Distribution Agreement

Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel in Manaus, Brazil

By

Gemma Parra, BS

Master of Public Health

Global Epidemiology

Scott Fridkin, MD

Committee Chair

Fernanda Lessa, MD, MPH

Committee Member

Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel in Manaus, Brazil

By

Gemma Parra

B.S., University of Arizona, 2020

Thesis Committee Chair: Scott Fridkin, MD

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2022

Abstract

Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel in Manaus, Brazil

By Gemma Parra

Introduction: Brazil experienced one of the worst public health crises in their history as their health system was overwhelmed by a second wave of COVID-19 infections, caused by the SARS-CoV-2 virus. This second wave coincided with the emergence of the gamma variant in the Amazonian region of Manaus. The World Health Organization has identified gamma as a variant of concern due to its high transmissibility and antibody escape. In Manaus, a large burden of the COVID-19 response has fallen to Healthcare personnel (HCP), who are a high-risk population that needs to be protected due to their extensive exposure to COVID-19 patients.

Methods: To identify potential risk factors for SARS-CoV-2 infection among HCP in Brazil, we conducted a longitudinal cohort study of HCP from two hospitals in Manaus. We collected demographic and occupational data through baseline and weekly questionnaires and weekly antigen tests from 771 HCP over a four-week follow up period.

Results: We identified 16 incident cases of SARS-CoV-2 infection and a SARS-Co-V-2 attack rate of 2%. We were unable to identify any demographic characteristics, or exposures that were significantly associated with the risk of acquiring SARS-CoV-2 infection. When adjusting for variables identified to be risk factors for infection in other studies conducted on HCP in the United States and Brazil, we found no significant exposures for SASRS-CoV-2 infection in any models, whether they included a subset of covariates selected a priori or all potential covariates (i.e., fully saturated).

Conclusion: The lack of significant findings is likely attributable to the low attack rate and high immunity from previous infection or vaccination in our study population. Additional longitudinal research on risk factors for SARS-CoV-2 infection in HCP in Brazil is still necessary.

Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel in Manaus, Brazil

By

Gemma Parra

B.S., University of Arizona, 2020

Thesis Committee Chair: Scott Fridkin, MD

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University
in partial fulfillment of the requirements for the degree of
Master of Public Health
in Global Epidemiology
2022

Acknowledgments

First and foremost I would like to thank my CDC supervisor, Kelly M. Hatfield, for her invaluable mentorship, guidance, and support throughout my entire master's program. Her immense knowledge, expertise, and patience have shown me what it is to be good scientist. I want to extend my gratitude to Dr. Fernanda Lessa and Dr. Scott Fridkin for the opportunity to work on this project and providing me with great guidance as thesis advisors. I would also like to thank OPRE in the CDC's Division of Healthcare Quality Promotion for their assistance and feedback while developing my analytic plan. Additionally, to Nyawung Asonganyi for proofreading my thesis and providing thoughtful edits. I would also like to acknowledge the Brazil Healthcare Personnel COVID-19 research team and the dedicated healthcare workforce from Hospital Pronto Socorro 28 de Agosto and Hospital Pronto Socorro Platão Araújo, who volunteered for this study and were on the frontline of the COVID-19 response in Manaus.

I would like to thank Dr. Carlos Del Rio, Dr. Jeannett Guarne, and faculty and friends of Dr. Reynaldo Martorell, for creating and funding The Reynaldo Martorell Endowed Scholarship which allowed me to attend Emory University. I am also grateful for Emory's Hatchery Center for Innovation as it was an inspiring work environment to complete my thesis.

Lastly, I would like to extend my immeasurable gratitude to my parents and brother. Without their support this would not have been possible. I am also extremely appreciative of my friends, and the rest of my family who have encouraged me throughout my studies.

Table of Contents

Abstract

Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel in Manaus, Brazil

Introduction: Brazil experienced one of the worst public health crises in their history as their health system was overwhelmed by a second wave of COVID-19 infections, caused by the SARS-CoV-2 virus. This second wave coincided with the emergence of the Gamma variant in the Amazonian region of Manaus. The World Health Organization has identified Gamma as a variant of concern due to its high transmissibility and antibody escape. In Manaus, a large burden of the COVID-19 response has fallen to healthcare personnel (HCP), who are a high-risk population that needs to be protected due to their extensive exposure to COVID-19 patients.

Methods: To identify potential risk factors for SARS-CoV-2 infection among HCP in Brazil, we conducted a longitudinal cohort study of HCP from two hospitals in Manaus. We collected demographic and occupational data through baseline and weekly questionnaires and weekly antigen tests from 771 HCP over a four-week follow up period.

Results: We identified 16 incident cases of SARS-CoV-2 infection and a SARS-Co-V-2 attack rate of 2%. We were unable to identify any demographic characteristics, or exposures that were significantly associated with the risk of acquiring SARS-CoV-2 infection. When adjusting for variables identified to be risk factors for infection in other studies conducted on HCP in the United States and Brazil, we found no significant exposures for SASRS-CoV-2 infection in any models, whether they included a subset of covariates selected a priori or all potential covariates (i.e., fully saturated).

Conclusion: The lack of significant findings is likely attributable to the low attack rate and high immunity from previous infection or vaccination in our study population. Additional longitudinal research on risk factors for SARS-CoV-2 infection in HCP in Brazil is still necessary.

Introduction

Brazil has the second highest death toll in the world from COVID-19, behind the United States as of June, 2021 [1]. After the first wave of cases in May 2020, Brazil experienced one of the worst public health crises in their history as their health system was overwhelmed in a second wave of COVID-19 infections, caused by the SARS-CoV-2 virus [2]. The initial wave of cases peaked on May 30, 2020, with a daily case rate of 32,321; however, during the second wave in March 2021, daily cases reached over 98,000 [3]. The March 2021 wave was associated with the emergence of a new variant, P.1 later classified by the World Health Organization as Gamma strain. The Gamma variant emerged from the city of Manaus, Brazil, in December 2020 and raised concerns due to its high transmissibility and antibody escape (ability to cause infections among those with prior COVID-19)[4].

In Manaus, a large burden of the COVID-19 response has fallen to Healthcare personnel (HCP), as they treat and work in overwhelmed healthcare settings experiencing shortages in supplies and staff. Due to their extensive exposure to COVID-19 patients, HCP are a high-risk population that needs to be protected.

Studies in the United States have investigated risk factors for SARS-CoV-2 infection in HCP and there is supporting evidence that certain occupations are at a higher risk of infection, such as nurses and nursing assistants [5, 6] and environmental cleaning staff [7, 8]. Similarly, in Brazil researchers have described differences in risk of infection by occupation in HCP, with cleaning personnel experiencing the highest attack rates [9]. This relationship may be correlated with personal protective equipment (PPE) use and occupational duties, such as performing aerosol generating procedures (AGPs), but this relationship has not been observed in the US [6] and has not been examined in Brazil. While longitudinal cohort studies have been conducted among HCP in the US, most research in other countries has been cross-sectional. Therefore, there remains a critical need for longitudinal data on potential risk factors for SARS-CoV-2 infection among HCP in Brazil.

Literature Review

COVID-19 in Brazil

As of May 2021, 400,000 Brazilians have died from COVID-19, making up 13% of the world's COVID-19 deaths [10]. Several factors contribute to the large burden of COVID-19 in Brazil, one of which is the politically-driven federal response. Brazil has had four Health Ministers since March 2020, two of which President Jair Bolsonaro fired due to their disagreement with his support of anti-malarial drugs as a prevention measure for COVID-19 and refusal to implement national lockdown measures [11]. The federal government has discouraged the use of facemasks and social distancing. Within Brazil, some state and local leadership have imposed recommended prevention and control measures which contributed to localized reduction of cases and deaths from COVID-19 [1].

Brazil's public health system, *Sistema Unico de Saude* (SUS), is one of the largest health systems in the world and provides 78% of the Brazilian population with free universal access to healthcare [3, 11]. Brazil's publicly-funded immunization program is one of the most successful in the world with more than 95% of the population vaccinated against TB, diphtheria, polio, and hepatitis [11]. Brazil's COVID-19 vaccination initiatives were deterred by Bolsonaro, who publicly stated vaccines from China were unsafe and repeatedly refused to purchase them [3]. Since the beginning of March 2021, Bolosnaro has endorsed the purchase of COVID-19 vaccines and production of a COVID-19 vaccine in Brail.

On January 17, 2021, Coronavac and Astrazeneca were the first two vaccines against COVID-19 approved for emergency use in Brazil [3]. CoronaVac is a whole inactivated virus vaccine developed by the Chinese company Sinovac and is being produced by Instituto Butantan in Sao Paulo, Brazil. This vaccine requires two doses with a three-to-four-week interval between each dose and has an efficacy of 50.7% (95% Confidence Interval: 36.7-81.52) 14 days after the second dose [12]. The AstraZeneca vaccine delivers a chimpanzee adenovirus encoding of the SARS-CoV-2 spike glycoprotein and also requires two doses [3]. Phase III clinical trials in Brazil, South Africa, and the UK found an efficacy of 55.1% when doses were less than six weeks apart and 81.3% when doses were 12 or more weeks apart [13, 14]. As of July 18, 2021, 42.5% of the Brazilian population was partially immunized and 16.2% was fully immunized [3]. Of the 117,787,993 doses administered, 46.7% were AstraZeneca and 39% were CoronaVac [3]. The Brazilian National Vaccination Campaign has prioritized vaccine roll-out among institutionalized people ages 60 years or older, institutionalized people living with disabilities, Indigenous Peoples living in Indigenous lands, and healthcare workers, in that order [3].

After an initial wave of COVID-19 in May 2020, Brazil experienced a large resurgence of COVID-19 cases and deaths that occurred between December 2020 and March 2021 [2]. Throughout this period, Brazil experienced healthcare worker shortages, limited testing supplies, oxygen shortages, and high death rates across the country [1]. By March 2021, the country experienced the most severe health and hospital collapse in their history, with most states reaching a 90% ICU occupancy rate and over 4,000 daily deaths [1, 3]. This second wave was first noticed in the city of Manaus, which is located in the Northern Amazonian region of Brazil and has been one of the most heavily affected regions of the pandemic [15].

COVID-19 in Manaus

Manaus is the capital of the state of Amazonas and is the largest city in the Amazonian region with a population of 2 million people [16]. The first case of COVID-19 in Manaus was reported in March of 2020 in a traveler from Spain [15]. Epidemiologic data from surveillance of severe acute respiratory illness in Manaus suggest that the first wave of the epidemic occurred from March 2020 to May 2020, but in late December cases began to grow exponentially [17]. During the first wave in May 2020, around 80 confirmed COVID-19 deaths were reported each day, but by January 2021, the number of deaths each day exceeded 100 [18]. A surge in COVID-19 hospitalizations led to oxygen shortages and collapsed the city's healthcare system resulting in many preventable COVID-19 deaths [1].

The second wave of cases was not anticipated due to the severe first wave that should have left a large proportion of Manaus's population with natural immunity against COVID-19. A study using data from blood donors in Manaus estimated that the first wave infected 76% of the city's population by October 2020 [16]. These results suggested that the theoretical threshold for herd immunity was reached at the end of 2020, leading many experts to hypothesize a second wave would not occur so soon. There are many possible explanations for why this second wave occurred, including a theory that the estimated seroprevalence rate was an overestimate; therefore, a large enough proportion of the population was still susceptible to infection. However, this is likely not the case since using this seroprevalence rate to model the expected case fatality rate yields a similar number of actual reported deaths in Manaus. This leads most researchers to assume that the rapid transmission in a previously infected population was due to the emergence of a new variant of concern (VOC) [17].

Gamma Variant

The second wave of cases coincided with the emergence of a new lineage of SARS-CoV-2, P.1. or Gamma strain. This variant was first detected in Amazonas on December 4, 2020, and was first reported in four travelers from Brazil in January 2021 [17]. Genomic and epidemiologic data suggest that this variant emerged in Amazonas around November 2020. The Gamma variant has 17 mutations with three in the spike protein and has been labeled as a variant of high concern by the World Health Organization (WHO) [19].

SARS-CoV-2 Gamma infections are associated with higher viral loads and there is evidence that Gamma could be more transmissible than earlier lineages [4]. Naveca and colleagues used real-time RT-PCRT cycle threshold (Ct) scores as a proxy for viral load to compare Gamma positive and negative samples from the upper respiratory tract. They found significantly lower Ct scores in Gamma -infected subjects compared to non- Gamma infected subjects. This difference reflects a tenfold higher viral load in Gamma infections than non-Gamma infections. They observed this relationship in all adult individuals, regardless of sex and age [17]. Another study using genomic and mortality data estimated that Gamma may be 1.7 to 2.4-fold more transmissible [19].

Another concerning trait of the Gamma lineage is that it may be able to evade immunity from previous infection and cause reinfection in convalescent individuals. A modeling study estimated that previous non- Gamma infection provides 54 to 79% of the protection against infection with Gamma that it provides against non- Gamma lineages [19]. While this study can help explain why the surge in Manaus occurred, it lacks supporting evidence to conclude that the Gamma lineage can evade immunity from previous infection. The same modeling study estimated that infections were 1.2 to 1.9 times more likely to result in mortality after the emergence of Gamma, but this could be correlated with the city's strained healthcare system. Subject matter experts believe that this viral strain emerged due to the limited public health measures in place to prevent the spread of COVID-19, allowing for a large number of cases and the opportunity for more mutations. This is important to understand as new strains and lineages continue to emerge as the COVID-19 pandemic evolves.

COVID-19 in HCP in Brazil

A large burden of SARS-CoV-2 infections during both waves of disease has been placed on healthcare personnel (HCP) [20]. As of May 2021, there were 10,870 infections among healthcare workers in the state of Amazonas. PPE shortages, fears of infection, exposure to SARS-CoV-2 patients, and staff shortages are heightened during a surge in cases. Ensuring the protection of HCP is essential for any country's COVID-19 response. In Brazil, it is imperative to protect HCP since the country must increase its healthcare capacity in response to this increase in cases. Identifying the risk factors for SARS-CoV-2 infection in HCP is needed to better protect HCP as the pandemic continues to evolve.

Cross-sectional studies have found that HCP who provide direct patient care or work in COVID-19 dedicated units are at a higher risk for SARS-CoV-2 infection [7, 8]. There is also evidence of differences in risk by occupation with environmental cleaning staff and nursing assistants having the highest risk [7, 8]. However, these observations are inconsistent with findings from longitudinal research [21]. These studies found that contact with a COVID-19 case outside of the workplace was the only risk factor for infection in HCP [8, 21, 22]. A case-control study conducted in healthcare facilities in five US states found that factors associated with SARS-CoV-2 included having close contact with persons with COVID-19 outside of the workplace, having contact with COVID-19 patients in the workplace, and assisting COVID-19 patients with activities of daily living [23]. Contact with COVID-19 patients as a risk factor for infection may be related to occupational duties such as performing aerosol generating procedures (AGPs). Performing AGPs has been identified as a potential risk factor but the only evidence is from research on SARS-CoV-1 [24].

Research assessing risk factors for SARS-CoV-2 infection in HCP in Brazil is limited. A serological survey conducted in Rio de Janeiro examined socioeconomic and occupational characteristics among HCPs. There was a 30% serum prevalence among the 1,141 enrolled HCPs. Non-white workers with lower income and schooling had the highest infection rates. Hospital support workers, particularly cleaning personnel, had the highest infection rates among different occupations [9]. Comparable to the studies conducted in the US, these researchers found that community exposure to COVID-19 was accountable for more infections in HCP than transmission within the hospital [8, 21, 23]. This study also highlights that there are inequalities between subgroups of HCP in Brazil, but it does not investigate specific occupation-related activities as risk factors for SARS-CoV-2.

These cross-sectional studies are helpful in guiding future research, but they reveal a lack longitudinal data on these relationships. Understanding what procedures or exposures are associated with infection is necessary to properly protect HCP. The goal of this study is to evaluate the risk factors related to patient care activities for the acquisition of SARS-CoV-2 among HCP in Manaus, Brazil.

Methods

Healthcare Provider Longitudinal Cohort

All eligible HCP from two hospitals in Manaus, Brazil (Platao, hospital A and 28 de Agosto, hospital B) and were recruited for a prospective, observational cohort study. HCP were defined as persons providing care to patients or having contact with patient surroundings. HCP were eligible to enroll if they had been on active duty since December 2020, worked at least 20 hours a week, and were at least 18 years of age. Eligible HCP completed a baseline questionnaire and provided blood sample collected on filter paper for serology testing using Luminex assay. During weekly follow-ups, a shorter questionnaire on occupational exposures and vaccination was administered. At baseline and weekly visits, self-collected nasal swabs were provided by HCP for RT-PCR testing. Self-collected nasal swabs were placed in viral transport medium and transported to LACEN Manaus for real-time reserve transcriptase polymerase chain reaction (RT-PCR) for SARS-CoV-2.

Data Collection

At enrollment, participating HCPs completed a detailed questionnaire on demographic data on occupation, comorbidities, household size, vaccination status, and previous SARS-Co-V-2 infection. HCP also self-reported PPE use in the last 14 days and any COVID-19 exposures (patient, coworker, household, community or other) in the last seven days. Participating HCP completed three follow-up questionnaires that assessed exposures from the previous week and any change in vaccination status. The weekly questionnaires included a section on occupational task section where HCP were asked if they performed 12 different potential AGPs (three-level responses of performed, was present, did not perform). The 12 potential AGPs were then grouped as having high, medium, and low exposure risk as listed in Table A1. These categorizations were determined using WHO guidelines for AGPs and potential AGPs [25]. A weekly exposure status for HCP was determined as the highest risk level AGP performed or present for, and each HCP-week was categorized as high risk, medium risk, low risk, and no risk (i.e., not having performed any potential AGPs) (Table A1).

HCP who reported caring for a suspected or confirmed COVID-19 patient were asked about PPE use in the previous 7 days. The response was collected on a 4 point Likert scale (rarely, occasionally, most of the time, always) which we then coded as non-compliant for rarely and occasionally responses and compliant for most of the time and always responses.

Vaccination status was self-reported and then verified by study staff using hospital vaccination records and was determined at each visit. Participant's vaccination status was categorized at baseline and each follow-up assessment: fully vaccinated (if >=14 days after dose 2), partially vaccinated (if >=14 days after dose 1 and <14 after dose 2) and unvaccinated (<14 days after dose 1, or having received no doses) . Baseline serology levels were also used as an indicator for immunity (either from previous infection or vaccination). We categorized serology levels as non-reactive (I.e., measure of < 35.2 BAU/ml), reactive low titer (I.e., 38.8-260.02 BAU/ml), and reactive high titer (>260.03 BAU/mL) [26].

Statistical Analysis

We summarized HCP characteristics by hospital using frequencies for categorical variables and medians and interquartile ranges for continuous variables overall and for the positive cases. HCP were determined to be susceptible to infection if they had not tested positive for SARS-CoV-2 at baseline or in the previous study visits. Attack rates were calculated as the number of new infections per 1000 susceptible HCP-weeks. Logistic regression using generalized estimating equations (GEEs) was used to calculate risk ratios across exposures for our primary outcome of positive RT-PCR-confirmed SARS-CoV-2 infection. These nested models allow for clustering at the facility level and for repeated measures for each HCP across the study period [27].

We utilized multivariable logistic regression using GEEs to examine associations between variables and SARS-CoV-2 infection, while adjusting for potential confounders. Variables included in model 1 were determined *a prior* based on studies conducted in HCP in the US and Brazil [7-9, 21-23] and included age (categorized as <60 and 60+ years), occupation, vaccination, and exposure to a COVID-19 case outside of the hospital. To further explore whether any exposures were associated with SARS-CoV-2 infection, we ran a fully saturated model (model 2) that included all predictors (sex, age, occupation, number of healthcare facilities employed at, comorbidities, household size, prior SARS-CoV-2 infection, vaccination status, hospital unity, contact with a suspected or confirmed COVID-19 patient, exposure to a COVID-19 patient outside of the hospital, direct contact with the environment of a COVID-19 patient, and highest AGP exposure risk that week). Lastly, we ran a similar fully saturated model (model 3) that included baseline serology values instead of vaccination status and only included HCP fully vaccinated at baseline. All analyses were performed using SAS version 9.4 (SAS Institute; Cary, NC).

Results

Cohort Characteristics

Our cohort included 771 participating HCP, 388 (50%) were enrolled from Platão Araújo and 383 (50%) were enrolled from 20 de Agosto (Table 1). The median age of the cohort was 40 years of age and most HCP were female (78%), non-smokers (91%) and had no chronic medical conditions (86%). About half of the participants were individuals that regularly provide hands-on medical care (55%) and the median hours of patient face-to-face contact in a typical work week was 25. The cohort was mostly made up of nurse assistants (43%), nurses (15%), security (9%), and environmental cleaning staff (9%). More than half of the cohort reported a COVID-19 infection prior to study enrollment (60%). At baseline, 76% of HCP were fully vaccinated, 7% were partially vaccinated, and 16% were unvaccinated (Table 1).

Occupational Exposures among HCP

Across the study period, 38% of HCP reported caring for a suspected or confirmed COVID-19 patient in the previous two weeks at enrollment and in the previous seven days at each visit (Table 2). Among those, 91% reported wearing a cloth mask most of the time or always, compared to 34% and 22% that reported wearing medical masks and N95 respirators, respectively. HCP reported consistently wearing face shields (69%) but only 7% reported wearing gloves and 10% reported wearing gowns (Table 3). Overall, 70% of HCP did not perform or were not present for any of the potential AGPs assessed, 18% of HCPs performed or were present for a high risk exposure at least once during the study period 8% had a medium exposure risk, 4% had a low exposure risk.

SARS-CoV-2 Positive HCP

SARS-CoV-2 infection was confirmed by RT-PCR testing in 16 (2%) participants (Table 4). Among these cases, the median age was 43.5 and 6 (43%) reported a previous infection. Most cases were breakthrough infections: 13 (75%) occurred when the HCP was fully vaccinated, 3 (19%) occurred in unvaccinated HCP, and 1 (6%) case occurred when the HCP was partially vaccinated. The majority of cases were HCP that regularly provide hands-on medical care (56%) and 5 (31%) reported a chronic medical condition. Only 4 (25%) of the cases reported providing care for a suspected or confirmed COVID-19 patient (Table 4). Among those four, one HCP reported not using PPE at all the week prior to the positive test, and the remaining three reported only the use of a cloth face mask with no other PPE.

Risk of SARS-Co-V-2 infection among HCP

The overall attack rate among HCP in the study period was 5.2 cases per 1000 HCP-weeks. By job category, the attack rate was highest among environmental cleaning staff and nurse assistants (7.7 and 6.9 per 1000 HCP-weeks, respectively) (Table 2). The risk of SARS-Co-V-2 infection among nurse assistants, registered nurses, security officers, and environmental cleaning staff was not statistically significantly different when compared to all other occupations (Table 2). The highest crude risk ratios (RR_c) were observed among nurse assistants (RR_c 2.6, 95% CI 0.57 – 12.06) and environmental cleaning staff (RR_c 2.9, 0.41-20.8) compared to other job types, but neither of these associations were statistically significant (Table 2).

HCP that reported regularly working in intensive care units did not have statistically significant difference in risk compared with those that did not (RR_c 1.95 95% CI 0.71-5.33). Neither direct contact with patient environment nor performing high risk AGPs were associated with a statistically significant different risk of infection.

HCP with a reported chronic medical condition was associated with a non-significant difference in the risk of infection (RR_c 2.75, 95% CI 0.96-7.91). Household crowding was also not statistically significantly associated with risk for infection, though the RR point estimate suggests a trends towards decreased risk (RR_c 0.43 95% CI 0.05-3.73). Having reported a previous infection with SARS-CoV-2 was protective by 50% (95% CI 0.19-1.34). In this cohort, HCP who were fully vaccinated or partially vaccinated had non-significant unadjusted differences in risk compared to those that were unvaccinated (RR = 0.95 (95% CI 0.27-3.37) for fully vaccinated, RR_c 0.73 (95% CI 0.08-7.08) for partially vaccinated). Reactive baseline serology levels were not statistically significantly associated with a risk of infection. HCP with high-titer reactivity were estimated to have 56% (95% CI 0.05-3.73) lower risk of SARS-CoV-2 infection and those with low-titer reactivity had 33% (95% CI 0.08-5.35) lower risk.

When adjusting for age, occupation, vaccination status, and COVID-19 exposure outside of the hospital, none of the associations were found to be statistically significant (Model 1, Table 5). Similarly, no significant associations were observed for the fully saturated model (Model 2, Table 6) which included all predictors except baseline serology levels. When limiting the outcome to breakthrough infections, none of the associations were found to be significant in model 3 (Table 7), which included baseline serology instead of vaccination.

Discussion

In this large prospective cohort study following 771 HCP over four weeks from two hospitals in Manaus, Brazil, we identified 16 incident cases of SARS-CoV-2 infection and a SARS-Co-V-2 attack rate of 2%. We were unable to identify any demographic characteristics, or exposures that were significantly associated with the risk of acquiring SARS-CoV-2 infection. When adjusting for variables identified to be risk factors for infection in other studies conducted on HCP in the United States and Brazil, we found no significant exposures for SASRS-CoV-2 infection in any models, whether they included a subset of covariates selected a priori or all potential covariates (i.e., fully saturated).

There are many possible explanations to our lack of significant findings in this study. The low attack rate in this cohort limits the statistical power necessary to reveal any significant relationships between exposure and risk of infection. This attack rate is notably lower than what was observed in Brazil during the two major waves of infection on May 2020 and March 2021 (32,000 and 98,000, respectfully) [3]. The low attack rate observed in this cohort is attributable to the high immunity at baseline; either from previous infection of vaccination. At enrollment, 76% of the cohort was fully vaccinated and 60.7% had reported a previous SARS-CoV-2 infection. Baseline serology data also provides insight on the susceptibility of this population. 96% of HCP had a reactive Ct value (> 25.2 BAU/ml) with half of those being a high titer (>260 BAU/ml). These data all support the idea that much of the cohort had some form of immunity against SARS-CoV-2 infection at enrollment.

Fully-vaccinated individuals should have a higher protection against infection than partially vaccinated individuals [12-14], and that was not observed. Both previous infection and baseline serology levels were better predictors of immunity in this dataset. This observation could be due to interaction between serology, priori infection, and vaccination. Contact with a COVID-19 case outside of the hospital has been found to be associated with a higher risk of SARS-Co-V-2 infection in HCP [9, 21], but we did not observe that relationship in this cohort. It should however, be noted that among the six cases that reported contact with a COVID-19 case outside of the hospital, all of them occurred at another healthcare facility. This limited our ability to assess whether HCP are being infected with SARS-CoV-2 from exposures in the community rather than the healthcare facility.

Some results in this study are suggestive of relationships that could have been significant had there been enough statistical power and they warrant further investigation. For example, the RR_c estimates comparing nurse assistants, nurses, and environmental cleaning staff to other HCP are all much higher, as suggested in the literature [7-9]. These potential findings can guide and justify future studies.

This study has many strengths, one being that it is likely the first longitudinal cohort study investigating risk factors among HCP working in a heavily affected region. A limitation in this study is the survey design for how we assessed PPE use. Data on the frequency of PPE use was only collected for HCP that reported having cared for a SARS-CoV-2 in the previous 14 days at baseline or previous seven days at follow-up visits. This further limited the number of cases in this group and prevented us from calculating measures of associations for PPE use. Another limitation for the data collected in this survey was that we did not collect any data on the racial and ethnic characteristics of the cohort. In the United States, being black was one of the few characteristics consistently associated with a higher risk of SARS-CoV-2 infection across multiple studies [5, 6, 8, 21]. Similarly, in a HCP cohort study conducted in Rio de Janeiro, non-white HCP showed the highest infection rates [9]. Therefor race/ethnicity still needs to be investigated in this population.

Despite these limitations, this study describes important characteristics of HCP in one of the highest COVID-burdened regions of Brazil. The high immunity in this cohort from either previous infection or vaccination resulted in a low SARS-CoV-2 attack rate in this population across the study period. However, descriptive data on AGPs and PPE across different occupations and hospital units are useful in understanding the possible differences in exposures to SARS-CoV-2 and henceforth the risk of infection.

Transmission of SARS-Co-V-2 occurs in healthcare settings between HCP and between patients and HCP. Our study highlights the demographic and occupational characteristics of HCP in Manaus which can guide future research on how they relate to risk of SARS-CoV-2 infection. Identifying the risk factors for SARS-CoV-2 infection among HCP can help create guidelines to protect them from becoming infected or spreading SARS-CoV-2 in the workplace. Similarly, defining immunity and susceptibility to infection using serology, previous infection, or vaccination status can help categorize target groups for vaccine rollout and other infection control practices.

References

1. Silva, S.J.R.d. and L. Pena, *Collapse of the public health system and the emergence of new variants during the second wave of the COVID-19 pandemic in Brazil.* One Health, 2021. **13**: p. 100287.
2. Dong, E., H. Du, and L. Gardner, *An interactive web-based dashboard to trackk COVID-19 in real time.* The Lancet Infectious Diseases, 2020. **20**(5): p. P533-534.
3. Bernardeau-Serra, L., et al., *The COVID-19 Vaccination Strategy in Brazil—A Case Study.* Epidemiologia, 2021. **2**(3): p. 338-359.
4. Sabino, E.C., et al., *Resurgence of COVID-19 in Manaus, Brazil, despite high seroprevalence.* Lancet, 2021. **397**(10273): p. 452-455.
5. Dube, W.C., et al., *Quantifying Risk for SARS-CoV-2 Infection Among Nursing Home Workers for the 2020-2021 Winter Surge of the COVID-19 Pandemic in Georgia, USA.* J Am Med Dir Assoc, 2022.
6. Howard-Anderson, J.R., et al., *Occupational risk factors for severe acute respiratory coronavirus virus 2 (SARS-CoV-2) infection among healthcare personnel: A 6-month prospective analysis of the COVID-19 Prevention in Emory Healthcare Personnel (COPE) Study.* Infect Control Hosp Epidemiol, 2022: p. 1-8.
7. Shepard, J., et al., *The prevalence of COVID-19 in healthcare personnel in an adult and pediatric academic medical center.* Am J Infect Control, 2021. **49**(5): p. 542-546.
8. Eyre, D.W., et al., *Differential occupational risks to healthcare workers from SARS-CoV-2 observed during a prospective observational study.* elife, 2020. **9**: p. e60675.
9. Correia, R.F., et al., *SARS-CoV-2 seroprevalence and social inequalities in different subgroups of healthcare workers in Rio de Janeiro, Brazil.* The Lancet Regional Health - Americas, 2022. **7**: p. 100170.
10. Taylor, L., *Covid-19: How the Brazil variant took hold of South America.* BMJ, 2021. **373**: p. n1227.
11. Malta, M., et al., *Political neglect of COVID-19 and the public health consequences in Brazil: The high costs of science denial.* EClinicalMedicine, 2021. **35**: p. 100878-100878.
12. Palacios, R., et al., *Efficacy and Safety of a COVID-19 Inactivated Vaccine in Healthcare Professionals in Brazil: The PROFISCOV Study* 2021.
13. Voysey, M., et al., *Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK.* The Lancet, 2021. **397**(10269): p. 99-111.
14. Voysey, M., et al., *Single-dose administration and the influence of the timing of the booster dose on immunogenicity and efficacy of ChAdOx1 nCoV-19 (AZD1222) vaccine: a pooled analysis of four randomised trials.* The Lancet, 2021. **397**(10277): p. 881-891.
15. Nascimento, V.A.D., et al., *Genomic and phylogenetic characterisation of an imported case of SARS-CoV-2 in Amazonas State, Brazil.* Mem Inst Oswaldo Cruz, 2020. **115**: p. e200310.
16. Buss, L.F., et al., *Three-quarters attack rate of SARS-CoV-2 in the Brazilian Amazon during a largely unmitigated epidemic.* Science, 2021. **371**(6526): p. 288-292.
17. Naveca, F.G., et al., *COVID-19 in Amazonas, Brazil, was driven by the persistence of endemic lineages and P.1 emergence.* Nature Medicine, 2021. **27**(7): p. 1230-1238.
18. Taylor, L., *Covid-19: Is Manaus the final nail in the coffin for natural herd immunity?* BMJ, 2021. **372**: p. n394.

19. Faria, N.R., et al., *Genomics and epidemiology of the P.1 SARS-CoV-2 lineage in Manaus, Brazil.* Science, 2021. **372**(6544): p. 815-821.
20. Bandyopadhyay, S., et al., *Infection and mortality of healthcare workers worldwide from COVID-19: a systematic review.* BMJ Glob Health, 2020. **5**(12).
21. Jacob, J.T., et al., *Risk Factors Associated With SARS-CoV-2 Seropositivity Among US Health Care Personnel.* JAMA Network Open, 2021. **4**(3): p. e211283-e211283.
22. Baker, J.M., et al., *Quantification of Occupational and Community Risk Factors for SARS-CoV-2 Seropositivity Among Health Care Workers in a Large U.S. Health Care System.* Ann Intern Med, 2021. **174**(5): p. 649-654.
23. Chea, N., et al., *Risk Factors for SARS-CoV-2 Infection Among US Healthcare Personnel, May-December 2020.* Emerg Infect Dis, 2022. **28**(1): p. 95-103.
24. Tran, K., et al., *Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review.* PLoS One, 2012. **7**(4): p. e35797.
25. World Health Organization, *Infection prevention and control during health care when coronavirus disease (COVID-19) is suspected or confirmed: interim guidance, 12 July 2021*. 2021, World Health Organization: Geneva.
26. Food and Drug Administration, *Euroimmun Anti-SARS-CoV-2 S1 Curve ELISA (IgG).* 2021.
27. Liang, K. Y. and Zeger, S.L., *Longitudinal data analysis using generalized linear models.* Biometrika, 1986. **73**(1): p. 13-22.

Table 1. Demographic Characteristics of Cohort by Hospital

	Hosp A n = 388	**Hosp B n = 383**	**Total (%) n = 771**
Age, Median [IQR]	40 [15]	41 [18]	40 [17]
Sex			
Male	104	67	171 (22.18)
Female	279	321	600 (77.82)
Occupation			
Nurse Assistant	198	130	328 (42.5)
Registered Nurse	66	52	118 (15.3)
Security	10	59	69 (8.9)
Environmental Cleaning Staff	30	36	66 (8.6)
Administrative Staff	12	15	27 (3.5)
Physical Therapist	7	17	24 (3.1)
Physician	6	15	21 (2.7)
Other	59	59	118 (15.3)
Number of healthcare facilities working at			
1	289	303	592 (76.8)
2	96	78	174 (22.6)
3	3	2	5 (0.65)
Number of hours with patient face to face contact during typical work week [1-80], Median [IQR]	30 [25]	20 [20]	25 [29]
HCP that regularly provides hands-on medical care			
Yes	184	241	425 (55.1)
No	199	147	346 (44.9)
Smoking Status			
Every day	20	11	31 (4)
Somedays	21	16	37 (4.8)
Not at all	342	361	703 (91.2)
Participated in physical activity in the last 30 days			
Yes	146	132	278 (36.1)
No	237	256	493 (63.9)
Comorbidities			
Yes	56	55	111 (14.4)
No	332	328	660 (85.6)
COVID-19 infection prior to study enrollment			
Yes- 90 or more days ago	210	168	378 (49)
Yes – within the previous 90 days	36	54	90 (11.7)
No	139	166	305 (39.6)
Vaccine type among those fully or partially vaccinated at study enrollment			
CoronaVac	311	311	622 (80.1)
AstraZeneca	9	7	16 (2.08)
Unvaccinated	68	65	133 (17.3)

*Hosp A = Platao; Hosp B = 28 de Agosto

Table 2. Attack Rates per 1000 HCP-weeks and Crude Risk Ratios

	HCP-weeks	**New Cases**	**Attack Rate (per 1000 HCP-weeks)**	**Crude Risk Ratio**	**95% CI**	
Sex						
Male	676	4	5.92	REF		
Female	2385	12	5.03	0.8505	0.27	2.63
Age						
< 60	2953	15	5.08	REF		
60+	108	1	9.26	1.82	0.25	13.32
Occupation						
Nurse assistant (nurse technician)	1302	9	6.91	2.62	0.57	12.06
Registered nurse	469	2	4.26	1.62	0.23	11.42
Security officers	273	1	3.66	1.39	0.13	15.36
Env. cleaning staff	259	2	7.72	2.93	0.41	20.79
Others	758	2	2.64	REF		
Number of Healthcare Facilities Employed at						
1	2348	14	5.96	REF		
2	693	2	2.89	0.48	0.11	2.12
3+	20	0	0	-	-	-
Comorbidities						
No	2627	11	4.19	REF		
Yes	434	5	11.52	2.75	0.96	7.91
Household Size						
< 5	2649	15	5.66	REF		
5+	412	1	2.43	0.43	0.06	3.21
Prior COVID-19 Infection*						
No previously reported	1201	9	7.49	REF		
Previous infection	1860	7	3.76	0.5	0.19	1.34
Baseline Serology						
Non-reactive	108	1	9.26	REF		
Reactive low titer	1473	9	6.11	0.67	0.08	5.35
Reactive high titer	1479	6	4.06	0.44	0.05	3.73
Vaccination Status						
Unvaccinated	530	3	5.66	REF		
Partially Vaccinated	242	1	4.13	0.73	0.08	7.08
Fully Vaccinated	2234	12	5.37	0.95	0.27	3.37
Hospital Unit						
Non-ICU	2340	10	4.27	REF		
ICU	715	6	8.39	1.95	0.71	5.33

Attack Rates for Weekly Exposures

	HCP-weeks	New Cases	Attack Rate	Crude Risk Ratio	95% CI	
Direct contact with a suspected or confirmed COVID-19 Patient						
No	1841	12	6.52	*REF*		
Yes	1114	4	3.59	0.55	0.18	1.7
Exposure to a confirmed or suspected COVID-19 case outside of hospital						
No	1679	10	5.96	*REF*		
Yes	1222	6	4.91	0.82	0.3	2.27
Direct contact with patient environment						
No	2114	11	5.20	*REF*		
Yes	787	5	6.35	1.22	0.42	3.51
Highest Procedure Risk Category that week						
No AGPs	2357	13	0.01	*REF*		
Low Risk**	96	0	0.00	-	-	-
Medium Risk ***	172	0	0.00	-	-	-
High Risk	420	3	0.01	1.29	0.37	4.54

Table 3. PPE Use among HCP that reported caring for a suspected or confirmed COVID-19 case throughout the study follow-up

	Baseline		**Week 1**		**Week 2**		**Week 3**		**Overall**	
PPE item	n=	411	n=	278	n=	225	n=	203	n=	1117
Medical Mask	138	34%	100	34%	73	32%	72	35%	521	34%
N95 Respirator	80	19%	71	26%	50	22%	46	23%	327	22%
Cloth Mask	363	88%	254	91%	210	93%	195	96%	1385	91%
Gloves	28	7%	20	7%	13	6%	12	6%	101	7%
Gowns	43	10%	28	10%	19	8%	21	10%	154	10%
Face shield	277	67%	196	71%	160	71%	142	70%	1052	69%

Table 4. Characteristics of 16 SARS-CoV-2 Positive HCP

		Total N=16 (%)
Hospital		
	A	9 (56)
	B	7 (44)
Age (Median, IQR)		43.5 (17)
Vaccination Status		
	Vaccinated	13 (75)
	Unvaccinated	3 (18.75)
	Partially Vaccinated	1 (6.25)
Previous Infection		6 (37.5)
HCP that regularly provides hands-on medical care		9 (56)
Reported any comorbidities		5 (31.3)
Reported caring for a suspected or confirmed COVID-19 patient		4 (25)

Table 5. Model 1: Risk Ratios adjusted for age, occupation, vaccination status, and COVID-19 exposure outside of hospital

		Adjusted Risk Ratio	95% CI	
Sex				
	Male	*REF*	-	-
	Female	0.62	0.18	2.1
Age				
	< 60	*REF*	-	-
	60+	2.15	0.26	18
Occupation				
	Nurse assistant (nurse technician)	2.68	0.6	12.09
	Registered nurse	1.69	0.21	13.28
	Security officers	1.3	0.1	16.19
	Env. cleaning staff	2.89	0.41	20.3
	Others	*REF*	-	-
Number of Healthcare Facilities Employed at				
	1	*REF*	-	-
	2	0.47	0.1	2.27
	3+*	-	-	-
Comorbidities				
	No	*REF*	-	-
	Yes	2.53	0.81	7.92
Household Size				
	< 5	REF	-	-
	5+	0.37	0.05	2.86

Prior COVID-19 Infection*			
No previously reported	*REF*	-	-
Previous infection	0.47	0.18	1.27
Baseline Serology			
Non-reactive	*REF*	-	-
Reactive low titer	0.58	0.08	4.23
Reactive high titer	0.38	0.05	3.22
Vaccination Status			
Unvaccinated	*REF*	-	-
Partially Vaccinated	0.56	0.05	5.87
Fully Vaccinated	0.79	0.21	2.91
Hospital Unit			
Non-ICU	*REF*	-	-
ICU	1.97	0.65	5.93
Direct contact with a suspected or confirmed COVID-19 Patient			
No	*REF*	-	-
Yes	0.54	0.17	1.73
Exposure to a confirmed or suspected COVID-19 case outside of hospital			
No	*REF*	-	-
Yes	0.89	0.32	2.51
Direct contact with patient environment			
No	*REF*	-	-
Yes	1.37	0.42	4.54
Highest Procedure Risk Category that week			
No AGPs	*REF*	-	-
Low Risk*	-	-	-
Medium Risk *	-	-	-
High Risk	1.39	0.34	5.78
***RR not assessed**			

Table 6. Model 2: Full-sink model (adjusted for sex, age, occupation, number of healthcare facilities employed at, comorbidities, household size, prior SARS-CoV-2 infection, vaccination status, hospital unity, contact with a suspected or confirmed COVID-19 patient, exposure to a COVID-19 patient outside of the hospital, direct contact with the environment of a COVID-19 patient, and highest AGP exposure risk that week)

	Adjusted Risk Ratio	95% CI	
Sex			
Male	*REF*	-	-
Female	0.54	0.15	1.97
Age			
< 60	*REF*	-	-
60+	1.28	0.12	13.77
Occupation			
Nurse assistant (nurse technician)	3.69	0.65	20.86
Registered nurse	2.23	0.25	19.72

Security officers	0.87	0.08	9.65
Env. cleaning staff	2.44	0.28	2128
Others	REF	-	-
Number of Healthcare Facilities Employed at			
1	*REF*	-	-
2	0.49	0.1	2.34
3+	-	-	-
Comorbidities			
No	*REF*	-	-
Yes	3.04	0.9	10.3
Household Size			
< 5	*REF*	-	-
5+	0.31	0.03	2.88
Prior COVID-19 Infection*			
No previously reported	*REF*	-	-
Previous infection	0.52	0.18	1.51
Vaccination Status			
Unvaccinated	*REF*	-	-
Partially Vaccinated	0.51	0.04	6.12
Fully Vaccinated	0.7	0.15	3.13
Hospital Unit			
Non-ICU	*REF*	-	-
ICU	2.06	0.63	6.74
Direct contact with a suspected or confirmed COVID-19 Patient			
No	*REF*	-	-
Yes	0.47	0.11	0.19
Exposure to a confirmed or suspected COVID-19 case outside of the hospital			
No	*REF*	-	-
Yes	1.09	0.31	3.87
Direct contact with patient environment			
No	*REF*	-	-
Yes	1.22	0.36	4.17
Highest Procedure Risk Category that week			
No AGPs	*REF*	-	-
Low Risk*	-	-	-
Medium Risk *	-	-	-
High Risk	1.22	0.29	5.09
***RR not assessed**			

Table 7. Full-sink model for breakthrough infections (adjusted for sex, age, occupation, number of healthcare facilities employed at, comorbidities, household size, prior SARS-CoV-2 infection, vaccination status, hospital unity, contact with a suspected or confirmed COVID-19 patient, exposure to a COVID-19 patient outside of the hospital, direct contact with the environment of a COVID-19 patient, and highest AGP exposure risk that week. Limited to HCP that were fully vaccinated at baseline)

	Adjusted Risk Ratio*	95% CI	
Sex			
Male	*REF*	-	-
Female	0.56	0.15	2.02
Age			
< 60	*REF*	-	-
60+	1.21	0.11	13.86
Occupation			
Nurse assistant (nurse technician)	3.64	0.66	20.16
Registered nurse	2.27	0.25	20.8
Security officers	1.04	0.09	12.25
Env. cleaning staff	2.56	0.31	21.5
Others	*REF*	-	-
Number of Healthcare Facilities Employed at			
1	*REF*	-	-
2	0.45	0.09	2.2
3+	-	-	-
Comorbidities			
No	*REF*	-	-
Yes	2.96	0.9	9.79
Household Size			
< 5	*REF*	-	-
5+	0.33	0.04	2.94
Baseline Serology			
Non-reactive	*REF*	-	-
Reactive low titer	0.54	0.08	3.73
Reactive high titer	0.38	0.05	2.91
Vaccination Status			
Unvaccinated	*REF*	-	-
Partially Vaccinated	0.6	0.05	7.95
Fully Vaccinated	0.84	0.17	4.01
Hospital Unit			
Non-ICU	*REF*	-	-
ICU	2.36	0.77	7.23
Direct contact with a suspected or confirmed COVID-19 Patient			
No	*REF*	-	-
Yes	0.45	0.11	1.79

Exposure to a confirmed or suspected COVID-19 case outside of the hospital			
No	*REF*	-	-
Yes	1.05	0.29	3.87
Direct contact with patient environment			
No	*REF*	-	-
Yes	1.54	0.48	5.01
Highest Procedure Risk Category that week			
No AGPs	*REF*	-	-
Low Risk*	-	-	-
Medium Risk *	-	-	-
High Risk	1.2	0.29	4.91
***RR not assessed**			

Table 8. Procedures Performed by HCP throughout the entire study period

	Week 1		Week 2		Week 3		Overall	
Procedure	n =	749	n=	728	n=	716	n=	2193
Airway suctioning	144	19%	123	17%	104	15%	371	17%
Non-invasive ventilation (positive pressure)	95	13%	62	8%	62	9%	219	10%
Non-invasive ventilation (high flow O2)	113	15%	88	12%	60	8%	261	12%
Manual ventilation	68	9%	57	8%	42	6%	167	8%
Nebulizer treatment	88	12%	71	10%	54	8%	213	10%
Intubation	94	12%	87	12%	74	10%	255	12%
Extubation	58	8%	39	5%	38	5%	135	6%
Code/CPR	65	9%	61	8%	49	7%	175	8%
Chest physiotherapy	70	9%	51	7%	50	7%	171	8%
Bronchoalveolar Lavage	6	0.80%	7	1%	4	1%	17	1%
Sputum induction	25	3%	16	2%	8	1%	49	2%
Bronchoscopy	3	0.40%	2	0.30%	3	0.40%	8	0%

Table 9. Procedures Performed by HCP grouped by risk level throughout the study period

	Week 1		Week 2		Week 3		Overall	
Procedure Risk Level	n =	771	n=	771	n=	771	n=	2313
High Exposure Risk	160	21%	137	18%	129	17%	426	18%
Medium Exposure Risk	73	9%	57	7%	44	6%	174	8%
Low Exposure Risk	39	5%	35	5%	23	3%	97	4%
No exposure	499	65%	542	70%	575	75%	1616	70%

Table A1. Exposure Risk Grouping for Potential Aerosol Generating Procedures

Risk Group for Potential Aerosol Generation among selected procedures
High
Tracheal Intubation
Noninvasive ventilation
Cardiopulmonary resuscitation
Manual ventilation before intubation
Bronchoscopy
Sputum induction
Medium
Nebulization
High-flow O2
Low
Airway suctioning
Extubation
Respiratory physiotherapy
Bronchoalveolar lavage