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COVID-19-Related Maternal Mortality and Morbidity in Brazil:

An Exploration of Individual, Municipal, and State Factors

A dissertation submitted in partial satisfaction of the

requirements for the degree Doctor of Philosophy

in Health Policy and Management

by

Mary Catherine Cambou

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ABSTRACT OF THE DISSERTATION

COVID-19-Related Maternal Mortality and Morbidity in Brazil:

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Professor James A. Macinko Jr., Chair

Persons infected with SARS-CoV-2 during pregnancy are at increased risk of severe COVID-19, including hospitalization, mechanical ventilation, and death. The effects of the pandemic on maternal mortality and morbidity in Brazil, a country disproportionately impacted by COVID-19, have not been well-characterized. We set out to quantify the effect of the COVID-19 pandemic on maternal mortality in Brazil, as well as identify individual, municipal, and state factors that impacted COVID-19-related maternal mortality and morbidity during the pandemic. Using publicly-available databases through the Brazilian Ministry of Health, we estimated 4,995 maternal deaths from January 1, 2020 to December 31, 2021. Using two complementary forecast models, we demonstrated that the observed maternal mortality ratio (MMR) in 2021 was more than double the predicted MMR based on historical maternal mortality data. From January 1, 2021 to December 31, 2021, there were 10,435 pregnant or postpartum persons hospitalized with COVID-19 in Brazil, of which 1,059 (10.1%) resulted in death. Using a random effects model, a single dose of an approved COVID-19 vaccine prior to hospitalization reduced the odds of maternal death by 66%, and estimated state vaccine coverage $\geq$90% reduced the odds of

maternal death by 89%. Among this hospitalized population, 3,055 individuals required an intensive care unit (ICU) admission. Using nested logistic regression models (LRMs) and multilevel models (MLMs) to incorporate both individual-level and municipal-level factors, we found that COVID-19 vaccination reduced the odds of maternal ICU admission by 38%. Municipal-level health factors, including high family health strategy coverage and ICU bed rates, were not significantly associated with protection against ICU admission when controlling for clustering in the LRM, or in the MLM with inclusion of municipal-level factors. The national COVID-19 vaccination campaign, including targeting pregnant and postpartum individuals, should remain a cornerstone of the Brazilian public health armamentarium in efforts to reduce the national MMR, and protect against maternal death and ICU admissions due to COVID-19.

The dissertation of Mary Catherine Cambou is approved.

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Curriculum Vitae

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4/24/2023 – 3/31/2024	Infant Immunologic and Neurologic Development Following Maternal Infection in Pregnancy During Recent Epidemics, NIAID (R56AI72252). Role: Investigator (PI: Nielsen-Saines, K and Jung, J).
7/05/2023 – 06/30/2028	SARS-CoV-2 in Pregnancy: Comparison of Natural Infection and Hybrid Immunity in Mother-Infant Pairs, NIAID (K23AI77952). Awarded 07/05/2023. Role: PI (Primary Mentor: Nielsen-Saines, K).

RESEARCH PAPERS

Publications I would like to highlight:

Cambou MC, Copeland TP, Nielsen-Saines K, Macinko J. Insurance status predicts self-reported influenza vaccine coverage among pregnant women in the United States: A cross-sectional analysis of the National Health Interview Study Data from 2012 to 2018. Vaccine. 2021 Mar 17:S0264-410X(21)00294-2. doi: 10.1016/j.vaccine.2021.03.026. Epub ahead of print. PMID: 33744045.

Cambou MC, Saad E, McBride K, Fuller T, Swayze E, Nielsen-Saines K. Maternal HIV and syphilis are not syndemic in Brazil: Hot spot analysis of the two epidemics. PLoS One. 2021 Aug 3;16(8):e0255590. doi: 10.1371/journal.pone.0255590. PMID: 34343219; PMCID: PMC8330908.

Cambou MC, Liu CM, Mok T, et al. Longitudinal Evaluation of Antibody Persistence in Mother-Infant Dyads Following SARS-CoV-2 Infection in Pregnancy. J Infect Dis. 2023 Jan 11;227(2):236-245. doi: 10.1093/infdis/jiac366. PubMed PMID: 36082433; PubMed Central PMCID: PMC9494415.

Complete List of Published Work in MyBibliography:
https://www.ncbi.nlm.nih.gov/myncbi/1tuyXkJWIfcwzr/bibliography/public/

Chapter 1 Introduction

> "Pandemics don't approach like wars, with the distant thud of artillery growing louder every day and flashes of bombs on the horizon. They arrive in retrospect, essentially."

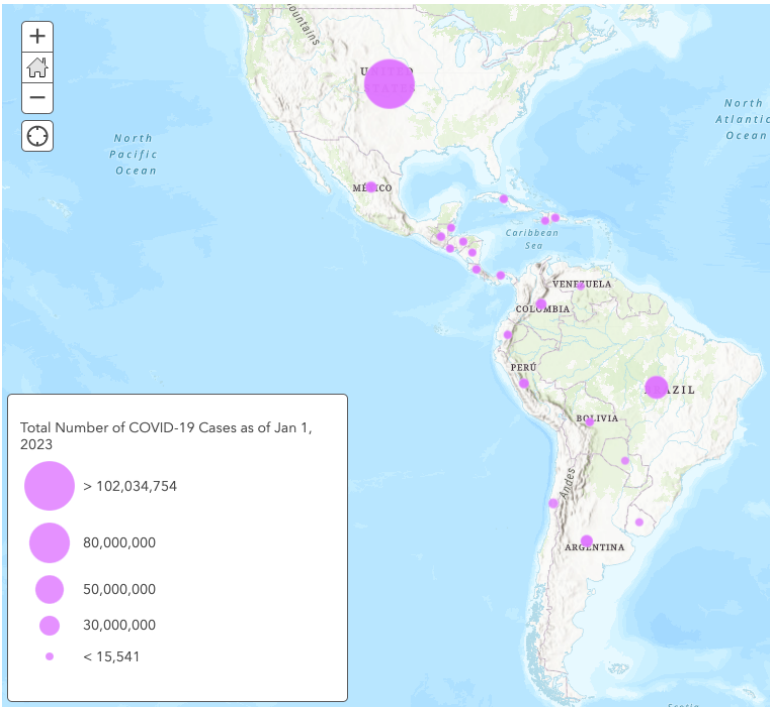
- Emily St. John Mandel, *Sea of Tranquility*

Background

COVID-19 Epidemiology in Brazil

Since the discovery of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the novel virus responsible for the COVID-19 pandemic[1] in December, 2019, there have been over 650 million cases and 6.5 million deaths globally[2, 3]. Early on in the pandemic, Brazil emerged as the COVID-19 epicenter in South America (Figure 1.1): as of January 1, 2023, the country had the fifth highest prevalence of SARS-CoV-2 infections in the world, with over 35 million documented cases, and 690,000 attributable deaths, the third highest count after the U.S. and India[2, 3].

Figure 1.1 Cumulative cases of COVID-19 based on data available for the Pan American Health Organization (PAHO) countries. Adapted from JHU COVID-19 Dashboard[4].



The high burden of COVID-19 in Brazil is likely multi-factorial in etiology, including national, state, and municipal-level health services related factors, ranging from political conflict[5] to the distribution of less effective vaccines[6] to differences in regional public health responses correlating with socioeconomic inequities[7, 8]. Similar to influenza epidemics[9], the relationship between urban density and cases is driven by a balance between sustained transmission due to population size and spatial structure, and increased access to health services, including intensive care unit (ICU) beds, referred to as the urban health advantage[7, 10].

COVID-19 in Pregnancy

COVID-19 disproportionately impacts vulnerable populations[11], including pregnant persons[12-14]. Both non-biological and biological factors amplify risk in maternal viral infections[15-17], including SARS-CoV-2: not only do sociopolitical forces influence viral transmission patterns and overall maternal health[18], but the immunologic paradox of pregnancy further complicates the course of COVID-19 in the relatively immunocompromised host[19, 20]. Maternal-fetal tolerance refers to the dynamic immunologic changes that occur during pregnancy, allowing for the growth of an antigenically distinct fetus, which would otherwise be rejected by the maternal immune system[21]. These immune changes are poorly understood, but render women more susceptible to highly pathogenic respiratory viruses during pregnancy[15, 16, 22].

Persons infected with SARS-CoV-2 during pregnancy are at increased risk of severe COVID-19, including hospitalization, mechanical ventilation, and death[12, 14, 23]. In a Centers for Disease Control (CDC) surveillance study of 400,000 cis-gender women with symptomatic COVID-19, pregnant women had a 70% increased risk for death compared to non-pregnant women, in addition to higher odds of ICU admissions and mechanical ventilation[24]. SARS-CoV-2 infection in pregnancy is associated with a three-fold increased odds of preeclampsia[25, 26], a hypertensive disorder of pregnancy (HDP), and leading cause of maternal morbidity and mortality worldwide. Furthermore, COVID-19 in pregnancy is associated with other adverse pregnancy outcomes, including up to a two-fold increased risk of preterm delivery and stillbirth[25, 27, 28].

COVID-19 Vaccines in Pregnancy

Due to the heightened risk of severe and critical COVID-19 in pregnancy, the leading global obstetrical societies recommend that all eligible persons, including pregnant and lactating individuals, complete the COVID-19 vaccine series[29-31]. The messenger RNA (mRNA) vaccines, BNT162b2 and mRNA-1273, are recommended for pregnant people over the single-dose adenovirus-vector vaccine, AD26.COV2.S, due to the Food and Drug Administration (FDA) warning of increased risk of thrombosis with thrombocytopenia syndrome[30]. Currently, the primary mRNA vaccine series consists of two monovalent doses, followed by a booster, preferably a bivalent dose. While pregnant individuals were excluded from the original clinical trials to test the safety and immunogenicity of the mRNA vaccines[32], studies to-date demonstrate that the vaccines do not confer an increased risk of adverse pregnancy events[33-38], although long-term monitoring is needed. Furthermore, transplacental transfer of functional antibodies is critically important during the first six months of infant life, particularly as the COVID-19 vaccines are not approved for this age group[39]. In addition to maternal protection, evidence suggests that administration of the mRNA COVID-19 vaccine during pregnancy may prevent COVID-19-related hospitalizations in infants less than six months of age[40].

Unfortunately, the COVID-19 vaccines were not readily available in Brazil until 2021, and recommended only later in the pandemic to pregnant persons[41]. While there are currently seven approved COVID-19 vaccines in Brazil, a national COVID-19 immunization program was started in January, 2021, consisting primarily of the inactivated CoronaVac (Sinovac) and adenovirus-vector ChAdOx1 (AstraZeneca) vaccines (both two-dose series), followed by the mRNA vaccine BNT162b2 (Pfizer). A case-control study among persons with a history of previous COVID-19 using the national COVID-19 notification data in Brazil demonstrated that vaccine effectiveness against symptomatic re-infection for CoronaVac and ChAdOx1 were 39.4% and 56.0%, respectively, compared to 65% for BNT162b2[42]. However, effectiveness against hospitalization

and death two weeks from the vaccine series completion was comparable for ChAdOx1 (89.9%) and BNT162b2 (89.7%).

COVID-19 and Maternal Health in Brazil

All pandemics are destabilizing events, with both immediate and long-term effects that continue to impact public health systems for years. Preventive services in Brazil, including prenatal care, were highly disrupted by the pandemic[43]. Not only were pregnant persons at higher risk of severe COVID-19[44], but the pandemic itself impacted their ability to access health services in a timely fashion for other maternal issues[45], such as HDP[46]. In addition, COVID-19 itself has been found to be a trigger of HDP, further complicating maternal health outcomes[14, 26].

The World Health Organization (WHO) defines maternal death as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of the cause[47]. Late maternal death is defined as death more than 42 days up to one year postpartum[47]. Maternal mortality is inversely related to access to high-quality health care, and is often used as an indicator of health services availability, measured as clinical indicators of maternal care quality (MCQ). While maternal mortality in Brazil is relatively higher when compared to similar middle-income countries, the maternal mortality ratio (MMR) decreased from 71 in 2000 to 63 per 100,000 live births in 2015[48]. However, studies at the regional and state levels in Brazil demonstrated an unexpected rise in MMR since the onset of the COVID-19 pandemic[49], likely due to a combination of COVID-19 related maternal deaths, and increasing barriers to access to prenatal and perinatal care impacting MCQ[50]. The Family Health Strategy (FHS)[51], a community-based multi-professional primary care model, particularly in rural Brazil, play a pivotal role in providing high-quality preventive healthcare, including prenatal and antenatal care, throughout the country[51-53]. Austerity measures, such as reduction in funding for the FHS program, likely affected health care delivery and quality.

Theory

Guided by the social-ecological model[54, 55], the goal of this dissertation is to explore how state, municipal and individual-level factors contributed to COVID-19 related maternal mortality and morbidity. First introduced by McLeroy in 1988[56] (Figure 1.2), the social-ecological model rejects the claim that an individual is solely responsible for their health condition. Instead, the framework acknowledges the multiple, intertwined levels of individual and environmental factors that influence health outcomes, thereby reducing the burden of responsibility on the individual. This shift away from the individual highlights the roles of historical institutions, environment, and policies that shape health profiles[56].

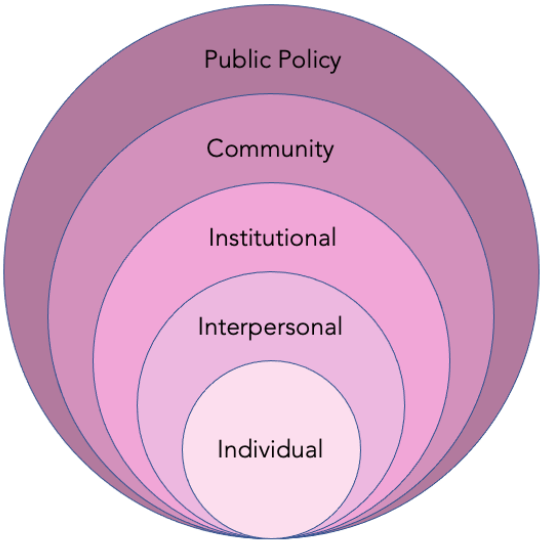


Figure 1.2 *Social-Ecological Model. Adapted from McLeroy, K.R. et al. The social ecology of health promotion interventions. Health Education Quarterly. 1988 15(4):351-377.*

An evaluation of COVID-19-related maternal mortality and morbidity in Brazil requires a nuanced understanding of the interplay of geography, health system infrastructure, infectious diseases epidemiology, and institutional ethnoracism. Brazil consists of five macroregions: the North, Northeast, Central-West, Southeast, and South. The 26 states and the Federal District, for a total of 27 federative units, form the macroregions. The states are further divided into 5,570 municipalities, each with its own autonomous local government, including a mayor, municipal chamber, and health secretariat responsible for local management and delivery of healthcare in facilities other than hospitals (which are mostly state or federally owned)[57]. While healthcare is a constitutional right in Brazil and the public health system (Sistema Único de Saúde, SUS) is available free of

charge in most settings, income, social and health inequities are widespread throughout Brazil, with persistent regional differences in employment, educational attainment, and access to basic services[58, 59].

The COVID-19 pandemic further exacerbated these gaps, particularly in the Northeast and Amazonia regions[60]. The Amazon has the highest population of Indigenous inhabitants and lowest human development index (HDI) scores in the country. In addition to the existing inequities, the Gamma (P.1) variant of concern emerged in Manaus, the capital city of the state of Amazonas, in November, 2020, which caused widespread infection in the region as a result of enhanced immune evasion[7, 60, 61]. The impact of COVID-19 on the health system infrastructure in the state of Amazonas lead to a decline of 3.5 years in the life expectancy at birth (e_o) in 2020, more than double the rate in the country as a whole[60]. In 2020, there were 1,496 excess deaths among women recorded in the Amazonas, representing a 95% increase[61]. This drastic increase highlights the intersectional issue of gender and race that influence maternal health in Brazil as well[62].

Historical systemic and institutional ethnoracism in Brazil continues to exacerbate poor maternal and infant outcomes in Black and Indigenous populations[63-67]. The risk of maternal mortality is estimated to be two to four-fold higher among Black and Indigenous women compared to white women in Brazil, driven by reduced access to high-quality prenatal care, high rates of HDP, and postpartum complications[62, 68, 69]. Racial differences across regions reflect these discrepancies in maternal health outcomes, with high MMR in the North and Northeastern regions, compared to relatively lower MMR estimates in the South[66, 68, 70]. The inequities in maternal health transition into neonatal and infant outcomes across ethnoracial lines: a recent population-based study using the national birth and death registry data from 2012 to 2018 found that compared to white children, the hazard of post-neonatal death (one month to one year of life) was 2.8 and 1.5 for children born to Indigenous and Black mothers, respectively[63].

The social-ecological model has been used throughout the pandemic to better elucidate the complex web of biological and social determinants that impact COVID-19 related outcomes[71, 72]. In every country, the pandemic brought to light pre-existing inequities that fueled disproportionate health outcomes across economic and racial lines[73, 74]. Brazil was no exception, with higher rates of COVID-19 morbidity and mortality among low-income families and persons of color[75, 76]. In one cross-sectional study that evaluated the association of income inequality as measured by the Gini index with COVID-19 mortality rates in Brazil using a mixed negative binomial model, one standard deviation (SD) increase in income inequality was associated with a 17% increase in COVID-19 mortality in the first 12 months of the pandemic[77]. Another cross-sectional study on hospital mortality from COVID-19 using a mixed-effects Cox regression found that mixed ethnicity (Pardo) and Black Brazilians had a 45% higher risk of death than hospitalized white Brazilians[78]. Through the lens of the social-ecologic framework, we will examine the impact of the pandemic on excess maternal mortality in Brazil, as well as health system predictors of severe COVID-19 in the pregnant population at a time when the public health infrastructure faced unprecedented stress.

Dissertation Aims

In order to evaluate the effect of the pandemic on excess maternal mortality, and identify factors that impacted COVID-19-related maternal mortality and morbidity in pregnancy in Brazil, we proposed the following:

Aim 1. To estimate the excess maternal mortality in Brazil from January 1, 2020 to December 31, 2021 based on an annual time series analysis of predicted MMR from 2008 to 2021.

We hypothesized that there was a significant relative increase in MMR in 2020 and 2021 compared to the projected MMR. We hypothesized that direct COVID-19 maternal deaths accounted for most maternal deaths.

Aim 2. To explore which individual and state-level health system infrastructure and utilization factors were associated with maternal death among hospitalized pregnant or postpartum persons with COVID-19 from January 1, 2021 to December 31, 2021, the time frame when vaccines were available to pregnant persons.

We hypothesized that compared with hospitalized pregnant or postpartum persons who did not receive a COVID-19 vaccine, receipt of at least one COVID-19 vaccine dose, regardless of type, protected against COVID-19-related maternal death in hospitalized pregnant or postpartum persons across the country, despite differences in health service factors at the state level.

Aim 3. To explore which individual and municipal-level factors were associated with maternal ICU admission among hospitalized pregnant or postpartum persons with COVID-19 from January 1, 2021 to December 31, 2021, the time frame when vaccines were available to pregnant persons.

We hypothesized that compared with hospitalized pregnant or postpartum persons who did not receive a COVID-19 vaccine, receipt of at least one COVID-19 vaccine dose, regardless of type, protected against COVID-19-related maternal ICU admission in hospitalized pregnant persons across the country, despite differences in health service factors at the municipal level.

Contributions to the Field

This dissertation adds to the global maternal health literature, the COVID-19 vaccine effectiveness literature, studies of health inequities, and will be of interest to those in the health services research, particularly in in the context of middle-income countries with universal healthcare coverage. First, the impact of the COVID-19 pandemic on excess maternal mortality in Brazil (Aim 1) has not been well-characterized to-date. As maternal mortality is often used as a proxy for health services availability, the findings of Aim 1 provide insight into both the direct and indirect effects of the pandemic on the healthcare infrastructure for the pregnant population. Second, quantifying the impact of vaccination on COVID-19 related maternal mortality, including individual vaccine receipt and state-level vaccine coverage, in the context of other state-level health system infrastructure factors (Aim 2) addresses the gap in knowledge around COVID-19 vaccine effectiveness in pregnancy in a real-world context. Third, an understanding of how municipal-level health services coverage and availability impacted maternal morbidity as measured by COVID-19-related ICU admissions for pregnant persons over the course of the pandemic (Aim 3) has important implications for health care resource allocation and public health campaigns to minimize COVID-19 related morbidity as the world shifts from a pandemic to endemicity[79].

Not only are the findings from this dissertation particularly relevant to Brazil, but they may inform strategies to optimize maternal health globally and meet the WHO sustainable development goal (SDG) target to reduce the global MMR to less than 70 per 100,000 live births[80], at a time when the pandemic disrupted much of the progress throughout the world[81]. These analyses may inform guidelines and policies on COVID-19 vaccine strategies in Brazil, and may serve as an important resource on care utilization throughout the Americas when the next pandemic arrives.

Chapter 2 Data Sources

Beginning in January, 2020, the publicly-available Sistema de Informação da Vigilancia Epidemiológica da Gripe (SIVEP-Gripe) database began tracking all COVID-19 hospitalizations in Brazil through the Unified Health System platform (DATASUS)[82]. The SIVEP-Gripe surveillance system was established in 2009 following the H1N1 influenza pandemic[83]. Since its inception, the database has served as the national surveillance system for influenza and other respiratory viruses of clinical concern[84]. Following the initial identification of SARS-CoV-2, the Brazilian Ministry of Health required notification of both suspected and confirmed cases by polymerase chain reaction (PCR) testing (the gold standard), and now antigen (Ag) testing[85]. Both public and private hospitals are required by law to report on COVID-19 hospitalizations via the electronic database within 24 hours of a suspected case[85]. Data collected include geographic location, medical co-morbidities, pregnancy and postpartum status, hospital course complications, and outcomes, including death. The annual databases, including reporting details and the data dictionary, are made available through the DATASUS platform[82]. The data are reviewed and cleaned weekly by the Ministry of Health National Immunization Program.

We used data from the following publicly available databases to complement the subset of SIVEP-Gripe data for the proposed analyses:

1) Brazilian Mortality Information System (SIM)[86] is a national database for microdata on deaths reported at the municipal level[87]. Data are transferred from municipalities to states, and subsequently managed at the national level by the Brazilian Ministry of Health[87]. We used aggregate data for maternal deaths, defined by the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of cause, and late maternal deaths, defined as death more than 42 days up to one year postpartum[47]. Several studies have documented undercounting and regional differences in mortality data via SIM compared to the National Statistics Office

(IBGE)[88-90], although estimates have improved over the past decade[91]. Only aggregate data at the national and state level were used.

2) The Brazilian Information System on Live Births (SINASC)[92, 93] is a national database for all live births reported at the municipal level[92]. Data are transferred to the Brazilian Ministry of Health. Aggregate data at the state and national levels were collected via the Integrated Health Surveillance (IVIS) platform[94].
3) The Institute for Health Metrics and Evaluation (IHME)[95] is a global health policy database independently managed by the University of Washington since 2007. The IHME stewards the Global Burden of Disease collaboration, and collects publicly available data across multiple sources, including Ministries of Health[96]. The IHME has been crucial in the advancement of COVID-19 research, serving as a universal database for health service indicators, including COVID-19 vaccine coverage, hospital bed use, and ICU capacity.
4) The Brazilian Institute for Studies for the Politics of Health (IEPS)[97] is an independent, non-profit database for municipal-level health data, including population, coverage by Family Health Strategy, and health system utilization rates (including physicians per capita, nurses per capita, and ICU beds per capita). The data are managed by a multidisciplinary, unpaid Advisory Board. IEPS collects data from across multiple publicly available data sources in Brazil, including the Ministry of Health National Health System (Sistema Único de Saúde, DATASUS) and the National Registry of Healthcare Facilities (Cadastro Nacional de Estabelecimentos de Saúde, CNES)[98].

This study used de-identified, publicly available data, therefore was IRB exempt per review by the UCLA Office of Human Research Protection Program (IRB #23-000145).

Chapter 3 Maternal Mortality During the First Two Years of the COVID-19 Pandemic: A Time Series Analysis of Predicted Maternal Mortality Ratio Estimates in Brazil

Abstract *(199 words):*

The effects of the COVID-19 pandemic on maternal mortality in Brazil have not been well-characterized. Using publicly available data from the Brazilian Mortality Information (SIM) and Information System on Live Births (SINASC) databases, we used two complementary forecasting models to estimate predicted maternal mortality ratios (MMR) based on data from 2008 to 2019. From January 1, 2020, to December 31, 2021, there were an estimated 4,995 maternal deaths. The observed MMR in 2021 was more than double the predicted MMR based on the non-seasonal Holt-Winters exponential smooth and autoregressive integrated moving average models (113.8 versus 55.23 and 54.28 per 100,000 live births, respectively). We found persisting sub-national variation in maternal mortality, with some regions experiencing far higher maternal deaths than others both before and during the pandemic. Standardized mortality ratio (SMR) estimates ranged from 1.75 (95% confidence interval [CI] 1.63 – 1.87) in the Northeast to 2.62 (95% CI 2.36 – 2.88) in the South in 2021. The observed MMR in 2021 is the highest MMR in Brazil in the past three decades, highlighting the impact of COVID-19 on maternal mortality and morbidity. Increased resources may be needed in regions with high MMR pre-COVID-19 in order to reverse the national MMR.

Background

Maternal mortality, defined as death during pregnancy, childbirth or within 42 days postpartum or termination (regardless of cause), remains a leading cause of death among women globally[99]. The majority of maternal deaths are due to postpartum hemorrhage, infection, and hypertensive disorders of pregnancy (HDP), the latter of which is the cornerstone of modern prenatal care[100]. While the 50% reduction in the global maternal mortality ratio (MMR) between 1990 and 2015 is a testament to the collective effort worldwide to improve maternal health, this progress fell short of the Millennium Development Goal (MDG) of a 75% reduction in the global MMR over this period[101]. The new World Health Organization (WHO) Sustainable Development Goal (SDG) target calls for a global MMR less than 70 maternal deaths per 100,000 live births by 2030[102]; it is currently 223 maternal deaths per 100,000 live births[103].

The COVID-19 pandemic slowed the progress made in MMR reduction in many countries, including in Brazil, although the true extent of this setback is unknown[103]. Pandemics are destabilizing events with both direct and indirect immediate and long-term effects. Not only are pregnant persons at higher risk of severe COVID-19[44], but the pandemic itself impacted their ability to access health services in a timely fashion. Preventive services in Brazil, including prenatal care, were highly disrupted by the pandemic[43], including the identification and treatment of HDP, a leading cause of maternal mortality and morbidity worldwide[46]. SARS-CoV-2, the virus responsible for COVID-19, is a trigger of HDP, further complicating maternal health outcomes during the pandemic[14, 26]. In addition, hospital resources normally designated for prenatal care were diverted to accommodate the unprecedented strain that was placed on the healthcare system as a result of the COVID-19 surges, particularly in 2021[104].

Before to the pandemic, Brazil made great strides in improving maternal care quality through several designated public health programs[51, 105, 106]. While maternal mortality in Brazil is relatively higher compared to similar middle-income countries, the MMR decreased from an estimated 84.5 per 100,000 live births in 1990 to 65.4 per 100,000 live births in 2015[48]. However,

studies at the regional and state levels in Brazil demonstrated an unexpected rise in MMR during the first year of the COVID-19 pandemic[49], likely due to a combination of COVID-19-related maternal deaths, and increasing barriers to perinatal care access impacting maternal care quality[50].

The excess burden of COVID-19 on maternal deaths in Brazil during the first two years of the pandemic has not been well-characterized. In order to estimate excess maternal mortality in Brazil in 2020 and 2021 due to COVID-19, we used a combination of (1) two forecasting methods, the non-seasonal Holt-Winters exponential smoothing (HES) model and autoregressive integrated moving average (ARIMA) model, to predict the MMR in 2020 and 2021 based on time series data from 2008 to 2019, and (2) the Standardized Mortality Ratio (SMR) at the national and regional levels for 2020 and 2021. We hypothesized that (1) there was a significant relative increase in MMR in 2020 and 2021 compared to the projected MMR, and (2) direct COVID-19 maternal deaths accounted for the majority of maternal deaths.

Methods

Data Source

The Brazilian Mortality Information System (SIM)[86] is a national database for microdata on deaths reported at the municipal level[87]. Data are transferred from municipalities to states, and subsequently managed at the national level by the Brazilian Ministry of Health[87]. Aggregate data for maternal deaths, defined by the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of cause, and late maternal deaths, defined as death more than 42 days up to one year postpartum[47]. The Brazilian Information System on Live Births (SINASC)[92, 93] is a national database for all live births reported at the municipal level[92]. Aggregate data at the state and national levels were collected via the Integrated Health Surveillance (IVIS) platform[94].

Beginning in January, 2020, the publicly-available Sistema de Informação da Vigilancia Epidemiológica da Gripe (SIVEP-Gripe) database began tracking all COVID-19 hospitalizations in Brazil through the Unified Health System platform (DATASUS)[82]. The SIVEP-Gripe surveillance system was established in 2009 following the H1N1 influenza pandemic[83]. Since its inception, the database has served as the national surveillance system for influenza and other respiratory viruses of clinical concern[84]. Following the initial identification of SARS-CoV-2, the Brazilian Ministry of Health required notification of both suspected and confirmed cases by polymerase chain reaction (PCR) testing (the gold standard), and now antigen (Ag) testing[85]. Both public and private hospitals are required by law to report on COVID-19 hospitalizations via the electronic database within 24 hours of a suspected case[85]. Data collected include geographic location, medical co-morbidities, pregnancy and postpartum status, hospital course complications, and outcomes, including death. The annual databases, including reporting details and the data dictionary, are made available through the DATASUS platform[82]. The data are reviewed and cleaned weekly by the Ministry of Health National Immunization Program.

Statistical Analysis

We used national aggregate data from the SIM[86] and SINASC[93] databases to calculate the annual observed MMR per 100,000 live births in Brazil from 2008 to 2021.

$$Annual\ MMR = \frac{Observed\ maternal\ deaths\ in\ a\ given\ year\ (from\ SIM)}{Total\ live\ births\ in\ a\ given\ year\ (from\ SINASC)}\ x\ 100{,}000$$

We used the non-seasonal HES model, a forecasting time series method, based on time series data of MMR from 2008 to 2019, to predict MMR for 2020 and 2021. The HES model is used often for forecasting time series[107, 108]. It builds on the simple exponential smoothing (SES) method:

$$L_t = \alpha y_t + (1 - \alpha) L_{t-1}$$

where "y_t is the value at current time step t, L_t is the level estimate for t, L_{t-1} is the previous level estimate, and α is a smoothing constant"[107, 108].

The HES model is considered a second exponential smoothing method, as the approach incorporates trend into the SES model:

$$F_{t+k} = L_t + kT_t$$

where "L_t is the level estimate for time t, k is the number of forecasts into the future, and T_t is the trend at time t"[108]. We used the iterative process to define the smoothing parameters.[109, 110] Predicted MMR and observed MMR with 95% confident intervals (CIs) from 2008 to 2021 were plotted. We then conducted a sensitivity analysis with an ARIMA model to test whether the findings were sensitive to the HES model[111, 112]. The ARIMA model parameters (p: lag order, d: degree of differencing, q: order of moving average) were selected based on minimizing Akaike Information Criteria (AIC) and Bayesian Information Criterion (BIC)[113].

Next, we plotted the maternal deaths at the national level, from 2008 to 2021. To explore geographic variation, maternal deaths were categorized and plotted by the five macro-regions in Brazil: the poorer North and Northeast, and wealthier South, Southeast, and Central-West. We calculated national and regional standardized mortality ratio (SMR) estimates[114] in 2020 and 2021, using maternal deaths in 2019 as the reference[115].

$$SMR = \frac{Observed\ deaths\ (in\ a\ study\ population)}{Expected\ deaths\ (in\ a\ study\ population)}$$

We then calculated the national regional SMR estimates for comprehensive maternal deaths (SMRc), defined as the sum of maternal deaths and late maternal deaths, up to one year postpartum[47]. The 95% CIs for each SMR and SMRc estimate were calculated using the Vandenbroucke method[116]. Statistical analysis was performed with STATA version 16. This study used de-identified, publicly available data, therefore was IRB exempt per review by the UCLA Office of Human Research Protection Program (IRB #23-000145).

Results

From January 1, 2020, to December 31, 2021, there were an estimated 4,995 maternal deaths, and 5,541 comprehensive maternal deaths in Brazil, with the majority occurring in 2021. Among deaths in this period, 1,336 were attributed to COVID-19 in pregnancy, with the majority (79.2%) occurring in 2021.

Figure 3.1 shows the Holt-Winters forecast of predicted MMR compared to observed MMR in Brazil from 2008 to 2021. While the model predicted a downward slope from 2019 to 2021, the observed MMR estimates in 2020 and 2021 increased from 71.97 to 113.18 per 100,000 live births, respectively. The observed MMR was more than double the predicted MMR in 2021 based on the Holt-Winters forecast estimate (113.18 versus 55.23 per 100,000 live births).

Figure 3.2 shows the ARIMA forecast of predicted MMR compared to observed MMR in Brazil from 2008 to 2021. The ARIMA model predicted MMR estimates of 56.78 and 54.28 in 2020 and 2021, respectively. The MMR estimates were comparable to those predicted by the Holt-Winters forecast. The observed MMR was again more than double the predicted MMR in 2021 based on the ARIMA estimate (113.18 vs 54.28 per 100,000 live births).

Figure 3.3 shows the maternal deaths from 2008 to 2021 at the national and regional levels. Geographic disparities present prior to the pandemic persisted across the five macro-regions: the highest number of maternal deaths were concentrated in the Northeast (consisting of the states of Alagoas, Bahia, Ceará, Maranhão, Paraíba, Pernambuco, Piauí, Rio Grande do Norte, and Sergipe) and the Southeast (consisting of the states of Espiríto Santo, Minas Gerais, Rio de Janeiro and São Paulo), while the Central-West (consisting of the states of Goiás, Mato Grosso, Mato Grosso do Sul and Distrito Federal) had the lowest. This trend continued during the first two years of the pandemic, with the highest recorded maternal deaths (1,055) observed in the Southeast in 2021.

The observed maternal deaths increased from 2020 to 2021 across all macro-regions. Table 3.1 compares maternal deaths, estimated percentage due to COVID-19, and SMR at the

national and regional levels from 2019 to 2021. In 2020, there were 1,965 maternal deaths, of which approximately 14.10% were due to COVID-19. In 2021, the maternal deaths increased to 3,030, of which an estimated 34.95% were attributed to COVID-19. The proportion of maternal deaths due to COVID-19 in 2021 ranged from 24.34% in the Northeast to 42.04% in the Central-West region. The national SMR estimates for maternal deaths were 1.25 (95% CI 1.19 – 1.30) in 2020 and 1.92 (95% CI 1.85 – 1.99) in 2021. The SMR estimates ranged from 1.75 (95% CI 1.63 – 1.87) in the Northeast, to 2.62 (95% CI 2.36 – 2.88) in the South during the second year of the pandemic.

Table 3.2 compares comprehensive maternal deaths, and SMRc at the national and regional levels from 2019 to 2021. The national SMRc estimates for comprehensive maternal deaths were 1.23 (95% CI 1.17 – 1.29) in 2020 and 1.96 (95% CI 1.89 – 2.03) in 2021. There were 3,403 total comprehensive maternal deaths in 2021, with the highest SMRc in the South Region (2.70, 95% CI 2.45 – 2.96).

Discussion

Consistent with our hypothesis, there was a significant relative increase in MMR in Brazil in 2020 and 2021 compared to the projected MMR based on both the HES and ARIMA models. Guimarães and colleagues estimated a 40% increase in excess maternal mortality in 2020 based on a Poisson model with robust variance, slightly higher than the our estimate[117]. In 2021, the observed MMR in Brazil was more than double the predicted MMR in 2021 based on our Holt-Winters forecast and ARIMA model estimates (113.18 versus 55.23 per 100,000 live births and 54.28 per 100,000 live births, respectively). Scheler and colleagues also demonstrated a relative increase in maternal deaths in Brazil during the first half of 2021 compared to 2020, reporting a two-fold increase in the mortality rate among hospitalized pregnant and postpartum individuals with COVID-19[118]. However, we used the most current SIM and SINASC data, representing the most up-to-date mortality and live birth data available in Brazil.

The sharp rise in maternal deaths in Brazil mirrors the trend in several countries, including the United States: in 2021, there were an estimated 1,205 maternal deaths, compared to 754 deaths in 2019[119]. However, the estimated MMR in the United States in 2021 was 32.9 per 100,000 live births, representing less than one-third the MMR in Brazil in 2021. This stark difference highlights the severity of maternal mortality in Brazil, where the 2021 MMR is the highest estimate observed in the country in the past three decades[120]. Furthermore, we used a conservative definition for the MMR estimates, excluding late maternal deaths (after 42 days postpartum) and garbage codes, per the WHO definition of MMR per 100,000 live births. Our observed MMR estimate in 2015, for example, was lower than that from the Global Burden of Disease (GBD) Study (57.59 vs 65.4 per 100,000 live births), although the GBD redistributed cause-specific and garbage ICD-10 codes to capture maternal deaths that were not counted as official[48].

We found persisting sub-national variation in maternal mortality, with some regions experiencing far higher maternal deaths than others both before and during the pandemic. At the

state-level, de Carvalho-Sauer and colleagues demonstrated that the 2020 MMR estimate in Bahia state based on a Holt-Winters forecast of time series data from 2011 to 2019 was 49 per 100,000 live births (95% CI: 38 to 59 per 100,000 live births), significantly lower than the observed MMR of 78 per 100,000 live births that year[50]. Orellana and colleagues demonstrated that in the North, South and Central-West regions, excess maternal mortality was not significant during 2020[49]. However, our estimates used the most current data, and suggest that all macro-regions except for the South had significantly higher maternal deaths compared to 2019.

Surprisingly, direct COVID-19-related maternal deaths did not account for the majority of maternal deaths as we hypothesized, although the proportion due to COVID-19 more than doubled from 2020 to 2021. Guimarães and colleagues demonstrated that COVID-19-related maternal deaths in 2020 did not account for all excess maternal mortality at the national level, pointing to indirect causes of the pandemic on maternal care quality, including interruption of prenatal care[117]. In the United States, a Government Accountability Office report from October, 2022 on maternal deaths during the pandemic to congressional addresses found that COVID-19 was the cause in 25% of maternal deaths in 2020 and 2021, but the pandemic worsened disparities affecting access to care, transportation, and living environment, leading to downstream effects on maternal health[121].

While the highest proportions of maternal deaths and comprehensive maternal deaths were concentrated in the Northeast and Southeast, the macro-region with the largest population, the South and Central-West regions witnessed the largest relative increase in SMR and SMRc in 2021.The high MMR in the Southeast, North, and Northeast are consistent with historical maternal mortality data, driven by economic inequities and structural racism[66, 120]. The increase in SMR in the South and Central-West was unexpected, and points to the overwhelming impact of COVID-19 on the healthcare system throughout the country during the second year of the pandemic. Orellana and colleagues found that while there was variation by region and maternal age group during the first 14 months of the pandemic, there was a significant increase in maternal deaths

across all five regions during the March to May period of 2021[49], coinciding with the SARS-CoV-2 variant Gamma becoming the primary circulating variant of concern.

The Gamma surge during the first half of 2021 in Brazil lead to an unprecedented strain on the healthcare system in Brazil[122], with profound implications for maternal care quality and the treatment of COVID-19 in pregnancy. Giovanetti and colleagues demonstrated that the Gamma variant accounted for over 95% of cases in the country during the first half of 2021[123]. During the first three months of 2021, 15 states reported >90% ICU bed capacity, and several states reported 100% ICU bed capacity[122, 124], leading to denial of or delays in ICU-level care for thousands of Brazilians[122]. A qualitative study by Diniz and colleagues provide context for how such disruptions may have affected maternal health by documenting the frustration of family members attempting to access care for their pregnant or postpartum relatives who ultimately died from COVID-19[125]. Many of them cited multiple unsuccessful attempts to access outpatient care before hospitalization, the dismissal of COVID-related symptoms, and significant delays in both hospitalizations and ICU admission due to health care system strain when COVID-19 progressed to severe disease[125]. While maternal deaths directly attributed to COVID-19 increased from the first to the second year of the pandemic, the significant increase in excess maternal mortality resulting from non-COVID causes in 2021 highlights the negative impact of the pandemic on maternal care quality.

Our study has several limitations. First, MMR estimates are notoriously difficult to capture due to inaccurate reporting of maternal death[126]. While SIM uses the standardized definition of maternal death up to 42 days after delivery, maternal death is likely under-reported worldwide with increasing duration of postpartum days. Several studies have documented undercounting and regional differences in mortality data via SIM compared to the National Statistics Office (IBGE)[88-90]. While mortality estimates have improved over the past decade[91], there are concerns about completeness, particularly from rural areas and the Northern region[89]. However, the Brazilian Ministry of Health has invested significant resources into improving the collection and

dissemination of maternal mortality data. Regardless, we suspect that the documented MMR estimates in 2020 and 2021 are lower than the true values.

Second, estimates of maternal deaths due to COVID-19 range across studies[49, 117, 118]. We used the most conservative definition of COVID-19 in pregnancy, based on laboratory confirmation with a positive PCR or antigen test. Therefore, while our study shows a significant increase in MMR and SMR due to COVID-19 in pregnancy, these values likely underestimate the true burden of COVID-19 on maternal mortality in Brazil due to racial and economic disparities in laboratory testing[127].

Third, forecasting depends on historical time series points, therefore the accuracy of the predictions rely on both the quantity and quality of the time series data. We addressed this by using 12 data points to forecast two MMR values; and used the HES method, which is robust and frequently used for forecasting in surveillance[128]. While time series models are vulnerable to over-fitting[129], we addressed this by running a sensitivity analysis with an ARIMA model, which produced similar MMR estimates.

Fourth, the significance of associations in a time series observational study should be interpreted with caution since the possibility of confounding cannot be excluded. However, given the increased risk of mortality with SARS-CoV-2 infection in pregnancy and its impact on maternal health care delivery, it is reasonable to assume that the increased MMR in Brazil in 2020 and 2021 was driven primarily by COVID-19.

Conclusions

During the first two years of the COVID-19 pandemic, there were nearly 5,000 maternal deaths in Brazil. Using two complementary forecasting models, we estimated that the observed MMR was more than double the predicted MMR in 2021. Excess maternal mortality at the national level increased by over 92% during the second year of the pandemic, with over one-third of the maternal deaths in 2021 due directly to COVID-19 in pregnancy or in the postpartum period. While there was significant geographic variation in SMR estimates, excess maternal mortality surpassed 75% in all macro-regions in 2021, coinciding with the Gamma surge during the first half of 2021[130].

The observed MMR in Brazil in 2021 is the highest MMR in the past three decades[66]. While preliminary maternal mortality rates suggest an improvement in 2022[131] due to less severe COVID-19 in pregnancy resulting from a combination of hybrid immunity and vaccination[132] (and a possible lessening of the severe impacts to the health system), the long-term effects of previous SARS-CoV-2 infection and subsequent development of HDP in pregnancy remain unclear[14, 19, 26, 133]. Furthermore, it is unknown how quickly the health care system in Brazil will recover in order to meet the WHO SDG of MMR <70 per 100,000 live births by the year 2030[101]. Increased resources may be needed to strengthen the delivery of high-quality perinatal and postpartum care, with particular focus on the states with high MMR pre-COVID-19, in order to reverse the national MMR. In addition, the Brazilian Ministry of Health should continue to encourage eligible pregnant and postpartum individuals to complete COVID-19 vaccination, including boosters, as the world transitions to SARS-CoV-2 endemicity.

Figure 3.1 Holt-Winters forecast of predicted MMR compared to observed MMR in Brazil from 2008 to 2021.

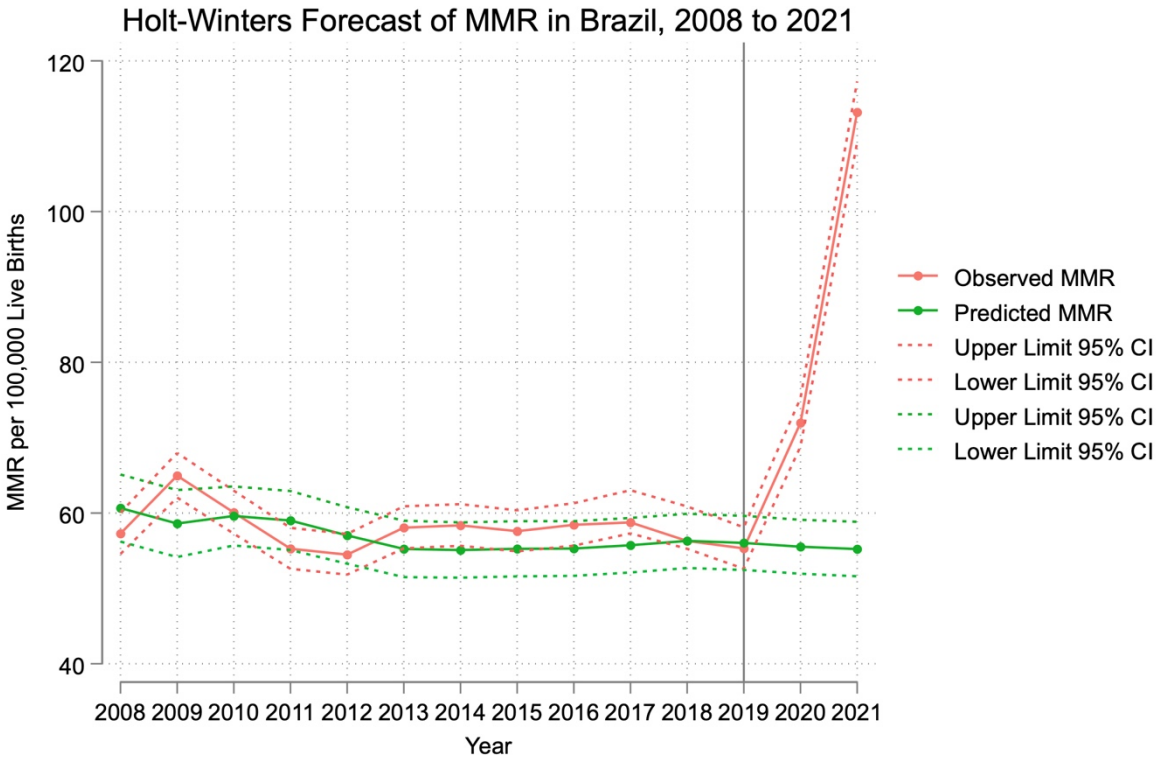


Figure 3.2 ARIMA forecast of predicted MMR compared to observed MMR in Brazil from 2008 to 2021.

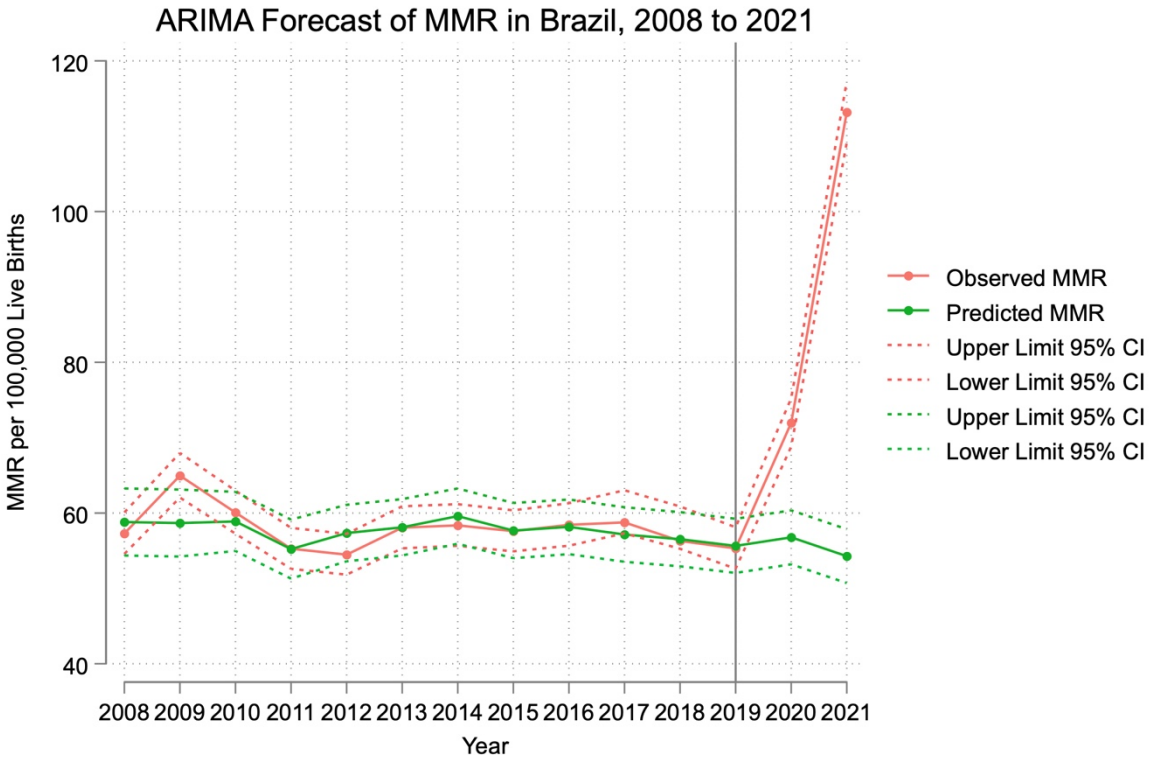


Figure 3.3 Maternal deaths[a] at the national and regional levels[b] from 2008 to 2021.

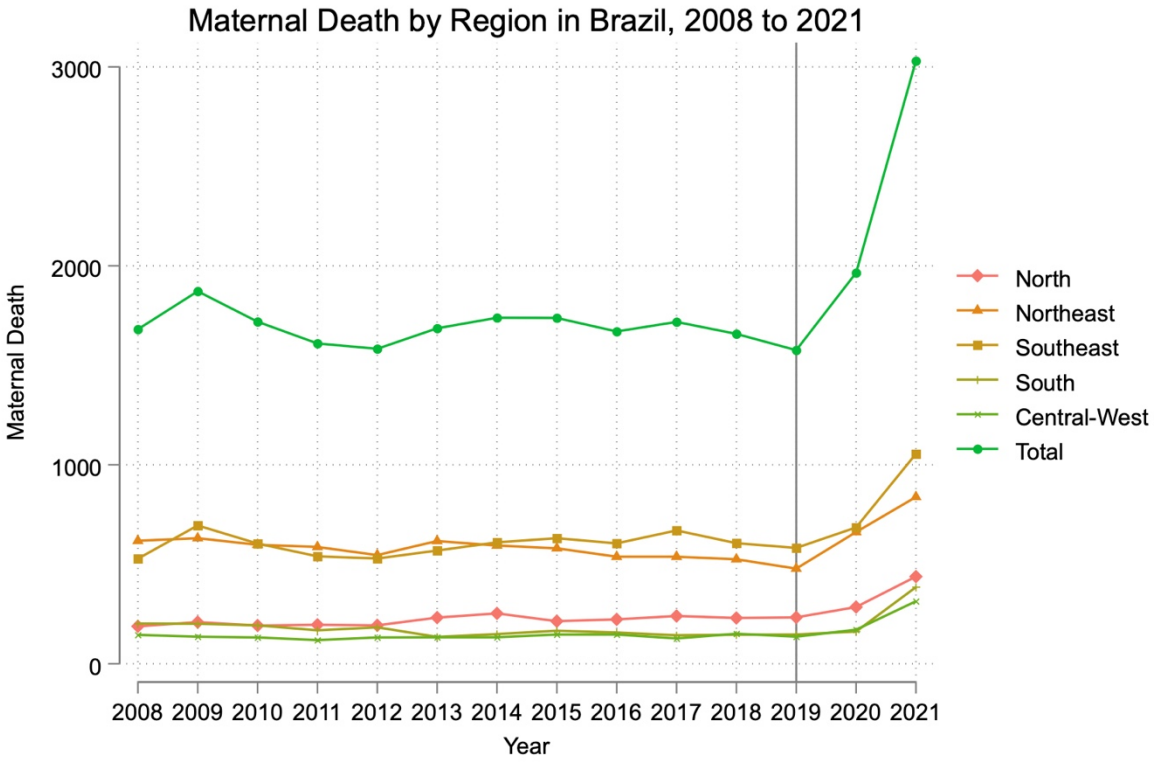


Table 3.1 Comparison of maternal deaths[a] and SMR[b] at the national and regional levels, 2019 to 2021.

Year	Region	Maternal Deaths	COVID-19 Death in Hospital	% Due to COVID-19	SMR (95% CI)[c]
2019	**Total**	**1,576**	**N/A**	**N/A**	**Reference**
2019	North	233	N/A	N/A	Reference
2019	Northeast	478	N/A	N/A	Reference
2019	Southeast	582	N/A	N/A	Reference
2019	South	147	N/A	N/A	Reference
2019	Central-West	136	N/A	N/A	Reference
2020	**Total**	**1,965**	**277**	**14.10**	**1.25 (1.19, 1.30)**
2020	North	285	36	12.63	1.22 (1.08, 1.37)
2020	Northeast	662	82	12.39	1.38 (1.28, 1.49)
2020	Southeast	685	113	16.50	1.17 (1.09, 1.27)
2020	South	162	16	9.88	1.10 (0.93, 1.27)
2020	Central-West	171	39	22.81	1.26 (1.07, 1.45)
2021	**Total**	**3,030**	**1,059**	**34.95**	**1.92 (1.85, 1.99)**
2021	North	438	132	30.14	1.88 (1.70, 2.06)
2021	Northeast	838	204	24.34	1.75 (1.63, 1.87)
2021	Southeast	1,055	432	40.95	1.81 (1.70, 1.92)
2021	South	385	159	41.30	2.62 (2.36, 2.88)
2021	Central-West	314	132	42.04	2.31 (2.05, 2.56)

a. Defined according to the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of cause.
b. SMR = (Observed deaths/Expected deaths), using 2019 as the reference.
c. 95% CI calculated using the Vandenbroucke metho

Table 3.2 Comparison of comprehensive maternal deaths and SMRc at the national and regional levels, 2019 to 2021.

Year	Region	Comprehensive Maternal Deaths	SMRc
2019	**Total**	**1,736**	**Reference**
2019	North	250	Reference
2019	Northeast	546	Reference
2019	Southeast	627	Reference
2019	South	161	Reference
2019	Central-West	152	Reference
2020	**Total**	**2,138**	**1.23 (1.17, 1.29)**
2020	North	310	1.24 (1.10, 1.38)
2020	Northeast	697	1.28 (1.18, 1.37)
2020	Southeast	763	1.22 (1.13, 1.30)
2020	South	187	1.16 (1.00, 1.33)
2020	Central-West	181	1.19 (1.02, 1.36)
2021	**Total**	**3,403**	**1.96 (1.89, 2.03)**
2021	North	479	1.92 (1.74, 2.09)
2021	Northeast	954	1.74 (1.64, 1.86)
2021	Southeast	1,205	1.92 (1.81, 2.03)
2021	South	435	2.70 (2.45, 2.96)
2021	Central-West	330	2.17 (1.94, 2.41)

a. Defined according to the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of cause.
b. SMR = (Observed deaths/Expected deaths), using 2019 as the reference.
c. 95% CI calculated using the Vandenbroucke method

Chapter 4 Individual Receipt of the COVID-19 Vaccine and High State-Level Vaccine Coverage Protects Against Maternal Mortality in Brazil Despite Differences in Epidemiologic and Health Service Delivery Factors at the State Level

Abstract (330 words):

Pregnancy is an established risk factor for severe COVID-19, including death. The leading global obstetrical societies recommend that all eligible persons, including pregnant and postpartum individuals, adhere to the annual COVID-19 vaccine schedule. Few studies have accounted for differences in state-level epidemiologic and health services factors when evaluating the impact of individual-level health factors on COVID-19 related maternal death, including receipt of the COVID-19 vaccine. We used the publicly available Sistema de Informação da Vigilancia Epidemiológica da Gripe (SIVEP-Gripe) database to analyze individual-level factors, including receipt of a vaccine, associated with maternal death among pregnant or postpartum individuals (up to 42 days after birth) hospitalized with COVID-19 in Brazil from January 1 to December 31, 2021. State-level variables were collected from the Institute for Health Metrics and Evaluation (IHME) and the Federal Council of Medicine databases. We calculated the crude and adjusted odds ratios (AOR) using two random effects (RE) models, first fitting a model that included only individual factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for clustering across 27 states, and a second model that included all possible factors. We conducted a sensitivity analysis using two additional fixed effects (FE) models to account for heterogeneity not adjusted by the state level variables. From January 1, 2020 to December 31, 2021, there were 10,435 pregnant or postpartum individuals hospitalized with COVID-19. Among those hospitalizations, there were 1,059 (10.15%) maternal deaths. In both the RE and FE models, pregnant persons who received a single dose of an approved COVID-19 vaccine prior to hospitalization had significantly reduced odds of maternal death (AOR 0.34, 95% CI 0.25 to 0.46). In the RE model, estimated state vaccine coverage of $\geq$90% was

associated with an 89% reduction in odds of maternal death. As Brazil faces the highest rates of maternal mortality observed in three decades, continued investment in the COVID-19 national vaccination campaign is a potential intervention to protect against COVID-19-related death in pregnant and postpartum populations.

Background

Pregnancy is an established risk factor for severe COVID-19 disease, including death[12, 24, 134]. Growing data support the safety and efficacy of the COVID-19 vaccines in pregnancy[135]. The leading global obstetrical societies recommend that all eligible persons, including pregnant and postpartum individuals, adhere to the annual COVID-19 vaccine schedule[29]. Despite these recommendations, vaccination rates among pregnant populations globally remain suboptimal[136]. The COVID-19 vaccines were not readily available in Brazil until 2021, and recommended only in July, 2021 to pregnant and postpartum individuals considered high-risk with underlying co-morbidities[137].

There are seven approved COVID-19 vaccines in Brazil, including one mRNA-based vaccine, BNT162b2[138]. Of the approved vaccines in Brazil, BNT162b2 is the most effective against multiple variants of concern and death[139-142]. The protection offered by the adenovirus-vector vaccines are variable depending on the predominantly circulating variable, and even less so with the most widely available vaccine in Brazil, the inactivated vaccines CoronaVac[143]. A national COVID-19 immunization program was started in January, 2021, consisting primarily of the inactivated CoronaVac and adenovirus-vector ChAdOx1 vaccines (both two-dose series), followed by the mRNA vaccine BNT162b2. There are data to suggest that even a single vaccine dose is protective against COVID-19 related mortality[42], including in pregnancy and postpartum.

Individual level health factors, including increasing age, co-morbidities (specifically pre-pregnancy obesity, diabetes mellitus, and hypertension) and urbanicity are linked to maternal death due to COVID-19 in Brazil and globally[14, 28, 144]. However, studies from multiple countries also describe the impact of epidemiologic and health services factors at the state level on poor COVID-19 outcomes, including high COVID-19 prevalence, low vaccine coverage, low mask usage, and extreme ICU strain[145-148].

Brazil consists of five macroregions: the North, Northeast, Central-West, Southeast, and South. The 26 states and the Federal District, for a total of 27 federative units, form the

macroregions. Across the macroregions, there are persistent geographic differences in social and health inequities impacting COVID-19 outcomes throughout, which have also impacted maternal mortality and morbidity. A population-based ecological study by Siqueira et al. found that COVID-19 related maternal mortality was clustered in municipalities with higher social inequities and lower healthcare utilization[149]. Studies among non-pregnant populations have come to similar conclusions [150].

Few studies have accounted for differences in state-level epidemiologic and health services factors when evaluating the impact of individual-level health factors on COVID-19 related mortality. In order to address this gap in the literature, we analyzed individual- and state-level factors associated with maternal death among pregnant and postpartum individuals hospitalized with COVID-19 in Brazil. To our knowledge, this is the first study to describe the protective effect of the COVID-19 vaccine on maternal mortality in Brazil once the vaccine became widely available, while accounting for other individual- and state-level factors also known to impact maternal mortality.

Methods

Aim and Study Design

The purpose of this analysis is to characterize which factors protected against maternal death among pregnant women hospitalized with COVID-19 in Brazil. By accounting for differences at the state level, we hope to provide a more nuanced understanding of the how epidemiologic and health care infrastructure impacted maternal mortality during the peak of the COVID-19 pandemic. The study's conceptual model (Figure 4.1) illustrates the posited relationship between these variables. Our hypothesis was that receipt of a single COVID-19 vaccine dose would strongly protect against maternal death due to COVID-19 in the hospital.

Data Source

Beginning in January 2020, the publicly-available Sistema de Informação da Vigilancia Epidemiológica da Gripe (SIVEP-Gripe) database began tracking all COVID-19 hospitalizations in Brazil through the Sistema de Informação de Agravos de Notificação (SINAN), the national reporting system for notifiable diseases of the Brazilian Ministry of Health[151-153]. The SIVEP-Gripe surveillance system was established by SINAN in 2009 in response to the H1N1 influenza pandemic[83]. Since its inception, the database has served as the national surveillance system for influenza and other respiratory viruses of clinical concern. Following the initial identification of SARS-CoV-2, the virus responsible for COVID-19, the Brazilian Ministry of Health required notification of both suspected and confirmed cases by polymerase chain reaction (PCR) testing (the gold standard), and more recently, antigen (Ag) testing. Both public and private hospitals are required by law to report COVID-19 hospitalizations to SIVEP-Gripe within 24 hours of a suspected case[154]. Each hospitalization includes information on the person's age, receipt of COVID-19 vaccine and type, trimester of infection (for pregnant persons), self-identified race, education level, geographic location, medical co-morbidities, pregnancy and postpartum status, and outcomes, including death. The annual databases, including reporting details and data dictionary, are made publicly available through the Ministry of Health SUS platform (DATASUS)[152,

[153]. The data are reviewed and cleaned weekly by the Ministry of Health National Immunization Program.

For state-level data, we used the Institute for Health Metrics and Evaluation (IHME)[95], and the Federal Council of Medicine. The IHME is a global health policy database independently managed by the University of Washington since 2007. The IHME stewards the Global Burden of Disease collaboration, and collects publicly available data across multiple sources, including Ministries of Health. The IHME has been crucial in the advancement of COVID-19 research, serving as a universal database for health service indicators, including state COVID-19 prevalence, COVID-19 vaccine coverage, and reported mask usage. For ICU bed capacity, we used 2020 estimates from the Federal Council of Medicine.

Variables

The predictor of interest, receipt of an approved COVID-19 vaccine prior to the hospitalization, was dichotomized (Yes = 1, No or Unknown= 0). The primary outcome was maternal death, defined by the World Health Organization (WHO) as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of the cause.

Age was dichotomized as <30 vs $\geq$30 years. Trimester of infection was operationalized as a categorical variable: first, second, third, or unknown. Although race is a social construct, we chose to include race in the model given the history of systemic racism in Brazil and its well-established impact on poor maternal outcomes[155]. Race was operationalized as a categorical variable: white, Black, and other (including indigenous, and mixed race). Education was dichotomized as less than high school vs high school and higher. Location of residence was dichotomized as rural vs urban. Season was dichotomized as January to June, vs July to December. In our study, season served as a proxy for the dominant variant in circulation. Gamma was the primary circulating variant of concern from January to June, and responsible for approximately 96% of cases during that time. Gamma was replaced by the Delta variant beginning in July, 2021. Cardiovascular risk and diabetes were dichotomized (Yes = 1, No = 0) according to

the SIVEP-Gripe variables. Obesity was categorized as pre-gestational body mass index (BMI) >30 kg/m^2. Missing data was high for race and educational attainment (both >25%). We assumed this nonresponse pattern reflected a missing at (MAR) pattern, and therefore used multiple imputation for race and educational attainment (see Appendix).

For state level epidemiologic and health services, the estimated percent of population infected with COVID-19 was dichotomized as <60% vs ≥60%, based on initial estimates for herd immunity[156]. State vaccine coverage was operationalized based on the estimated proportion of the state population that received at least one dose of the vaccine by the end of the year (10, 20, 30, 40, 50, 60, 70, 80, 90, 100%). State mask usage was operationalized based on the proportion of the state population reporting always wearing a mask when leaving the home (10, 20, 30, 40, 50, 60, 70, 80, 90, 100%). The state ICU bed capacity variable was dichotomized as <2 vs ≥2 per 10,000 inhabitants based on previous studies examining the relationship between ICU bed capacity and death[147].

Data Analysis

Total COVID-19 related hospitalizations in Brazil from January 1, 2020 to December 31, 2021, were stratified by pregnancy status. Pregnant or postpartum individuals in Brazil hospitalized for COVID-19 between January 1, 2021 and December 31, 2021 were included in the analysis. The association between maternal death and vaccine status among hospitalized pregnant or postpartum patients in Brazil in 2021 was assessed via Pearson's correlation. Descriptive statistics (frequency and percentage) of individual levels factors for the main study population in 2021 were calculated among those who did and did not experience maternal death. We conducted a logistic regression model for state-level epidemiologic and health services factors associated with maternal death among pregnant or postpartum persons hospitalized with COVID-19 in Brazil in 2021. We calculated the crude and adjusted odds ratios (OR) using a random effects (RE) model for factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for clustering at the state level (27). The

first RE model was constructed by backward removal of non-significant covariates ($p<0.10$) in the initial multivariate model, including all individual and state-level health factors, including dummy state variables. The second RE model included all individual level factors based on the conceptual model.

We ran a sensitivity analysis using two fixed effects (FE) models. An advantage of the RE model is that the RE estimator accounts for both within and between-cluster variation, while the FE estimator, which only accounts for within-cluster variation. We used a Hausman-Wu test to determine whether an FE or RE model was more appropriate (since the FE model is generally consistent, but the RE model is generally more efficient). Statistical analysis was performed with STATA with statistical significance defined using a two-sided $\alpha < 0.05$.

Results

From January 1, 2020 to December 31, 2021, there were 1,917,541 COVID-19 related hospitalizations in Brazil (Figure 4.2). In 2021, there were 1.2 million COVID-19 related hospitalizations, of which 10,435 (0.83%) were pregnant or postpartum. Among those hospitalizations, there were 1,059 (10.15%) maternal deaths (Figure 4.2). In Distrito Federal (DF), Mato Grosso do Sul, and the Southern states, except for Rio Grande do Sul, a higher prevalence of maternal vaccination among hospitalized pregnant or postpartum individuals correlated with a low prevalence of maternal death (Figure 4.3). In the Northern and Central West states, there was a higher prevalence of maternal death, which correlated with lower rates of maternal vaccination among the hospitalized population (Figure 4.3). Among the pregnant or postpartum individuals hospitalized with COVID-19, 1,234 (13.2%) of those who survived received the vaccine, compared to only 49 (4.6%) among the 1,059 maternal deaths (Figure 4.3, Pearson chi-square $p<0.0001$).

Table 4.1 shows the descriptive statistics of the 10,435 pregnant or postpartum individuals hospitalized with COVID-19 from January 1, 2021 to December 31, 2021. Hospitalized pregnant or postpartum individuals who died compared to those who survived were more likely to be $\geq$30 years of age, infected with COVID-19 during the 2nd trimester, live in a rural area, diagnosed in the first half of the year (January to June), and have at least one co-morbidity. Hospitalized pregnant or postpartum individuals who died compared to those who survived were less likely to have received the COVID-19 vaccine. There were no significant differences in racial or educational categories between those who died or survived.

Supplemental Table 4.1 is the correlation matrix of state level factors, presented as Pearson correlation coefficients. State mask usage and state vaccine coverage were highly correlated ($r = 0.7031$), while correlations between other variables ranged from –0.4697 to 0.4892. Supplemental Table 4.2 shows the nested regression models for individual-level factors associated with maternal death. Table 4.2 shows the nested logistic regression models for state

level epidemiologic and health services factors associated with maternal death among pregnant or postpartum persons hospitalized with COVID-19 in Brazil in 2021. In Model 4, only State Mask Usage was associated with maternal survival, although the impact was modest.

Table 4.3 shows the adjusted OR (AOR) from the random effects model for factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021. Controlling for other factors, pregnant or postpartum individuals who received a single COVID-19 vaccine prior to hospitalization had significantly reduced odds of maternal death (AOR 0.34, 95% CI 0.25 to 0.46). At the state level, estimated state vaccine coverage of 80% was associated with a 72% reduction in odds of maternal death (AOR 0.28, 95% CI 0.16 to 0.49). Estimated state vaccine coverage of ≥90% was associated with an 89% reduction in odds of maternal death. Age ≥30 years (AOR 1.63, 95% CI 1.42 to 1.87), January to June season (AOR 1.33, 95% CI 1.10 to 1.60), maternal co-morbidities (AOR 2.21, 95% CI 1.89 to 2.57) and the state-level factor ≥2 ICU beds per 10,000 inhabitants (AOR 3.02, 95% CI 1.94 to 4.69) were associated with an increased odds of maternal death. There was significant variation with the state of residence. Alagoas, Amazonas, Amapá, Bahia, Ceará, Distrito Federal, Minas Gerais and Mato Grosso were associated with a significantly reduced odds of maternal death among hospitalized pregnant women with COVID-19, while Espírito Santo and Rio Grande do Norte were associated with significantly increased odds of maternal death. Supplemental Table 4.3 shows the crude and adjusted ORs from the random effects model for individual-level factors associated with maternal death. The values are similar between crude and adjusted ORs, and comparable to the first RE model. The only variable that is significant in the second model that was not in the first RE model is second trimester of infection (AOR 1.40, 95% CI 1.07 to 1.84). Race, education and urbanicity were not significant predictors of maternal death.

Table 4.4 shows the AOR from the FE model for factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for within-cluster variation at the state level. Controlling for other factors, women who received a single COVID-19

vaccine prior to hospitalization had significantly reduced odds of maternal death (AOR 0.34, 95% CI 0.25 to 0.46). Age ≥30 years (AOR 1.63, 95% CI 1.42 to 1.87), January to June season (AOR 1.33, 95% CI 1.10 to 1.60), and maternal co-morbidities (AOR 2.20, 95% CI 1.89 to 2.57) were associated with an increased odds of maternal death, nearly identical to the RE model. Supplemental Table 4.4 shows the crude and adjusted odds ratios from the FE model for individual-level factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021. The values were nearly identical to the first FE model, except second and unknown trimester of infection (AOR 1.40 and 1.52, respectively) were associated with increased odds of maternal death.

Discussion

Among the 10,435 pregnant or postpartum individuals hospitalized with COVID-19 in Brazil in 2021, 10.15% of these resulted in maternal death. This staggeringly high case fatality rate mirrored COVID-19-related maternal mortality in the United States, where SARS-CoV-2 infection at delivery conferred a 14-fold higher odds of maternal mortality[157]. Among the pregnant or postpartum individuals hospitalized with COVID-19 in this dataset, 13.2% of those who survived received the vaccine, compared to only 4.6% among the 1,059 maternal deaths (Pearson chi-square $p<0.0001$), representing a 66% reduction in odds of maternal death due to COVID-19.

Consistent with our findings, studies in other countries have demonstrated the protective effect of the vaccine on COVID-19-related maternal deaths, including during surges with new variants of concern[135]. The INTERCOVID-2022 prospective observational study evaluated the effectiveness of COVID-19 vaccines among 4,618 pregnant women across 41 hospitals in 18 countries, including Brazil, during the Omicron surge from November 2021 to June 2022. In the subset of pregnant women with confirmed COVID-19, vaccine effectiveness (defined as the reduction in confirmed SARS-CoV-2 infections among vaccinated compared to unvaccinated pregnant persons) to prevent maternal mortality and morbidity was 74% (95% CI 48 to 87) and 91% (95% CI 65 to 98) after the booster dose. While mRNA vaccines were the most effective, the adenovirus-vector vaccines also protected against maternal morbidity and mortality[135]. In a retrospective cohort also using SIVEP-Gripe data between May and November of 2021, de Freitas Paganoti et al. found that completion of two approved vaccine doses compared to unvaccinated pregnant or postpartum women with COVID-19 reduced the odds of maternal mortality by 82%[158]. These estimates likely differ from our study due to our definition of vaccination (a single approved dose only), inclusion of those with an unknown vaccine status, and inclusion of the entire year of 2021, including the Gamma surge in the first half.

Our study highlights the benefit of individual receipt of the COVID-19 vaccine in protection against maternal death, as well as the impact of high state-level vaccine coverage ($\geq$90%),

underscoring the need for an ongoing national COVID-19 vaccination campaign. A retrospective study using SIVEP-Gripe from January 2020 to November 2021 to evaluate individual-level and healthcare-related factors on maternal mortality among pregnant and postpartum women hospitalized with COVID-19 in Brazil by Leung et al. found that that COVID-19 vaccination, region (the Central-West and South), urbanicity, and access to a designated obstetric center were protective against maternal death. We expanded on these analyses by utilizing FE and RE models integrating both individual-level and state-level variables to account for tremendous epidemiologic and health services variation at the state level. In our analyses, $\geq$2 ICU beds per 10,000 inhabitants was associated with increased odds of maternal death at the state level, likely indicative of reverse causality.

A surprising finding from our study was that high state-level vaccine coverage protected against maternal death due to COVID-19. Other studies from the US support our finding of the community level benefit of high vaccine coverage: a CDC study of 2,558 counties across 48 states found an 8% reduction in COVID-19 mortality rates for every 10% increase in vaccination coverage at the county level[159]. The mechanism by which high population-level vaccine coverage protects the individual is not understood, but may be driven by herd immunity impacting shedding kinetics and reduced viral load in human-to-human transmission as a result[160].

Maternal co-morbidities, January to June season, and age $\geq$30 years were associated with increased odds of maternal death. The presence of at least one maternal co-morbidity (maternal cardiovascular risk, diabetes, or pre-pregnancy obesity) conferred a two-fold increased odds of maternal death, consistent with several studies in both pregnant[133] and non-pregnant populations[161, 162]. As expected, the odds of maternal death was 30% higher during the Gamma surge (first half of 2021), a time of unprecedented healthcare strain as a result of the increasing COVID-19 incidence throughout the country. A Bayesian modeling study by Brizzi et al. found that the high in-hospital fatality rates during the Gamma wave were highly associated with differences in pandemic healthcare pressure and resource allocation across 14 state capitals[163].

However, the study excluded all vaccinated persons, which may explain why epidemiologic and healthcare utilization factors at the state level were not significant in our analyses, other than high vaccine coverage at the state level. Surprisingly, maternal race and education were not significant factors in the model. While there was a high rate of missingness for both variables, we used multiple imputation to address this.

Continued investment in the country-wide COVID-19 immunization program could be a cost-effective policy intervention to reduce COVID-19-related maternal mortality. A susceptible-vaccinated-exposed-infectious-recovered (SVEIR) model constructed by Augustovski et al. to evaluate the cost-effectiveness of the COVID-19 vaccines in seven Latin American countries, including Brazil, projected that vaccination campaigns would be cost-effective in the seven countries, and cost-saving in all of the countries except Chile. Furthermore, other public health campaigns and efforts to re-allocate resources may not be as effective since mask usage and ICU capacity were not protective against COVID-19-related maternal mortality in our study.

Limitations

There are several limitations to this analysis. First, while the RE and FE models are based on primary literature, the available datasets lack important variables, such as receipt of prenatal care, therefore omitted variable bias may threaten the internal validity of the study. In addition, we cannot exclude the possibility of collider bias, since we are analyzing the relationship between COVID-19 vaccination and death in a sample of hospitalized patients with COVID-19[164]. Second, a cross-sectional analysis may fail to capture the longitudinal effects throughout the year, particularly given the dynamic changes in healthcare utilization in 2021, and time-variant factors such as daily ICU capacity and state-level vaccine coverage. However, we addressed this by incorporating the season, which was a surrogate for the primary circulating variant of concern. Third, the state-level variables were based on crude estimates from IHME and the Federal Council of Medicine. However, these two datasets are frequently used in the literature[165], and represent the most accurate estimates of real-time epidemiologic and health services data available. Last, given the high rate of missing values for the type and doses of the COVID-19 vaccine (mRNA vs adenovirus-vector based), we did not include these variables in the analysis. Nevertheless, our study demonstrated that even a single vaccine dose, regardless of type, was protective against maternal death in hospitalized pregnant and postpartum individuals with COVID-19.

There are several advantages to using the RE and FE models. First, both models accommodate nested data with complex error structures. Second, RE models account for both within and between-cluster variation, leading to a population average estimate, and therefore a more efficient estimator of the coefficients. However, one of the limitations is the assumption that the explanatory variables do not correlate with the random effects[166]. In that case, the coefficients are biased, and the model is inconsistent. To address this, we ran a sensitivity analysis with an FE model, and also ran additional FE and RE models based only on the conceptual model.

Conclusions

Receipt of a single dose of an approved COVID-19 vaccine in pregnant and postpartum individuals prior to hospitalization for COVID-19 was associated with a 66% reduction in odds of maternal death in Brazil in 2021, despite major differences in epidemiologic and healthcare delivery factors at the state level that might have affected mortality during this time, such as ICU capacity. The only state-level variable found to be protective against COVID-19-related maternal mortality was high vaccine coverage, associated with an 89% reduction in odds of maternal death.

These findings have important health policy implications as Brazil faces the highest maternal mortality rates in three decades. While many individual-level health factors are difficult to modify, and the impact of other state-level factors on COVID-19-related mortality are unclear, continued vaccination is a potential strategy to reduce maternal mortality in Brazil. A notable finding is that even a single dose of the vaccine was protective against COVID-19-related maternal mortality, underscoring the potential impact of an effective nationwide vaccination campaign on efforts to tackle the rise in maternal mortality. Further research is needed to measure more precisely the impact of the national immunization program on COVID-19-related maternal mortality in Brazil.

Figure 4.1 Conceptual model.

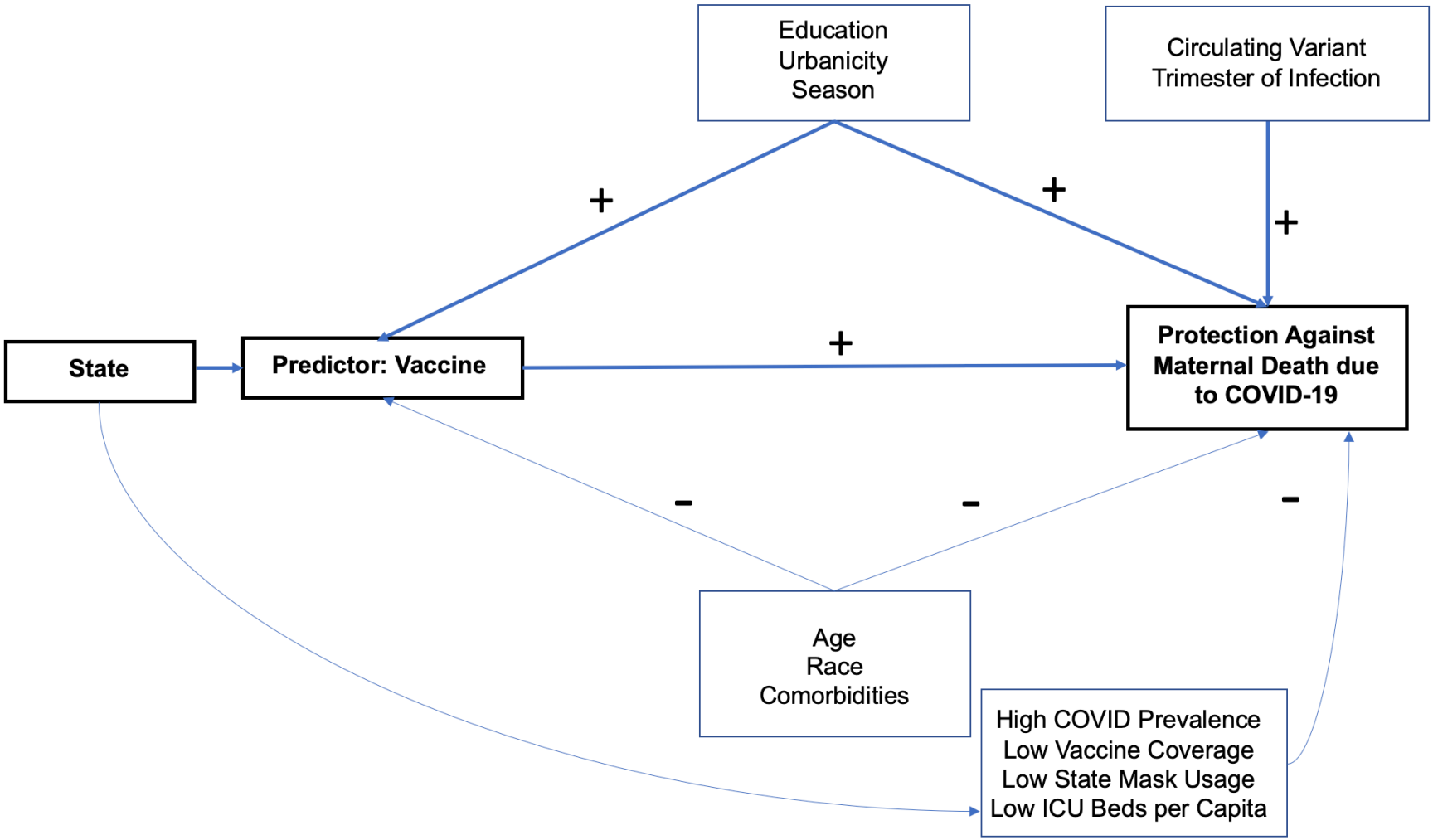
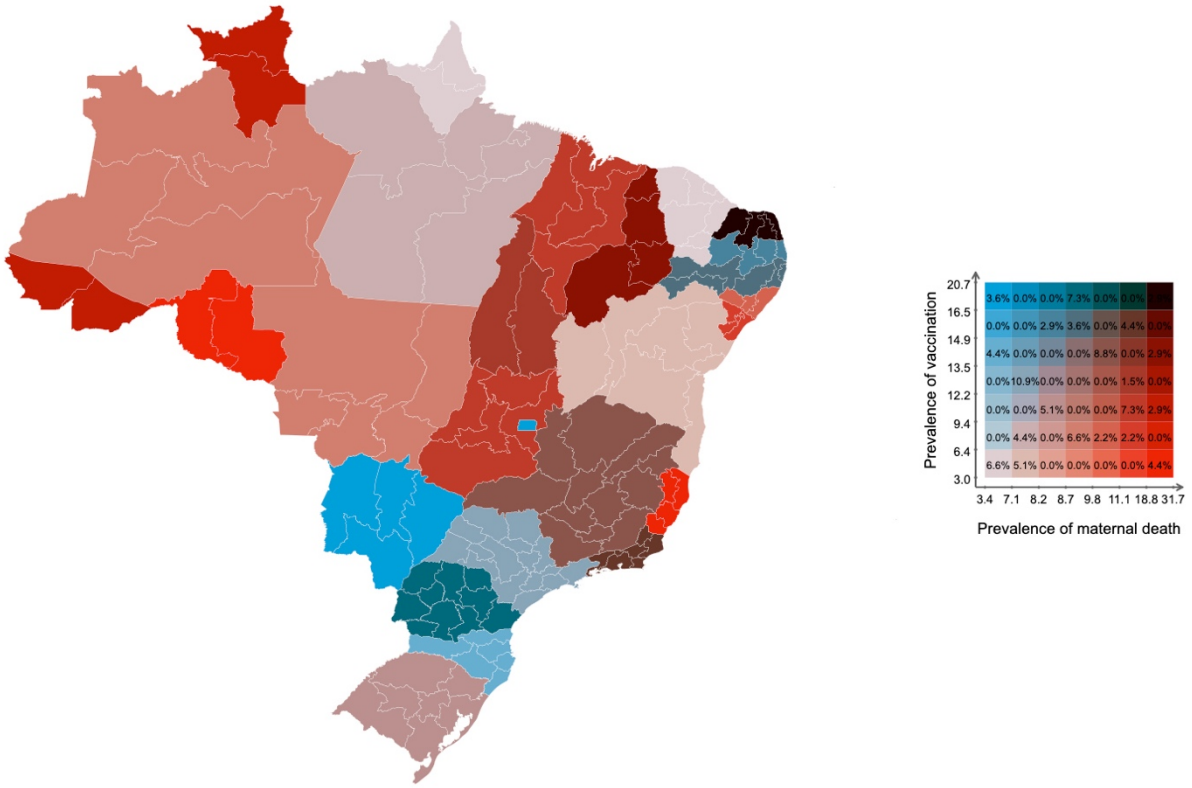


Figure 4.2 Total COVID-19 related hospitalizations in Brazil from January 1, 2020 to December 31, 2021, stratified by pregnancy status and maternal death.

Year	2020	2021	Total
Total	672,672	1,244,869	1,917,541
Pregnant or Postpartum[a] n (% total)	5,347 (0.79)	10,435 (0.83)	15,782 (0.82)
Maternal Deaths[b] n (% pregnant)	277 (5.18)	1,059 (10.15)	1,336 (8.47)

a. Pregnant or postpartum, defined as the period up to 42 days following birth.
b. Maternal death, defined by the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of the cause.

Figure 4.3 Bivariate map of prevalence of maternal vaccination[a] and prevalence of maternal death[b] among hospitalized pregnant or postpartum[c] patients in Brazil by state, January 1 to December 31, 2021.



a. Maternal vaccination: defined as a single dose of any approved COVID-19 vaccine prior to hospitalization for COVID-19.
b. Maternal death: defined by the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of the cause.
c. Postpartum: defined as the period up to 42 days following birth.
d. Red is associated with low prevalence of vaccination and high prevalence of maternal death, while teal is associated with low prevalence of maternal death and high prevalence of vaccination.

Figure 4.4 Association between maternal death[a] and vaccine status[b] among hospitalized pregnant or postpartum patients in Brazil in 2021.

	Maternal Deaths n (%)[d]		
COVID-19 Vaccine	**No**	**Yes**	**Total**
No	8,142 (86.8%)	1,010 (95.4%)	9,152 (87.7%)
Yes	1,234 (13.2%)	49 (4.6%)	1,283 (12.3%)
Total	9,376	1,059	10,435

Pearson chi-square p<0.0001

a. Maternal death, defined by the WHO as death during pregnancy, childbirth or within 42 days postpartum or termination, regardless of the cause.
b. Maternal vaccination defined as a single dose of any approved COVID-19 vaccine prior to hospitalization for COVID-19.
c. Pregnant or postpartum, defined as the period up to 42 days following birth.
d. Pearson chi-square by frequency (column percentage).

Table 4.1 Descriptive statistics of pregnant or postpartum persons hospitalized with COVID-19 in Brazil in 2021, stratified by maternal death.

N = 10,435		**Survived**	**Maternal Death**	**p-value[a]**
n (%)		9,376 (89.9%)	1,059 (10.1%)	
Age	Median (IQR)	30 (25, 35)	32 (27, 37)	<0.001
	<30 years	4,445 (47.4%)	365 (34.5%)	<0.001
	≥30 years	4,931 (52.6%)	694 (65.5%)	
COVID-19 Vaccination[b]	No	8,142 (86.8%)	1,010 (95.4%)	<0.001
	Yes	1,234 (13.2%)	49 (4.6%)	
Trimester of Infection	First	840 (9.0%)	75 (7.1%)	<0.001
	Second	2494 (26.6%)	329 (31.1%)	
	Third	5,607 (59.8%)	589 (55.6%)	
	Unknown	435 (4.6%)	66 (6.2%)	
Race	White	3,615 (44.6%)	399 (41.6%)	0.21
	Black	438 (5.4%)	57 (5.9%)	
	Other[c]	4,050 (50.0%)	502 (52.4%)	
Education	Less than HS	1,076 (27.4%)	159 (30.0%)	0.21
	HS and Higher	2,853 (72.6%)	371 (70.0%)	
Urbanicity	Rural	1,508 (16.1%)	196 (18.5%)	0.04
	Urban	7,868 (83.9%)	863 (81.5%)	
Season	Jan to Jun	7,238 (77.2%)	895 (84.5%)	<0.001
	Jul to Dec	2,138 (22.8%)	164 (15.5%)	
Cardiovascular Risk	No	8,905 (95.0%)	967 (91.3%)	<0.001
	Yes	471 (5.0%)	92 (8.7%)	
Diabetes	No	8,787 (93.7%)	954 (90.1%)	<0.001
	Yes	589 (6.3%)	105 (9.9%)	
Obesity[d]	No	8,833 (94.2%)	897 (84.7%)	<0.001
	Yes	543 (5.8%)	162 (15.3%)	
Co-Morbidities[e]	No	8,067 (86.0%)	774 (73.1%)	<0.001
	Yes	1,309 (14.0%)	285 (26.9%)	

a. Continuous variables are compared using Wilcoxon rank-sum, and categorical variables are compared using Pearson's chi-squared.
b. Defined as at least one approved vaccine dose prior to hospitalization.
c. Includes indigenous, mixed, and other racial categories.
d. Defined as pre-gestational BMI >30.
e. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity

Table 4.2 Nested logistic regression models for state level epidemiologic and health services factors associated with maternal death among pregnant or postpartum persons hospitalized with COVID-19 in Brazil in 2021[a].

	Model 1	**Model 2**	**Model 3**	**Model 4**
State COVID-19 Prevalence[b]	1.26* (1.03, 1.55)	1.12 (0.90, 1.41)	1.04 (0.81, 1.32)	1.03 (0.81, 1.31)
State Vaccine Coverage[c]		0.99* (0.98, 0.99)	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)
State Mask Usage[d]			0.99* (0.98, 0.99)	0.98* (0.97, 0.99)
State ICU Beds per Capita[e]				1.05 (0.97, 1.13)
LR chi^2	*4.69**	*10.53***	*14.97***	*16.45***

***p < 0.001; **p < 0.01; *p < 0.05

a. Presented as ORs and 95% CIs.
b. Estimated percent of the population infected with COVID-19, dichotomized as <60% and ≥60% (source: IHME Policy Briefing for Brazil, December 2021).
c. Estimated percent of the population who received at least one COVID-19 vaccine dose (source: IHME Policy Briefing for Brazil, December 2021).
d. Proportion of the population reporting always wearing a mask when leaving the home (source: IHME Policy Briefing for Brazil, December 2021).
e. ICU beds per 10,000 inhabitants (source: Federal Council of Medicine, 2020).

Table 4.3 Adjusted odds ratios (OR) from the random effects model for factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for clustering at the state level[a].

N = 10,435		**Adjusted OR [95% CI]**
Individual Level Factors		
Age	<30 years	Reference
	≥30 years	1.63 [1.42, 1.87]*
COVID-19 Vaccination[b]	No	Reference
	Yes	0.34 [0.25, 0.46]*
Season	Jan to Jun	1.33 [1.10, 1.60]*
	Jul to Dec	Reference
Co-Morbidities[c]	No	Reference
	Yes	2.21 [1.89, 2.57]*
State Level Factors		
State Vaccine Coverage[d]	50%	Reference
	60%	1.77 [0.82, 3.86]
	70%	0.75 [0.39, 1.43]
	80%	0.28 [0.16, 0.49]*
	90%	0.11 [0.06, 0.22]*
	100%	0.11 [0.06, 0.20]*
State ICU Beds Per Capita[e]	<2 per 10,000	Reference
	≥2 per 10,000	3.02 [1.94, 4.69]*
	Santa Catarina	Reference
	Acre	0.73 [0.22, 2.47]
	Alagoas	0.27 [0.11, 0.69]*
	Amazonas	0.27 [0.13, 0.59]*
	Amapá	0.08 [0.01, 0.40]*
	Bahia	0.17 [0.08, 0.39]*
	Ceará	0.16 [0.08, 0.35]*
	Distrito Federal	0.27 [0.17, 0.44]*
	Espírito Santo	2.00 [1.03, 3.86]*
	Goiás	0.81 [0.58, 1.14]
	Maranhão	1 (omitted)
	Minas Gerais	0.53 [0.39, 0.70]*
	Mato Grosso do Sul	1.08 [0.57, 2.07]
	Mato Grosso	0.20 [0.09, 0.45]*
	Pará	0.22 [0.10, 0.47]
	Paraíba	0.51 [0.26, 1.00]
	Pernambuco	0.61 [0.28, 1.34]
	Piauí	1.32 [0.63, 2.74]
	Paraná	1.33 [0.92, 1.94]
	Rio de Janeiro	1 (omitted)

	Rio Grande do Norte	2.11 [1.05, 4.25]*
	Rondonia	1.29 [0.64, 2.58]
	Roraima	1 (omitted)
	Rio Grande do Sul	1 (omitted)
	Sergipe	1 (omitted)
	São Paulo	1 (omitted)
	Tocantins	1 (omitted)
σ_μ		0.0005 [0.0000, 22611.04]
ρ		0.0000 [0.0000, 1]

*p<0.05

a. The final model was constructed by backward removal of nonsignificant covariates in the initial multivariate model, including individual, state-level health factors, and state dummy variables.
b. Defined as at least one approved vaccine dose prior to hospitalization.
c. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.
d. Upper limit of the estimated decile of vaccine coverage (source: IHME Policy Briefing for Brazil, December 2021).
e. ICU beds per 10,000 inhabitants (source: Federal Council of Medicine, 2020

Table 4.4 Adjusted OR from the fixed effects model for factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for within-cluster variation at the state level[a].

N = 10,435		**Adjusted OR [95% CI]**
Individual Level Factors		
Age	<30 years	Ref
	≥30 years	1.63 [1.42, 1.87]*
Vaccinated	No	Ref
	Yes	0.34 [0.25, 0.46]*
Season	Jan to Jun	1.33 [1.10, 1.60]*
	Jul to Dec	Ref
Co-Morbidities	No	Ref
	Yes	2.20 [1.89, 2.57]*

*p<0.05

a. The final model was constructed by backward removal of nonsignificant covariates in the initial multivariate model, including individual and state-level health factors.
b. Defined as at least one approved vaccine dose prior to hospitalization.
c. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.

Supplemental Table 4.1 Correlation matrix of state level factors.

	State COVID-19 Prevalence	**State Vaccine Coverage**	**State Mask Usage**	**State ICU Beds per Capita**
State COVID-19 Prevalence	1			
State Vaccine Coverage	-0.3968***	1		
State Mask Usage	-0.4697***	0.7031***	1	
State ICU Beds per Capita	-0.2158***	0.4892***	0.4728***	1

***p < 0.001; **p < 0.01; *p < 0.05

a. Values are presented as Pearson correlation coefficients.

Supplemental Table 4.2 Comparison of nested regression analysis models for individual-level factors associated with maternal death[a].

	Model 1	**Model 2**	**Model 3**	**Model 4**	**Model 5**	**Model 6**	**Model 7**	**Model 8**
Vaccinated	-0.072 (0.008)***	-0.075 (0.008)***	-0.075 (0.008)***	-0.066 (0.009)***	-0.068 (0.009)***	-0.068 (0.009)***	-0.065 (0.010)***	-0.080 (0.015)***
Co-Morbidities		0.093 (0.008)***	0.087 (0.008)***	0.087 (0.008)***	0.087 (0.008)***	0.087 (0.008)***	0.089 (0.008)***	0.097 (0.013)***
Age			0.041 (0.005)***	0.040 (0.005)***	0.040 (0.005)***	0.040 (0.005)***	0.042 (0.006)***	0.045 (0.009)***
Season				0.016 (0.007)*	0.016 (0.007)*	0.016 (0.007)***	0.024 (0.008)**	0.023 (0.012)
Urbanicity					-0.015 (0.007)	-0.014 (0.007)	-0.018 (0.008)*	-0.037 (0.015)*
Trimester of Infection						0.002 (0.004)	-0.0004 (0.004)	0.005 (0.007)
Race							0.006 (0.003)*	0.011 (0.005)*
Education								-0.008 (0.011)
F	*64.65****	*98.59****	*82.65****	*63.22****	*51.31****	*42.80****	*33.81****	*17.70****
Adjusted R-squared	*0.0061*	*0.0184*	*0.0229*	*0.0233*	*0.0235*	*0.0235*	*0.0247*	*0.0299*

***p < 0.001; **p < 0.01; *p < 0.05

a. Values are presented as β coefficients and standard errors.

Supplemental Table 4.3 Crude and adjusted OR from the random effects model for individual level factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for clustering at the state level[a].

N = 10,435		Crude OR [95% CI]	Adjusted OR [95% CI]
Age	<30 years	Ref	Ref
	≥30 years	1.74 [1.52, 1.99]*	1.63 [1.42, 1.87]*
COVID-19 Vaccination[b]	No	Ref	Ref
	Yes	0.32 [0.24, 0.43]*	0.34 [0.25, 0.46]*
Trimester of Infection	First	Ref	Ref
	Second	1.42 [1.09, 1.85]*	1.40 [1.07, 1.84]*
	Third	1.19 [0.92, 1.53]	1.23 [0.95, 1.60]
	Unknown	1.60 [1.12, 2.29]*	1.53 [1.06, 2.19]
Race[c]	White	Ref	Ref
	Black	1.01 [0.75, 1.36]	1.04 [0.76, 1.41]
	Other	0.97 [0.82, 1.15]	1.00 [0.84, 1.18]
Education	Less than HS	Ref	Ref
	HS and Higher	0.91 [0.73, 1.14]	0.93 [0.73, 1.17]
Urbanicity	Rural	Ref	Ref
	Urban	0.85 [0.71, 1.00]	0.87 [0.74, 1.04]
Season	Jan to Jun	1.70 [1.43, 2.03]*	1.32 [1.10, 1.59]*
	Jul to Dec	Ref	Ref
Co-Morbidities[d]	No	Ref	Ref
	Yes	2.29 [1.97, 2.66]*	2.19 [1.88, 2.56]*
σ_μ			0.51 [0.36, 0.72]
ρ			0.07 [0.04, 0.14]

*p<0.05

a. Final model was constructed based on individual level factors in the conceptual model.
b. Defined as at least one approved vaccine dose prior to hospitalization.
c. Includes indigenous, mixed, and other racial categories.
d. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.

Supplemental Table 4.4 Crude and adjusted OR from the fixed effects model[+] for factors associated with maternal death among pregnant persons hospitalized with COVID-19 in Brazil in 2021, corrected for within-cluster variation at the state level[a].

N = 10,435		Crude OR [95% CI]	Adjusted OR [95% CI]
Age	<30 years	Ref	Ref
	≥30 years	1.73 [1.51, 1.98]*	1.62 [1.41, 1.86]*
COVID-19 Vaccination[b]	No	Ref	Ref
	Yes	0.32 [0.24, 0.43]*	0.34 [0.25, 0.46]*
Trimester of Infection	First	Ref	Ref
	Second	1.40 [1.08, 1.83]*	1.40 [1.07, 1.83]*
	Third	1.19 [0.92, 1.53]	1.24 [0.96, 1.60]
	Unknown	1.59 [1.11, 2.27]*	1.52 [1.06, 2.19]*
Race[c]	White	Ref	Ref
	Black	0.99 [0.74, 1.34]	1.02 [0.75, 1.39]
	Other	0.95 [0.80, 1.13]	0.97 [0.82, 1.15]
Education	Less than HS	Ref	Ref
	HS and Higher	0.91 [0.73, 1.14]	0.93 [0.73, 1.18]
Urbanicity	Rural	Ref	Ref
	Urban	0.85 [0.72, 1.01]	0.88 [0.74, 1.04]
Season	Jan to Jun	1.70 [1.43, 2.03]*	1.32 [1.10, 1.59]*
	Jul to Dec	Ref	Ref
Co-Morbidities[d]	No	Ref	Ref
	Yes	2.28 [1.96, 2.65]*	2.18 [1.87, 2.55]*

*$p < 0.05$

a. Final model was constructed based on individual level factors in the conceptual model.
b. Defined as at least one approved vaccine dose prior to hospitalization.
c. Includes indigenous, mixed, and other racial categories.
d. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.

Chapter 5 Individual Receipt of the COVID-19 Vaccine Protects Against ICU Admissions Among Pregnant Persons Hospitalized with COVID-19 in Brazil Despite Differences in Health Service Delivery Factors at the Municipal Level

Abstract (Word Count: 268)

COVID-19 in pregnancy augments the likelihood of an intensive care unit (ICU) admission, an independent risk factor for a prolonged hospitalization and future mortality. We used the publicly available Sistema de Informação da Vigilancia Epidemiológica da Gripe (SIVEP-Gripe) database to analyze individual-level factors, including receipt of a vaccine, associated with an ICU admission among pregnant and postpartum individuals hospitalized with COVID-19 in Brazil from January 1 to December 31, 2021. Municipal-level variables were collected from the Instituto de Estudos para Políticas de Saúde (IEPS) 2021 database. We calculated the adjusted odds ratios (AOR) using nested logistic regression models (LRMs) and multi-level models (MLMs) for factors associated with maternal ICU admission among pregnant persons hospitalized with COVID-19 in Brazil in 2021. Among the 10,435 pregnant or postpartum persons hospitalized with COVID-19 in 2021, municipality data were available for 10,113 (96.91%). Among the 10,113 patients, 3,055 (30.2%) required an ICU admission. Receipt of a single dose of the COVID-19 vaccine was associated with a 38% reduced odds of maternal ICU admission in both the LRMs and MLMs, even when accounting for both individual-level and municipal-level health factors (AOR 0.62, 95% confidence interval 0.53 to 0.73). Municipal-level health factors, including high family health strategy (FHS) coverage and ICU bed rates, were not significantly associated with protection against ICU admission when controlling for clustering at the municipal level in the logistic regression model, or in the MLM with inclusion of municipal-level factors. Individual receipt of the COVID-19 vaccine protects against maternal ICU admission among pregnant and postpartum individuals hospitalized with COVID-19, despite health services differences at the municipal-level.

Background

COVID-19 in pregnancy augments the likelihood of an intensive care unit (ICU) admission[25, 167], an independent risk factor for a prolonged hospitalization and in-hospital mortality[168]. The long-term consequences of an ICU admission are well-documented, ranging from profound muscle wasting[169] to an increased risk of one-year mortality post-discharge[170]. In addition to the high morbidity associated with critical illness, ICU care is one of the most expensive and resource-dependent aspects of modern healthcare[171].

Several studies have demonstrated that receipt of an approved COVID-19 vaccine, regardless of type, protects against ICU admission in non-pregnant populations[172-174]. The data on vaccine effectiveness in the prevention of ICU admission among pregnant persons hospitalized with COVID-19 are mixed. In a meta-analysis of 14 observational studies of COVID-19 vaccination in pregnancy, receipt of the vaccine in pregnancy reduced the odds of an ICU admission by 42%, but the finding was not significant (odds ratio 0.58, 95% confidence interval 0.13 to 2.58)[175].

Furthermore, it is unclear how differences in health system infrastructure across regions, particularly healthcare utilization and critical care capacity measures, impact the effect of the COVID-19 vaccine on ICU admissions during pregnancy. The states are further divided into 5,570 municipalities, each with its own autonomous local government, including a mayor, municipal chamber, and health secretariat responsible for local management and delivery of healthcare in facilities other than hospitals (which are mostly state or federally owned)[57, 176]. The Family Health Strategy (FHS)[51], a community-based multi-professional primary care model, play a pivotal role in providing high-quality preventive healthcare, including prenatal and antenatal care, at the municipal-level[51-53]. In 2014, it was estimated that the FHS program covered 62% of the national population[106]. Austerity measures, such as reduction in funding for the FHS program, likely affected maternal care delivery and quality during the pandemic, although these municipal-level factors have not been adequately explored.

To address this gap in the literature, we evaluated individual-level and municipal-level health factors associated with the likelihood of maternal ICU admission among hospitalized pregnant or postpartum persons in Brazil with COVID-19 in 2021 using (1) nested logistic regression models (LRMs) and (2) multi-level models (MLM). We hypothesized that receipt of the COVID-19 vaccine prior to hospitalization protected against a maternal ICU admission, despite differences in health services at the municipal-level.

Methods

Data Source

Beginning in January, 2020, the publicly-available Sistema de Informação da Vigilancia Epidemiológica da Gripe (SIVEP-Gripe) database began tracking all COVID-19 hospitalizations in Brazil through the Unified Health System platform (DATASUS)[82]. The SIVEP-Gripe surveillance system was established in 2009 following the H1N1 influenza pandemic[83]. Since its inception, the database has served as the national surveillance system for influenza and other respiratory viruses of clinical concern[84]. Following the initial identification of SARS-CoV-2, the Brazilian Ministry of Health required notification of both suspected and confirmed cases by polymerase chain reaction (PCR) testing (the gold standard), and now antigen (Ag) testing[85]. Both public and private hospitals are required by law to report on COVID-19 hospitalizations via the electronic database within 24 hours of a suspected case[85]. Data collected include geographic location, medical co-morbidities, pregnancy and postpartum status, hospital course complications, and outcomes, including death. The annual databases, including reporting details and the data dictionary, are made available through the DATASUS platform[82]. The data are reviewed and cleaned weekly by the Ministry of Health National Immunization Program.

For municipal-level data, we used the Instituto de Estudos para Políticas de Saúde (IEPS) 2021 database[97]. IEPS is a national health policy database managed by a non-government organization in Brazil. IEPS collects data from across multiple publicly available data sources in Brazil, including the Ministry of Health National Health System (Sistema Único de Saúde, DATASUS) and the National Registry of Healthcare Facilities (Cadastro Nacional de Estabelecimentos de Saúde, CNES)[98].

Variables

The predictor of interest, receipt of an approved COVID-19 vaccine prior to the hospitalization, was dichotomized (Yes = 1, No or Unknown= 0). The primary outcome was an intensive care unit (ICU) admission (Figure 5.1).

Age was dichotomized as <30 vs ≥30 years. Trimester of infection was operationalized as a categorical variable: first, second, third, or unknown. Although race is a social construct, we chose to include race in the model given the history of systemic racism in Brazil and its well-established impact on poor maternal outcomes[155]. Race was operationalized as a categorical variable: white, Black, and other (including indigenous, and mixed race). Education was dichotomized as less than high school vs high school and higher. Location of residence was dichotomized as rural vs urban. Season was dichotomized as January to June, vs July to December. In our study, season served as a proxy for the dominant variant in circulation. Gamma was the primary circulating variant of concern from January to June, and responsible for approximately 96% of cases during that time. Gamma was replaced by the Delta variant beginning in July, 2021. Cardiovascular risk and diabetes were dichotomized (Yes = 1, No = 0) according to the SIVEP-Gripe variables. Obesity was categorized as pre-gestational body mass index (BMI) >30 kg/m^2. Missing data was high for race and educational attainment (both >25%). We assumed this nonresponse pattern reflected a missing at (MAR) pattern, and therefore used multiple imputation for race and educational attainment (see Appendix).

For municipal-level factors, four variables were evaluated: family health services (FHS) coverage (%), physician rate per 1,000 inhabitants, nursing rate per 1,000 inhabitants, and ICU beds per 10,000 inhabitants. A pearson correlation matrix demonstrated that nursing rates were highly correlated with physician rates and ICU bed rates ($r \geq 0.50$). Therefore, only FHS coverage, physician rate, and ICU bed rates were included in the models.

We constructed an ordinal FHS variable (none, <30%, 30 – 69.9%, ≥70%), based on previous work by Aquino and colleagues on the association between low municipal FHS coverage and increased infant mortality rates[177]. Physician rates were operationalized as ≥3 per 1,000 inhabitants and ICU bed rates were operationalized as ≥1 per 10,000 inhabitants based on previous literature examining the impact of health system infrastructure strain on COVID-19 mortality[168, 178].

Data Analysis

Pregnant or postpartum individuals hospitalized with COVID-19 in Brazil from January 1, 2021 to December 31, 2021 were included in the analysis. Descriptive statistics (frequency and percentage) of individual levels factors for the main study population in 2021 were stratified by maternal ICU admission. We calculated adjusted odds ratios (AOR) from nested LRMs and MLMs. We constructed three LRMs: (1) a naïve model constructed based on individual-level factors only, (2) a model with both individual-level and municipal-level factors, and (3) a model with both individual-level and municipal-level factors, controlling for clustering at the municipality. Next, we constructed two MLMs: (1) a naïve model consisting of individual-level factors only, and (2) a MLM consisting of both individual-level and municipal-level factors to account for hierarchical data[179]. Statistical analysis was performed with STATA with statistical significance defined using a two-sided $\alpha < 0.05$.

Results

From January 1, 2021 to December 31, 2021, there were 10,435 pregnant or postpartum individuals hospitalized with COVID-19 in Brazil. The municipality of residency data were available for 10,113 (96.91%) of the total. Table 5.1 shows the descriptive statistics of the 10,113 pregnant or postpartum individuals hospitalized with COVID-19, of which 3,055 (30.2%) required an ICU admission. Pregnant or postpartum individuals who were admitted to the ICU were more likely to be older, have a second-trimester infection, to identify as white, come from a rural place, and have co-morbidities. They were less likely to have received the COVID-19 vaccine. There were no significant differences in educational categories. Supplemental Table 5.1 is the correlation matrix of municipal-level factors, presented as Pearson correlation coefficients. Physician rate and nursing rate were highly correlated (r = 0.62), as were ICU beds per capita and nurse rate (r = 0.52).

Table 5.2 shows the nested LRMs regression models factors associated with maternal ICU admission among pregnant or postpartum persons hospitalized with COVID-19 in Brazil in 2021. In the naïve model, controlling for other individual level factors, pregnant persons who received a single dose of the COVID-19 vaccine prior to hospitalization had significantly reduced odds of a maternal ICU admission (AOR 0.63, 95% CI 0.54 to 0.73). Urbanicity and the first half of the year were associated with a reduced odds of maternal ICU admission. Age $\geq$30 years, second and third trimester infections, and the presence of co-morbidities were associated with an increased odds of a maternal ICU admission. Infection in the second-trimester conferred nearly a two-fold increased odds of ICU admission. In model 2, with the addition of municipal-level factors, FHS coverage $\geq$70% reduced the odds of maternal ICU admission by 22% (AOR 0.78, 95% CI 0.67 to 0.89). The individual-level factors were comparable across model 1, 2, and 3. However, while the individual factors remained the same, no municipal-level factors were significant in model 3, when controlling for clustering at the municipal level ($F = 17.21$, $p<0.001$).

Table 5.3 shows the AOR from the MLMs for individual and municipal-level factors associated with maternal ICU admission among pregnant persons hospitalized with COVID-19 in Brazil in 2021. The naïve MLM was comparable to the naïve LRM: the COVID-19 vaccine prior to the hospitalization reduced the odds of maternal ICU admission by 38% (AOR 0.62, 95% CI 0.53 to 0.73). With the addition of municipal-level factors, the same individual-level factors remained significant, but none of the municipal-level factors were significant.

Discussion

Among the 10,113 pregnant or postpartum individuals hospitalized with COVID-19 in Brazil in 2021, 30.2% required an ICU admission, a remarkably high rate even for those with severe maternal morbidity. A recent study of 27 obstetrical centers in Brazil by Soares and colleagues estimated that the maternal ICU rate was approximately 2.5% for all births, compared to 21.5% among pregnant persons with severe maternal morbidity[180]. This high maternal ICU admission rate highlights the resources needed to appropriately care for the pregnant population hospitalized with COVID-19.

A potential strategy to protect the pregnant population from maternal ICU admissions as SARS-CoV-2 becomes endemic in Brazil is continued vaccine campaigns targeting women of reproductive age. While the data on vaccine effectiveness in the prevention of ICU admission among pregnant persons hospitalized with COVID-19 are mixed[175], receipt of a single dose of the COVID-19 vaccine was associated with an approximate 38% reduced odds of maternal ICU admission across the models in our study. In an analysis by de Freitas Paganoti and colleagues of pregnant and postpartum individuals hospitalized with COVID-19 in Brazil between May and November 2021, propensity score matching estimated that completion of the two-dose vaccine series reduced the odds of a maternal ICU admission by 46% (OR 0.54, 95% CI 0.34 to 0.85)[158]. Not only did our analysis include all of 2021, as opposed to seven months in the study by de Freitas Paganoti, but we also defined vaccination by a single dose, as opposed to two doses. This may explain the differences we observed between the two analyses, but also highlights the protective effect of a single vaccine dose in the prevention of a maternal ICU admission among pregnant persons with COVID-19.

Consistent with prior data, SARS-CoV-2 infection in the second and third trimesters[181], and the presence of maternal co-morbidities[182] were associated with more severe disease, as measured by a maternal ICU admission. Surprisingly, the first half of 2021 was associated with an approximate 20% reduction in odds of a maternal ICU admission. However, this coincided with

the Gamma surge and the resulting unprecedented healthcare strain, when over half of the states had ICUs at over 90% capacity[183, 184]. Therefore, this may represent collider bias since ICU beds were prioritized for those with the most severe disease.

A notable finding of our study was that municipal-level factors (family health strategy coverage, physician rate and ICU bed rate) were not significant predictors of ICU admission when controlling for clustering at the municipal level in the LRM (model 3), nor in the MLM with both individual-level and municipal-level factors. While critical care capacity and other healthcare utilization factors were anticipated to impact morbidity and mortality at the beginning of the pandemic, it is striking that these healthcare utilization factors were not protective, both when controlling for clustering in the LRM, or when accounting for a hierarchical data structure in the MLM.

There are limitations to this analysis. First, we cannot exclude the possibility of collider bias in analyzing the relationship between COVID-19 vaccination and maternal ICU admission in a sample of patients who were hospitalized for COVID-19. However, we attempted to address this by running nested models, since the data limit our ability to define a different inclusion criteria. Second, it is difficult to disentangle the impact of ICU bed stress on the likelihood of ICU admission. However, we attempted to address this by incorporating season, a surrogate for the Gamma surge and ICU bed stress, as well as ICU bed rates by municipalities. Last, given the high rate of missing values for the type and doses of the COVID-19 vaccine (mRNA vs adenovirus-vector based), we did not include these variables in the analysis. Nevertheless, our study demonstrated that even a single vaccine dose, regardless of type, was protective against maternal ICU admission among hospitalized pregnant or postpartum individuals with COVID-19.

Out study has several strengths. First, MLMs accommodate nested data with complex error structures and produce more efficient estimators of the coefficients[185]. Second, we were able to analyze a large study population of over 10,000 pregnant and postpartum individuals by

accessing public databases. Third, this is the first study to our knowledge that linked individual and municipal-level factors in Brazil to evaluate the association between vaccination and maternal ICU admission.

Conclusions

Individual receipt of a single dose of an approved COVID-19 vaccine prior to hospitalization was associated with a 38% reduction in odds of maternal ICU admission among pregnant and postpartum persons hospitalized with COVID-19 in Brazil in 2021, despite differences in healthcare delivery factors at the municipal level. While health system infrastructure factors were of interest at the beginning of the pandemic, particularly high ICU bed rates and other critical care capacity measures, our study suggests that municipal-level health services factors were not protective against maternal ICU admissions when controlling for vaccine status. As Brazil transitions to SARS-CoV-2 endemicity with unpredictable COVID-19 surges, continued investment in regional vaccine campaigns with special attention to pregnant and postpartum individuals will likely result in lower maternal ICU admissions due to COVID-19.

Figure 5.1 Conceptual model.

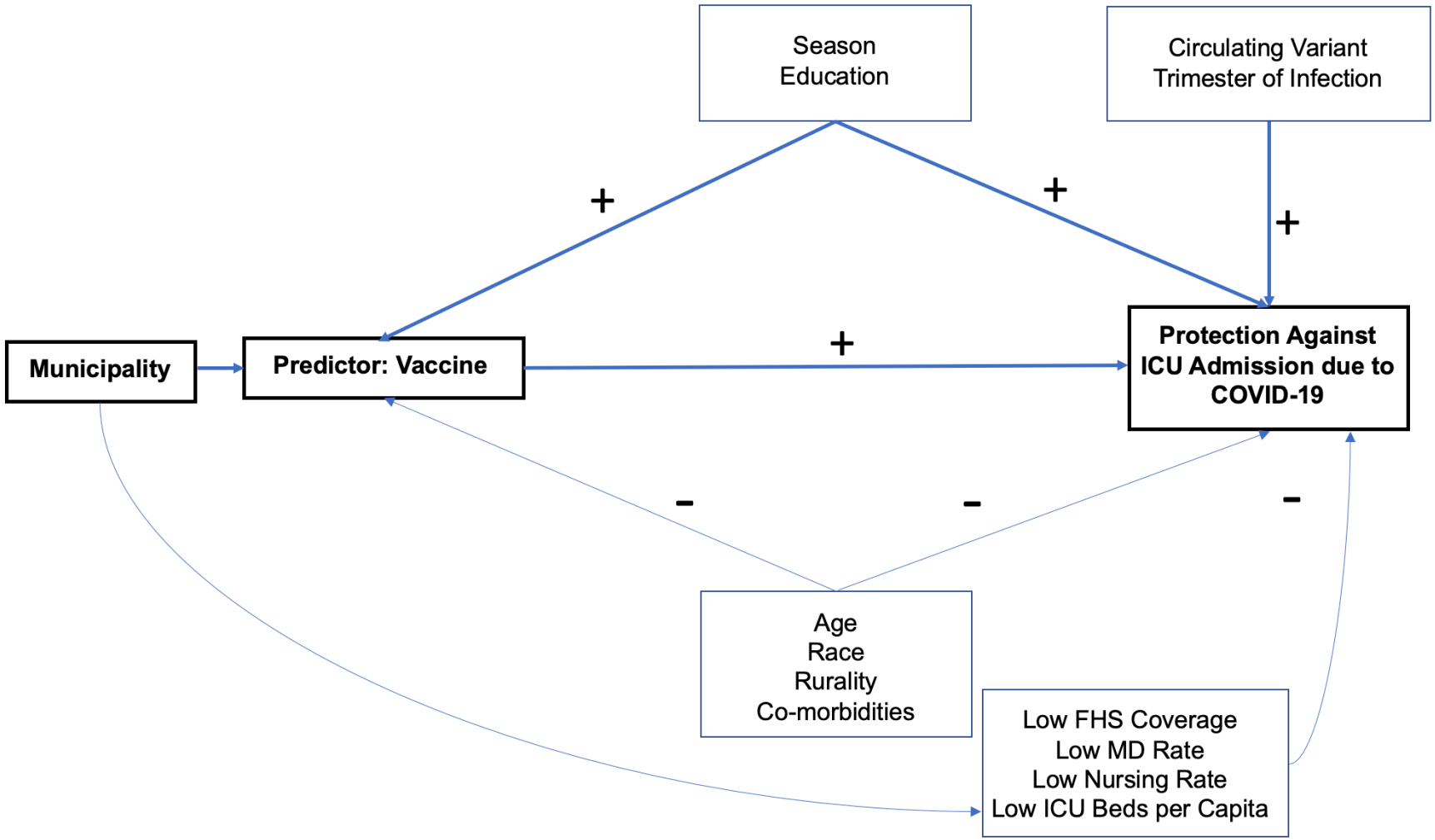


Figure 5.2 Association between maternal ICU admission[a] and vaccine status[b] among hospitalized pregnant or postpartum[c] patients in Brazil in 2021.

	Maternal ICU Admissions n (%)[d]		
COVID-19 Vaccine	**No**	**Yes**	**Total**
No	6,133 (68.99%)	2,757 (31.01%)	8,890
Yes	925 (75.63%)	298 (24.37%)	1,223
Total	7,058 (69.79%)	3,055 (30.21%)	10,113

Pearson chi-square p<0.0001

a. Maternal ICU admission included all pregnant and postpartum individuals hospitalized with COVID-19.
b. Maternal vaccination defined as a single dose of any approved COVID-19 vaccine prior to hospitalization for COVID-19.
c. Pregnant or postpartum, defined as the period up to 42 days following birth.
d. Pearson chi-square by frequency (row percentage).

Table 5.1 Descriptive statistics of pregnant or postpartum persons hospitalized with COVID-19 in Brazil in 2021, stratified by maternal ICU admission.

N = 10,113		**No ICU**	**ICU Admission**	**p-value**
n (%)		7,058	3,055	
Age	Median (IQR)	30 (24, 35)	32 (26, 36)	<0.001
	<30 years	3,475 (49.2%)	1,168 (38.2%)	<0.001
	≥30 years	3,583 (50.8%)	1,887 (61.8%)	
COVID-19 Vaccination[b]	No	6,133 (86.9%)	2,757 (90.2%)	<0.001
	Yes	925 (13.1%)	298 (9.8%)	
Trimester of Infection	First	705 (10.0%)	188 (6.2%)	<0.001
	Second	1,806 (25.6%)	951 (31.1%)	
	Third	4,153 (58.8%)	1,812 (59.3%)	
	Unknown	394 (5.6%)	104 (3.4%)	
Race	White	2,714 (43.6%)	1,264 (47.3%)	0.006
	Black	344 (5.5%)	140 (5.2%)	
	Other[c]	3,171 (50.9%)	1,271 (47.5%)	
Education	Less than HS	899 (28.4%)	336 (26.1%)	0.12
	HS and Higher	2,268 (71.6%)	952 (73.9%)	
Urbanicity	Rural	1,122 (15.9%)	543 (17.8%)	0.019
	Urban	5,936 (84.1%)	2,512 (82.2%)	
Season	Jan to Jun	5,549 (78.6%)	2,364 (77.4%)	0.17
	Jul to Dec	1,509 (21.4%)	691 (22.6%)	
Co-Morbidities[d]	No	6,163 (87.3%)	2,414 (79.0%)	<0.001
	Yes	895 (12.7%)	641 (21.0%)	

a. Continuous variables are compared using Wilcoxon rank-sum, and categorical variables are compared using Pearson's chi-squared.
b. Defined as at least one approved vaccine dose prior to hospitalization.
c. Includes indigenous, mixed, and other racial categories.
d. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.

Table 5.2 Adjusted odds ratios (OR) from logistic regression models for factors associated with maternal ICU admission among pregnant persons hospitalized with COVID-19 in Brazil in 2021.

N = 10,113		**Model 1[a]**	**Model 2[b]**	**Model 3**
Individual Level Factors		*AOR [95% CI]*	*AOR [95% CI]*	*AOR [95% CI]*
Age	<30 years	Ref	Ref	Ref
	≥30 years	1.53 [1.40, 1.67]***	1.52 [1.40, 1.66]***	1.52 [1.38, 1.68]***
COVID-19 Vaccination[d]	No	Ref	Ref	Ref
	Yes	0.63 [0.54, 0.73]***	0.63 [0.54, 0.73]***	0.62 [0.53, 0.73]***
Trimester of Infection	First	Ref	Ref	Ref
	Second	1.96 [1.63, 2.35]***	1.96 [1.63, 2.35]***	1.98 [1.62, 2.40]***
	Third	1.70 [1.43, 2.02]***	1.70 [1.43, 2.02]***	1.76 [1.47, 2.12]***
	Unknown	0.95 [0.73, 1.25]	0.96 [0.73, 1.26]	1.03 [0.76, 1.38]
Race	White	Ref	Ref	Ref
	Black	0.91 [0.75, 1.12]	0.92 [0.75, 1.12]	0.89 [0.71, 1.11]
	Other[e]	0.90 [0.82, 0.99]*	0.94 [0.85, 1.03]	0.96 [0.85, 1.08]
Education	Less than HS	Ref	Ref	Ref
	HS and Higher	1.13 [0.98, 1.30]	1.13 [0.98, 1.31]	1.12 [0.96, 1.30]
Urbanicity	Rural	Ref	Ref	Ref
	Urban	0.85 [0.76, 0.95]**	0.84 [0.74, 0.94]**	0.83 [0.73, 0.95]**
Season	Jan to Jun	0.79 [0.70, 0.88]***	0.78 [0.70, 0.87]***	0.80 [0.70, 0.90]***
	Jul to Dec	Ref	Ref	Ref
Co-Morbidities[f]	No	Ref	Ref	Ref
	Yes	1.79 [1.59, 2.00]***	1.78 [1.59, 2.00]***	1.81 [1.60, 2.06]***
Municipal Level Factors				
FHS Coverage[g]	<30		Ref	Ref
	30 – 69		0.92 [0.81, 1.06]	0.81 [0.62, 1.05]

	≥70		0.78 [0.67, 0.89]***	0.82 [0.64, 1.06]
Physician Rate per Capita[h]	<3 per 1,000		Ref	Ref
	≥3 per 1,000		1.10 [0.98, 1.23]	1.07 [0.90, 1.28]
ICU Beds per Capita[i]	<1 per 10,000		Ref	Ref
	≥1 per 10,000		0.87 [0.77, 0.97]*	0.93 [0.77, 1.12]
F		27.18***	21.55***	17.21***

*p<0.05; **p<0.01; ***p<0.001

a. The naïve model was constructed based on individual-level factors only.
b. The model consists of individual-level and municipal-level factors.
c. The model consists of individual-level and municipal-level factors, controlling for clustering at the municipality.
d. Defined as at least one approved vaccine dose prior to hospitalization.
e. Includes indigenous, mixed, and other racial categories.
f. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.
g. FHS coverage at the municipal level (source: IEPS, 2021).
h. Physicians per 1,000 inhabitants (source: IEPS, 2021).
i. ICU beds per 10,000 inhabitants (source: IEPS, 2021).

Table 5.3 Adjusted odds ratios (OR) from multilevel models for factors associated with maternal ICU admission among pregnant persons hospitalized with COVID-19 in Brazil in 2021.

N = 10,113		**Model 1[a]**	**Model 2[b,c]**
Individual Level Factors			
Age	<30 years	Ref	Ref
	≥30 years	1.52 [1.38, 1.68]***	1.52 [1.38, 1.68]***
COVID-19 Vaccination[d]	No	Ref	Ref
	Yes	0.62 [0.53, 0.73]***	0.62 [0.53, 0.73]***
Trimester of Infection	First	Ref	Ref
	Second	1.97 [1.62, 2.40]***	1.98 [1.63, 2.41]***
	Third	1.76 [1.46, 2.12]***	1.76 [1.47, 2.12]***
	Unknown	1.02 [0.76, 1.37]	1.03 [0.76, 1.38]
Race	White	Ref	Ref
	Black	0.89 [0.71, 1.10]	0.89 [0.71, 1.11]
	Other[e]	0.95 [0.85, 1.06]	0.96 [0.85, 1.08]
Education	Less than HS	Ref	Ref
	HS and Higher	1.11 [0.96, 1.30]	1.12 [0.96, 1.30]
Urbanicity	Rural	Ref	Ref
	Urban	0.83 [0.73, 0.95]**	0.83 [0.73, 0.95]**
Season	Jan to Jun	0.80 [0.70, 0.90]***	0.80 [0.70, 0.90]***
	Jul to Dec	Ref	Ref
Co-Morbidities[f]	No	Ref	Ref
	Yes	1.82 [1.60, 2.06]***	1.81 [1.60, 2.06]***
Municipal Level Factors			
FHS Coverage[g]	<30		Ref
	30 – 69		0.81 [0.62, 1.05]
	≥70		0.82 [0.64, 1.06]
Physician Rate per Capita[h]	<3 per 1,000		Ref
	≥3 per 1,000		1.07 [0.90, 1.28]
ICU Beds per Capita[i]	<1 per 10,000		Ref
	≥1 per 10,000		0.93 [0.77, 1.12]
F		22.59***	17.21***

*p<0.05; **p<0.01; ***p<0.001

a. The naïve model was constructed based on individual-level factors only.
b. The model consists of individual-level and municipal-level factors.
c. Of the 5,570 municipalities in Brazil, 2,186 (39.2%) were listed as municipalities of residence.

d. Defined as at least one approved vaccine dose prior to hospitalization.
e. Includes mixed, indigenous and other.
f. Co-morbidities defined as the presence of cardiovascular risk, diabetes, or obesity.
g. FHS coverage at the municipal level (source: IEPS, 2021).
h. Physicians per 1,000 inhabitants (source: IEPS, 2021).
i. ICU beds per 10,000 inhabitants (source: IEPS, 2021).

Supplemental Table 5.1 Correlation matrix of municipal level health services factors[a].

	Family Health Strategy Coverage	Physician Rate	Nurse Rate	ICU Beds per Capita
Family Health Strategy Coverage	1			
Physician Rate	-0.3782*	1		
Nurse Rate	-0.1562*	0.6168*	1	
ICU Beds per Capita	-0.1819*	0.4290*	0.5173*	1

*p<0.05.

e. Values are presented as Pearson correlation coefficients.

Chapter 6 Conclusions

In this dissertation, we set out to quantify the effect of the COVID-19 pandemic on maternal mortality in Brazil, as well as identify individual, municipal, and state-level factors that impacted COVID-19-related maternal mortality and morbidity during the pandemic. Our findings suggest that national and regional COVID-19 vaccination campaigns targeting pregnant and postpartum individuals should remain a cornerstone of the Brazil public health armamentarium in efforts to reduce the national MMR, and protect against COVID-19-related maternal death and ICU admissions.

In the first analysis, using two complementary forecast models, we demonstrated that the observed MMR in 2021 was more than double the predicted MMR. From January 1, 2020 to December 31, 2021, there were approximately 4,995 maternal deaths in Brazil, an extraordinarily high national two-year estimate. The SMR estimates ranged from 1.75 to 2.62 across the macroregions in 2021, highlighting the profound impact of the pandemic on maternal mortality throughout the country. While COVID-19 augmented disparities at the regional level, high-resource regions with historically better health outcomes were not protected from the devastating impact of the pandemic on maternal mortality. The South is the second-wealthiest macro-region in Brazil, yet had the highest SMR and SMRc (2.62 and 2.70, respectively). The majority of maternal deaths were not a direct cause of COVID-19, although the percentage attributed to COVID-19 increased to 35% in 2021. This finding underscores the indirect impact of the pandemic on maternal care and delivery, with devastating downstream effects.

In the second analysis, we hypothesized that a single dose of the vaccine was highly protective against maternal death due to COVID-19 among hospitalized pregnant and postpartum individuals, despite differences in epidemiologic and health service delivery factors at the state level. From January 1, 2021 to December 31, 2021, there were 10,435 pregnant or postpartum persons hospitalized with COVID-19 in Brazil, of which 1,059 (10.15%) resulted in death. In both the RE and FE models, a single dose of an approved COVID-19 vaccine prior to hospitalization

reduced the odds of maternal death by 66%. In the RE model, estimated state vaccine coverage ≥90% reduced the odds of maternal death by 89%, although other state-level variables, including specific states, were not protective against maternal death.

In the third analysis, we hypothesized that a single dose of the COVID-19 vaccine was highly protective against maternal ICU admission due to COVID-19 among hospitalized pregnant and postpartum individual, despite differences across municipalities. Of the 10,435 pregnant and postpartum individuals hospitalized with COVID-19 in 2021, municipality data was available for 10,113 (96.91%). Among this hospitalized population, 3,055 (30.2%) required an ICU admission. Using nested LRMs and MLMs to incorporate both individual-level and municipal-level factors, we found that COVID-19 vaccination reduced the odds of maternal ICU admission by 38%. Municipal-level health factors, including high family health strategy coverage and ICU bed rates, were not significantly associated with protection against ICU admission when controlling for clustering in the LRM, or in the MLM with inclusion of municipal-level factors.

The main findings of this dissertation include:

1) The observed maternal deaths during the first two years in Brazil were higher than predicted based on historical data;

2) Maternal death and ICU admission due to COVID-19 among hospitalized pregnant and postpartum individuals were high (10% and 30%, respectively), representing a life-threatening condition to current and future pregnant and postpartum populations;

3) A single dose of the COVID-19 vaccine prior to hospitalization was highly protective against death in pregnancy and in the postpartum period, despite differences in epidemiologic and healthcare delivery factors across the states;

4) High state vaccine coverage (≥90%) was associated with reduced odds of maternal death, although other state-level variables did not protect against maternal mortality;

5) A single dose of the COVID-19 vaccine prior to hospitalization was highly protective

against maternal ICU admission in pregnancy and in the postpartum period, despite differences in health care delivery and capacity care measures across the municipalities.

As the world transitions to SARS-CoV-2 endemicity, COVID-19 will continue to impact the health of pregnant and postpartum persons. While the indirect effects on healthcare quality and delivery will fade as we move away from the pandemic phase, the risk of infection in pregnancy will persist, with consequences including increased rates of hypertensive disorders of pregnancy, mechanical ventilation, and maternal-fetal death[26, 28, 134, 181, 182]. Following years of progress in reducing the national MMR, Brazil now faces the daunting task of reversing the MMR, while simultaneously addressing the new threat of an endemic SARS-CoV-2. In addition to COVID-19-specific programs, increased resources to optimize perinatal and maternal care delivery may be needed in states and municipalities with persistently high MMR.

Early on in the pandemic, epidemiologic factors such as mask usage and COVID-19 prevalence, and health services factors such as ICU capacity and physician rates per capita, were of great interest and hypothesized to impact COVID-related-mortality. Surprisingly, our studies suggested that these factors did not significant impact COVID-19 maternal deaths and ICU admissions when controlling for individual receipt of the COVID-19 vaccine. Furthermore, high state-level vaccine coverage was highly protective against maternal death due to COVID-19, underscoring the individual and public health benefits of effective COVID-19 vaccine campaigns. With unpredictable COVID-19 surges expected in the future, efforts should focus on vaccination, not necessarily increasing ICU capacity or physician rates per capita.

One strategy to protect against maternal death and maternal ICU admissions includes ongoing government support for national and regional vaccination campaigns, with an emphasis on pregnant, postpartum and lactating individuals, as well as other persons capable of pregnancy. This could bolster state vaccine coverage, a state-level factor found to be protective against maternal death in our study, as well as vaccination rates in pregnancy. Several studies demonstrate the success of coordinated COVID-19 vaccination campaigns: a modeling study by

Watson and colleagues estimates that the COVAX mechanism prevented 14.4 million deaths across 185 countries in the first year the vaccines became available[186]. A smaller, complementary study by Santos and colleagues to evaluate the impact of the national vaccination campaign in Brazil in 2021 estimates that 875,846 cases of severe COVID-19 and 303,129 deaths among adults were averted as a result of the roll-out[187].

While 80% of Brazil had received at least one dose of the COVID-19 vaccine by the beginning of 2022[188], vaccination rates among pregnant persons remain subpar, driven largely by vaccine hesitancy[189]. As of January, 2023, the Brazilian Federation of Gynecology and Obstetrics Associations recommend the CoronaVac and BNT162b2 mRNA vaccines for all pregnant and lactating persons,[190] representing a major step in the implementation and uptake of the COVID-19 vaccine in pregnancy. Targeted public health campaigns to encourage COVID-19 vaccine uptake among pregnant, postpartum and lactating persons, as well as women and persons of reproductive age, has the potential to drastically maternal mortality and morbidity.

Appendix

We used a multiple imputation by chained equations (MICE) strategy. We assumed a multinomial distribution for race and binomial distribution for educational attainment. Ten imputations were added. The variables in the imputation model included the outcome variable, receipt of a vaccine prior to delivery, maternal age, race, educational attainment, presence of comorbidities, urbanicity, season, and trimester of infection. The random seed number was set as 54321.

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