Structural Racism as a Barrier to Influenza Vaccination Uptake during Pregnancy in the Americas

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On my honor as a University Student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments

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Structural Racism as a Barrier to Influenza Vaccination Uptake during Pregnancy and Influenza Modeling in the Americas

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Abstract

Disparities that disproportionately affect minorities persist in several avenues of healthcare in the Americas; analyzing solutions to address the factors causing these inequities is imperative for relevant public health measures. In this project, the team aimed to: 1) elucidate the effects of racial disparities in inactivated influenza vaccination (IIV) access among minority pregnant woman on birth outcomes in Brazil and Virginia, and 2) construct a vaccination schedule that can predict the time at which patients in Ceará, Brazil should receive IIVs. Wavelet decomposition analysis was utilized to capture periodicities in birth weight and gestation outcomes for all Brazilian states. It was found that more distinct fluctuations in birth weight and gestation are exhibited in northern states relative to southern states, as well as in the *pretos* ("black") class relative to the *branco* ("white") and *pardo* ("mixed") classes. Furthermore, through use of SIR modeling, a baseline model capturing the spatiotemporal spread of influenza in the state of Ceará was constructed, and this model was compared to an experimental model in which Brazil's national vaccination campaign begins 1 month earlier. The experimental model exhibited a smaller peak in influenza infections (412,803 relative to 2,516,746 individuals; -83.60% change), as well as this peak being observed later in the year (177 days relative to 53 days; +233.96% change), relative to the baseline model. Overall, the project's findings suggest that racial health disparities pertaining to IIV coverage in Brazil and influenza's associated adverse birth outcomes exist. The findings also suggest that earlier vaccination campaigns may further mitigate the spread of influenza in northern states of Brazil. The methodology utilized in this project should be extended to other infectious diseases (Hepatitis E, pertussis, tetanus, SARS-CoV-2, etc.), as well as other locales, for identification of racial health disparities and improvement in vaccination coverages.

Keywords: Racial Inequities, Influenza Vaccination, Computational Modeling, Epidemiology

Introduction

Background

Immunological changes during pregnancy increase the risk of contracting influenza infection, which can result in several complications for both the mother and fetus; these complications include hospitalizations, preterm birth, low birth weight, low infant APGAR score, and various neonatal respiratory diseases.[1,2] Moreover, in the Americas, these adverse health outcomes may have a disproportionately negative impact on minority pregnant populations relative to white pregnant populations due to the longstanding history of systemic racial disparities and institutional racism.[3] For example, recent United States studies have found that pregnant African-American women are 19% less likely to be offered the inactivated influenza vaccination (IIV) by their healthcare providers and 30% less likely to be immunized overall relative to their white counterparts.[4,5] This suggests that the African-American pregnant population possesses a higher chance of contracting influenza infections, and therefore, a higher chance of experiencing influenza's associated adverse birth outcomes.

Brazil and the United States have a shared history of colonization, slavery, structural racism, and racial health disparities, the effects of which continue to permeate each country's broader society.[6] In Brazil, racial health disparities among IIV coverage have also been observed, and they resemble the previously discussed inequities that are present in the United States.[7] To our knowledge, the effects of these racial health disparities in IIV coverage

during pregnancy on the quantity of adverse birth outcomes have yet to be elucidated. Thus, quantitatively analyzing the relationship of racial health disparities in IIV uptake during pregnancy and adverse birth outcomes experienced by minority patients is crucial to gain a better understanding of the urgent and pertinent need for improving influenza vaccination coverage among minority pregnant populations in the Americas.

The spatiotemporal spread of seasonal influenza in Brazil begins in the northern states before transitioning to the southern states.[8] One of the states present in this northern region is Ceará. Furthermore, Brazil's national influenza vaccination campaign is implemented for 8-10 weeks simultaneously across the country.[9] For instance, Brazil's 2018 campaign was conducted from April 23rd to June 1st.[10] This indicates that the campaign occurs over the same period for all states, which may intuitively lead to a lack of influenza vaccination coverage in the northern regions of the country—where influenza infection occurs earlier in the year—relative to the southern regions—where influenza infection occurs later in the year. Furthermore, when considering the fact that larger proportions of minorities and low-SES citizens reside in northern states of Brazil relative to southern states, this disproportionate coverage may be the reason why substantial racial health disparities relating to influenza infection and its adverse birth outcomes are continually observed from year to year in Brazil.[11–13] Brazil's national vaccination campaign does not start until the number of influenza cases has already peaked in Ceará.

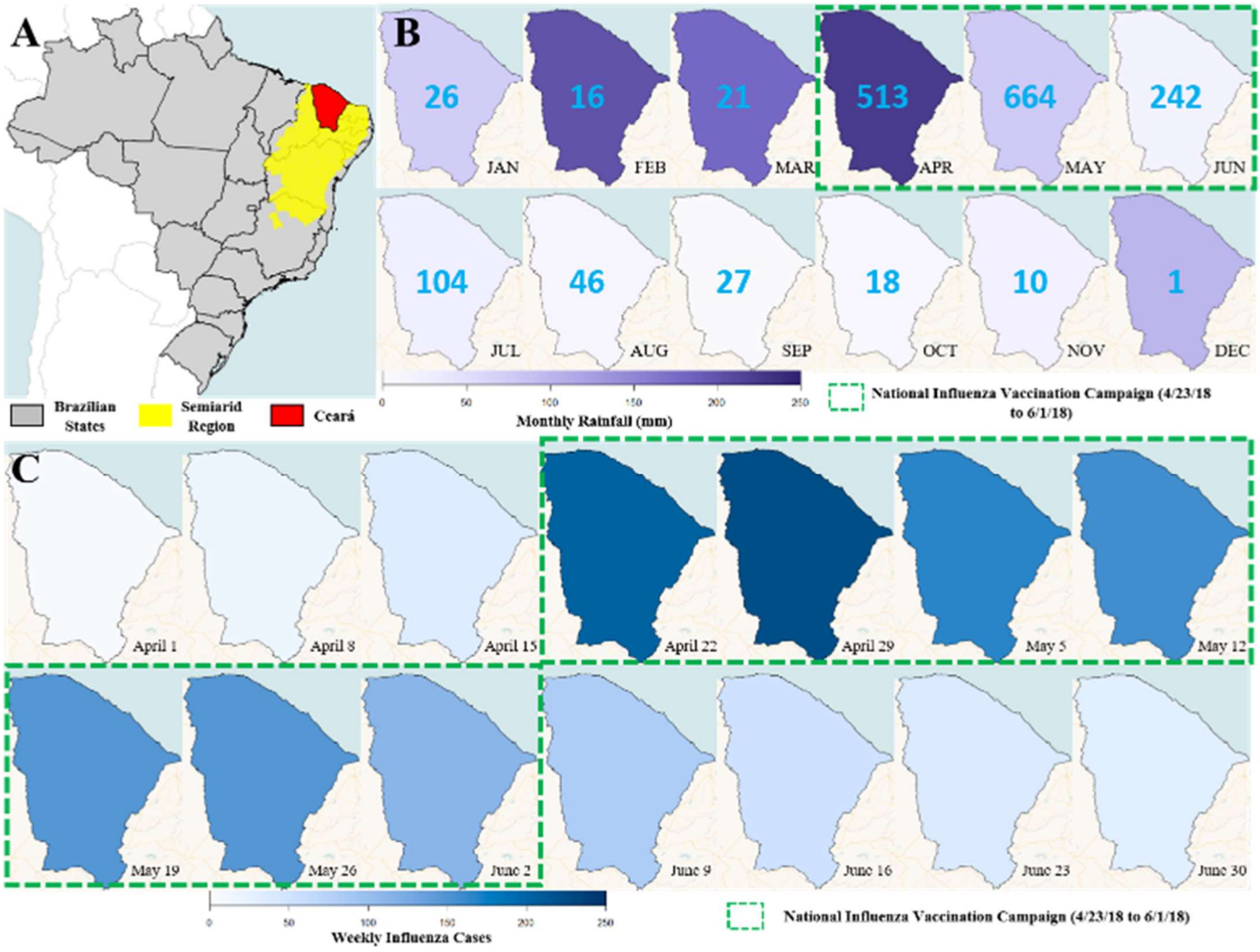

Figure 1. *Map of Ceará and visualizations of average monthly rainfall and weekly influenza cases in Ceará, 2018.*
(A) Ceará (red) in relation to Brazil's semiarid region (yellow) and other Brazilian states (light gray). **(B)** Visualizations of average monthly rainfall (mm) across the state of Ceará over the course of 2018 with total monthly influenza cases labeled in the center of each visualization. Brazil's National Influenza Vaccination Campaign (green bounded box) was conducted from April 23rd, 2018 to June 1st, 2018. Average monthly rainfall steadily increased from January to April and then decreased from April to September before increasing again at the end of the year. Monthly influenza cases drastically increased from March to April, peaking in May at 664 before decreasing throughout the remainder of the year. **(C)** Visualizations of weekly influenza cases before, during, and after Brazil's National Influenza Vaccination Campaign (green bounded box). Weekly cases quickly peaked two weeks into the campaign before beginning to steadily decrease throughout the remainder of the campaign and shortly thereafter.

The untimeliness of the national vaccination campaign can be observed qualitatively and quantitatively in **Figure 1** and **Figure 2**, respectively. The weekly incidence of influenza peaked two weeks into the 2018 vaccination campaign prior to steadily decreasing throughout the remainder of the campaign and shortly thereafter. These trends suggest that the vaccination campaign is ineffective for the state of Ceará, and consequently, the campaign may be relatively inconsequential in mitigating the adverse birth outcomes associated with influenza infection during pregnancy.

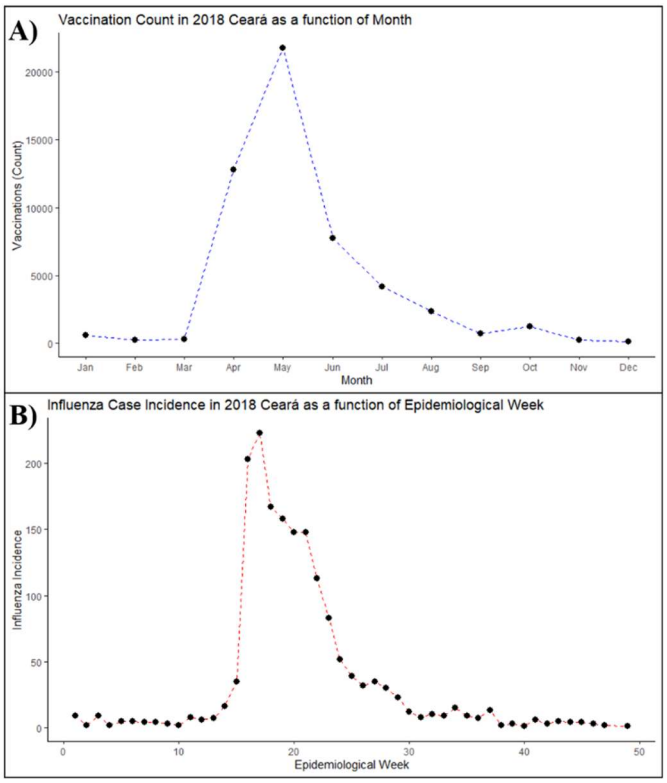

Figure 2. *2018 Vaccination Counts and Influenza Incidence in Ceará*
(A) Depicts vaccination count as a function of month in 2018 Ceará. **(B)** Depicts influenza incidence as a function of week in 2018 Ceará.

Although a meticulous task, constructing an effective and timely influenza vaccination schedule to improve IIV coverage in northern states such as Ceará—and by extension, influenza's associated adverse birth outcomes—is pertinent for the future of maternal and child healthcare quality in the South American country. Thus, to mitigate the racial health disparities experienced by minorities, properly timed influenza vaccination schedules and widespread participation of pregnant women in influenza vaccination campaigns throughout the country must be achieved.

The current state of research and collection of generated solutions pertaining to Brazil's insufficient national vaccination campaign possess several shortcomings, including the lack of quantitative analysis pertaining to the correlational and causal relationships of IIV racial health disparities during pregnancy and adverse birth outcomes. Additionally, there is an absence of spread modeling performed for influenza in Brazil, as well as the Americas in general, when compared to other viral diseases such as Zika and SARS-CoV-2.[14,15] As a result, timely IIV schedules in these continents do not exist. To address these shortcomings, two goals were established for this project: **1)** to quantify the effects of racial disparities in IIV access among African-American pregnant woman on adverse birth outcomes in Brazil and Virginia ***(Aim 1)***, and **2)** to construct a vaccination schedule that can predict the optimal time at which patients in Ceará should receive IIVs. ***(Aim 2)***.

Significance & Innovation

The exposure and dissemination of racial health disparities among IIV coverage during pregnancy and their causalities with birth outcomes may lead to a decreased quantity of adverse birth outcomes experienced by minority populations through increasing the awareness of both patients and healthcare providers in these locales. The quantitative research may also contribute to resolving the current state of racial health disparities in Brazil and specifically the state of Ceará, as it focuses on the harmful disparities faced by the minority pregnant population in this diverse locale. Constructing a computational model that can predict the optimal time at which pregnant women should be administered IIVs may aid in increasing IIV uptake for the minority pregnant populations of Brazil. Such an increase in IIV coverage among the pregnant population may also help minimize the incidence of influenza-related prenatal and maternal morbidities previously outlined in this section. Additionally, the analysis and modeling conducted in this project may be further expanded upon to address not only other racial health disparities, such as those characterizing palliative care, pain management, and cardiovascular disease death rates, but also additional pathogenic and viral infections that pregnant women must be protected against, including but not limited to Hepatitis E, pertussis, and tetanus.[1,2,16,17]

Overall, this design project aims to contribute to current research focused on decreasing incidence and prevalence of adverse birth outcomes related to influenza infection during pregnancy. In doing so, a schedule predicting the time at which patients should receive IIVs in Ceará will be constructed, and the effects of racial health disparities in IIV coverage among pregnant women on the quantity of adverse birth outcomes in Ceará will be elucidated.

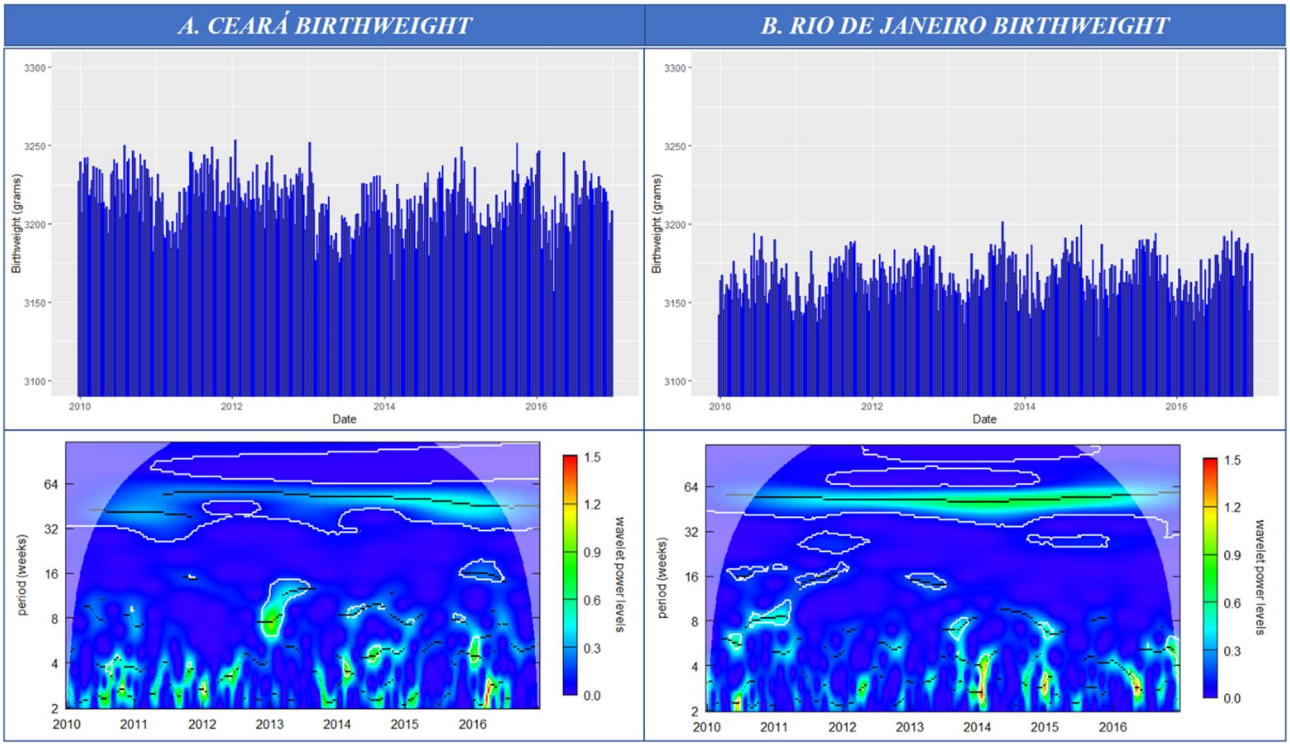

Figure 3. *Birth Weight Outcomes in Brazil from 2010 to 2016*
(A) Weekly birth weight outcomes as a function of time from 2010 to 2016 in the northern Brazilian state of Ceará (top row), and the wavelet analysis conducted on this data (bottom row). **(B)** Weekly birth weight outcomes as a function of time from 2010 to 2016 in the southern Brazilian state of Rio de Janeiro (top row), and the wavelet analysis conducted on this data (bottom row).

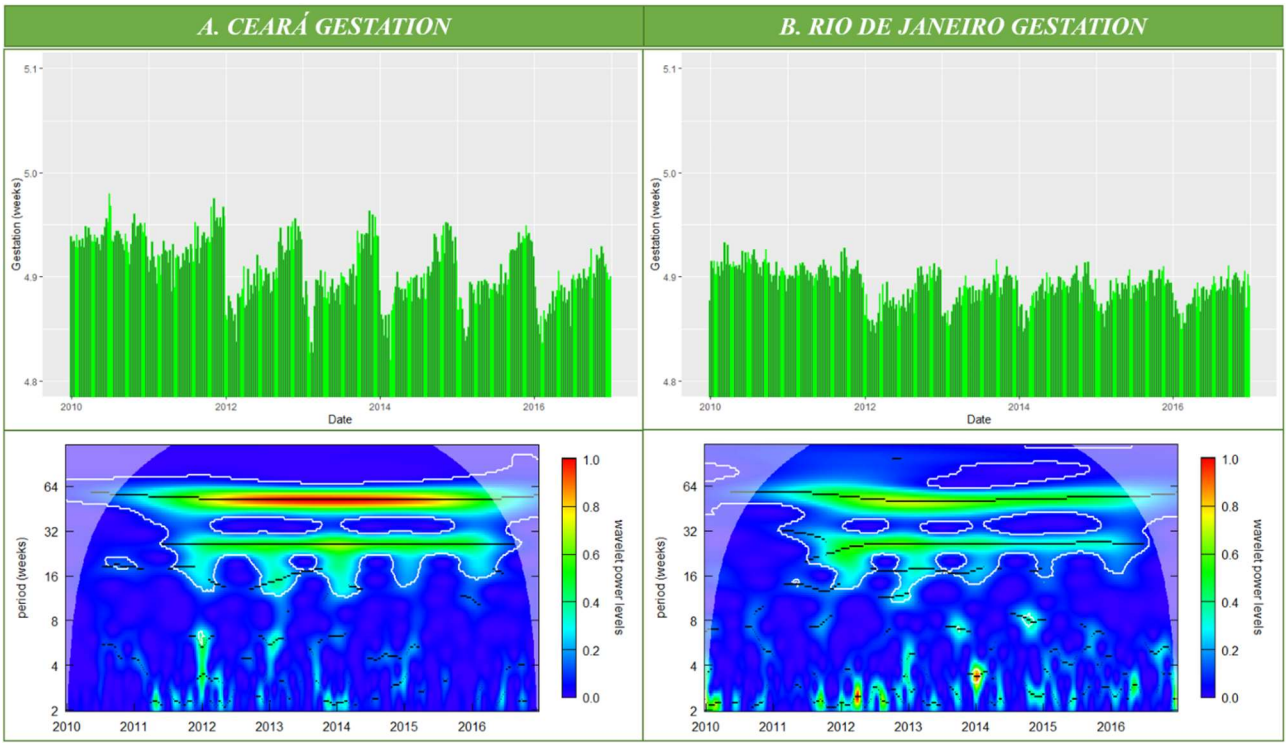

Figure 4. *Gestational Period Outcomes in Brazil from 2010 to 2016*
(A) Weekly gestational period outcomes as a function of time from 2010 to 2016 in the northern Brazilian state of Ceará (top row), and the wavelet analysis conducted on this data (bottom row). **(B)** Weekly gestational period outcomes as a function of time from 2010 to 2016 in the southern Brazilian state of Rio de Janeiro (top row), and the wavelet analysis conducted on this data (bottom row).

Results

Analysis of 2010-2016 Birth Outcomes in Brazil

The contents of this section showcase the results of a quantitative analysis of Brazil's weekly birth weight and gestational period outcomes from 2010 to 2016 through use of the Brazilian DataSUS population health database. As explained in the **Materials and Methods** section later in this report, 7-day rolling averages of birth weights and gestational periods in each state of Brazil were plotted as a function of time (2010-2016). Wavelet decomposition analysis was then conducted on these rolling averages to determine if any periodicity was present with respect to the incidence and prevalence of these birth outcomes.

Birth Weight Outcomes in Brazil (2010-2016)

As can be qualitatively and quantitatively depicted in **Figure 3**, birth weight outcomes did not reveal any distinct periodicities in both the northern and southern states of Brazil. However, interesting trends that were quantitively observed from the birth weight analysis included northern states possessing earlier peaks relative to those of southern states each year. Additionally, the magnitudes of these peaks in birth weight outcomes in the northern states were higher when compared to the southern states of Brazil. Furthermore, qualitatively, northern states possessed greater magnitudes of weekly birth weights across the board relative to the southern states.

Gestational Period Outcomes in Brazil (2010-2016)

In contrast to the relatively similar periodicities of birth weight outcomes between the northern states and southern states of Brazil, stark differences were found in the periodicities of weekly gestational period outcomes in the northern states relative to the southern states. Quantitatively depicted in the bottom row of **Figure 4**, the wavelet decomposition analysis resulted in near-maximum power levels at a periodicity of approximately 50-60 weeks (annually) for the weekly gestational period outcomes of Ceará (northern state; **Figure 4A**). On the other hand, the wavelet analysis conducted on weekly gestational period outcomes of Rio de Janeiro (southern state) did not exhibit high power levels in its findings (**Figure 4B**). This trend was consistent across the board when comparing the periodicities of weekly gestational period outcomes in northern Brazilian states and southern Brazilian states. As contextualized in the **Discussion** section later in this report, these findings suggest that influenza's seasonal incidence and lack of equal vaccination coverage may be the cause of these periodic incidences of poorer gestational trends in the northern states relative to the southern states.

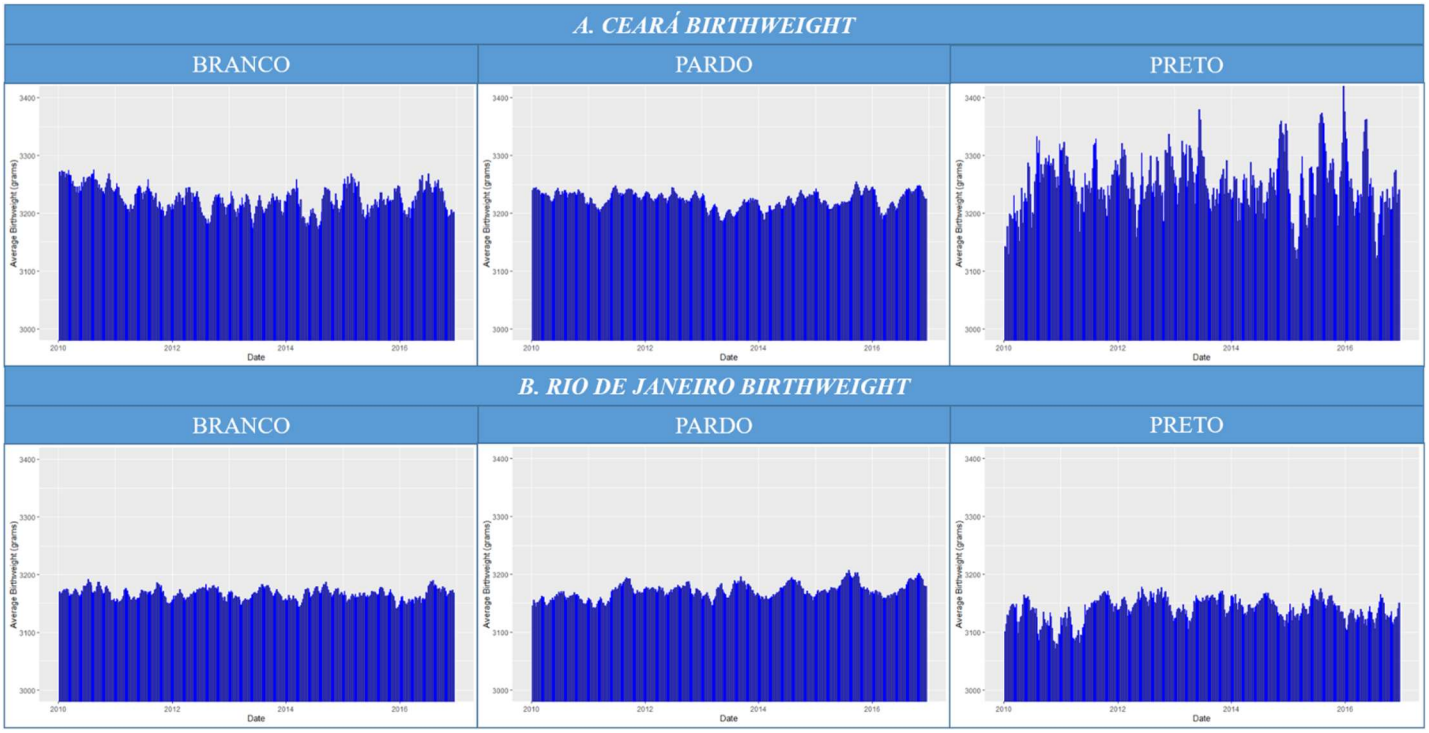

Figure 5. *Racial Disparities in Brazilian Birth Weight Outcomes for Ceará and Rio de Janeiro from 2010 to 2016.*
(A) Weekly birth weight outcomes of the *branco* ("white"; left), *pardo* ("mixed"; middle) and *preto* ("black"; right) racial classes in Ceará, Brazil (northern state) from 2010 to 2016. **(B)** Weekly birth weight outcomes of the *branco* ("white"; left), *pardo* ("mixed"; middle) and *preto* ("black"; right) racial classes in Rio de Janeiro, Brazil (southern state) from 2010 to 2016.

Racial Disparities in Birth Weight Outcomes

As can be observed qualitatively in **Figure 5A**, the *preto* ("black") racial group in Ceará (northern state) possesses much more distinct fluctuations in birth weight outcomes relative to those of the *branco* ("white") and *pardo* ("mixed") racial groups. In contrast, the weekly birth weights of the *branco* and *pardo* classes of Ceará exhibit less volatile and more mean-reverting fluctuations in birth weight outcomes. However, as can be seen qualitatively in **Figure 5B**, there were not as many distinct differences in the fluctuations of birth weight outcomes in Rio de Janeiro among the three racial categories. Across all three racial classes, fluctuations were non-volatile and quickly mean-revert. However, slightly more volatility was still observed among the *preto* birth outcomes in Rio de Janeiro relative to the birth outcomes of the *branco* and *pardo* racial categories, especially around the year of 2011.

Racial Disparities in Gestational Period Outcomes

Similar to the racial health disparities observed in birth weight outcomes, the *preto* racial group in Ceará possessed much more distinct fluctuations in gestational period outcomes relative to those of the *branco* and *pardo* racial groups. This can be qualitatively observed in **Figure 6A**. Meanwhile, the gestational period outcomes of the *branco* and *pardo* racial groups are much more mean-reverting and less volatile, which is similar to what was observed in the birth weight outcomes for these groups in Ceará. With regard to Rio de Janeiro, the qualitative findings exhibited rapid mean-reversions and non-volatility in gestational period outcomes across all three racial groups (**Figure 6B**). Moreover, these findings were similar to what was observed in the birth weight outcome fluctuations for all three racial classes in Rio de Janeiro, as qualitatively, the *preto* racial group still exhibited slightly more volatility than the *branco* and *pardo* categories with respect to gestational period outcomes.

Modeling Influenza Incidence and Prevalence in Ceará

The contents of this section first showcase the results of performing population-based SIR compartment modeling with respect to the current spatiotemporal spread of influenza in Ceará using 2018 vaccination documentation data. Also included in this section are the results of an experimental vaccination schedule inputted into this baseline SIR model, in which the national vaccination campaign is conducted 1 month earlier. The intricacies and processes behind the SIR compartment modeling methodology are explained in the **Materials and Methods** section later in this report.

Figure 6. *Racial Disparities in Brazilian Gestational Period Outcomes for Ceará and Rio de Janeiro from 2010 to 2016.*
(A) Weekly gestational period outcomes of the *branco* ("white"; left), *pardo* ("mixed"; middle) and *preto* ("black"; right) racial classes in Ceará, Brazil (northern state) from 2010 to 2016. **(B)** Weekly gestational period outcomes of the *branco* ("white"; left), *pardo* ("mixed"; middle) and *preto* ("black"; right) racial classes in Rio de Janeiro, Brazil (southern state) from 2010 to 2016.

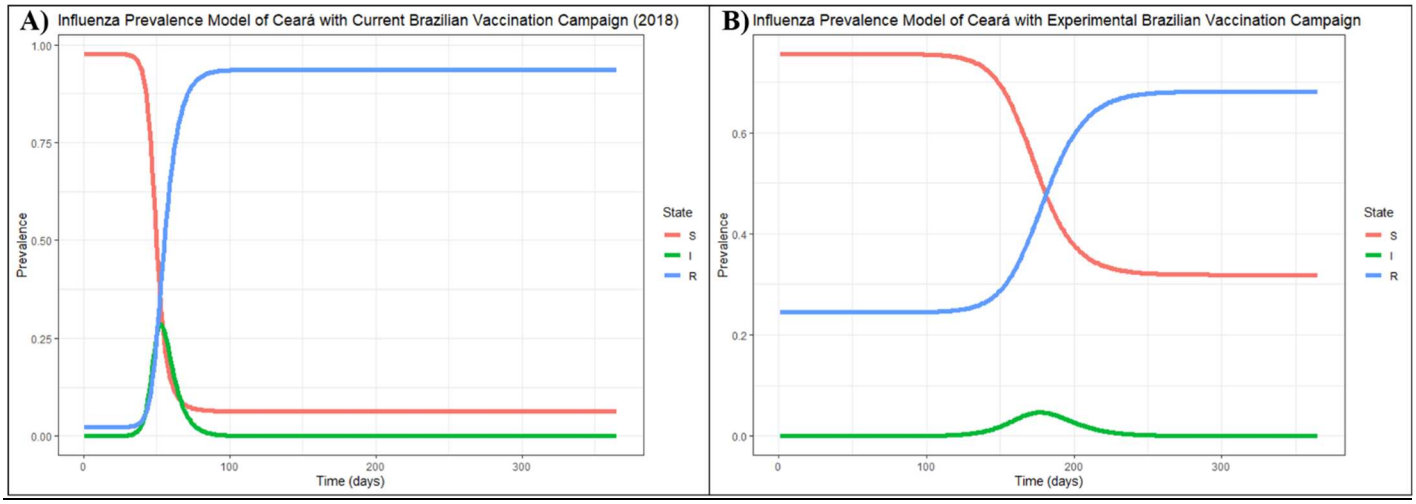

Figure 7. *SIR Models of Current and Experimental Influenza Spread in Ceará*
(A) Depiction of the SIR model reflecting the current spread of influenza in Ceará using data obtained from 2018 vaccination records. **(B)** Depiction of the SIR model reflecting the spread of influenza in Ceará using an experimental vaccination schedule in which the national vaccination campaign starts 1 month earlier. Both sections (**A** and **B**) track the individuals comprising the *S* (Susceptible; red), *I* (Infected; green), and *R* (Recovered; blue) compartments of the SIR model as a function of time. Furthermore, the prevalence is obtained by dividing the quantity of individuals in each compartment at any given time by the total population of Ceará (8,843,000).

Baseline Influenza Spread Model of Ceará

Figure 7A depicts the SIR model capturing the current spread of influenza in the state of Ceará. In other words, this showcases the SIR model utilizing 2018 vaccination data and that year's national vaccination campaign strategy. The model found that the peak of 2,516,746 individuals infected with influenza occurs 53 days after the first person is infected in Ceará. This corresponds to a prevalence of 28.36% when influenza is at its peak in the semiarid state.

Experimental Vaccination Schedule of Ceará

Figure 7B depicts the SIR model capturing the theoretical spread of influenza in the state of Ceará after accounting for an experimental vaccination schedule in which Brazil's national vaccination campaign begins approximately 1 month earlier. This model found that the peak of 412,803 individuals infected with influenza occurs 177 days after the first person is infected in Ceará. This corresponds to a prevalence of 4.66% when influenza is at its peak.

When comparing the experimental vaccination schedule SIR model with the baseline influenza spread SIR model, the peak of influenza prevalence occurs 124 days later in the experimental model compared to the baseline model. Furthermore, the peak's magnitude is decreased by 2,103,942 individuals, or by 23.7% of Ceará's total population, from the baseline influenza spread model to the model accounting for the experimental vaccination schedule. Overall, this results in a -83.60% change in the total magnitude of individuals infected by influenza in Ceará from the baseline spread model—reflecting Brazil's current vaccination schedule—to the experimental spread model—reflecting a theoretical vaccination schedule in which the National Vaccination Campaign is conducted 1 month earlier than it currently is each year. The experimental spread model also results in a +233.96% change in when the peak influenza case count occurs in the year relative to the baseline spread model.

Qualitative Study Outcomes

The qualitative portion of this project is pending results that will be compiled after IRB approval has been achieved. As of May 1st, 2021, the IRB application for this portion of the project is in its final stages of review. Once this approval is obtained, participant recruitment may begin. Moreover, once 30 people who fit the study's criteria—being older than 18, Black or African-American, and pregnant or pregnant within the past 3 years—have consented to participation in the team's qualitative study, the team can then schedule and conduct surveys and interviews with each individual participant. Each survey and interview session will be audio-recorded and transcribed using the auto-transcription feature in Cisco WebEx. The transcriptions will be analyzed for results corresponding to the most highly cited reasonings, motivations, and opinions surrounding influenza vaccination during pregnancy. These results will be acquired through analysis of the interview and survey responses using Health Belief Model coding tactics. The Health Belief Model is a sociocultural and psychological health belief evaluation model that strives to explain and predict health related behaviors and choices related to health services.[18] This model allows evaluation of

the qualitative cohort's stance on susceptibility, severity, benefits, barriers, and uptake relating to influenza vaccination during pregnancy. The statements related to these categories will be identified, grouped, and analyzed according to significance and prevalence amongst all study participants. The impending results may demonstrate novel findings and insights regarding the Black pregnant population and IIV uptake. With these findings, qualitative underpinnings behind decreased vaccination coverage among minority pregnant populations can then be contextualized at both the individual and societal levels.

Discussion

Gestational Period and Birth Weight Outcome Analysis

Interpretation of Results

When analyzing the birth weight and gestational period outcomes of Brazilian states, the team observed distinct indications of seasonal periodicities. With specific regard to the gestational period outcomes, wavelet analyses bolstered support of these qualitative fluctuations with high power values for the northern states relative to the southern states of Brazil. Most strikingly, longer gestational periods were observed later in the year with a periodicity of approximately 50-60 weeks in Ceará. Since Ceará is a relatively less wealthy state and possesses higher proportions of minorities compared to Rio de Janeiro, the distinct fluctuations in gestational period outcomes (**Figure 4**) suggest that these outcomes are seasonal; specifically, the suggested seasonality is that shorter gestational periods are present in the earlier months of the calendar year and longer gestational periods are present in the latter months of the calendar year. Furthermore, when considering that influenza infection begins in northern states of Brazil before transitioning to southern states, these findings support previous research suggesting that northern states possess lower overall IIV coverage relative to southern states. Moreover, the findings indicate that influenza infection during pregnancy is associated with a higher quantity of adverse birth outcomes such as preterm birth, which is characterized by smaller gestational periods. Thus, effective administration of IIVs to the pregnant population is an urgent necessity to mitigate these adverse birth outcomes.

After making this analysis more granular by breaking down the population of each state into the *branco* ("white"), *pardo* ("mixed"), and *preto* ("black") racial groups, it was found that the *preto* racial category experienced more distinct fluctuations when compared to the *branco* and *pardo* racial categories with respect to both birth weight and gestation outcomes in both the northern states and the southern states (**Figure 5** and **Figure 6**). However, the fluctuations were far more pronounced in the northern states for the *preto* class relative to the southern states. Overall, this suggests two overarching things regarding racial health disparities in Brazil. First, the findings indicate that racial health disparities are associated with these adverse birth outcomes, and when accounting for influenza's seasonal nature, that these disparities may be the result of the substantial lack of IIV coverage among pregnant minorities (*preto*) relative to pregnant patients belonging to majority groups (*pardo* and *branco*). Secondly, the findings suggest that the minorities in the northern states, which are generally less wealthy and underdeveloped, are affected more by these adverse birth outcomes and racial disparities in IIV coverage relative to minorities in the southern states of Brazil.

Finally, higher volatilities of birth weight and gestational period found in the *preto* racial category could possibly be attributed to the smaller amount of available data collected on this group, which in of itself demonstrates a racial health disparity. The high volatility and fluctuation of gestational period and birth weight may also indicate that women in the *preto* category are being impacted by other factors in society that lead them to experience wider ranges of birth outcomes. In accordance with past research, some of these outside factors include racial health disparities in IIV coverage during pregnancy, since the fluctuations coincide during peak influenza seasons in these locales. However, other extraneous variables include lower socioeconomic status and holding resistant attitudes and beliefs towards the country's healthcare system.

Limitations

There are several limitations associated with the gestational period and birth weight outcome analysis. Primarily, the analysis was performed on data obtained from 2010 to 2016, and this data may not be representative of current birth weight and gestation outcomes. Furthermore, the DataSUS population health database suffers from a general lack of documentation with respect to these outcomes, and if other outcomes exist that were not documented in the database, the analysis might have yielded different results. Moreover, with specific regard to the analysis of the *preto* racial category with respect to gestation and birth weight outcomes, the distinct fluctuations observed in this group may be indicative of higher noise due to a disproportionate lack of documented incidences among *pretos* relative to *brancos* and *pardos*. Finally, the most pronounced limitation in this analysis concerns itself with the relationship to influenza infection during pregnancy. After all, it is impossible to discern whether these fluctuations are

due to influenza infection during pregnancy or other confounding variables including SES, standard of living, and likelihood of consulting with a healthcare provider.

Future Avenues

In order to establish a causality regarding influenza infection during pregnancy and adverse birth outcomes, a more granular analysis is needed at the individual level. However, the team was not granted IRB approval for such a quantitative analysis in time for the results of this study. Therefore, analyzing individual cases of influenza during pregnancy and determining whether a higher quantity of adverse birth outcomes result from these infections is prudent in order to further contribute to research regarding racial health disparities. Furthermore, population-based birth outcome analysis broken down by racial categories should be extended not only to other locales such as the United States, but also other viral diseases that cause adverse birth outcomes if contracted during pregnancy.

Specifically, analyzing disparities surrounding COVID-19 vaccination uptake during pregnancy would be the intuitive next step relevant to current times. There has already been indications that COVID-19 vaccine hesitancy is disproportionately impacting minority groups.[19] Therefore, it can be expected that pregnant women may have the same hesitancy towards COVID-19 vaccination uptake as IIV uptake unless relevant research is conducted that supports its use for the pregnant population. If our methods were used to elucidate the effects of COVID-19 infection on birth outcomes and used to create COVID-19 seasonal spread models, then pregnant women may be further encouraged to get their vaccinations. Similarly, further research into racial health disparities associated with other viral infections and their vaccinations during pregnancy, such as Hepatitis E, Pertussis, and Tetanus, would be beneficial to society as well. Examining the disparities surrounding health education, vaccination, and accessibility for these diseases could upregulate the number of pregnant women and infants that are protected from these debilitating health outcomes.

SIR Modeling of Influenza Spread in Ceará

Interpretation of Results

The decrease in influenza infection peak (2,516,746 to 412,803 individuals; -83.60% change), as well as increase in the number of days where the peak is in the year (53 days to 177 days; 233.96% change), indicates that starting the vaccination schedule 1 month earlier in Ceará would indeed be effective in mitigating the spatiotemporal spread of influenza. This may pose several epidemiological benefits to not only the population of the state overall, but also the racial health disparities pertaining to influenza that permeate the state. Furthermore, the quantity of adverse birth outcomes associated with influenza in Ceará may in turn be mitigated due to moving the start date of the vaccination schedule 1 month earlier.

Limitations

The primary limitation affecting the interpretation of the computational modeling results is the use of an SIR model. As explained in the **Materials and Methods** section below, SIR models are population-based, which results in an oversimplification of disease spread. In other words, SIR models do not consider individual contact mechanisms, age differences of the population, re-infection rates of the disease, and transportations networks. As a result, the intricacies behind the spread of infectious diseases in the real world are far too complex to be comprehensively reflected in an SIR model. However, the SIR model was utilized in this project due to the lack of granular, quantitative data regarding influenza infection in Ceará.

Nevertheless, the method utilized to validate the experimental IIV schedule with respect to effectiveness and timeliness also possessed inherent limitations. Firstly, due to the lack of empirical influenza spread models present in the infectious disease field, the baseline SIR model reflecting the current spread of influenza was one that the team constructed. Thus, validating the experimental IIV schedule through inputting it into the baseline model may simply propagate the error that the baseline model inherently possesses. As a result, the findings of the modeling portion of this project may be inaccurate and non-generalizable to the entire state of Ceará.

Future Avenues

Primary future avenues of research pertaining to spatiotemporal modeling of seasonal influenza include utilizing comprehensive and complex modeling methods. In 2017, the University of Virginia Biocomplexity Institute leveraged hybrid agent-based modeling techniques to capture the spread of Zika virus in the United States.[14] Such modeling tactics serve as a prudent method of comprehensively reflecting person-to-person transmission mechanisms, social networks, and mixing patterns to better capture accurate infectious disease dynamics.[20] Consequently, hybrid agent-based modeling may be more accurate when modeling the spatiotemporal spread of influenza in Ceará. Furthermore, future modeling approaches should use more granular data, such as influenza infection incidence at the individual level and the specific characteristics of the individual contracting or not

contracting the infection, to more accurately capture influenza spread. Finally, these modeling approaches should be extended to other infectious diseases, as well as other populations to determine whether more effective vaccination schedules are necessary. For example, SARS-CoV-2 viral spread models may use these methods to account for the two-dose mRNA vaccines currently being implemented. Furthermore, if the SARS-CoV-2 virus becomes seasonal in its dynamics, modeling techniques would help better predict the optimal time at which vaccination campaigns should begin each year.

Impending Qualitative Analysis

Current Interpretation of Preliminary Results

As previously stated, the outcomes from the Qualitative portion of the project will be added after IRB approval has been obtained for the team to begin conducting surveys and interviews. Analysis of these qualitative findings may demonstrate new insights behind the relationships of Black pregnant women and their healthcare providers, and the perceived importance of an IIV during pregnancy.

Limitations

Although the qualitative data collection process has not begun, the team has identified several future limitations of the methodology once it is implemented. First, while survey and interview questions were constructed by the team in an effort to be trauma-informed, ethically conscious, and non-leading, there may still be some unconscious bias implanted by the team members conducting the surveys and interviews towards participants. Additionally, although there have been several repeated iterations of question generation and approval after mock interviews, future participants may feel as if the team is actively looking for a particular type of answer. This phenomenon is called survey/response bias, and it is impossible to eliminate in a qualitative study. Moreover, in the context of these qualitative methods, survey bias may lead participants to hold mistrust, or resentment, to the survey and interview conductors since this study will be associated with the UVA Health System. In combination with the longstanding history of clinical atrocities and unethical investigations disproportionately affecting minority patients in the Americas, this may lead them to provide fewer forthcoming responses.

Additionally, the target sample size of the qualitative methodology is 30 participants from the Blue Ridge health region of Virginia. However, this relatively small sample size may not be representative of the entire Black pregnant population in neither the Blue Ridge region nor Virginia overall. Furthermore, since the surveys and interviews will be conducted over a UVA Health IT arranged Cisco WebEx account to maintain HIPAA compliance, subjects who lack the technological equipment necessary to participate in these qualitative studies may indirectly be excluded. Since these excluded subjects would likely belong to low socioeconomic status classes—a population already known to have lower IIV coverage—this may skew impending findings and make them even less generalizable.[21]

Finally, the Health Belief Model does not account for habitual health practices or actions performed to be socially acceptable; it also assumes that individuals have equal access to information on health and disease. However, due to the relative lack of IIV information available to individuals of lower socioeconomic status, the Health Belief Model poses limitations to impending qualitative results due to the team's use of it to code interviews and surveys.

Future Avenues

Implementation of the qualitative methodology will begin in the summer of 2021 after IRB approval is finally obtained. The team is currently in the final iterations of the IRB review process, the culmination of which will allow recruitment to be conducted for surveys and interviews. Findings will potentially impact the Black pregnant population of the Blue Ridge region of Virginia, as this research attempts to elucidate the understanding of IIVs and the motivations behind receiving or not receiving one while being pregnant. The findings of this research may also help healthcare providers, the Black pregnant community, and others involved in the public health field to understand how to encourage vulnerable communities to obtain IIVs. In summary, this research may aid in promoting influenza education and prevention for this vulnerable population in the Blue Ridge region of Virginia and beyond.

Materials and Methods

Birthweight & Gestational Period Methodology

Brazilian datasets containing birth outcome documentation were obtained through the Brazilian DataSUS population health database, as well as existing records obtained from the team's collaborators in Brazil. Furthermore, the team expanded upon existing R code developed by previous work of these aforementioned collaborators conducted in Brazil.[7] Specifically, the code was extended to visualize trends of 7-day rolling average weekly birth weight and gestational period outcomes in all states of Brazil from 2010 to 2016. Wavelet decomposition analysis was also performed to identify potential periodicities in these outcomes at all given times. Wavelet analysis results in power levels for a

possible periodicity at any given time; these power levels are represented by the heat scales in the bottom rows of **Figure 3** and **Figure 4**. Higher magnitudes of wavelet power levels correspond to a higher likelihood of periodicity being present at a specified time (x-axis) for a certain number of weeks (y-axis). In the figures, higher power levels are represented by longer-wavelength colors of the visible light spectrum, while smaller magnitudes of wavelet power levels are represented by shorter-wavelength colors of the visible light spectrum.

Computational Modeling of Influenza Spread

Overview of SIR Model

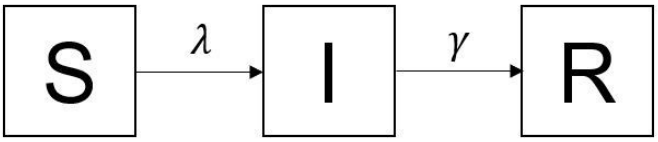

Figure 8. *Depiction of SIR Model Compartments*
Individuals in the population move directionally from the Susceptible (*S*) compartment to the Infected (*I*) compartment to the Recovered (*R*) compartment in an SIR model of an infectious disease. Differential equations govern the rate of directional movement between the Susceptible and Infected compartments (λ, also referred to as β), as well as between the Infected and Recovered compartments (γ).

SIR models form the cornerstone for modeling in the modern-day infectious disease field.[22] As such, it is a prudent technique to leverage when evaluating the spatiotemporal spread of viral diseases such as influenza.

The SIR model is a population-based model that partitions individuals in a certain locale into three different compartments. These compartments, governed by their differential equations, are outlined as follows: 1) Susceptible (S), 2) Infected (I), and 3) Recovered (R). The Susceptible compartment is comprised of individuals in the populations who are susceptible to infection by the disease. The Infected compartment is comprised of individuals in the population who are actively infected with the disease. Finally, the Recovered compartment is comprised of those individuals in the population who have already contracted and recovered from the infection. The movement of individuals between compartments is qualitatively depicted in **Figure 8**.[23]

$$\frac{dS}{dt} = -\beta S\frac{I}{N} \quad [1]$$

$$\frac{dI}{dt} = -\beta S\frac{I}{N} - \gamma I \quad [2]$$

$$\frac{dR}{dt} = \gamma I \quad [3]$$

$$N = S + I + R \quad [4]$$

Assumptions of the SIR model pertaining to the spread of an infectious disease include the population being homogenous, being well-mixed, and having recovered immunity forever.[24] The homogeneous assumption characterizes all individuals in the population as being subject to the same hazards. The well-mixed assumption posits that all individuals in the population possess the same risk of contracting the disease. Finally, the immunity forever assumption states that all individuals in the population who have recovered from the disease—and are therefore placed within the Recovered compartment—are immune to the disease for the remainder of their lives. These assumptions lead to the construction of a set of differential equations that govern unidirectional movement of individuals in the population between the Susceptible, Infected, and Recovered compartments (**Equations 1-4**).[23] In the differential equations, *S*, *I*, and *R* are utilized to represent the number of susceptible, infected, and recovered individuals in each compartment, respectively. *N* represents the total quantity of individuals in the population, and *N* is intuitively the sum of *S*, *I*, and *R* at any given time. β and γ represent the infection rate and recovery rate, respectively. Finally, *t* represents the time (in days) that the model seeks to capture. Together, **Equations 1-4** were utilized in the computational analysis to form the basis of the SIR model.

$$S = (1-p)(N-1)\ at\ t = 0 \quad [5]$$

$$I = 1\ at\ t = 0 \quad [6]$$

$$R = p(N-1)\ at\ t = 0 \quad [7]$$

From there, the initial conditions shown in **Equations 5-7** were utilized to solve the differential equations and obtain equations of *S*, *I*, and *R* representing the number of individuals in each respective compartment at any given time *t* (days). In the initial conditions, *p* represents the proportion of individuals who have already received an IIV, with the assumption that the IIV is perfectly effective in protecting any given individual against influenza.

Baseline SIR Model for Influenza Spread in Ceará

In order to model the current spread of influenza in Ceará, the team first took into consideration the effects of Brazil's current vaccination campaign. As previously mentioned in the **Introduction** section of this report above, Brazil uses an annual 8-10 week vaccination strategy simultaneously across the entirety of the country. Using vaccination incidence records obtained from the team's collaborators in Brazil, it was found that at the start of 2018's national vaccination campaign, 1,246 individuals documented in the state of Ceará had received an IIV (January, February, and March). Through dividing this with a quotient of 52,432—the total quantity of individuals documented to receive an

IIV in 2018 Ceará—a p of 0.0228 was obtained. Furthermore, through an extensive literature review, it was found that a person who has contracted influenza is infectious for 6 days on average, and that an infected individual infects another person every 3 days on average.[25] Taking the inverse of these values, β and γ were found to be 0.33 and 0.167, respectively. Finally, 8,843,000 was utilized as N, as this is the most recent documentation of Ceará's total population by the Brazilian Census.[26]

Experimental IIV Schedule for Ceará

It was hypothesized that a prudent and intuitive method to mitigate the spread of influenza in Ceará is to begin vaccinating individuals in the state 1 month earlier. The reasoning behind this hypothesis is outlined in **Figure 1B**, which shows the peak influenza incidence of 2018 Ceará occurring in May while the vaccination campaign started in April. Consequently, we added the vaccination counts of April to the vaccination count of 1,246 individuals utilized in the baseline model of influenza spread. This yielded a value of 12,814 total individuals that would be vaccinated if the schedule was moved 1 month earlier in its start date. This value was then similarly divided by the total number of individuals documented to receive an IIV in 2018 Ceará—52,432—to obtain an experimental p of 0.2443, which represents the proportion of individuals in Ceará that would be vaccinated if the national vaccination campaign began 1 month earlier. Using this value, the SIR model's differential equations were solved with new initial conditions to obtain the predicted model of influenza spread when the experimental IIV schedule was utilized.

Qualitative Methodology

For the qualitative portion of ***Aim 1***, the team constructed survey and interview questions after multiple iterations of mock interviews and group discussions. These carefully crafted questions were non-leading, ethically conscious, and trauma-informed, which are important characteristics when working with vulnerable patients that may have faced various forms of trauma within the nation's healthcare system. The team also conducted practice interviews with each other to address confirmation bias or unconscious behavior that may encourage participants to answer untruthfully. The survey and interview questions are depicted in **Appendix S1** and **Appendix S2**, respectively.

In order to recruit participants, the team reached out to various support groups, healthcare organizations, and OBGYNs in the Blue Ridge health region of Virginia, and the team also created recruitment flyers for these groups to distribute to patients and post in online information boards. The recruitment flyer is depicted in **Appendix S3**; it is currently pending approval from the IRB. Once said approval is obtained, the flyer will be sent to these organizations for distribution to and recruitment of qualitative study participants.

During the interview process, the team of interviewers will make sure to remain as objective as possible in response to the participants' answers. For instance, if a participant expresses extremely negative sentiment regarding the IIV, the team will not say anything to negate the way the participant feels. This is because the team is not conducting these qualitative methods to debunk IIV myths and folklore, but rather to reveal the current state of understanding and opinions regarding IIVs during pregnancy within this vulnerable population.

The team will utilize audio cloud recording during the interviews, and this will allow automatic speech-to-text transcription. After conducting each interview, the team will cross-check the audio and transcription log to ensure that they match prior to coding each transcribed interview using the Health Belief Model. The team members have been training how to code using this model throughout the entire duration of this project in order to objectively analyze the responses provided by the voluntary participants. A statistical analysis will then be conducted to determine the significance of findings after all interviews and surveys have been collected.

End Matter

Author Contributions and Notes

S. Herron, H. Newland, and K. Sarnaik synthesized the report, conducted quantitative analysis and computational modeling, and constructed qualitative instruments involved in the study. S. Moore oversaw the year-long project and provided iterative feedback. I. Mathieu specifically oversaw the qualitative methodology outlined in this paper. Finally, G. Hanson provided feedback, scheduled weekly team meetings, and aided in the overall production of this project.

The authors declare no conflict of interest.

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Appendix – Qualitative Study Instruments Supplemental Items

S1) Demographic Survey

1. What is your age?
2. If you have a job, what is it?
3. How far did you go in school?
4. Did you have health insurance during your pregnancy?
5. Are you currently pregnant?
    a. If YES: Is/was this your first pregnancy? If not, how many times have you been pregnant? How many children have you given birth to?
    b. If NO: When did you most recently give birth? How many times have you been pregnant? How many children have you given birth to?

S2) In-Depth Interview Questions

1. What does a healthy pregnancy mean to you?
2. What factors do you think lead to a healthy pregnancy?
3. Do you think your current or most recent pregnancy was a healthy one? Why or why not?
4. Do you think vaccination is important in pregnancy? What about a flu shot?
5. If someone recommended a flu shot, who was it? What was/is your relationship with this person? What did you think about that recommendation?
6. Why do healthcare providers recommend flu shots to pregnant women? Is it more important for pregnant women than for other people? (Why (not)?)
7. Why did you decide (not) to get a flu shot during your pregnancy?
8. What concerns do you or people you know have about the flu shot (in general, not just in pregnancy)?
9. What benefits might the flu shot provide for pregnant women and their babies?
10. Do you trust your health care provider in pregnancy? What makes you (not) trust this person? How could they increase your trust?
11. Do you have any other thoughts you'd like to share about the flu shot in pregnancy or health during pregnancy in general?

S3) Recruitment Flyer

PARTICIPATE IN A NEW STUDY

UNIVERSITY OF VIRGINIA HEALTH STUDY

A UVA Health team is looking for interview participants to discuss health disparities faced by Black & African-American pregnant women in the Blue Ridge region of Virginia

Are You..?

- **Currently Pregnant or Have Been Pregnant in the Last 3 Years?**
- **At Least 18 Years Old?**

AND

- **Black or African-American?**

If yes...

Contact Us At:
Email:
Phone:

UVA Health