and maximum vaccination level achieved, using mid-pandemic hesitancy in lieu of pre-pandemic measures, using OWID data without any cleaning, as well as limiting our analyses for MCV, DTP3, BCG, and Polio to those governmental trust locations for comparability. Additional analyses included looking at the era of vaccination prior to booster roll out and widespread vaccination to children and teens, which occurred circa May 2021 in many high-income countries,[171–173] looking only at those countries not meeting routine MCV coverage targets of 90% coverage,[5] considering interpersonal trust as a covariate of interest, and controlling for sociodemographic index. Results considering the alternate immunization metrics, the first six months of vaccine delivery, and

those countries not reaching target immunization are included in this manuscript. All additional analyses are available in appendix sections 5 (sensitivity analyses) and 6 (supplemental analyses).

RESULTS

Trends in national COVID-19 vaccination

Among the countries included in the analysis, the time to differing levels of at least one dose COVID-19 vaccination varied tremendously by region and income group (Figure 6). Moreover, the number of countries reaching each threshold was highly variable by region with much of the African continent not reaching 25% and additional countries in the Middle East and Eastern Europe not reaching 50% coverage. Time to various thresholds followed a similar trend, with many sub-Saharan African countries taking nearly a year or more to get to 5% coverage in contrast to many North American and western European countries taking four months or less to reach the same level. Subnational plots of time to 1%, 5% and 10% coverage are available in appendix section 3.8.

Figure 7 presents the results of our smoothed maximum daily dose analysis. In general, we see North America and western Europe having achieved, on average, higher numbers of daily persons vaccinated. However, this is not nearly as consistent as the time to vaccination maps. Some high-income countries like New Zealand, Israel, and United Arab Emirates had unsurprisingly large single-day dose roll outs while other less expected locations like Mongolia, Cuba, and Viet Nam were also in the highest tier of vaccinations given in a day. Similarly, other high-income countries like the United States, Sweden, the United Kingdom, and Australia more middling in their maximum dose distribution, despite all being among the top 10 most highly ranked countries for GHSI (appendix section 3.7). Figure 8 presents the results of estimating the highest level of at least one dose COVID-19 vaccination achieved in each country from our cumulative time series through December 1, 2022. This pattern appears to correlate highly with income, with much of North America, Europe and Australia reaching 80 to 90% overall vaccination, though much South America and parts of east and southeast Asia also performed highly in terms of overall vaccination levels achieved. Unsurprisingly, much of the African continent has fallen behind in terms of maximum coverage achieved, though a few exemplar countries appear in Botswana, Rwanda, Mozambique, and Liberia. For both the maximum daily dose analysis and maximum coverage, subnational trends were much less heterogeneous than those observed nationally.

Correlations with routine MCV coverage

Figure 9 presents the results of the models of our at-least-one-dose COVID-19 indicators versus one-dose MCV coverage. In looking first at the model of time to each of the three thresholds, one-dose MCV was significantly correlated with time to one-dose COVID-19 vaccine roll out such that increasing MCV coverage was related to shorter time to each threshold; similarly the maximum coverage achieved was significantly related to MCV coverage, such that higher MCV coverage was associated with higher one-dose COVID-19 maximum coverage. These findings also held true for the 53 countries with MCV coverage under the targeted 90%. In contrast, time to various thresholds was not significant in the analysis of the first six months of vaccine delivery, though the relationship with maximum coverage was still significant. Plots of each outcome variable (time to threshold, maximum daily doses, and maximum coverage) are all available in appendix sections 3.9 – 3.12 for the May 1, 2021 cut-off and appendix sections 3.12 – 3.14 for the sub-90% model. Looking next to the subnational analysis considering 165 locations across six countries, we observe a different picture of routine and pandemic immunization correlation. For all of our different indicators of vaccine delivery, we found no significance between one-dose COVID-19 vaccination and one-dose MCV vaccination across any of the data subsets.

Considering alternate measures of routine immunization

Our sensitivity analysis results looking at additional indicators of routine immunization were highly variable (Figure 9). For polio vaccination, results largely mirrored those of MCV vaccination, with all time to threshold models having significant, inverse relationships with one-dose COVID-19 vaccination at the national level such that increasing polio vaccine coverage was correlated with shorter times to roll out; similarly, no time to threshold model was significant at the subnational level. In addition, maximum coverage achieved was significant for both polio and MCV coverage at the national level; for polio alone, maximum daily doses administered also had a significant, positive relationship with routine immunization coverage. In contrast, for DTP3, only time to 1% coverage and maximum daily doses administered were significantly related to DTP3 coverage nationally, with no significance subnationally. For the subset of countries with BCG vaccine policies (n=103), both maximum daily doses administered and maximum overall coverage were significantly related with BCG coverage at a national level, but none of the time-to-threshold models proved significant. At the subnational level, again no significance was found. Last, in looking at adding trust as a covariate to the model (n=95 countries), we found that when controlling for trust, maximum one-dose COVID-19 coverage was significantly related to one-dose MCV coverage, but maximum daily doses and time-to-threshold models were not significant; in the model interacting trust and MCV coverage, we observed no significant relationships.

Discussion

We draw several conclusions from this work. First, we note that most heterogeneities in one-dose COVID-19 vaccine delivery were largely mirrored by one-dose MCV coverage at the national level: roll out time to reach 1%, 5% and 10% vaccinated were all shorter in places with higher MCV coverage and maximum one-dose COVID-19 vaccine coverage achieved by December 2022 demonstrated increasing coverage as MCV coverage increased; however, maximum daily doses per capita was not significantly tied to MCV coverage. This is the first analysis, to our knowledge, that considers how successfully one-dose MCV coverage correlated to at-least one-dose COVID-19 vaccination. While composite metrics have not been informative of COVID-19 successes,[26,28,29,86] this research demonstrates that existing immunization-specific preparedness indicators are indeed correlated with COVID-19 vaccine delivery at a national level, using MCV as the proxy for immunization readiness. Knowing that, at a national level, MCV coverage does correlate with pandemic vaccine delivery (as evidenced here by COVID-19 vaccination) allows us to refocus efforts and resources to those places not achieving high levels of immunization in order to both strengthen routine immunization but also quickly and equitably distribute vaccines and therapies in future pandemics. Additional research is needed to investigate other individual pandemic preparedness indicators to understand to what extent these correlated with pandemic outcomes, and how we can best measure and prepare for future threats, regardless of the pathogen. It is additionally important to highlight that by December 1, 2022, many countries in sub-Saharan Africa had not reached even 25% to 50% of the country vaccinated. While MCV coverage may explain how quickly a country will get doses of a vaccine, it is a measure of routine coverage and therefore does not fully capture the nuances and challenges of emergency vaccine or therapy delivery. In that sense, learning from emergency vaccine distribution or mop up campaigns such as those seen in poliovirus vaccine delivery in response to novel cases may provide tools for reaching those least served by current vaccination approaches. Future research is necessary to understand barriers to equitable delivery in these locations.

Second, in contrast to the national level, our subnational analysis across six countries revealed no significance between initial COVID-19 vaccination and routine one-dose MCV coverage. In addition, these results were persistent across all subsets of data, and held when looking at additional measures of routine immunization including DTP3, Polio, and BCG. This is consistent with previous research finding no major significant drivers of subnational variability in COVID-19 outcomes in Brazil and the United States. Moreover, that research found that after controlling for key sociodemographic and baseline risk

characteristics, outcomes appeared grouped more closely by country, suggesting that country-level policy, healthcare, and social factors may have a stronger influence on COVID-19 heterogeneities than subnational ones. Current pandemic preparedness indicators have focused on national-level preparedness, leaving gaps in our understanding of subnational capacities and how they influence pandemic outcomes. Future research is needed to better quantify subnational preparedness and response. It is important to note that this analysis only included the six countries with subnational COVID-19 and routine immunization data available, with further subsets for BCG-specific analyses and those countries not meeting the 90% target; future research is needed to understand if these patterns persist across a wider multitude of countries.

We considered a number of additional analyses in this manuscript to better understand the relationship between routine immunization and pandemic vaccine delivery. We first note that for countries not meeting the 90% target for routine immunization, one-dose MCV coverage was also significantly correlated with the time to 1%, 5%, and 10% one-dose COVID-19 vaccine coverage as well as the maximum level of coverage achieved. This suggests that even among those countries falling short of routine immunization targets, the correlation between MCV coverage and COVID-19 vaccination persist. Given that MCV is significantly, positively correlated with gross domestic product (GDP) per capita[174] and sociodemographic index (SDI, appendix 6.3), and since, on average, those higher-income countries with the highest routine immunization coverage scores were also those countries who reserved COVID-19 vaccine doses in advance, received the COVID-19 vaccine in its earliest days, or had the capacity and funding to develop and test novel vaccines,[175–177] we hypothesized that the relationship between MCV and COVID-19 vaccination might be largely mediated by SDI. While our time to threshold models controlling for SDI (appendix 6.4) did show non-significance when controlling for SDI, our findings from the under 90% MCV grouping suggest that there is utility in MCV as a proxy for time to vaccine roll out in pandemic settings. It is worth noting that while SDI and MCV were highly correlated, not all countries meeting the 90% threshold were high income, and, conversely, not all countries falling below that threshold were low- or middle-income. We next consider our analysis restricted to the time period before widespread booster roll out and vaccinations to children and teens (ie through May 1, 2021). Here, we find no significant correlations between one-dose MCV coverage and time to various thresholds of one-dose COVID-19 vaccination, nor maximum daily doses administered. This suggests that early in COVID-19, routine immunization was not predictive of pandemic vaccine delivery, suggesting that economics, health system capacity and access, and political buy-in may have been more influential.[178,179] Importantly, throughout the first six months, less than 30% of all low- and middle-income countries had received even 10% coverage of COVID-19 vaccination compared to nearly 90% of high-income countries.

Our analysis looking at different metrics of routine immunization revealed inconsistent results at a national level. Routine polio vaccination largely mirrored that of MCV vaccination, while DTP3 and BCG were more disparate. Investigating the policies for delivery of each of these vaccines may help inform why they were or were not correlated with COVID-19 vaccine delivery. Additional research is needed to better understand how these measures of routine immunization vary nationally and subnationally to better understand why some are predictive of pandemic vaccine delivery, while others are not. In addition, our analysis controlling for governmental trust suggests that only the maximum level of COVID-19 vaccination achieved was significantly related to MCV coverage, which corroborates findings that trust in the government may influence vaccine uptake at a national level.[86] However, our analysis of trust as a covariate was limited to only 95 locations with MCV coverage data, COVID-19 vaccination data, pre-pandemic hesitancy data, and governmental trust data. Moreover, our sensitivity analysis limiting our main results to just those 95 governmental trust locations founds similar results, suggesting that limited sample size may be largely driving these results (appendix 5.4).

Limitations

There are several limitations to this analysis. First, COVID-19 vaccination data, while well documented and researched for consistency and anomalies, are still subject to reporting pitfalls – the data are only as good as each location's reporting. While we have attempted to correct for major pitfalls like negative daily values, major spikes in data due to backlogs of reporting, and incomplete time series, undoubtedly issues remain. Investing in surveillance systems and reporting training now would pay dividends in improving data quality for future threats. We additionally try to adjust for some anomalous reporting by taking moving averages to smooth out noisy data and taking averages of the top days of data, but it is possible that anomalies remain. Our analysis of the maximum doses administered by day consider multiple approaches to averaging data to address this issue, with overall consistency in our results (appendix 5.1). Moreover, current data sources fail to account for the changing eligibility criteria individually for each country, meaning that data are not wholly comparable across all locations where some are allowing children while others have focused solely on adults. We attempted to control for this by limiting our analysis to the period before children and teens were able to get vaccines and before booster roll out (ie. May 1, 2021), but found no significant associations given that nearly half of our countries studied had not received even 10% coverage in those first six months. Second, while we propagated uncertainty in the modelled data and our analysis by using 100 simulations of our data, some covariates did not include uncertainty. Those that did included all routine immunization estimates and governmental trust. Results should be interpreted with caution where uncertainty was not available. Third, our measure of pre-pandemic hesitancy was only available for 134 countries, limiting our analysis to these specific countries. Importantly, the countries missing from the hesitancy analysis were not missing completely at random, with lower income countries and small island nations missing more frequently than high income and larger ones. However, our sensitivity analysis using mid-pandemic hesitancy allowed us to include a larger number of countries (n=166) and demonstrated equivalent results nationally and subnationally (appendix 5.2). Fourth, we modelled time to 1%, 5% and 10% to capture time to roll out, but considered including 25% and 50% as additional thresholds; however, many countries had not reached such thresholds by December 2022 and were therefore not missing at random from our linear analysis, introducing bias. They are therefore omitted from this analysis. Fifth, while high levels of interpersonal trust were found to be highly correlative of lower infection rates in previous research,[86] these data were plagued by heavy missingness and for this analysis where we relied on complete COVID-19 vaccination series and MCV coverage as well as hesitancy, data were too sparse to proceed; these results are available in appendix 6.1 but should be interpreted with caution. Sixth, we use this analysis to correlate reported COVID-19 vaccination versus MCV coverage as a proxy for routine immunization. Unlike routine immunization, however, countries approached pandemic COVID-19 vaccination differentially, with some countries prioritizing elderly persons, and other countries discontinuing vaccination once high levels of natural infection had been met. It may be in some cases that those countries having longer roll out periods or lower overall coverage levels chose not to pursue additional vaccinations, and in other cases, additional vaccinations were not available. Future research is needed to disentangle these two phenomena. Last, we prioritized the explanatory value of routine immunization coverage on COVID-19 vaccination and developed log-linear, logit-linear, and linear models rather than extensively studying the functional form of each variable and outcome, including non-linear effects or hierarchical models.

CONCLUSIONS

This retrospective on the relationship between routine immunization and pandemic COVID-19 vaccination suggests that MCV coverage is a significant correlate of vaccine roll out time and overall vaccination level achieved at the national level. This is the first analysis to our knowledge to demonstrate that routine

immunization pandemic preparedness coverage – via one dose MCV coverage – was significantly correlated with pandemic COVID-19 vaccination coverage. While overall pandemic preparedness metrics were not predictive of COVID-19 success,[86] this demonstrates that specific indices have particular usefulness in considering pandemic preparedness. Future research should consider how other indices map with COVID-19 outcomes to better understand which metrics were tied to this pandemic, which ones may be useful in other pandemics impacting other populations at risk (such as mpox or Zika), and which may not be useful altogether. In addition, we demonstrate that subnational variability in one-dose COVID-19 vaccination was not driven by routine MCV immunization, supporting previous studies finding limited significance with sociodemographics and policy variable subnationally for two countries.

Our world is becoming increasingly interconnected. Simultaneously, climate change and deforestation, human population growth, and infrastructure development increasingly influence our interactions with novel species.[4,10,11] As such, we are likely to see another pandemic in our lifetimes. As public health experts, we are increasing the pace at which we can develop new therapies or vaccines for novel threats.[180,181] Yet, these efforts at increasing the pace of development are not meaningful if distribution is not equitable and expedient globally. This analysis has demonstrated that routine MCV coverage is a successful correlate of vaccine delivery during a pandemic, but that both exhibit gaps in target coverage, particularly in low-income settings. Pandemic preparedness plans should consider not only how best to quantify vaccine delivery, but refocus efforts and resources to quickly and equitably distribute vaccines in future pandemics and beyond.

List of Tables and Figures

Figure 1: Different elements of initially vaccinated COVID-19 vaccine roll out over time

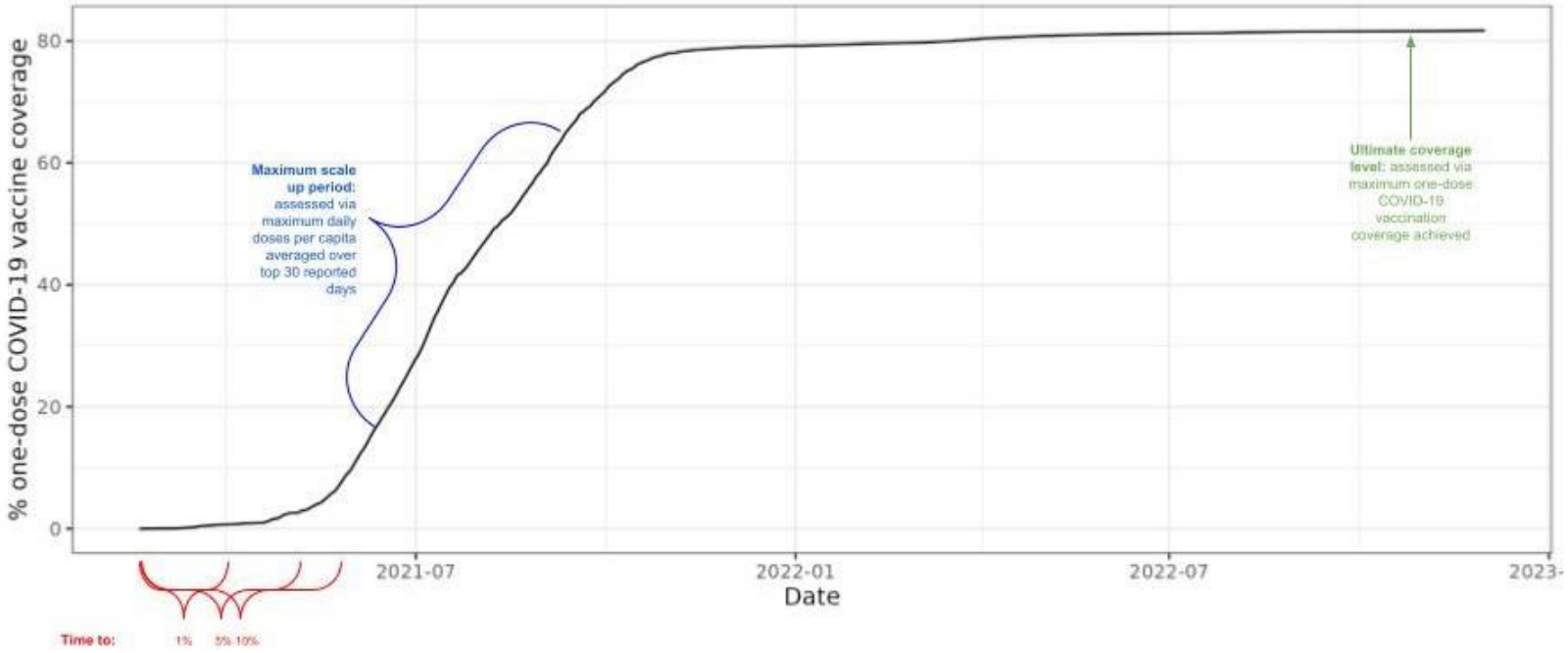


Figure 2: 2019 Measles containing vaccine one-dose 2019 coverage, national (A) and subnational (B)

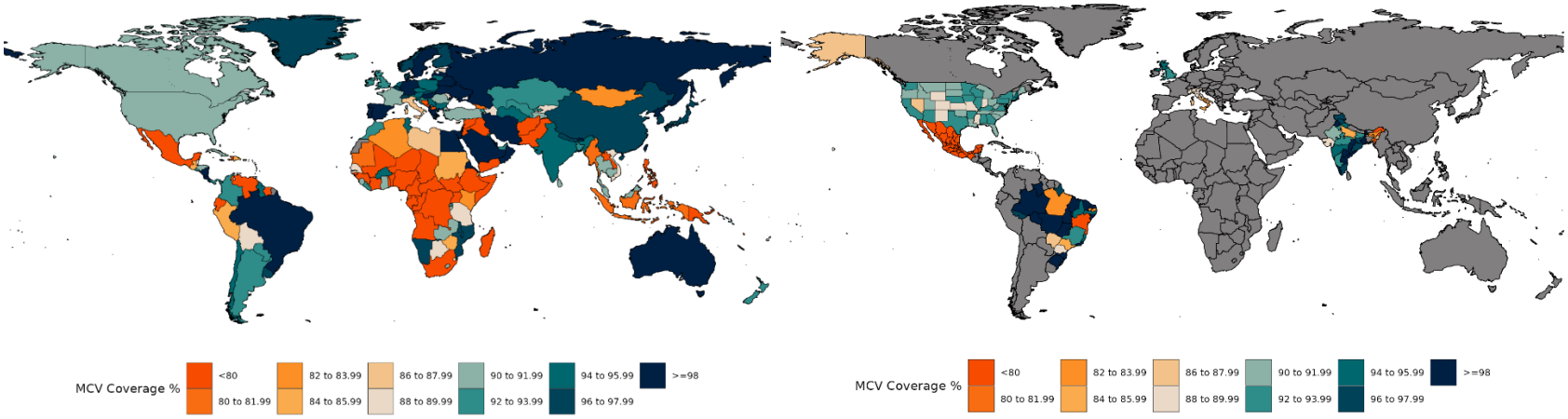


Figure 3: 2019 DTP3 vaccine three-dose 2019 coverage, national (A) and subnational (B)

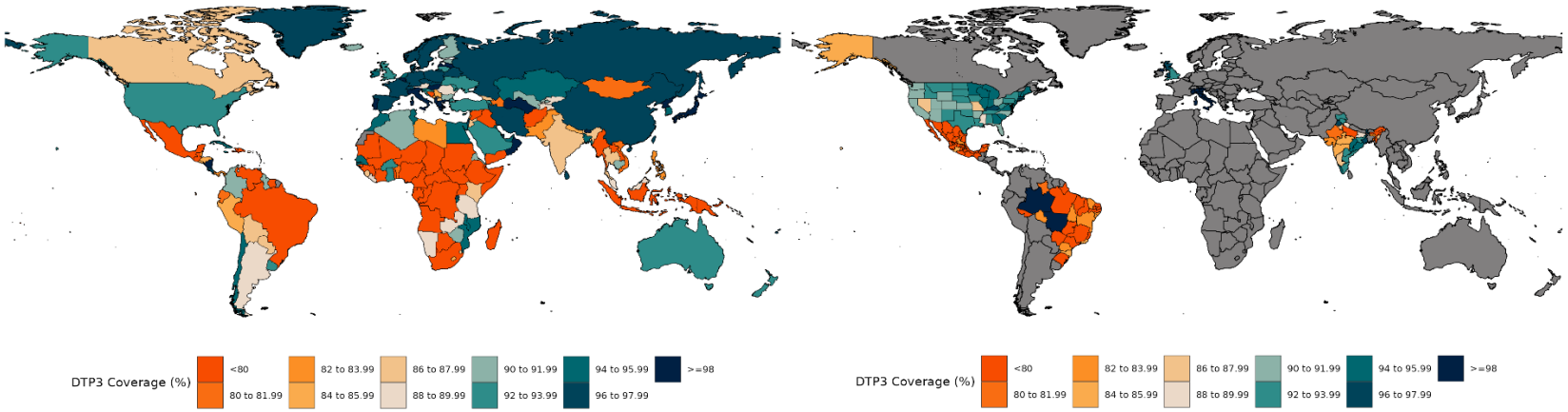


Figure 4: 2019 poliovirus vaccine three-dose 2019 coverage, national (A) and subnational (B)

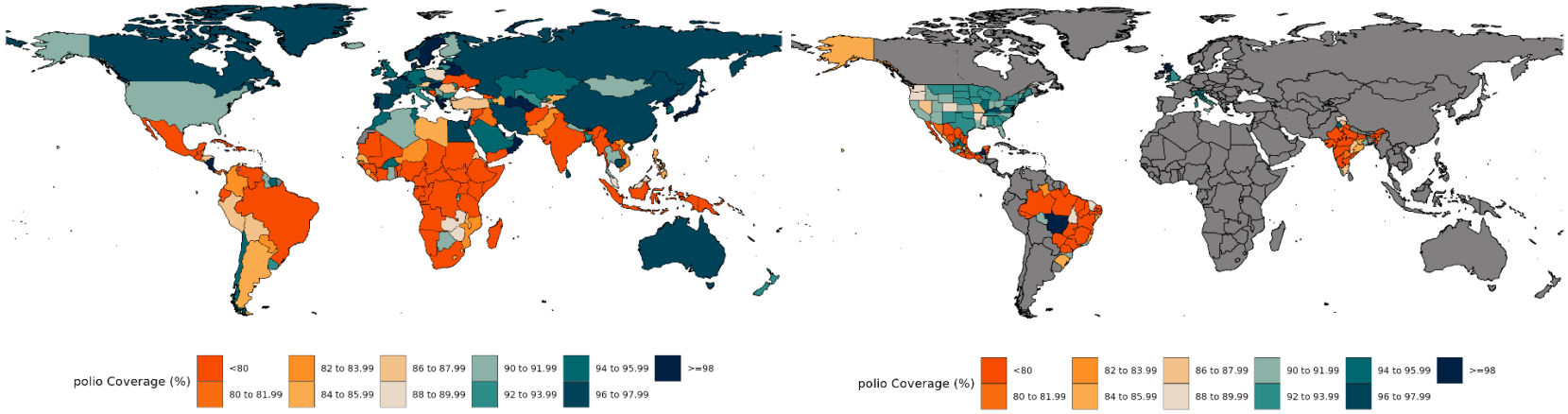


Figure 5: 2019 BCG one-dose 2019 coverage, national (A) and subnational (B), where indicated

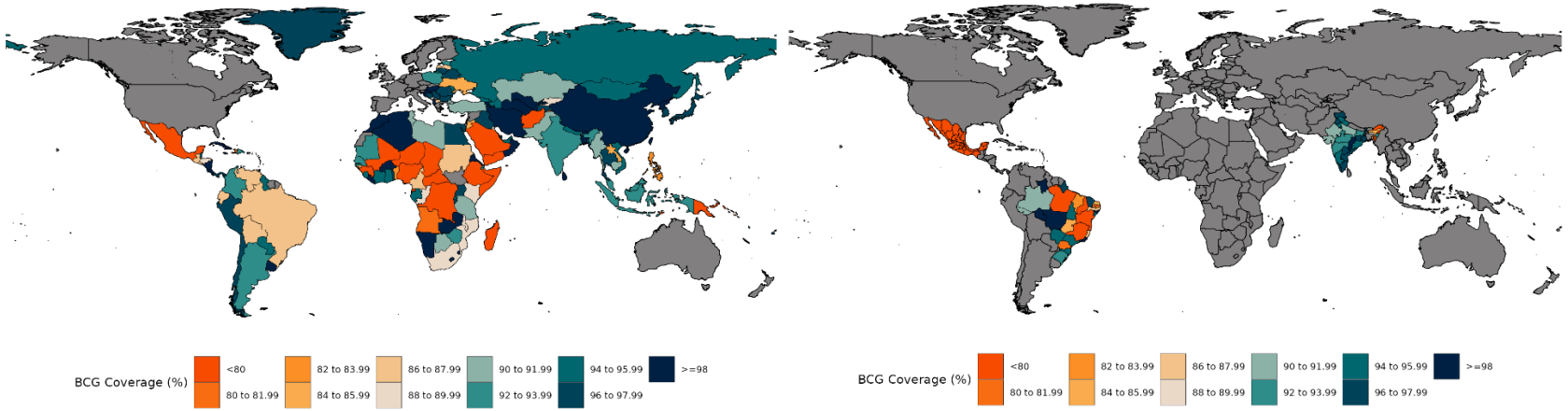


Figure 6: Time to 1%, 5%, and 10% coverage of one-dose COVID-19 vaccine, national locations

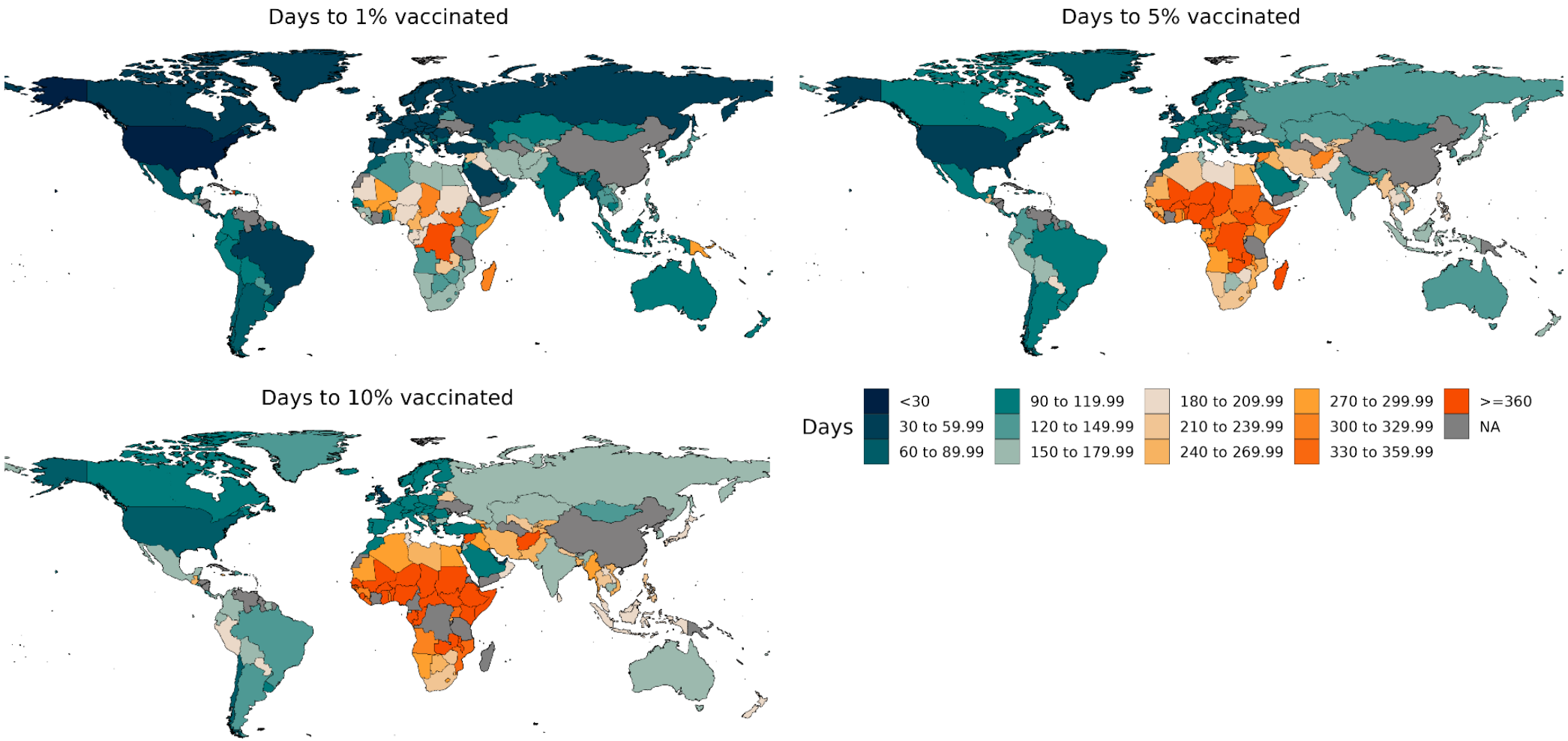


Figure 7: Maximum daily COVID-19 doses administered, smoothed and averaged, national (A) and subnational (B)

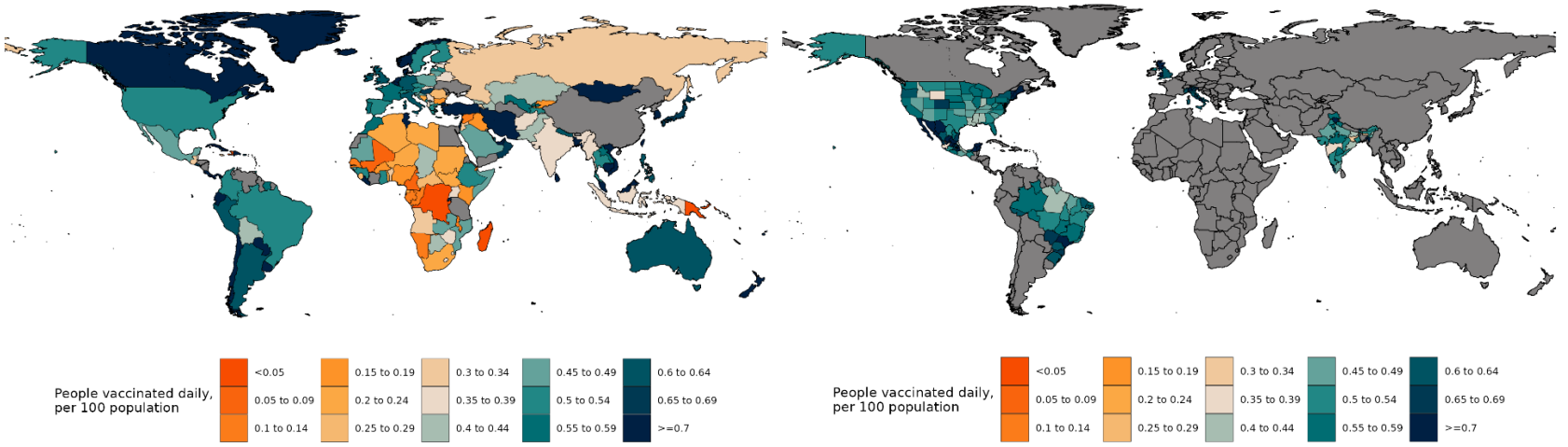


Figure 8: Maximum one-dose COVID-19 vaccination level achieved by December 2022, national (A) and subnational (B)

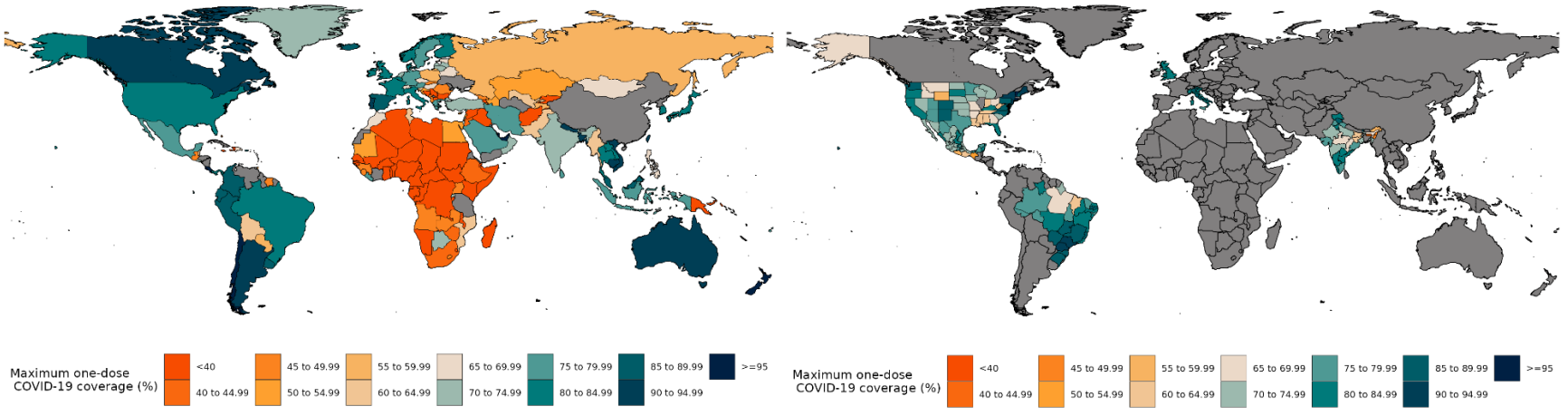
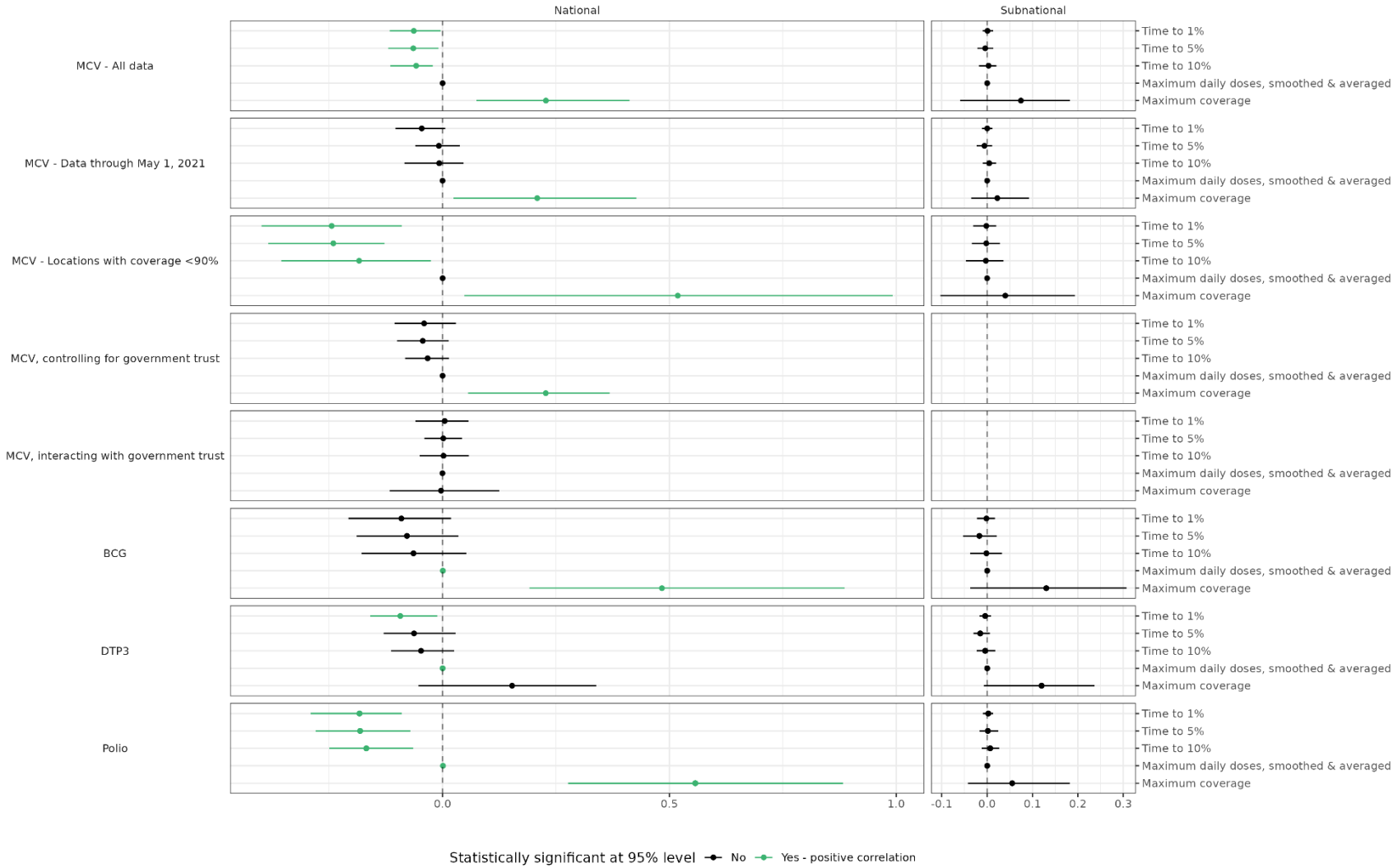


Figure 9: Correlations between routine immunization and one-dose COVID-19 vaccination, national and subnational


National
Subnational
MCV - All data
MCV - Data through May 1, 2021
MCV - Locations with coverage <90%
MCV, controlling for government trust
MCV, interacting with government trust
BCG
DTP3
Polio
Time to 1%
Time to 5%
Time to 10%
Maximum daily doses, smoothed & averaged
Maximum coverage
0.0
0.5
1.0
-0.1
0.0
0.1
0.2
0.3
Statistically significant at 95% level
No
Yes - positive correlation

SUPPLEMENTAL INFORMATION FOR CHAPTER 4

Section 1: Abbreviations

BMI: body-mass index

BCG: Bacille Calmette-Guérin

COVID-19: coronavirus disease 2019

DTP3: Diphtheria-tetanus-pertussis

GBD: Global Burden of Diseases, Injuries, and Risk Factors Study

GHS Index: Global Health Security Index

HAQ Index: Healthcare Access and Quality Index

IHME: Institute for Health Metrics and Evaluation

JEE: Joint External Evaluation

MCV: Measles containing vaccine

PCA: principal component analysis

SARS-CoV2: severe acute respiratory syndrome coronavirus 2
WHO: World Health Organization

UHC effective coverage index: universal health coverage effective coverage index

UI: uncertainty interval

Table 2.1: Checklist of information that should be included in new reports of global health estimates

Item #	Checklist item	Reported on page #
Objectives and funding		
1	Define the indicator(s), populations (including age, sex, and geographic entities), and time period(s) for which estimates were made.	Summary. Main Text: Introduction, Methods (Overview).
2	List the funding sources for the work.	N/A
Data Inputs		
For all data inputs from multiple sources that are synthesized as part of the study:		
3	Describe how the data were identified and how the data were accessed.	Main Text: Methods. Supplementary Appendix, Section 4.2
4	Specify the inclusion and exclusion criteria. Identify all ad-hoc exclusions.	Main Text: Methods.
5	Provide information on all included data sources and their main characteristics. For each data source used, report reference information or contact name/institution, population represented, data collection method, year(s) of data collection, sex and age range, diagnostic criteria or measurement method, and sample size, as relevant.	Main Text: Methods.
6	Identify and describe any categories of input data that have potentially important biases (e.g., based on characteristics listed in item 5).	Main text: Limitations section.
For data inputs that contribute to the analysis but were not synthesized as part of the study:		
7	Describe and give sources for any other data inputs.	N/A
For all data inputs:		
8	Provide all data inputs in a file format from which data can be efficiently extracted (e.g., a spreadsheet rather than a PDF), including all relevant meta-data listed in item 5. For any data inputs that cannot be shared because of ethical or legal reasons, such as third-party ownership, provide a contact name or the name of the institution that retains the right to the data.	Available through: http://ghdx.healthdata.org/ (upon publication)
Data analysis		
9	Provide a conceptual overview of the data analysis method. A diagram may be helpful.	Main text: Methods
10	Provide a detailed description of all steps of the analysis, including mathematical formulae. This description should cover, as relevant, data cleaning, data pre-processing,	Main text: Methods

	data adjustments and weighting of data sources, and mathematical or statistical model(s).	
11	Describe how candidate models were evaluated and how the final model(s) were selected.	Main Text: Methods; Supplementary Appendix
12	Provide the results of an evaluation of model performance, if done, as well as the results of any relevant sensitivity analysis.	Supplementary Appendix
13	Describe methods for calculating uncertainty of the estimates. State which sources of uncertainty were, and were not, accounted for in the uncertainty analysis.	Main Text: Methods
14	State how analytic or statistical source code used to generate estimates can be accessed.	Available through: http://ghdx.healthdata.org/ (upon publication)
Results and Discussion		
15	Provide published estimates in a file format from which data can be efficiently extracted.	Available through: http://ghdx.healthdata.org/ (upon publication)
16	Report a quantitative measure of the uncertainty of the estimates (e.g. uncertainty intervals).	Available through: http://ghdx.healthdata.org/ (upon publication)
17	Interpret results in light of existing evidence. If updating a previous set of estimates, describe the reasons for changes in estimates.	Main Text: Discussion
18	Discuss limitations of the estimates. Include a discussion of any modelling assumptions or data limitations that affect interpretation of the estimates.	Main Text: Limitations

Figure 3.1: Percentage of the population greater than 65 years of age, national

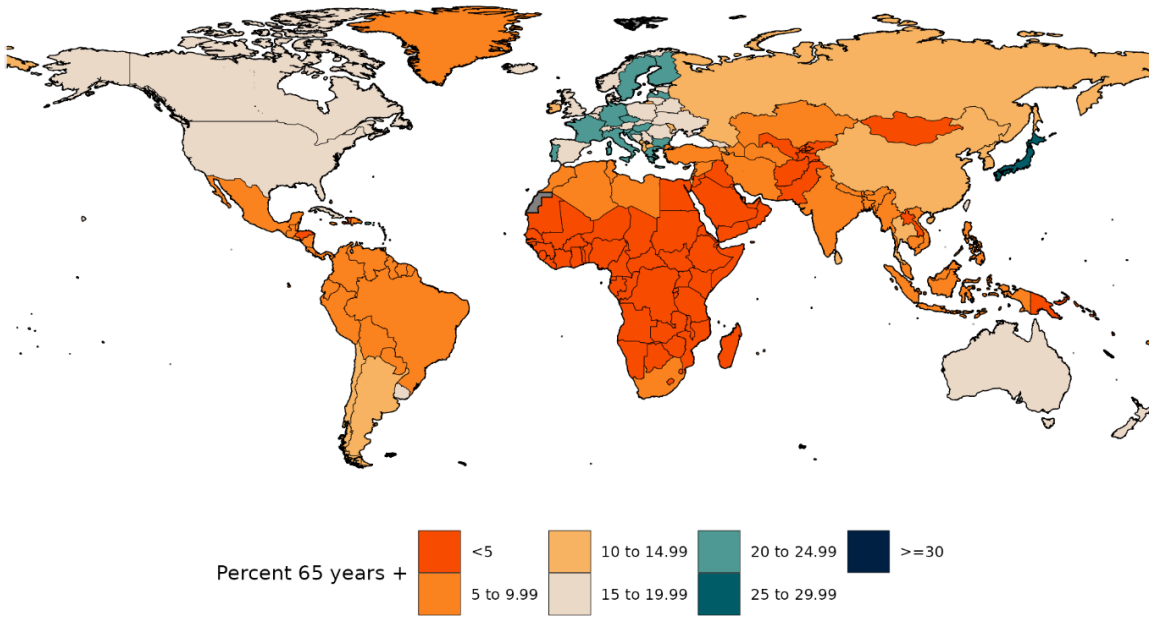


Figure 3.2: Percentage of the population greater than 65 years of age, subnational

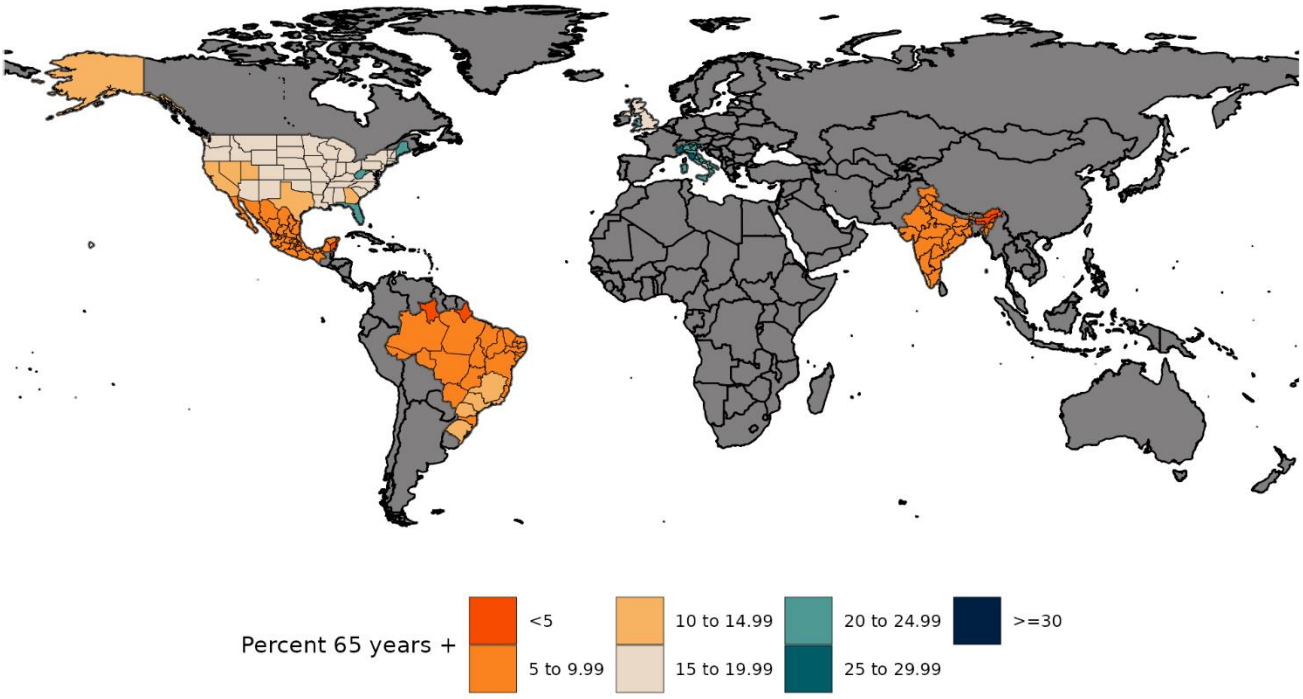


Figure 3.3: Pre-pandemic vaccine hesitancy percentage, national

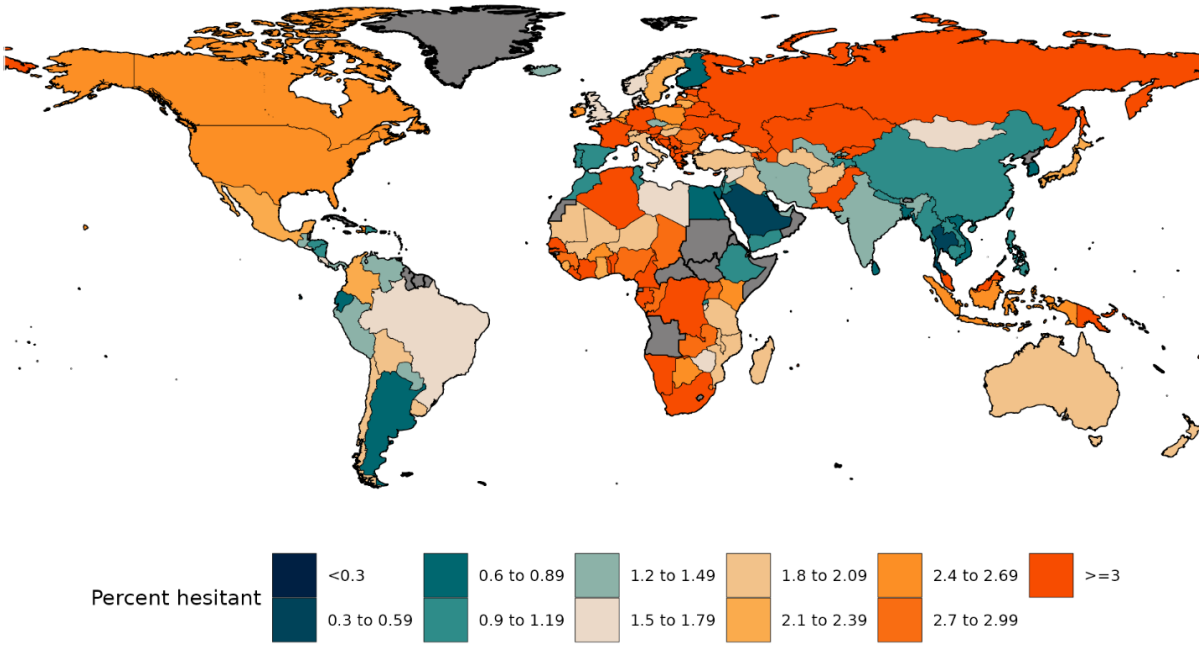


Figure 3.4: Mid-pandemic vaccine hesitancy percentage, national

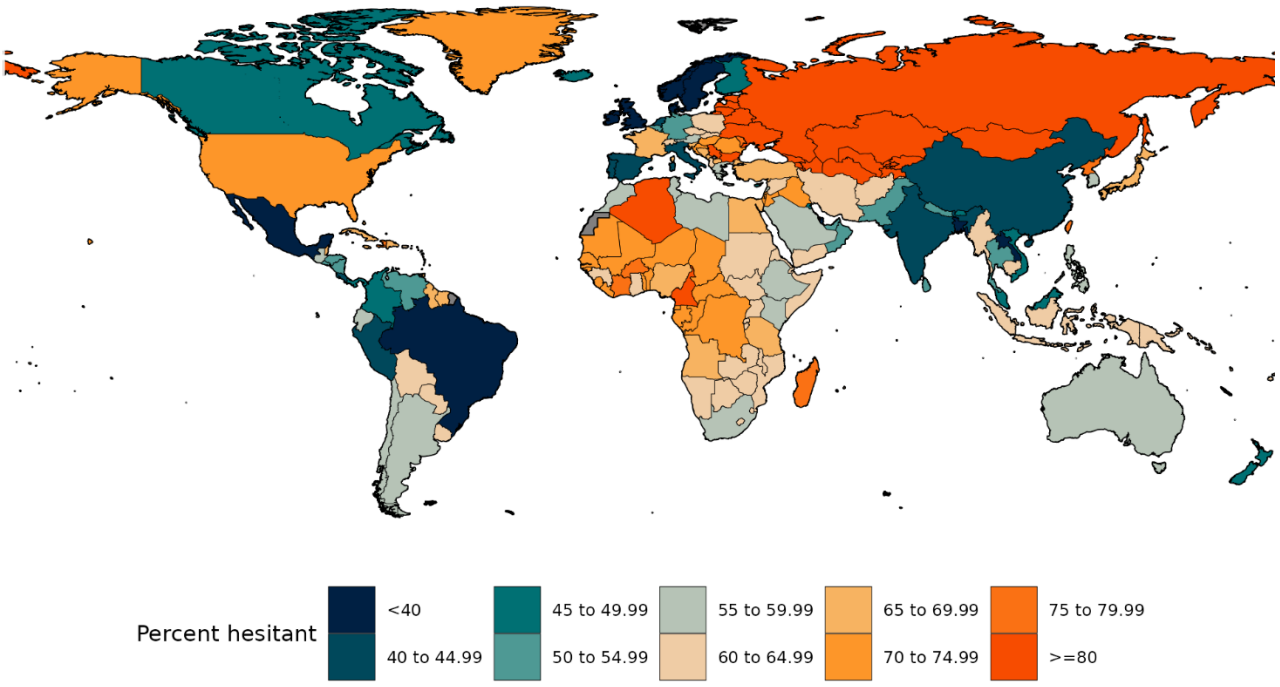


Figure 3.5: Mid-pandemic vaccine hesitancy percentage, subnational

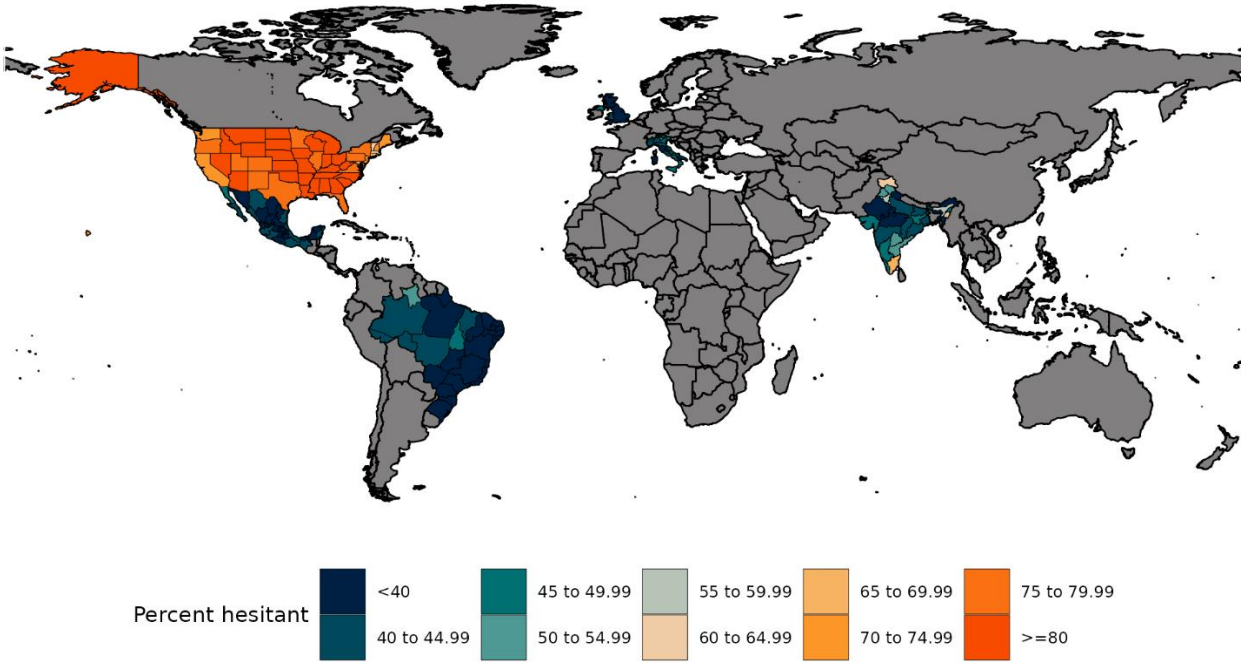


Figure 3.6: Governmental trust, centered and scaled PCA variable

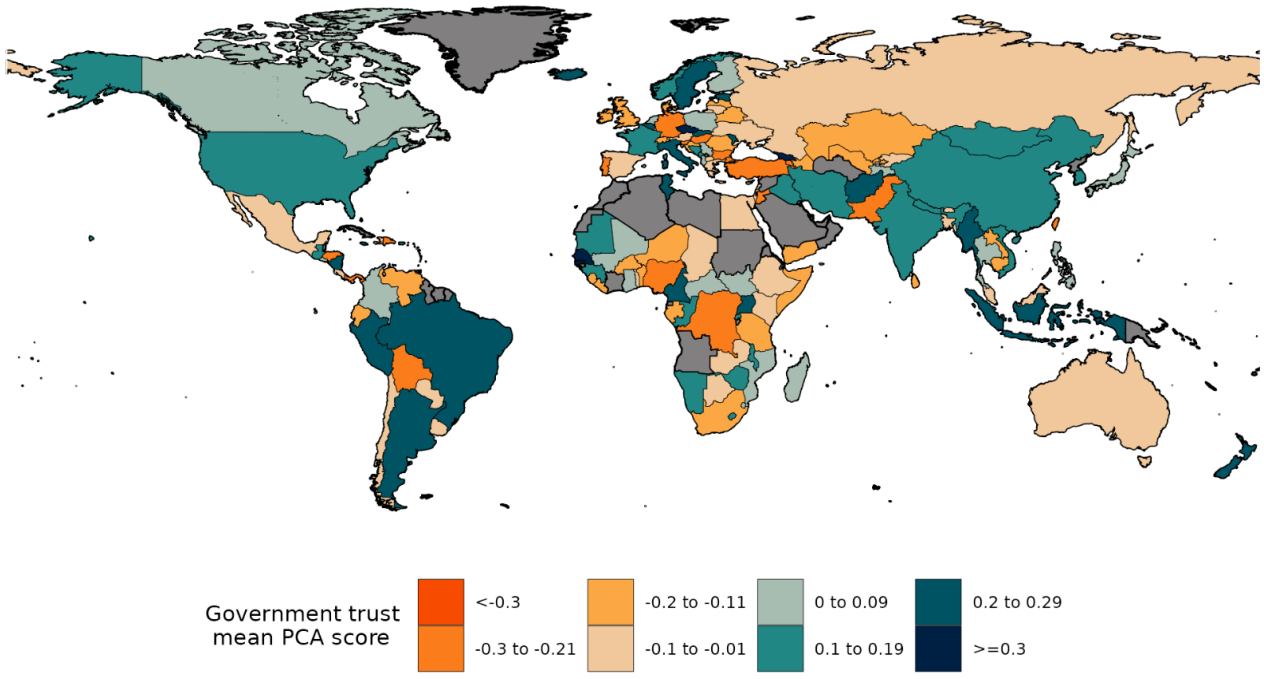


Figure 3.7: 2019 GHSI overall score

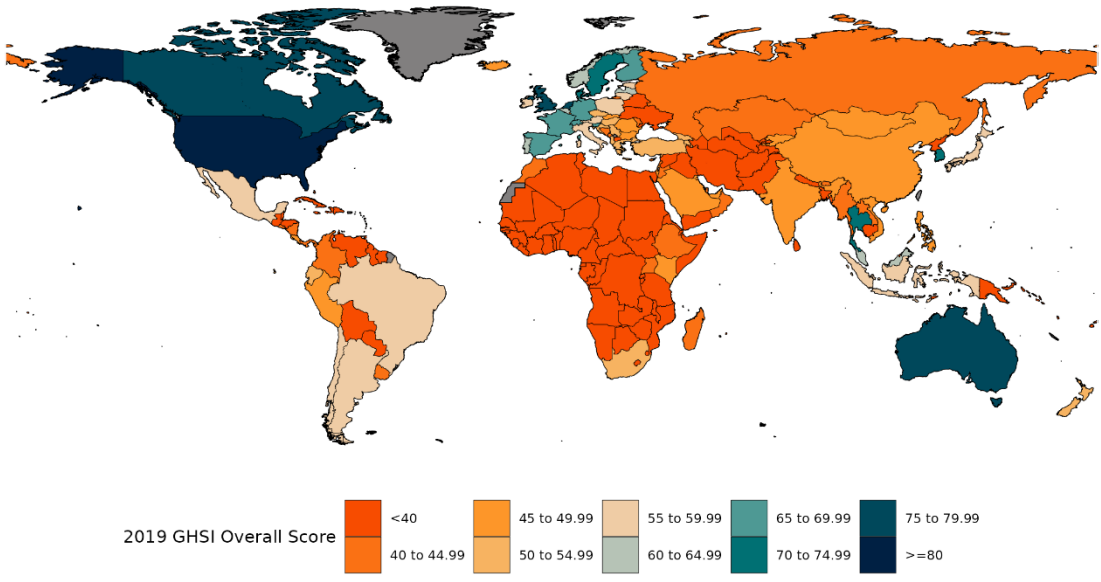


Figure 3.8: Time to 1%, 5%, and 10% coverage of one-dose COVID-19 vaccine, subnational

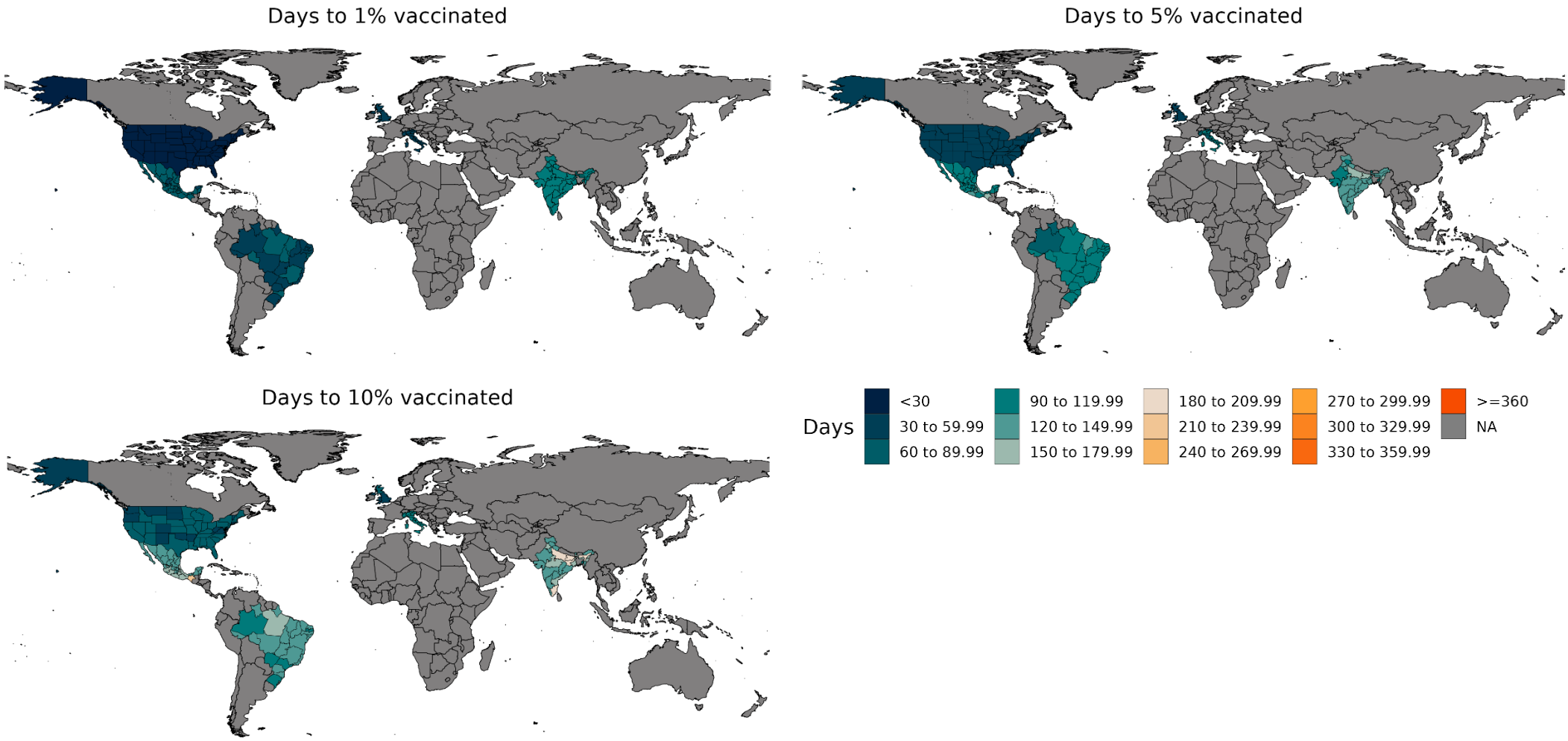
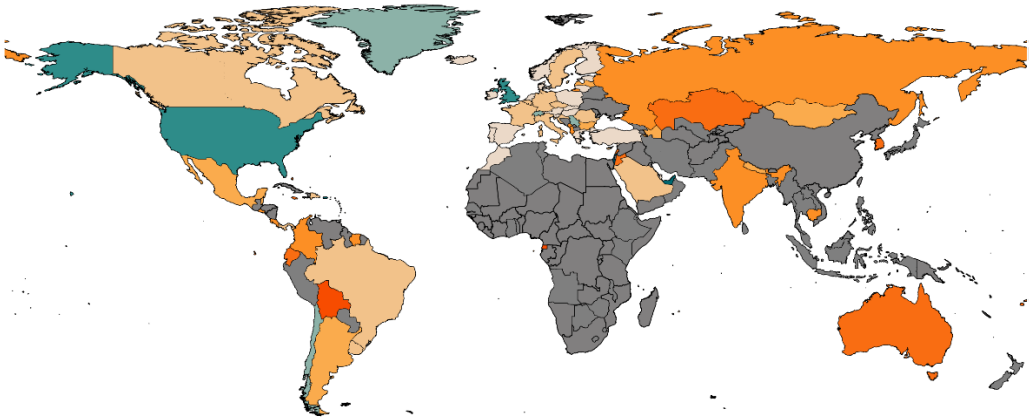
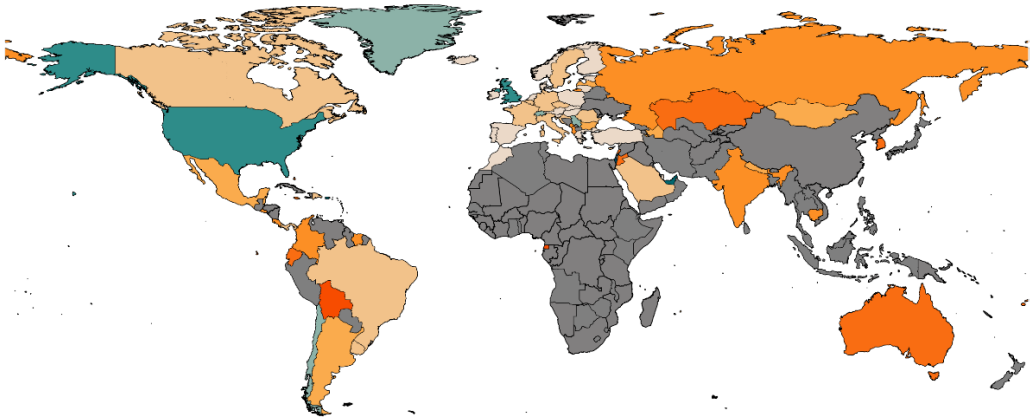


Figure 3.9: Time to 1%, 5%, and 10% one-dose COVID-19 vaccine coverage for the period to May 1, 2021, national locations

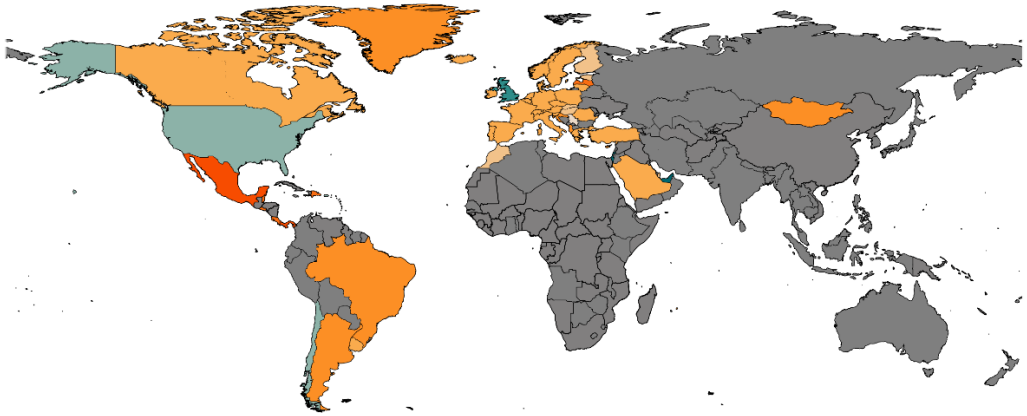
Days to 1% vaccinated



Days to 5% vaccinated



Days to 10% vaccinated



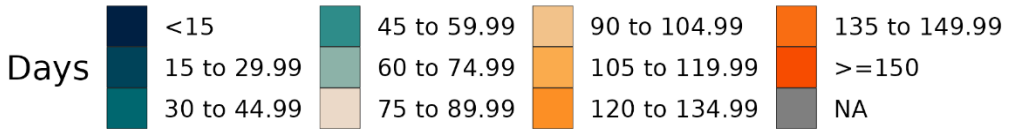


Figure 3.10: Maximum daily doses administered per capita, smoothed and averaged, for the period to May 1, 2021, national locations

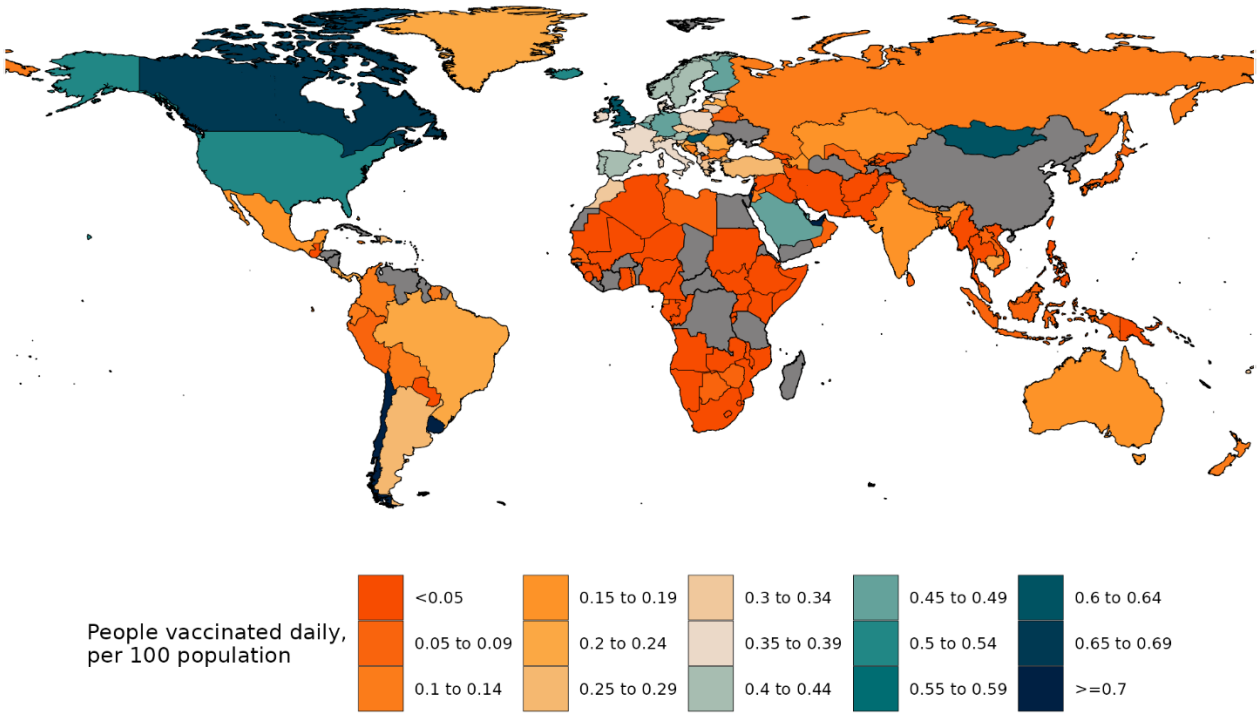


Figure 3.11: Maximum one-dose COVID-19 vaccine coverage for the period to May 1, 2021, national locations

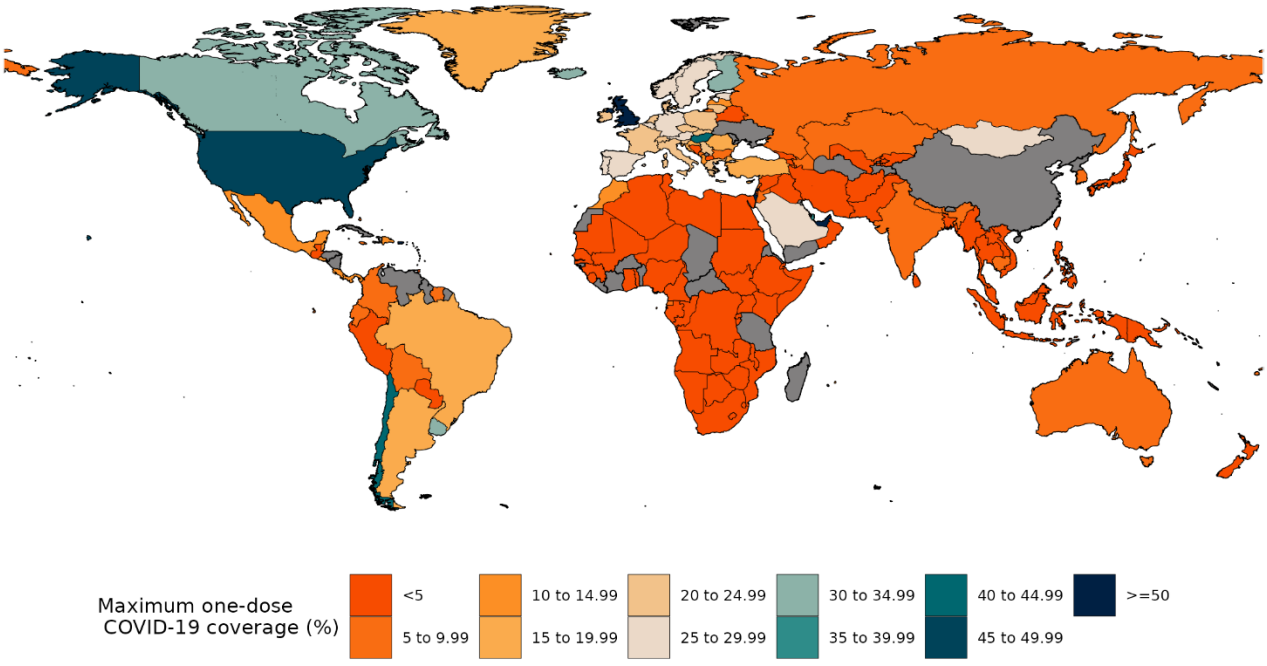


Figure 3.12: Time to 1%, 5%, and 10% one-dose COVID-19 vaccine coverage for those countries with routine MCV coverage less than 90%

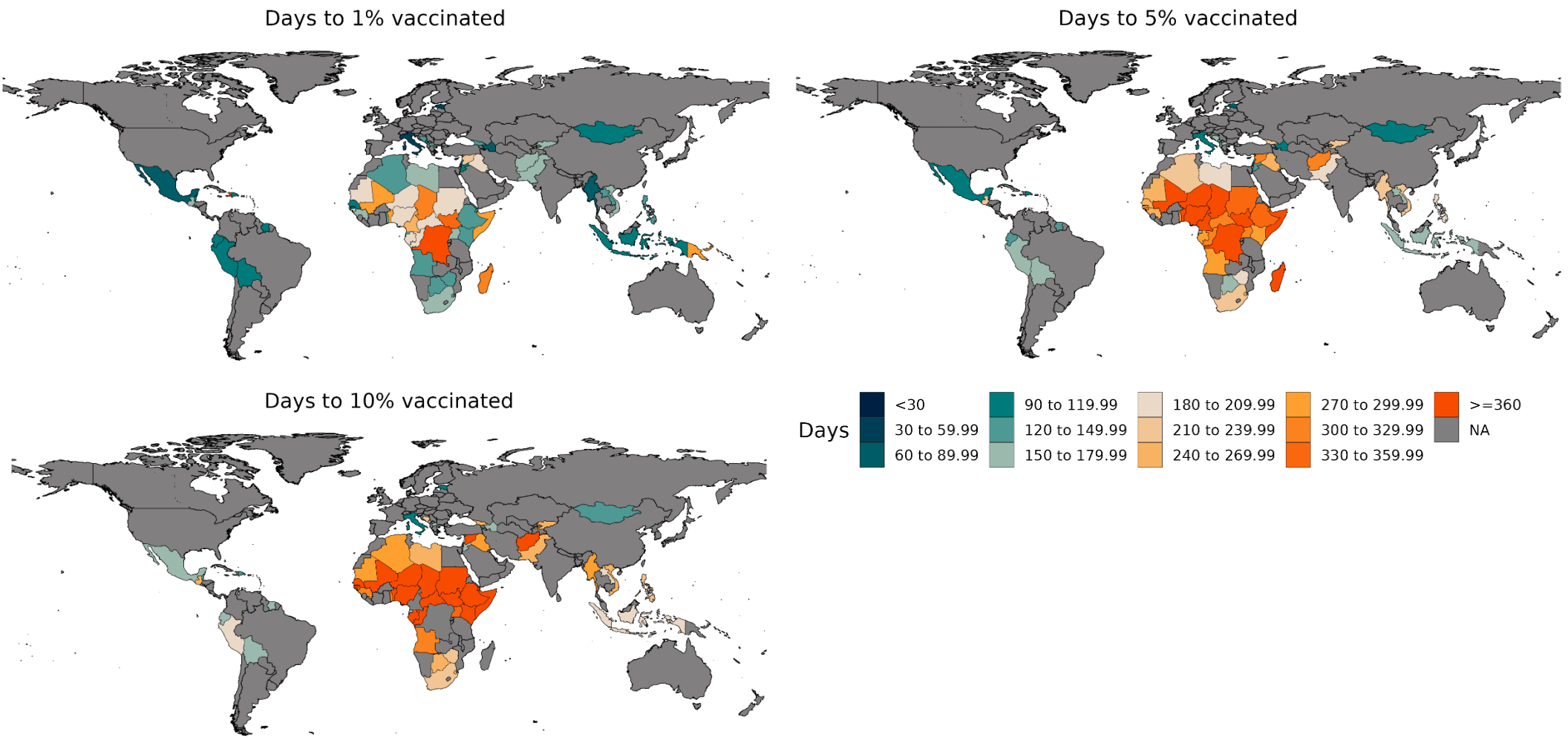


Figure 3.13: Maximum daily doses administered per capita, smoothed and averaged, for those countries with routine MCV coverage less than 90%

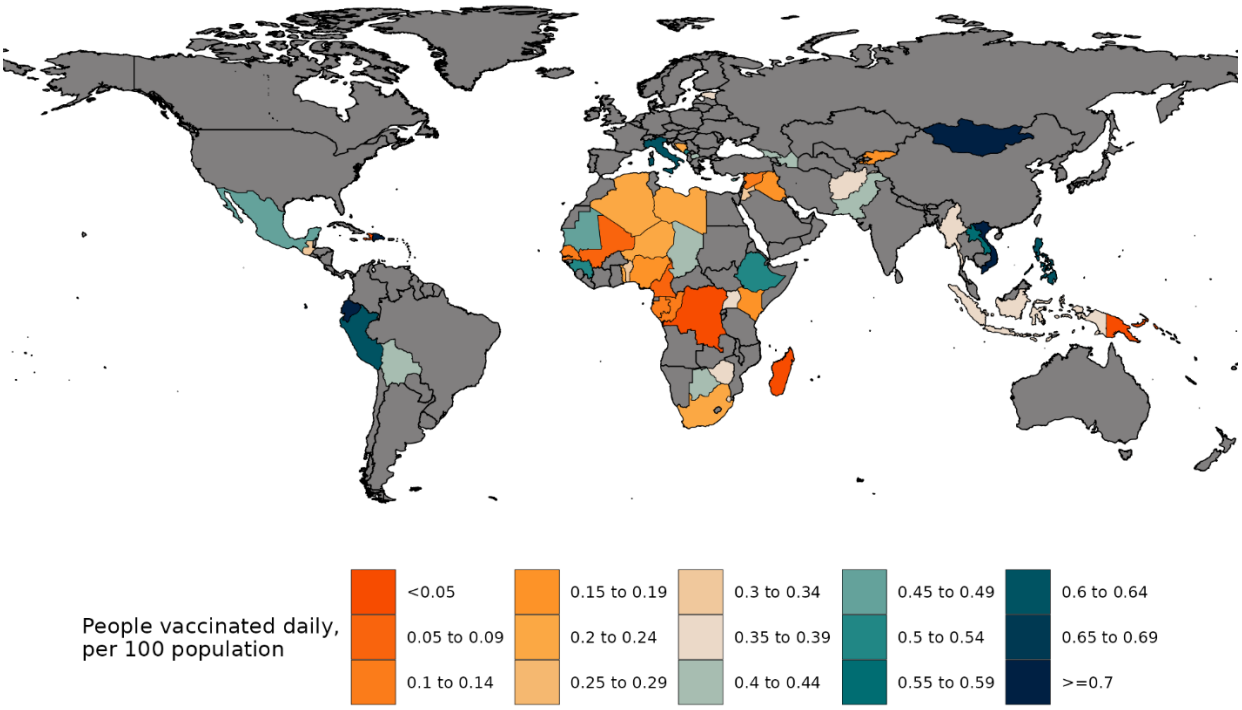


Figure 3.14: Maximum one-dose COVID-19 vaccine coverage for those countries with routine MCV coverage less than 90%

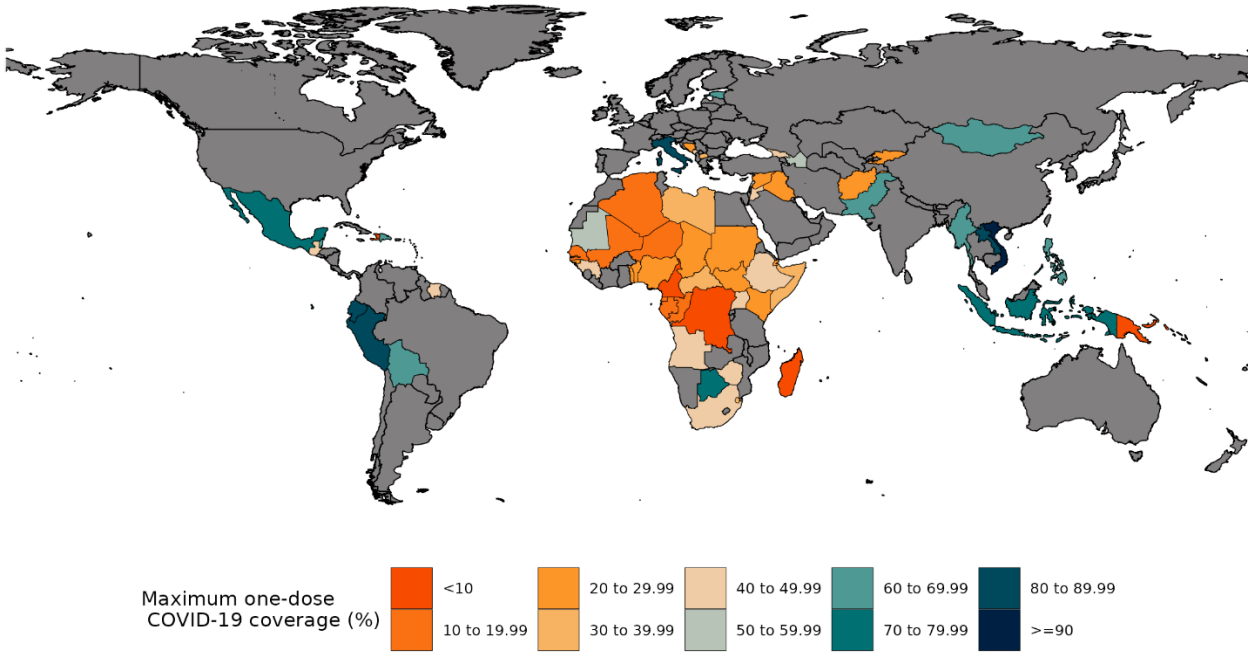


Figure 3.15: Scatterplot of one-dose MCV coverage (logit) versus time to 1% (log), n=134

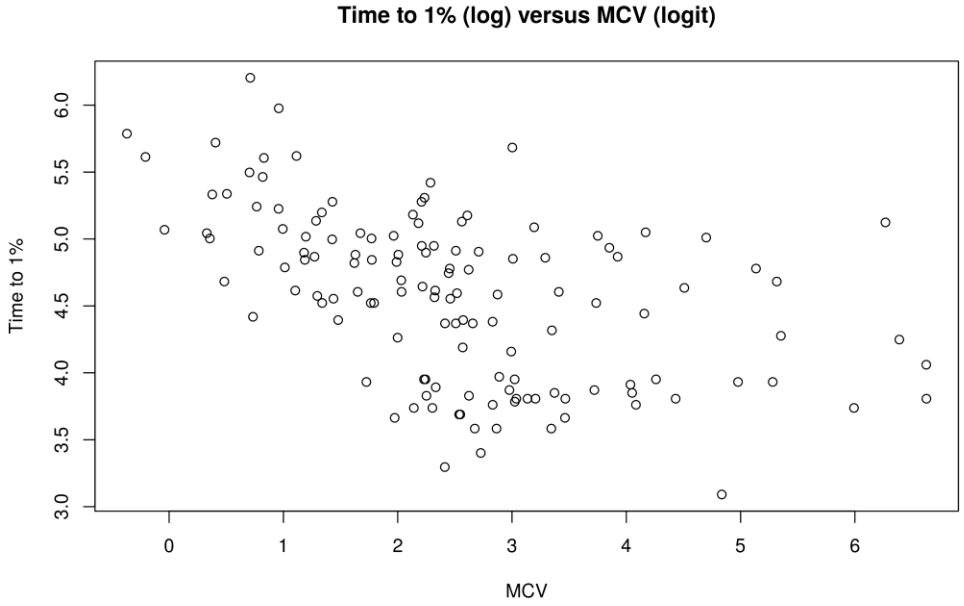


Figure 3.16: Scatterplot of one-dose MCV coverage (logit) versus time to 5% (log), n=132

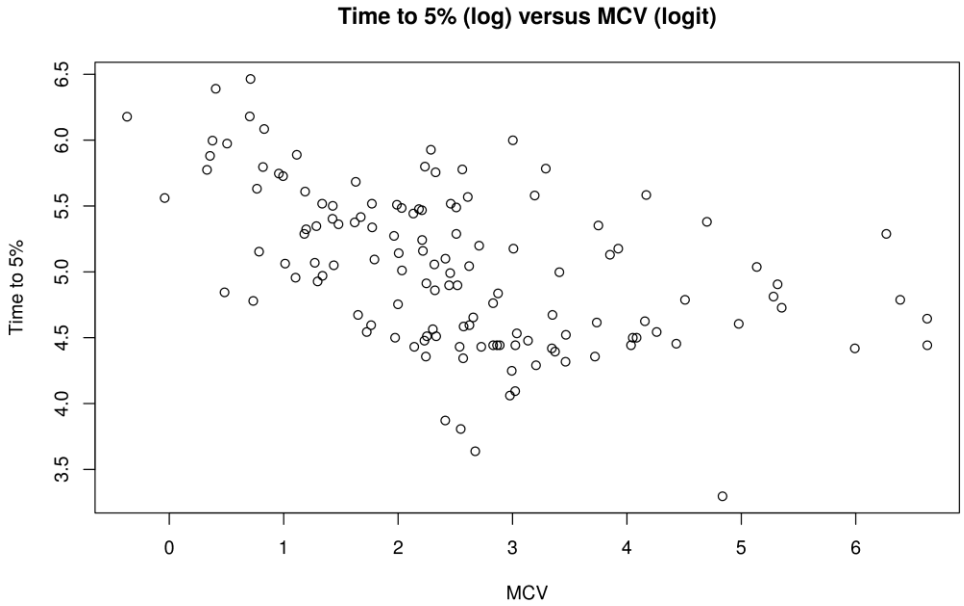


Figure 3.17: Scatterplot of one-dose MCV coverage (logit) versus time to 10% (log), n=129

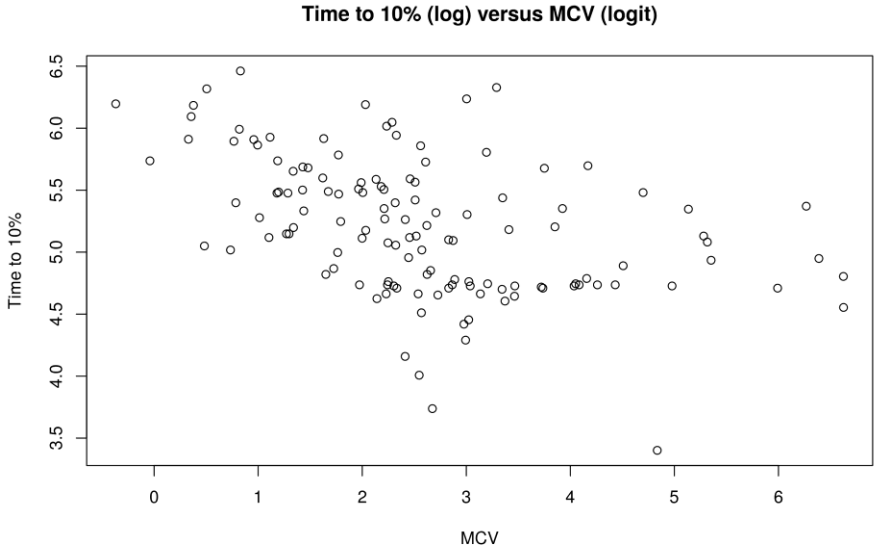


Figure 3.18: Scatterplot of one-dose MCV coverage (logit) versus time to 25% (log), n=116

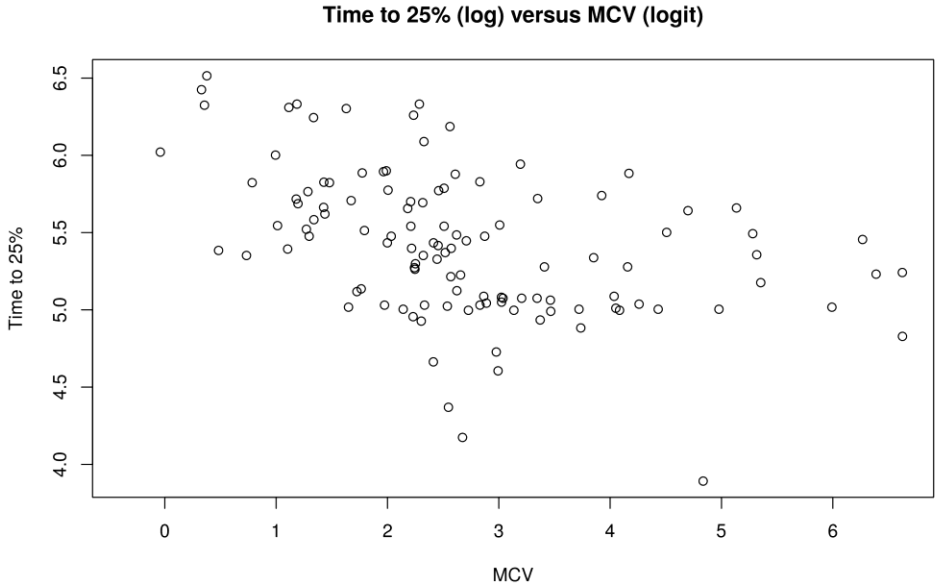


Figure 3.19: Scatterplot of one-dose MCV coverage (logit) versus time to 50% (log), n=87

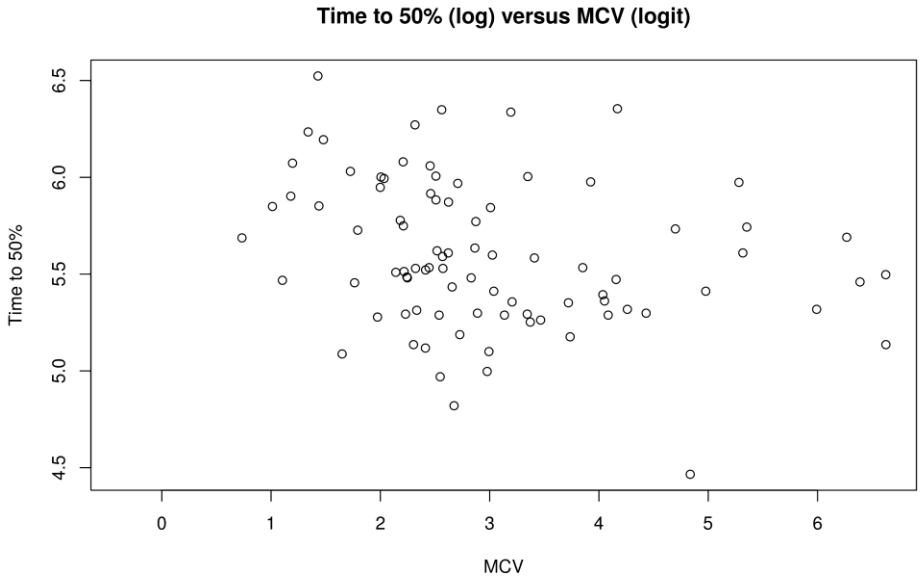


Figure 3.20: Scatterplot of one-dose MCV coverage (logit) versus maximum daily doses per capita (smoothed and averaged over 30 days), n=133

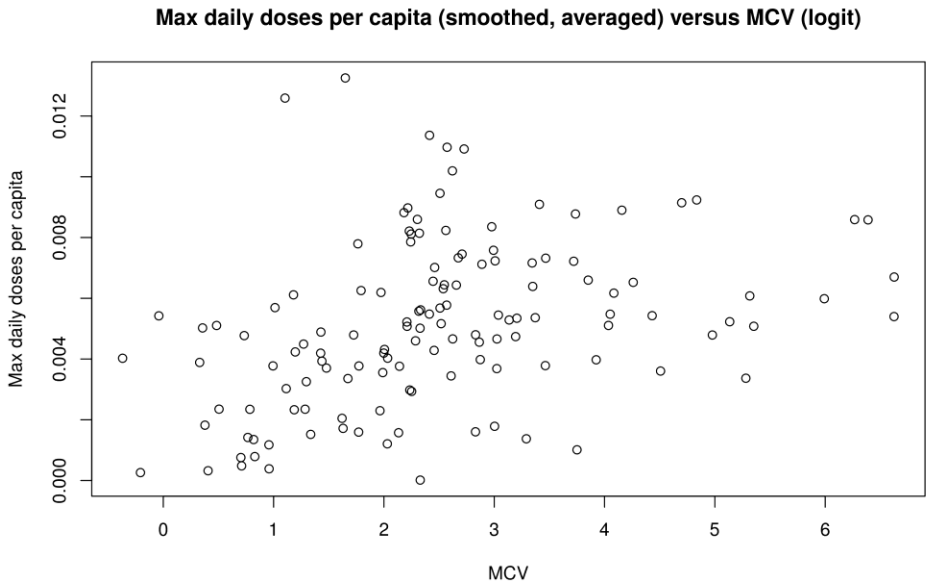


Figure 3.21: Scatterplot of one-dose MCV coverage (logit) versus maximum overall coverage (logit), n=134

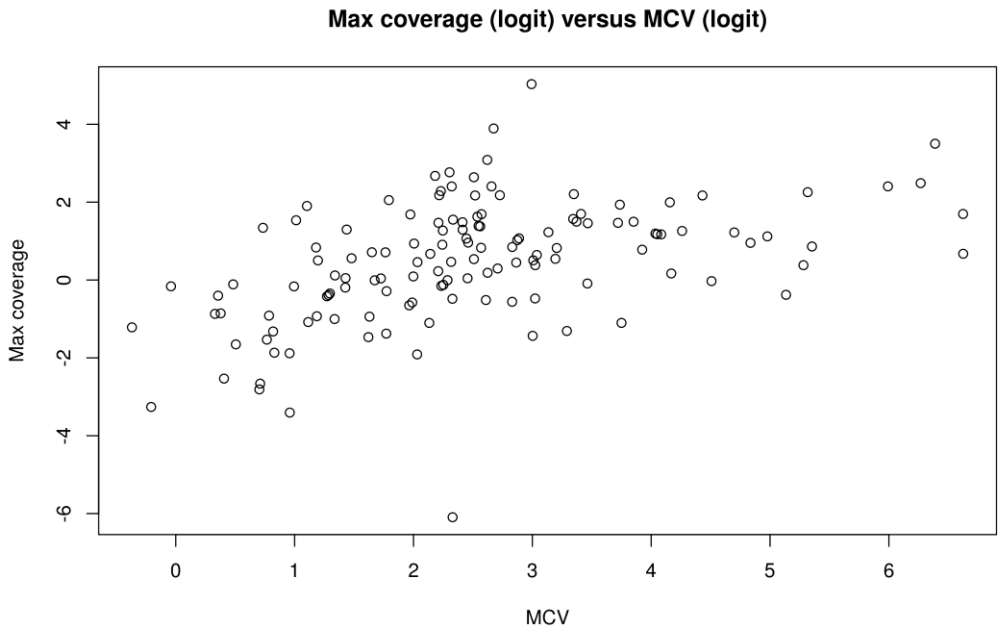
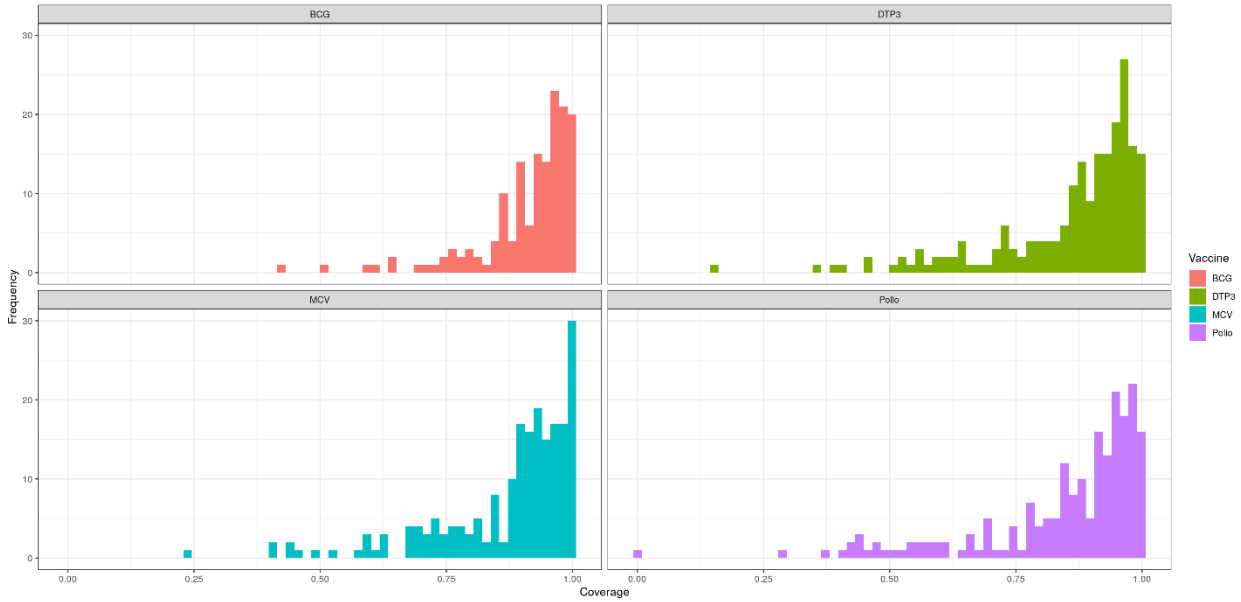


Figure 3.22: Histogram of coverage for each MCV1, DTP3, BCG, and polio vaccinations



Section 4: Additional methods

Section 4.1: PCA analysis for trust in government and corruption

We used principal component analysis (PCA) to create summary metrics that combine information about trust in government. The input variables were trust in government (WVS) and trust in government (Gallup). Using centered and scaled versions of the covariates, the summary metrics consist of the first principal component from each PCA analysis. The first component (of four) explained 92.6% of the variation. PCA requires that all variables have complete data, but some of the variables had missing data. We used the imputePCA function from the missMDA R package to impute missing values, but only used observations that had at least one of the two original observations. The package implements the iterative PCA method described in Josse and Husson (2010).[42]

Section 4.2: Our World in Data location-specific cleaning

For each location, we considered cumulative and daily vaccine curves over the entire study period. Specific fixes or reasons for dropping for each location are specified in the table below.

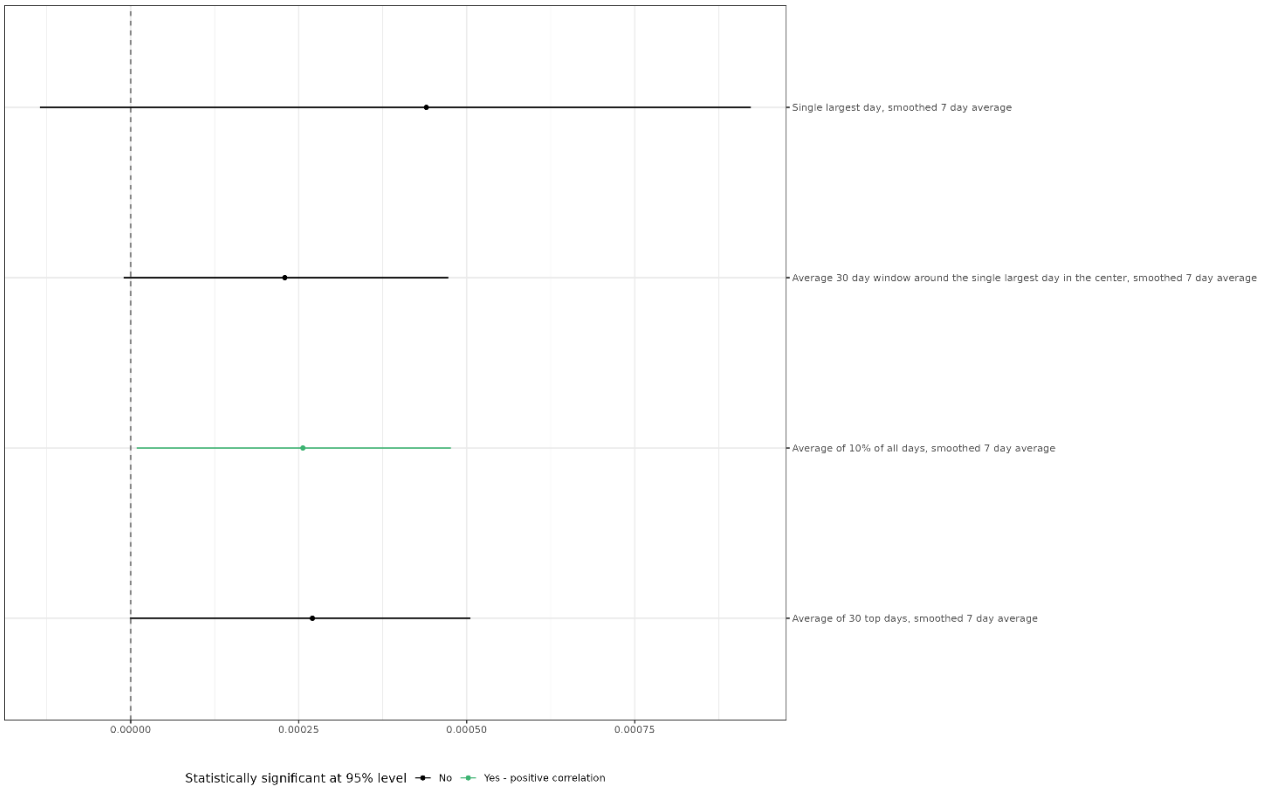
Table 4.2.1 Location-specific cleaning or omissions

Location	Reason
Eswatini	Cropped back data to 8-21-2022 before a large spike at the tail given unresolved provenance of spike
Cameroon	Cropped back data to 11-20-2022 before a large spike at the tail given unresolved provenance of spike
Guinea-Bissau	Cropped back data to 8-28-2022 before a large spike at the tail given unresolved provenance of spike
Niger	Cropped back data to 10-16-2022 before a large spike at the tail given unresolved provenance of spike
Egypt	Drop from analysis of maximum doses due to highly anomalous day on 6-29-2022
Lebanon	Drop from analysis of maximum doses due to highly anomalous day on 4-25-2022
United Arab Emirates	Cap vaccinations at 98% as UAE includes non-nationals in vaccination figures
Antigua and Barbuda	Drop from analysis: jump from 0 to >5% vaccinated in a single day
Cuba	Drop from analysis: jump from 0 to >5% vaccinated in a single day
Saint Kitts and Nevis	Drop from analysis: jump from 0 to >5% vaccinated in a single day
Saint Vincent and the Grenadines	Drop from analysis: jump from 0 to >5% vaccinated in a single day
Bhutan	Drop from analysis: jump from 0 to >5% vaccinated in a single day
Tuvalu	Drop from analysis: jump from 0 to >5% vaccinated in a single day
San Marino	Drop from analysis: jump from 0 to >5% vaccinated in a single day
Kiribati	Drop from analysis: erratic reporting, in part due to small population size
Samoa	Drop from analysis: erratic reporting, in part due to small population size
Solomon Islands	Drop from analysis: erratic reporting, in part due to small population size
Tonga	Drop from analysis: erratic reporting, in part due to small population size
Vanuatu	Drop from analysis: erratic reporting, in part due to small population size

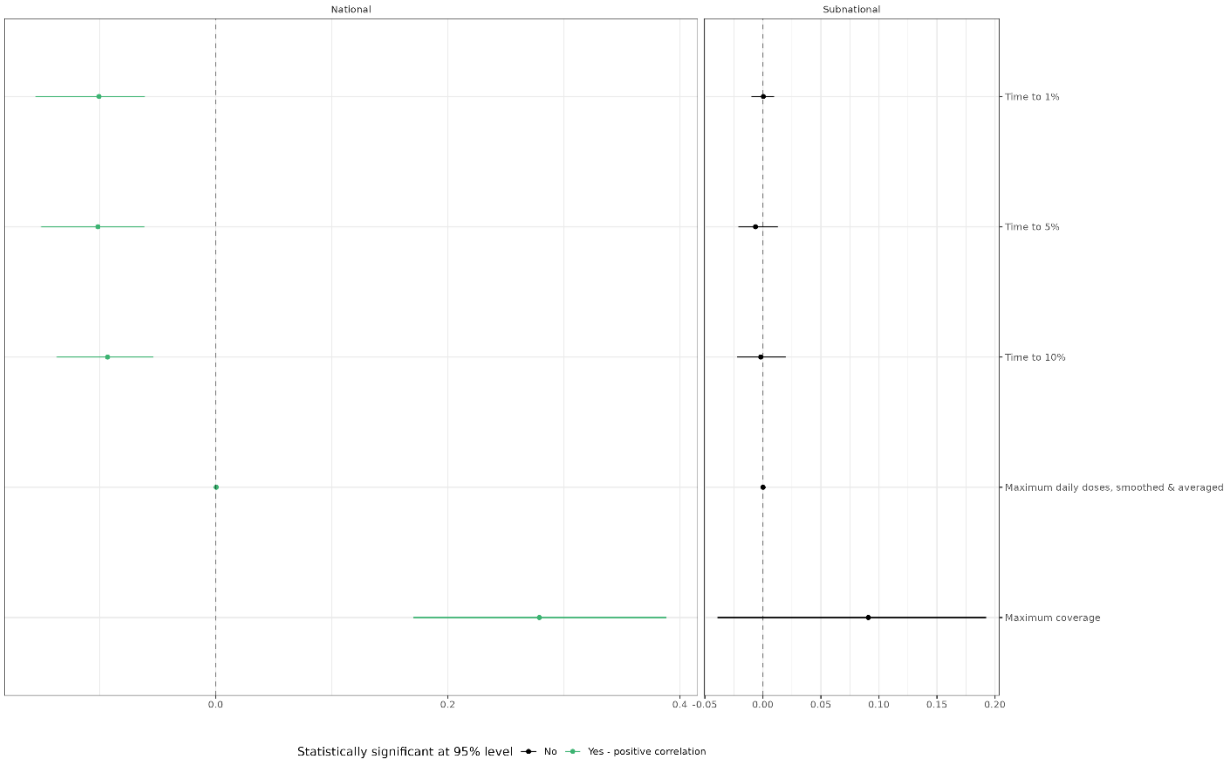
Turkmenistan	Drop from analysis: few data points
Dominica	Drop from analysis: erratic reporting, in part due to small population size
Guyana	Drop from analysis: erratic reporting, in part due to small population size
Saint Lucia	Drop from analysis: erratic reporting, in part due to small population size
Yemen	Drop from analysis: limited data due to conflict
United Republic of Tanzania	Drop from analysis: few data points
Cook Islands	Drop from analysis: erratic reporting, in part due to small population size
Nauru	Drop from analysis: erratic reporting, in part due to small population size
Niue	Drop from analysis: erratic reporting, in part due to small population size
Tokelau	Drop from analysis: erratic reporting, in part due to small population size
Kuwait	Drop from analysis: inconsistent reporting
China	Drop from analysis: inconsistent reporting
Honduras	Drop from analysis: inconsistent reporting
Nicaragua	Drop from analysis: inconsistent reporting
Venezuela	Drop from analysis: few data points
Ukraine	Drop from analysis: limited data due to conflict

Section 5: Sensitivity analyses

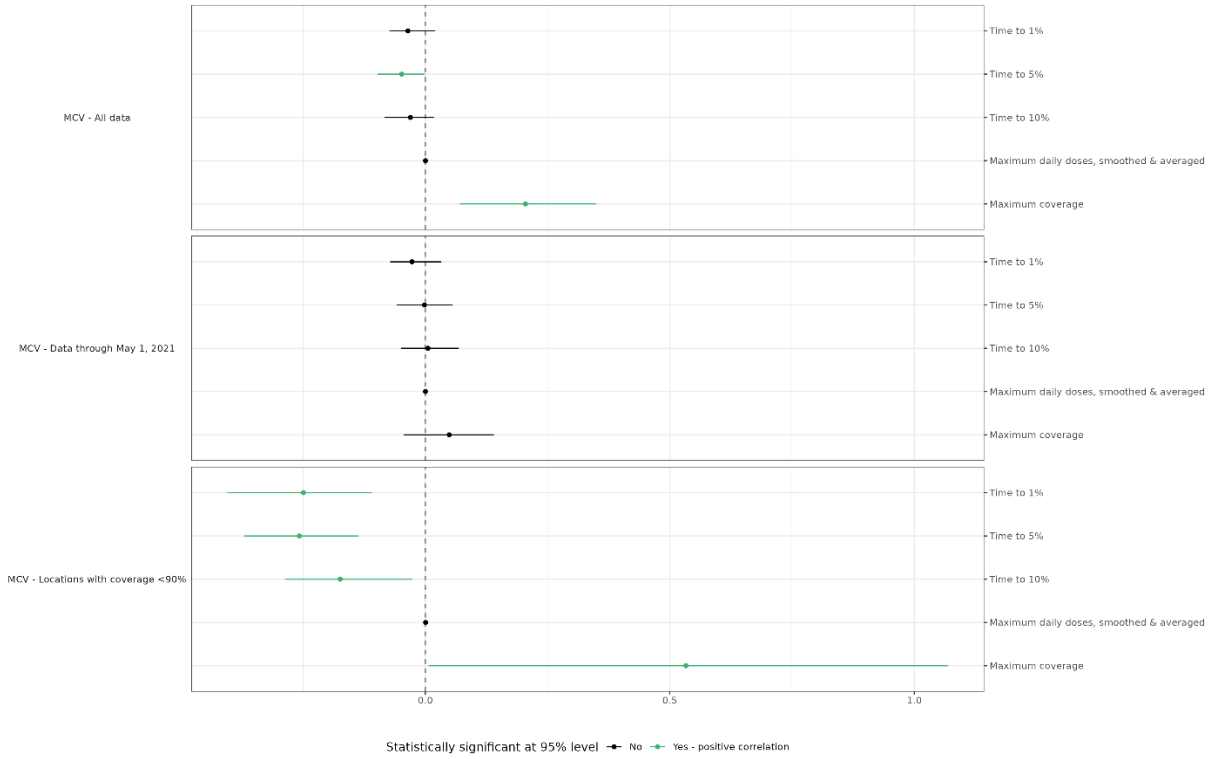
Section 5.1: Differing definitions for maximum daily doses versus MCV: A) Single-day maximum doses administered per capita, smoothed, versus MCV, B) Average thirty day window around maximum one-day vaccine administration per capita, smoothed and averaged, versus MCV, and C) Average top 10% of single-day vaccine doses administered per capita, smoothed and averaged, and D) Current best version: Average of top 30 days of vaccine doses administered per capita, versus MCV, national level only



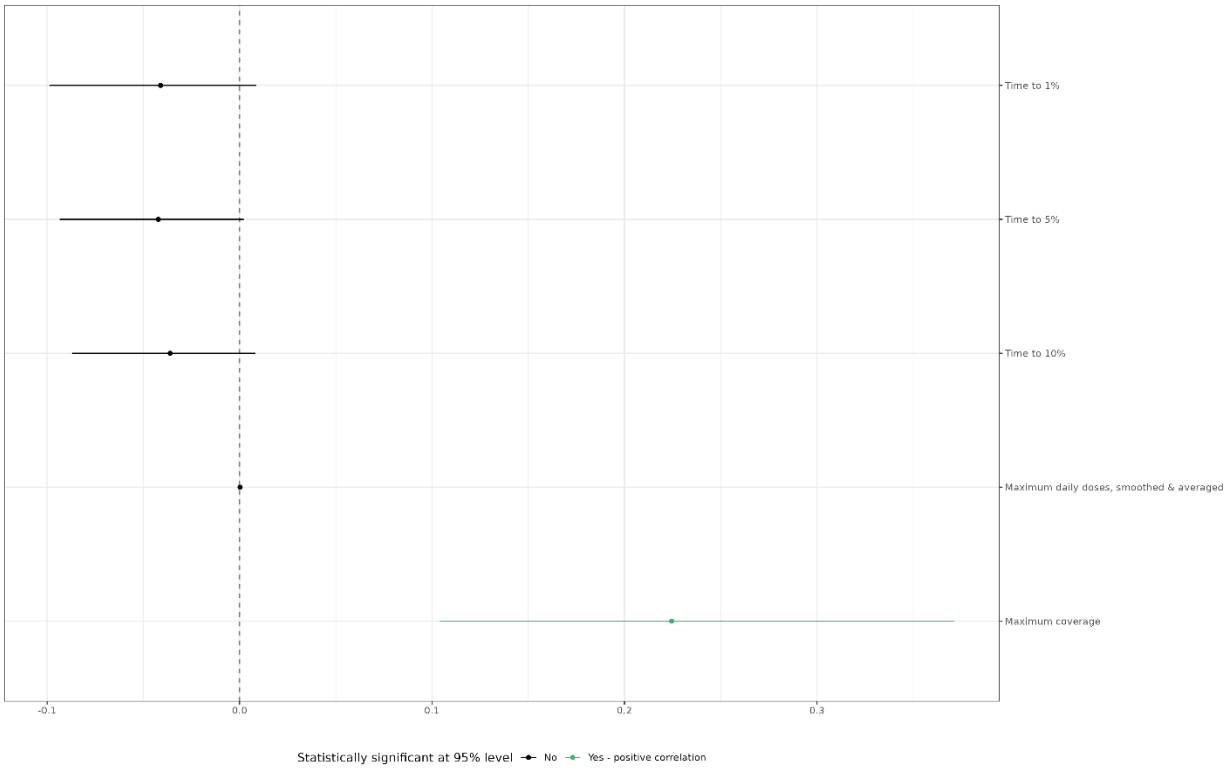
Section 5.2: National and subnational models using mid-pandemic vaccine hesitancy



Section 5.3: National models using raw OWiD data, extracted March 31, 2023

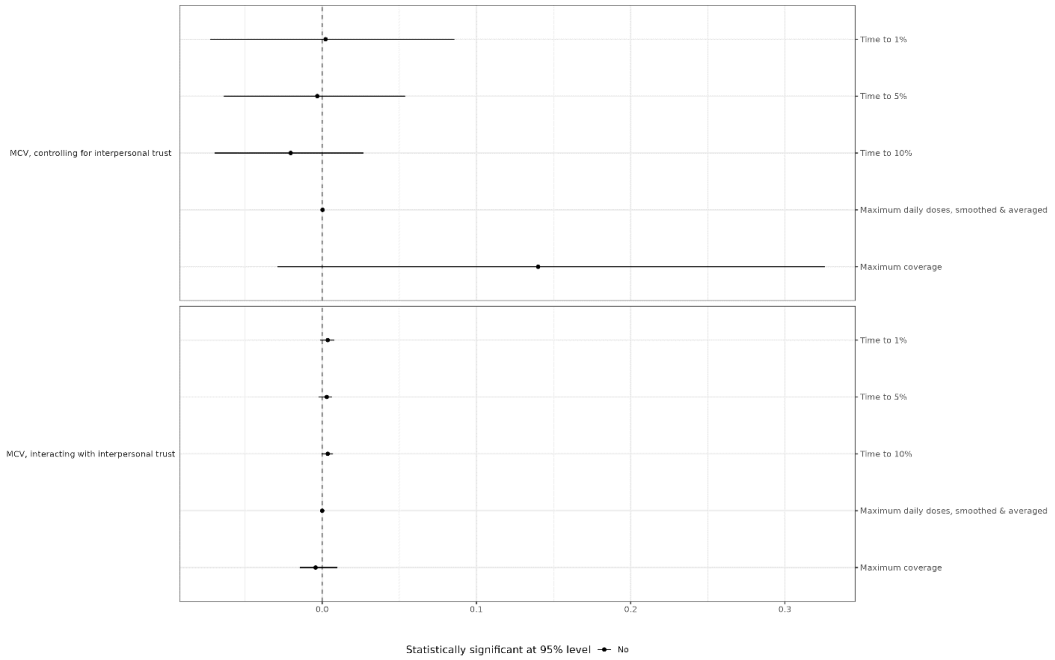


Section 5.4: MCV versus one-dose COVID-19 only for locations with government trust data (n=95)

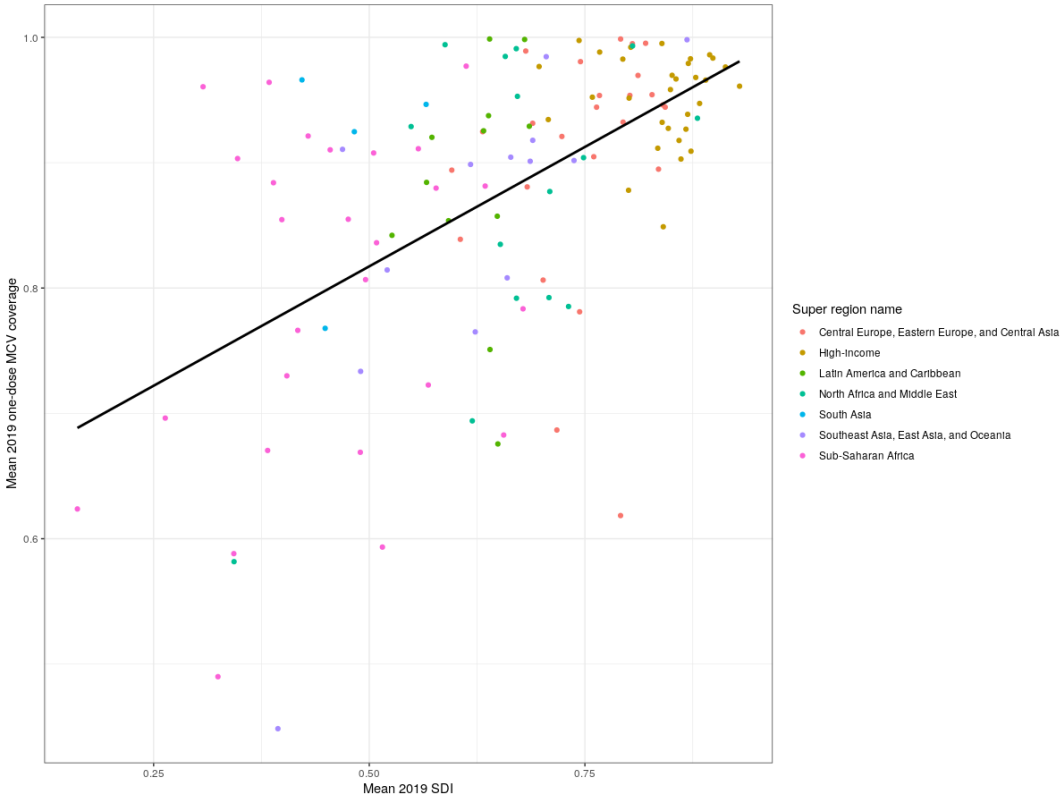


Section 6: Supplemental results

Section 6.1: Models of MCV versus one-dose COVID-19 controlling for and interacting with interpersonal trust, n=62 national locations

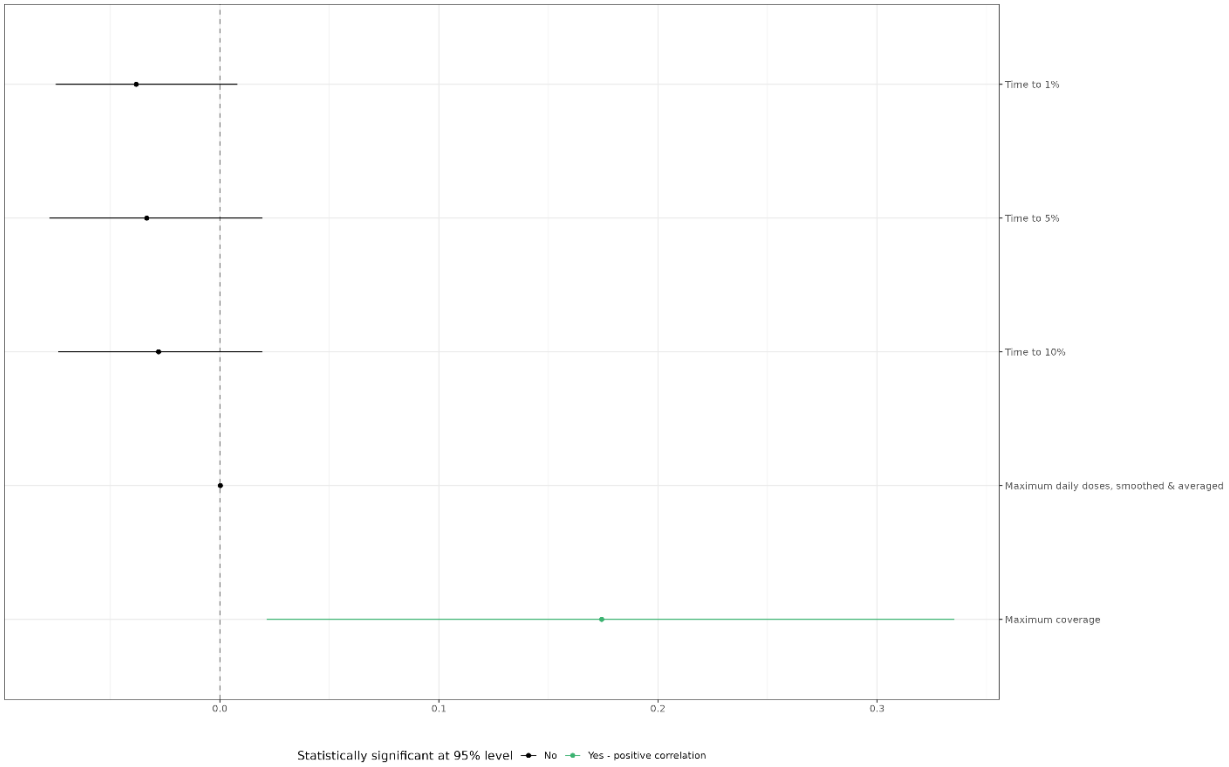


Section 6.2: Plot of sociodemographic index (SDI) versus MCV coverage, by super region



Linear model coefficient for SDI: 0.3811 (0.2809 – 0.4813)

Section 6.3: Models controlling for SDI, as well as age and hesitancy, with MCV



CHAPTER 5: CONCLUSIONS

SUMMARY

Despite years of research into pandemic preparedness via the capacity to prevent, detect, and respond to novel threats, zoonotic spillover, and outbreak resiliency, no country was wholly prepared for the COVID-19 pandemic. Moreover, those countries ranking mostly highly in pre-pandemic readiness were actually worse off than some other less-highly ranked countries. In addition, existing preparedness plans do not consider subnational variations in readiness. This dissertation aimed to quantify how these existing preparedness metrics correlated with COVID-19 outcomes both nationally and subnationally, and whether key indicators were particularly informative of various COVID-19 outcomes than others. As vaccination has played an essential role in managing the COVID-19 pandemic, exploring how MCV vaccine coverage - the existing measure of immunization readiness – correlated to COVID-19 vaccine delivery heterogeneities was of particular interest. The first aim demonstrates that composite pandemic preparedness metrics – via JEE scores and GHSI scores – were not informative of better COVID-19 outcomes. We identify a number of baseline characteristics correlated with COVID-19 infection and fatality rates, including environmental suitability and age structure, population density, BMI, GDP per capita, altitude, previous exposure to betacoronaviruses, smoking rates, and comorbid COPD and cancer prevalence. In addition, we emphasize higher trust in the government and in other people as a key predictor of reduced COVID-19 infections, likely through increased vaccine uptake as a mediator. These findings provide a number of avenues for improvement before the next pandemic such as enacting policies to reduce obesity or smoking rates, and ways to improve trust such as through improved transparency and clear communication, addressing mis- and dis-information, and increasing accountability among leadership. Given that trust is highly correlated with vaccine uptake, improving trust now is likely to have implications for all future threats.

In the second aim, we demonstrate again that composite pandemic preparedness was overall not predictive of better COVID-19 outcomes, this time subnationally in Brazil the United States. Some key metrics associated with national-level differences did not persist nationally, including BMI, comorbid COPD prevalence, and smoking prevalence. After standardizing state-level infection and fatality rates, marked heterogeneities within each country were minimized, and differences between the two countries became more apparent, suggesting that many national-level differences may be exacerbating existing subnational differences in outcomes. Trust in the government and in other people – a key finding from the national level analysis – was not a significant predictor of improved COVID-19 outcomes at a subnational level, though the data availability and quality were much lower subnationally for existing trust data. In our analysis of policy-amenable indicators for COVID-19 outcomes, only hospital beds per capita was significantly related to increased COVID-19 infections in the United States, though various indicators of health care coverage and access and GHSI risk environment were marginally suggestive of lower COVID-19 infections in both Brazil and the United States. Since health care quality and access are correlated with vaccine delivery, this suggests a pathway by which better health care may improve COVID-19 outcomes. We propose additional research into local trust and expanding this analysis globally and to the county-level to better understand subnational drivers in COVID-19 outcome heterogeneities. Moreover, we urge policymakers to consider how subnational variabilities in preparedness - which are presently not quantified nor considered in pandemic preparedness plans – could inhibit national level progress in readily preventing, detecting, and responding to novel threats.

In our third aim, we relate pandemic preparedness scores to initial COVID-19 delivery through the routine immunization readiness metric: MCV coverage. Vaccination played a huge role in influencing COVID-19 outcomes, and we wanted to retrospectively understand how this one essential element of pandemic preparedness tied into pandemic COVID-19 delivery and uptake. We find that MCV coverage is a significant correlate of one-dose COVID-19 outcomes for time to delivery – a proxy for the time out the door to shots in arms – as well as the maximum level of coverage achieved; in contrast, the maximum doses at scale up was not a significant correlate with MCV coverage. While overall pandemic preparedness metrics were not predictive of COVID-19 success, this analysis demonstrates that routine immunization specifically – as measured by MCV coverage – was significantly related to one-dose COVID-19 delivery at a national level. In addition, we demonstrate that subnational variability in one-dose COVID-19 vaccination was not driven by routine MCV immunization, supporting our findings from Aim 2 suggesting limited significance with sociodemographics and policy variable subnationally for two locations.

Future Directions

As this pandemic winds down, we need to focus resources on improving pandemic preparedness for novel threats. We identified that overall composite JEE and GHSI scores as well as aggregate subsections were not informative of national or subnational infections or deaths but that routine immunization via MCV coverage was informative of COVID-19 vaccine delivery nationally. Additional research to understand other indicators correlated with specific COVID-19 outcomes is needed in order to be able to identify which countries are well prepared in various capacities versus those that need additional resources and attention. The GHSI and JEE composite indices were created to summarize many facets of pandemic preparedness for generic future threats, but not all pathogens of international concern impact the same at-risk groups equally. For COVID-19, this dissertation has demonstrated that age structure was a larger driver of COVID-19 fatalities, but other pathogens like mpox and Zika unduly impact younger children and neonates. Similarly, behaviors and socioeconomics may be much more influential for other pathogens, like vector-borne diseases, and understanding which indicators within the JEE and GHSI map to other pandemic and outbreak variables is important for future plans. We acknowledge that the JEE, in particular, has value beyond quantifying preparedness. JEEs are conducted to identify gaps, leading to National Action Plans to target address noted vulnerabilities. Inclusion of actions to build trust, such as addressing mis- or dis-information and improving risk communication should be considered as additions to ongoing action plans in addition to the measurement of trust. In sum, additional research is needed to identify the risk profile for each pathogen, and map existing preparedness indicators to these risks, but steps can be taken now to introduce trust into pandemic plans via methods to improve communication prior to subsequent threats.

We identified trust in the government and in other people as a key predictor of both reduced COVID-19 infections as well as increased vaccine coverage. However, these findings were not replicable at a subnational level due to limited survey data and wide confidence intervals. Moreover, our observation of much less pointed variability in the subnational level trust data raise the question of whether measurement error is the root cause of this homogeneity, whether subnational distinctions in trust are far more nuanced, or whether the state-level estimate masks further county-level variability; we emphasize the need to consider all of these aspects in future analyses of subnational trust. Additionally,

data quality at the national level were varying, with many countries missing survey data, particularly for interpersonal trust. High quality, open-source data in trust both locally and nationally are of high importance to better quantify how influential trust is in driving pandemic and outbreak heterogeneities. Previous research into interpersonal trust – or social capital[182] – has highlighted the importance of our community ties in responding to disasters; additional research investigating these social networks and their impact on trust in the context of the COVID-19 pandemic would provide a wealth of new information on how our communities influence our resiliency in a disaster, and will further inform how best to build in such networks into plans for future threats. However, trust can also be shattered during disasters and pandemics, such as following the Dengvaxia Dengue vaccine roll out leading to a small degree of vaccine-harm among healthy children in Dengue-endemic countries,[183,184] as well is in Turkey following the Gaziantep earthquake of February 2023 where 'earthquake-proof' structures and 'earthquake taxes' appeared to have been futile in preventing catastrophic injury and death.[185] Understanding these contexts is equally important to avoid future ruptures of trust. Moreover, it is important to consider how trust changes overtime. Pandemic threats, preparedness, and current levels of trust are constantly changing;[186] ongoing efforts to assess the status of trust is equally as important as expanding the scope of current knowledge. In addition to our call for improved trust data worldwide, we also call for actions to address lack of trust now before the next pandemic. The COVID-19 pandemic is unlikely to be the last pandemic we experience in our lifetimes due to increasing interactions between humans and wildlife through climate change and urbanization. Focused attention now on building trust locally and federally will undoubtedly impact pandemic response behaviors in future threats.

In our second and third aims, we found few correlates with subnational COVID-19 heterogeneities. While we did identify that after controlling for sociodemographics and baseline risk factors, between-country heterogeneities were amplified versus within-country ones, we had limited policy, health care, and social data available for our analysis subnationally. We first need to expand these methods to a larger number of countries to understand whether these subnational patterns persist beyond the subset of countries investigated here. Additional research is essential to better quantify subnational heterogeneities in order to understand local drivers of differential pandemic outcomes. While studies like the Global Burden of Disease[62,169] have undertaken commendable efforts in quantifying risk factors and outcomes subnationally within several countries, more work is to be done to extend these analyses to all countries in the world; in addition, novel indicators like trust in local governments and interpersonal trust as well as measures of pandemic preparedness would provide essential tools for preparing not only locally, but extending preparedness plans to local governments and policy makers.

We will likely see another pandemic in our lifetimes. This dissertation has quantified how previous measures of pandemic preparedness have informed COVID-19 outcomes, and where gaps still exist. Unfortunately, our understanding of pandemic preparedness and response will continue to evolve with novel threats. Focused, ongoing research into the most appropriate quantifications will continue to guide the most appropriate allocation of resources and prioritization of therapies and help with focused prevention, detection, and response worldwide.

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