Distribution Agreement

In presenting this thesis or dissertation as a partial fulfillment of the requirements for an advanced degree from Emory University, I hereby grant to Emory University and its agents the non-exclusive license to archive, make accessible, and display my thesis or dissertation in whole or in part in all forms of media, now or hereafter known, including display on the world wide web. I understand that I may select some access restrictions as part of the online submission of this thesis or dissertation. I retain all ownership rights to the copyright of the thesis or dissertation. I also retain the right to use in future works (such as articles or books) all or part of this thesis or dissertation.

Signature:

_____ _____

Kristin Harrington Date

COVID-19 Mitigation Strategies: Implications for Pandemic Control and the Incidence of Drug-Resistant Tuberculosis

By

Kristin R. V. Harrington

Doctor of Philosophy

Epidemiology

_____

Neel R. Gandhi, MD

Advisor

_____ _____

Jason R. Andrews, MD

Committee Member

Sara C. Auld, MD, MSc

Committee Member

_____ _____

Samuel M. Jenness, PhD

Committee Member

Lance A. Waller, PhD

Committee Member

Accepted:

_____

Kimberly Jacob Arriola, Ph.D., MPH

Dean of the James T. Laney School of Graduate Studies

_____

Date

COVID-19 Mitigation Strategies: Implications for Pandemic Control and the Incidence of Drug-Resistant Tuberculosis

By

Kristin R. V. Harrington

BS, Biochemistry and Global Health, University of Wisconsin-Madison, 2014

Advisor: Neel R. Gandhi, MD

An abstract of

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Epidemiology

2022

Abstract

COVID-19 Mitigation Strategies: Implications for
Pandemic Control and the Incidence
of Drug-Resistant Tuberculosis

By

Kristin Harrington

COVID-19 is a major global health threat with over 440 million cases and 10.6 million deaths to date. Changes in social mixing patterns and shifting resources towards COVID-19 have had negative repercussions in the control of diseases such as tuberculosis (TB), the leading cause of infectious disease mortality in 2019, with 1.4 million deaths worldwide. The impact of efforts to curb the COVID-19 pandemic, and the impact of mitigation strategies on TB control require further study. The overarching goal of this dissertation was to evaluate local transmission dynamics of COVID-19 and the impact of mitigation strategies on both pandemic spread and drug-resistant TB control.

In the first study, we used a network-based model to study the relationship between contact tracing activities and hospital utilization. We found that no isolated or combined contact tracing intervention could prevent excess strain on ICU bed capacity in the state of Georgia. The positive effects of contact tracing were magnified within the period of time shortly after index case diagnosis, and plateaued after approximately 1 week.

In the second study, we utilized individual-level exposure histories collected through case investigation and contact tracing interviews to construct the contact tracing networks of COVID-19 at Emory University during the 2020-2021 school year. We found minimal clustering, a low proportion of asymptomatic cases, and higher secondary attack rates among contacts of symptomatic cases. Our results suggest it was unlikely that asymptomatic cases were missing from the observed network.

In the third study, we described changes in the number, spatial distribution, and neighborhood characteristics of drug-resistant TB cases before and after the COVID-19 national lockdowns in KwaZulu-Natal, South Africa. We observed a 29% reduction in drug-resistant TB cases diagnosed in the province after the lockdowns. Further, we observed that cases diagnosed after the lockdowns reported worse living conditions and fewer household resources.

The findings from this dissertation contribute to our understanding of the impact of contact tracing optimization on hospitalization and ICU utilization at a community level, important drivers of transmission in the setting of a university community, and the impact of COVID-19 mitigation strategies on drug-resistant TB control.

COVID-19 Mitigation Strategies: Implications for Pandemic Control and the Incidence of Drug-Resistant Tuberculosis

By

Kristin R. V. Harrington

BS, Biochemistry and Global Health, University of Wisconsin-Madison, 2014

Advisor: Neel R. Gandhi, MD

A dissertation submitted to the Faculty of the

James T. Laney School of Graduate Studies of Emory University

in partial fulfillment of the requirements for the degree of

Doctor of Philosophy

in Epidemiology

2022

ACKNOWLEDGEMENTS

There are so many individuals who have made it possible for me to reach this point in my life. I would like to acknowledge my dissertation committee for being with me every step of the way through this process. To Jason, whose tuberculosis modeling work inspired me to focus on this in my research; to Sam, whose immense knowledge in modeling and computational methods pushed me to become a stronger programmer than I ever would have imagined; to Lance, whose joy and excitement in research inspired me to pursue the questions I found fascinating and who always makes time for students, to Sara, who has always been someone I look up when it comes to rigor in research and balancing priorities, and who has always been there for me when things were so difficult. And most importantly to Neel, who has provided me with support, motivation, encouragement, and constructive criticism throughout these several years. You have made me a much better writer, scientist, and question asker, and you have never let me forget to also prioritize my personal wellbeing throughout it all. I appreciate you all so much, and it has been such an amazing experience to be able to work with you all. I will cherish all of the lessons learned from all of you throughout my career. Thank you for being such excellent mentors and for making my graduate school experience so impactful.

I would like to acknowledge my friends and for all of their support for me throughout all of these years. To my friends in graduate school who commiserated with me over homework assignments, writing, or the publication process; and to my friends outside of academia who still were there to provide empathy and support although they may not have been able to fully understand the details. Thank you for being there for me and for always listening.

To my family, who has encouraged me to pursue higher education (perhaps not *this* much) since I was a small child. To my parents, for filling the house with books of all kinds and for always being so curious in your work and never forgetting to question why things are the way they are. Thank you for always supporting my academic endeavors.

To my classmates in the Epidemiology PhD program as well as those in the MD/PhD program, you all are incredibly inspiring and motivate me to be a better researcher. It has been a such a surreal experience having the opportunity to learn from you as we have navigated coursework, exams, milestones, and research projects together. You are all so incredibly smart and I am lucky to be able to train alongside you all.

Table of Contents

List of Tables

List of Figures

Chapter 1: Introduction

1.1 Background and Significance – COVID-19

1.1.1 Coronavirus disease 2019 pandemic

COVID-19 natural history and transmission

Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), is a major global health threat with over 299 million cases and 5.4 million deaths to date.[1] In late 2019, several cases of an acute respiratory illness with unknown etiology were reported in Wuhan, Hubei province, China.[2,3] Similar disease presentations were subsequently identified in several other countries, and the causative agent, SARS-CoV-2, was identified in Wuhan in January 2020.[4] The emergence of COVID-19 in China coincided with the Chinese Lunar New Year, for which millions of individuals make almost 3 billion trips collectively to celebrate.[5] To limit the amount of spread throughout the country and the rest of Asia, the Chinese government halted all province-wide public transportation, and train and plane travel to and from Wuhan prior to the start of the holiday.[6] Following this, several other countries restricted travel to and from China,[7] and after 200 deaths had been confirmed globally by the end of January 2020, the World Health Organization (WHO) declared COVID-19 a Public Health Emergency of International Concern.[8] Of note, in February 2020, more than half of all global COVID-19 cases outside of China were on the Diamond Princess cruise ship, carrying over 3,700 passengers of which 712 cases were identified.[9] It was later discovered that this outbreak occurred due to a single introduction of the virus, that is, one infected person.[10] After quickly spreading to over 100 countries outside of China, COVID-19 was deemed a pandemic by the WHO in March 2020.[11,12]

Transmission of COVID-19 was known to occur between close contacts, but whether or not it was transmitted via the respiratory route, and if it was able to spread through aerosolized

droplets, was a point of contention for many months after the identification of SARS-CoV-2.[13–15] Understanding the specific route of transmission has implications for recommendations to reduce disease spread, including communication around mask wearing and the potential exposure range around an infected individual, which informed social distancing measures.[16,17] Through the combination of observational,[18–20] experimental,[21–23] and modeling studies,[24,25] there is now ample evidence to support transmission through the respiratory route via coughing, talking, or singing, and that airborne transmission through aerosolized droplets is possible.[26,27] Public health interventions such as mask wearing, social distancing measures, travel restrictions, national lockdowns, and school closures helped to limit the spread of COVID-19;[28–31] however, setting-specific differences in public health communication approaches combined with the evolving nature of this pandemic and conflicting political messaging have resulted in the varied timing of additional individual control measures.[32–36] Unique transmission characteristics of COVID-19 include the infectiousness of individuals 2-3 days prior to the onset of symptoms,[37] and the large proportion of infected individuals that remain asymptomatic;[38,39] both of which have challenged overall containment strategies.[40] Asymptomatic individuals are estimated to account for approximately 45% of all infections, with the potential for an extended timeframe (> 14 days) in which they are able to transmit to others.[41]

The average incubation period (time from initial exposure to symptoms) for COVID-19 is approximately 4-5 days, with almost all individuals who will go on to develop symptoms do so within 11.5 days of infection.[42–44] There is considerable diversity in the severity and clinical manifestations of disease,[45] with all age groups affected (albeit at differential rates), almost 20% of individuals experiencing severe to critical manifestations, and a preponderance (60-90%) of hospitalized individuals with concurrent comorbidities.[46–48] Common presenting symptoms include fever, cough, shortness of breath, gastrointestinal symptoms, and loss of taste and smell.[49–51]

Hospitalization courses are typically for weeks or longer (in contrast to days for many other viral syndromes), and cases requiring mechanical ventilation are not uncommon which have put a significant strain on the healthcare system.[52–55]

COVID-19 epidemiology in the United States

The first case of COVID-19 was confirmed in the U.S. on January 21st, 2020, and as of March 10th, 2022, there have been over 79 million confirmed cases and over 965,000 deaths.[1,56] Although the first cases were identified on the West coast, by mid-March of 2020 50 states and 4 territories had reported cases.[57] Genomic sequencing analyses demonstrated that trans-continental spread occurred early on and rapidly due to domestic travel.[58] Epidemiologic studies assessing the causes of seeded community transmission further implicated travel, limited testing capacity, and transmission by asymptomatic and pre-symptomatic persons in addition to large group gatherings (e.g., Mardi Gras, conferences, funerals) and introductions into vulnerable settings such as long-term care facilities that resulted in amplified transmission.[59]

In the first several months of the pandemic, greater incidence of confirmed COVID-19 was associated with metropolitan, populated areas with high proportions of minorities, and in counties closest to core airports.[56] Furthermore, there were dynamic patterns between socioeconomic status (SES) and COVID-19 incidence and mortality. Greater incidence was initially associated with higher SES early on in the pandemic, but this association later shifted to lower SES likely due to the ability of higher SES groups to shelter-in-place while lower SES individuals were more often essential workers with inadequate protections.[60]

Widespread diagnostic testing for COVID-19, which is essential for accurately tracking disease burden and identifying asymptomatic cases,[61] was not prioritized in the U.S. as compared to other countries,[62,63] which resulted in major underestimates in the total number of cases. Bias

analyses to account for limited testing and imperfect test accuracy estimated that the U.S. was underestimating cases in the first wave of the pandemic, with true numbers of infections likely 3 to 20 times higher than testing-based reports.[64] Further, limited testing capacity and protocols aimed at older individuals, those with travel history, or those with symptoms, albeit appropriate for identifying cases in high-risk individuals, nevertheless have the potential to severely bias estimates of true, underlying population-level disease burden.[65] These biased estimates had repercussions on our ability to correctly interpret epidemiological trends, which in turn influenced policy decisions.[66] While testing practices were implicated in biased estimates of transmission parameters,[67] the role of testing patterns in the shift in age distribution towards younger individuals observed in the latter half of 2020 was more complex;[68,69] disentangling these trends and others would likely have been more feasible with the early establishment of extensive testing infrastructure. Due to the potential bias in overall disease burden and reporting, it is important that epidemiological studies of COVID-19 take local testing practices and reporting into consideration.

The disordered and heterogenous (sometimes absent) local implementation of mask mandates, business closures, and social distancing orders across the country led to asynchronous reductions in transmission in counties, resulting in immensely complicated and limited options for disease containment as infections continued to be reintroduced into controlled areas by geographically nearby counties with sustained transmission.[70,71] Further, the political polarization of the U.S. carried over into the risk communication and mitigation responses of entire states and counties, which had resultant effects on mobility patterns and engagement in physical distancing.[72] In an analysis of mobility data in the U.S., it showed that these heterogeneous and sporadic state-level responses and mandates resulted in delayed yet significant effects on COVID-19 case reductions.[73] Social distancing policies and shelter-in-place mandates resulted in a 25% and 29% reduction in mobility, respectively, and a 10% reduction in mobility was associated

with a 17.5% decrease in COVID-19 cases after 2 weeks.[73] Statewide orders were also observed to have an effect on COVID-19 mortality; delayed emergency declarations and school closures were associated with higher mortality rates, with, on average, a 5% increase in mortality rates for every one extra day of delay.[74] These between and within state differences in the application and impact of mitigation strategies complicated the interpretation of national and even state-level studies examining methods to slow disease spread.

In comparison to many other high-income countries, the U.S. is a geographically large area with heterogeneous demographics such as age and race distributed across over 3,000 counties. This, coupled with a uniquely fragmented and expensive healthcare system with variable capacities and resources, has resulted in differential burdens placed on hospitals leading to inconsistent access to care and disproportionate impacts and excess deaths among specific communities including the elderly, immigrants, and racial minorities.[75–80]

1.1.2 Mitigation strategies and non-pharmaceutical interventions

The impact of mitigation strategies on transmission

In the context of infectious disease epidemiology, one of the most important metrics to describe transmission is the *basic reproductive number* (R_0), which represents the average number of people one infected person can infect in a completely susceptible population and can also be conceptualized as the approximate 'strength' of an epidemic.[81,82] The overarching goal of any containment strategy for infectious diseases is to achieve and maintain a reproductive number below 1, which would result in the extinguishing of sustained transmission.[83] R_0 was a practical parameter to estimate at the beginning of the COVID-19 pandemic as no one had been exposed to SARS-CoV-2 previously; there were widely varying approximations ranging from 1.4 to 6.5 in China,[84] 3.3 in Italy,[85] and 2.3 on the Diamond Princess cruise ship.[86] As more people

became infected and were no longer completely susceptible, the more practical metric has been the *effective reproductive number* at time *t*, (R_t), which does not assume complete susceptibility in the population, and can help assess the impact of intervention strategies on the control of spread and monitor transmission at a particular point in time and level of population-level infection.[87] This parameter can provide for a quantitative evaluation of interventions, taking into account their timing in an epidemic.[88] A similarly important metric for transmission is the *secondary attack rate*, which is the probability of susceptible persons becoming infected after *effective contact* (i.e., frequency, duration, and type of contact necessary for transmission) with an infected person.[89] This metric requires more specific estimation for reliable estimation, including information on exposure histories and accurate enumeration of close and casual contacts. Among the studies that have estimated the secondary attack rate for COVID-19, probabilities range from 12-53% for household contacts,[90–93] to 35% for individuals attending group events with an infected case.[94]

Mitigation strategies to reduce overall transmission include the implementation of non-pharmaceutical interventions (NPIs), i.e., applied methods to limit the spread of an infectious disease. The utilization of NPIs is distinct from the use of pharmaceuticals (e.g., vaccinations or antiviral drugs), which may not be available at the start of a pandemic. NPIs have been incorporated into pandemic preparedness plans by the WHO since 2005, for which the evidence base draws upon historical experience from the 1918 influenza pandemic.[95] During the 1918 pandemic, many countries across the world adopted measures such as isolating sick individuals, quarantining those who had been in contact with someone ill, closure of schools and businesses, and cancellation of large gatherings which were documented to have an effect in reducing transmission.[95] One study combining archival research and epidemiologic analyses observed that NPIs implemented in the U.S. during the 1918 pandemic had strong associations with lower

mortality rates, especially if these measures were implemented early and were sustained.[96] In addition to these more widespread public health interventions, individual-level measures such as social distancing and mask wearing (in the case of a respiratory pathogen) have been used to minimize effective contact between an infectious and susceptible individual. These alterations in human behavior are typically transient and associated with an individual's perceived personal risk, and helped explain waves in the epidemic curve observed during the 1918 pandemic not entirely explained through viral seasonality or different viral strains.[97]

Observational evidence from the current COVID-19 pandemic similarly shows beneficial impacts of implementing NPIs to reduce spread. Practices such as reducing the delay in isolating infected individuals, travel restrictions, and quarantining exposed persons have documented significant effects on decreasing transmission especially if implemented early on, estimated via a range of transmission parameters including incidence and R_t.[98–100] Modeling studies have been generally useful in assessing the impact of NPIs in various settings during previous pandemics, in addition to evaluating and forecasting the effects of different interventions throughout the current COVID-19 pandemic. For example, one study concluded that travel-related restrictions in the U.S. had little impact after community transmission of SARS-CoV-2 was widespread, while stronger transmission-reduction interventions (i.e., social distancing and shelter-in-place orders) and expanded testing capacity were more optimal to control disease spread.[101] Similarly, national lockdowns in France were estimated to have reduced the transmission rate by 76%.[102] Policy makers have relied on modeling studies to inform their decision-making around the implementation of mitigation strategies; an analysis across six different countries found that policy actions such as business restrictions, although potentially economically costly, had large and consistent beneficial impacts on preventing millions of cases and on achieving better health outcomes.[103] Estimated projections of hospital and critical-care bed utilization have provided

valuable evidence in support of intensive rather than moderate mitigation measures to avoid healthcare systems from being overwhelmed.[104] These cost-benefit analyses as well as insights into the necessary trade-offs required during a pandemic are able to help guide policy makers and public health programs on how to balance and prioritize their efforts.

During the COVID-19 pandemic, mitigation strategies utilized in previous pandemics have been leaned upon and further expanded. These relatively basic public health measures remain impactful, including mask wearing, social distancing, hand hygiene, and limiting large social gatherings.[105] Further measures, including expanded testing availability, case investigations and contact tracing, and widespread coverage of effective vaccines have been implemented during this pandemic and have been crucial to our efforts in disease containment.

Contact tracing history, process, and application

Contact tracing has been a staple control measure for the spread of many infectious diseases, including TB,[106,107] sexually transmitted infections,[108,109] and emerging outbreaks.[110,111] Typically, contact tracing is a paired alongside case investigations, in which probable and confirmed infected persons are interviewed by a public health worker to recall their activities and all of their close contacts during the time they were potentially infectious. After gathering this information, contacts of cases are notified of their potential exposure, educated on their risks and how to monitor themselves, and encouraged to quarantine themselves away from others. Contact tracers have scheduled follow-up communication with all contacts to help monitor their symptoms and provide further support, in addition to potentially shortening the contact's quarantine period depending on their test results and symptoms.[112]

The effectiveness of contact tracing programs is dependent on factors at the pathogen, individual, and population level, including transmissibility, timing of symptoms, and logistical

feasibility.[113,114] Disease-specific nuances such as the duration of infectiousness and the length of the incubation period as well as the practicality of conducting longer interviews with cases to collect more contact information have the potential to significantly impact the benefits of contact tracing.[114] Of note, there is a theoretical threshold for the proportion of contacts that must be traced to keep R_0 below 1, assuming homogenous mixing and all cases display symptoms: $1 - \frac{1}{R_0}$ (interestingly, this is also the equation for the standard herd immunity threshold, often used as a target for immunization coverage for an infectious disease[115]). For an infection with an R_0 of 2, contact tracing would have to reach at least 50% of contacts to be effective. Importantly, if there is a proportion (p) of untraceable contacts, that is, contacts cases would not know to report (as they are unknown to the case due to casual contact, such as is common for airborne diseases), the contact tracing threshold would increase for the remaining known contacts: $\frac{1}{1-p}\left(1 - \frac{1}{R_0}\right)$. So, in the previous case with an R_0 of 2, and if 30% of one's contacts were unknown to them, contact tracing would have to reach over 70% of contacts to be effective. In these cases, other interventions in addition to increasing the contact tracing threshold would be required to control spread. As transmission and logistical feasibility differ across public health programs, a better understanding of these thresholds at a local level can help guide which efforts to prioritize and focus on and where.

Contact tracing is known to be more effective in highly clustered environments and networks and is typically expected to work well in the context of airborne disease spread; however, as airborne transmitted infections have the potential to spread more easily, contact tracing must also be more efficient and more quickly performed. An important consideration for improving the efficiency of contact tracing is the trade-off between increasing the overall number of contacts collected from cases versus a targeted collection of contacts that are most likely to have had an effective exposure to the case. One strategy to improve tracing efficiency used for respiratory

pathogens such as influenza has been to quarantine entire households after the identification of one individual in the home as a contact.[116] The benefits of contact tracing are amplified when asymptomatic infections are possible (as more infections will be 'hidden' from detection), and the importance of contact tracing is positively associated with the proportion of new cases that are asymptomatic.[117] Since these individuals would not display symptoms and may not be detected at all, the contact tracing process can identify these persons through their contact networks to reduce the overall force of infection. Contact tracing is considered essential when every asymptomatic case gives rise to at least one more asymptomatic case ($R_{0_{asymptomatics}} \times p_{asymptomatic\ infection} > 1$).[117] In one modeling study aimed at determining the importance of R_0 and the proportion of asymptomatic transmission on case isolation and contact tracing procedures found that if the proportion of asymptomatic transmission is < $\frac{1}{R_0}$, case isolation would be enough to control the outbreak; however, if the proportion of asymptomatic transmission is > $\frac{1}{R_0}$, contact tracing must be used together with case isolation to control spread.[118]

Like any other intervention strategy, contact tracing has its limitations. If transmission is too widespread in a community and contact tracing cannot identify potentially exposed cases prior to becoming infectious, it becomes insufficient to reduce transmission.[118–120] As previously observed in a modeling analysis of smallpox, there is a 'race to trace' – in the case of smallpox, vaccinating contacts within a reasonable timeframe was the main goal, whereas for COVID-19 quarantining contacts in time is required.[121] Further, if testing infrastructure is not efficient and individuals are not informed of their test results within a reasonable time frame, infected persons unaware of their diagnosis can continue to spread the infection. This also hampers the efficiency of contact tracing, as cases interviewed later on in their disease course may not remember all of their contacts from over a week ago as accurately as their contacts from a few days prior.

On another level, there is the aspect of sharing one's contacts with a public health worker and trust in the national government.[122] Case investigations are typically performed over a public health worker's personal cell phone or a Google line, and many Americans are unwilling to answer phone calls from unknown numbers, let alone provide sensitive personal information to the individual on the other end of the line.[123] To make matters worse, scammers have posed as contact tracers during the COVID-19 pandemic to gather identifiable information from individuals.[124] Privacy concerns and circulating misinformation about COVID-19 have also created additional barriers for contact tracers to overcome in order to simply gain initial communication with cases and their contacts.[125] Further, there has been significantly reduced participation in contact tracing programs by groups disproportionately affected by the pandemic. Reasons for this include the politicization of the pandemic in the U.S., in addition to the earned distrust by minority populations in public health institutions due to historical research practices and discrimination.[126–128]

Although logistically arduous and with its other limitations, contact tracing is still able to provide some of the most valuable data for estimating transmission of an infectious disease, as it can produce individual-level exposure histories to inform both transmission parameters and epidemiologic links within a transmission network.[129,130] Further, although contact tracing steps are implemented at the beginning of an outbreak, contact tracing is also often a critical tool utilized in the final stages of an outbreak to reach elimination, such as was the case for the eradication of smallpox[131,132] and the Ebola outbreak in 2014.[133] Even within the context of an effective vaccine, contact tracing will continue to be an indispensable tool for controlling the pandemic, and its importance will inevitably increase as caseloads are potentially reduced by vaccinations.[134,135] Thus, assessments and modeling studies of contact tracing programs at earlier stages in the

pandemic when caseloads were much lower may serve as useful illustrations for eradication efforts.

Modeling contact tracing effectiveness

Modeling studies, as discussed previously, are useful in planning interventions as well as evaluating the impact of previous and future interventions.[136] Examinations of the impact of contact tracing in various settings have described variable success of programs during the COVID-19 pandemic, due to the various factors described above that can affect contact tracing effectiveness.[137,138] Many early studies to inform contact tracing programs at the beginning of the pandemic utilized models parameterized with data from initial cases in China or simulated populations.[139–142] Although conclusions from these studies are important, they commonly highlight limitations in their data sources and emphasize the need for more data to clarify epidemiologic parameters.[143] While previous studies emphasize minimizing testing delays and optimizing tracing coverage, this guidance is provided at a general rather than a local level.[144] Further, the size and capacity of the local public health workforce should be considered when determining feasible and sustainable programmatic goals.[145] There is scarce literature on targeted modeling studies utilizing local public health data; however, existing studies have been able to provide more specific estimates of the impact of local interventions given not only disease characteristics in the area, but also demographics and the local public health workforce.[146]

The majority of mathematical modeling studies of transmission have also used a compartmental framework, which is a foundational method used to represent the dynamics of infectious diseases. However, due to its underlying assumptions, this framework cannot directly incorporate individual-level variation within a population, such as the range of clinical variability in those infected, and does not feasibly represent distinct steps or potential delays in the contact

tracing process.[147,148] These simple models are excellent for initial hypothesis generation for disease transmission and control, but modeling an intervention such as contact tracing requires an accurate representation of contact network structure that can drive disease transmission.[149] For example, modeling methods capable of distinguishing between high-risk, close contacts and lower-risk, casual or unknown contacts may have more utility when estimating intervention impacts for respiratory infections. Further, the act of quarantine itself is an intrinsically individual-level action, and treatment of this behavior as a group-level process as compartmental models must do relies on a vast number of assumptions, such as a very large and well-mixed population.[150]

Individual-level models, rather than being comprised of different population compartments, include a synthetic simulated population, computational algorithms dictating social contact among this population, and a disease process framework.[151] The utility and validity of advanced modeling techniques such as individual-level models is enhanced by the integration of empiric data specific to the population of interest, and results must always be interpreted within the limits of the data inputs and assumptions made.[152] For these models to have the most useful impact during the COVID-19 pandemic, predictions and evaluations at the local level should be performed using data from the local level, rather than aggregated data from a different setting.[153]

1.1.3. School and university re-opening

Re-opening strategies globally and in the U.S.

Re-opening, or the loosening of stay-at-home orders and other restrictions on businesses and schools during the pandemic, inevitably changes the ways in which individuals interact and connect with others. Studies assessing the rate of interpersonal contact among individuals in the U.S. have shown that there were massive reductions across all ages during the first wave of the

pandemic, with subsequently increasing rates corresponding to the unbalanced lifting of social distancing measures across the country.[154] Contact rates have also been observed to be greater overall among certain demographic groups, including those < 45 years, and Black and Hispanic individuals.[154] In the limited data that exist on contact patterns specifically within the primary school setting, there were large reductions (53-80%) among students, teachers, and staff after re-opening compared to before the pandemic.[155] Modeling studies predicting the impact of re-opening in certain settings expected rebounds in incidence and mortality,[156] which were subsequently observed across the nation.[157] Methods such as local re-openings prior to larger-scale re-openings had more successful outcomes in modeling studies; however, this is under the assumption that areas flattened their epidemic curves before re-opening, which was not the case for the disparate and uncoordinated re-opening plans across the U.S.[158]

There is recent evidence to suggest that school and university re-openings increase COVID-19 spread due to their many communal spaces.[159–162] Safely re-opening universities requires a combination of strategies such as active screening on campus, quarantine protocols, dormitory regulation, mask and personal hygiene requirements, and air ventilation practices.[163] However, assessment of whether or not measures are sufficient to contain COVID-19 spread on campuses is dependent on local transmission. For example, South Korea, where the pandemic has been well-controlled compared to the U.S., did not observe an increase in the number of COVID-19 cases after re-opening schools, and had a successful transition from online to in-person teaching.[164] In modeling studies aimed at providing guidance for universities, it was found that a multi-faceted approach was more effective, with an emphasis on expanding testing infrastructure allowing for wide-spread randomized testing.[165] Specifically, one study modeling university transmission found that under a scenario in which 68% of contacts were traced, 75% of symptomatic individuals would need to be tested, with all positive cases isolated in order to

prevent a second COVID-19 wave after school re-opening; with only 40% of contacts traced, the testing requirement would increase to 87%.[166]

Impact of network characteristics on re-opening strategies

In a network, individuals are represented as 'nodes' and the connections between them are classified as 'edges' in the case of a respiratory pathogen which can be spread in either direction.[167] A node's position in a network can be defined by the number of connections it has to others in the network (degree) and the proportion of paths between other nodes that pass through it (betweenness).[167] Clustering in a network occurs when three or more nodes are connected in a network, and path length represents the number of connections that separate two nodes.[167] In the context of an outbreak, 'flattening the curve,' or mitigating further waves of a pandemic while re-opening can be done through increasing the path length (by increasing the number of connections) from an infected person to others in the network.[168] Social-distancing also helps to increase the average path length of the entire network, so differentiating between highly connected and less connected nodes in a network is crucial to adjust interactions in the context of re-opening.[168] Clustering, or maintaining isolated, small social circles also tends to reduce the spread of a disease within a network.[169]

In contrast to sexually transmitted infections which are spread through sexual networks, respiratory pathogens are able to spread through social and community contact networks. Thus, understanding the structure of an underlying network is crucial to the design of effective social distancing strategies. Attributes of a community, including the groups to which people belong and the number of contacts individuals have, influence the local transmission dynamics and can guide targeted and more effective mitigation strategies.[170] There is evidence to support transmission in a university setting from a transmission network perspective, as shared classrooms, dormitories,

laboratories, and other campus spaces allow for close and casual connections among students, faculty, and staff.[171,172] The specific structure of a network can provide insight into what factors may be important in spreading infection within a community. For example, one study of the transmission networks of COVID-19 at a university found that 91% of gatherings that took place in the context of COVID-19 restrictions were associated with sorority and fraternity events, with these events accounting for 72% of links among all gatherings on campus.[173] In response, the university banned gatherings of ≥ 10 persons, and other Greek-life events were held virtually. High-risk individuals and groups likely differ across different university settings, thus creation of these context-specific contact networks can inform targeted strategies.

Among the several studies that have documented social mixing patterns,[174–177] few have focused on examining patterns in school settings,[178,179] especially at the university-level.[180] There has been work to uncover the 'class size paradox', in which the experienced number of connections between students is typically greater than the average class size, due to the presence of large lecture courses in many students' schedules.[181] Further work has described that both high and low enrollment courses can act as powerful connectors of university students, and that certain types of students (e.g., pre-medical) may act as unique connectors across a network.[182] One recent study was aimed at exploring the characteristics of several university-level networks via transcript data, and how a hybrid mode of instruction (as a result of the COVID-19 pandemic) would impact these characteristics.[183] They found that all university settings were 'small worlds' in that they were highly clustered with short path lengths connecting students.[183] Interestingly, although switching all classes with ≥ 30 students to an online format significantly reduced student connectivity, > 50% of students were still connected in four steps within the network, suggesting that full online instruction was necessary to prevent COVID-19 transmission on campuses.[183] These studies have provided the necessary framework for further transmission

modeling work specific to the university setting. Specifically, as most of these studies have evaluated networks dichotomizing the existence of edges over time (edges are fixed or turnover), further studies utilizing methods that can incorporate a distribution of edge durations can build upon this work.

There are similarly scarce data extending school-level contact networks to infectious disease transmission networks. One study documented close proximity interactions using electronic sensors to construct social networks in a high school to understand network structures relevant for transmission of an influenza-like illness.[184] They found that in their small-world network[185] with short repeated interactions, little variability in the degree, number, and strength of interactions were most relevant for transmission. Further, their work supported previous findings which have found that long, right-tailed distributions in the number of social contacts (i.e., potential super-spreaders, or individuals with significantly more contacts than average) are not typically observed at the local community level, as they are for sexual contact networks.[186] Given the importance of underlying network structures to infectious disease transmission dynamics, it has been noted that further empirical studies are necessary, with a focus on estimating model parameters for more complex interactions; this could be done through collecting data on demographics of contacts in addition to location information of interactions.[187]

With the completion of the 2020-2021 school year, lessons learned should be applied to strategies for re-opening and disease containment, and to do so, a closer look at social network structures, risk factors for COVID-19 infection, and potentially under-surveilled groups will be required.

The impact of COVID-19 mitigation strategies was examined in relation to COVID-19 spread in Aims 1 and 2 of this dissertation, as well as in relation to the spread of another respiratory-transmitted infection, tuberculosis, in Aim 3.

1.2 Background and Significance – Tuberculosis

1.2.1 Global epidemiology of tuberculosis

The global burden, history, and transmission of TB

Tuberculosis (TB), caused by the bacillus *Mycobacterium tuberculosis*, is a major public health burden worldwide as the leading cause of death from an infectious agent and one of the top ten causes of death worldwide, with the exception of the year 2020 during the COVID-19 pandemic.[188] Approximately 10 million individuals were infected with TB just in 2019, with 1.4 million deaths, including over 200,000 deaths among people with HIV.[188] Although any individual is at risk for TB, 30 high-burden countries account for almost 90% of all new TB cases.[189] TB is also a disease of poverty, with individuals typically managing not only their disease course, but also food insecurity, housing instability, and discrimination.[190,191] The WHO's End TB Strategy's goals include a 20% reduction in new TB cases worldwide between 2015–2020; however, we have only achieved a global cumulative reduction of 9% in cases by 2019.[188] The 2025 goals have been set at a 50% reduction in incidence compared to 2015 which will require an even more accelerated rate of decline;[192] clearly, these goals will not be achieved without new, targeted strategies aimed at reducing transmission in high-incidence settings.[193–195]

The causative agent of TB, *Mycobacterium tuberculosis,* was first discovered by Robert Koch in 1884.[196] At that time, there were no pharmaceutical treatments available for TB, and instead, presumed infected individuals were typically sent to a sanatorium, or an isolated institution where patients were encouraged to rest and had continuous access to open-air

spaces.[197] The first vaccine for TB, the bacille Calmette-Guérin (BCG) vaccine, was distributed in 1921 to children, and remains the most commonly used vaccine in the world.[198] Unfortunately, due to its relatively low efficacy,[199,200] its use has been limited to high-burden TB countries for children to prevent severe disease, for which it remains a cost-effective intervention.[201,202] The first treatment for TB was found in 1944 with the discovery of streptomycin, followed by the rapid development of para-aminosalicyclic acid, isoniazid, pyrazinamide, cycloserine, ethionamide, ethambutol, and rifampicin.[203] After a long lull in drug discovery, there have been recent additions to potential drug treatments for TB including bedaquiline, pretomanid, and delamanid.[204–206]

Transmission of TB occurs via the airborne route, which makes population-level conditions such as poverty and crowding relevant to disease transmission.[207] Bacteria are transmitted via airborne droplets after activities such as talking, coughing, and singing.[208] After TB is transmitted to an individual, there are two disease progression pathways possible. Approximately 2-5% of individuals will develop active TB disease within a couple of years after infection, which results in the presentation of common symptoms including fever, cough, weight loss, and hemoptysis.[209] The majority of individuals (> 95%) who become infected with TB will never become ill with TB disease. Instead, these individuals will clear the infection or develop latent TB infection (LTBI), which is a state of persistent immune response lacking the clinical manifestation of symptoms. An infected person is not believed to transmit the bacteria in the LTBI state.[210] If left untreated, individuals with LTBI may harbor this latent infection for their entire lives, or they may develop active TB disease, otherwise known as re-activation. The lifetime risk of this occurring is approximately 10%, and there are groups for which this risk is increased, including very young children and the elderly, immunosuppressed populations (e.g., those with HIV or on TNF-alpha inhibitors), and persons with silicosis or diabetes.[211]

It is estimated that approximately one-quarter of the world's population (~1.7 billion individuals) is latently infected with TB, and this group remains a large reservoir for incident active TB cases.[212] TB mainly manifests in the lungs as pulmonary TB but is also capable of affecting other body sites such as the brain and spine (known as extrapulmonary TB).[209] The vast majority of individuals (~85%) who contract TB can be successfully treated and cured with a 6-month drug regimen; appropriate and consistent treatment is also able to prevent onward transmission from an infected individual.[188] As a 6-month treatment course can be difficult for an individual to follow and maintain, programs such as directly observed treatment, short course (DOTS) implemented by the WHO have provided for a standardized framework in TB treatment courses, allowing for community health care workers to monitor and check in on TB patients daily.[213]

Drug-resistant TB

Very shortly after the first treatments were discovered for TB, drug resistance was documented in *M. tuberculosis* strains.[214] Through both experimental and observational studies, differences in drug-resistant (DR) TB clinical outcomes and the need for combination treatments were reported, and these remain extremely important concepts today.[215,216] Almost fifty years after DR TB strains were discovered, the WHO, in collaboration with the International Union against Tuberculosis and Lung Disease, created the Global Project on Anti-Tuberculosis Drug Resistance Surveillance to track the spread of drug resistance worldwide, which remains the largest and longest-running initiative for antimicrobial drug resistance in the world.[217] In 2019, approximately 50% of all DR TB cases were located in India, China, and the Russian Federation.[188]

TB drugs are classified into first-line and second-line drugs, largely based upon usage priority (i.e., first-line drugs prioritized over second-line) regarding the efficacy, risks, and bactericidal activity associated with the drugs. First-line drugs include isoniazid, rifampin,

ethambutol, and pyrazinamide, which comprise the staple treatment package for individuals with drug-susceptible TB. Second-line drugs, which typically carry more side-effects, are more expensive, and are prescribed for a much longer period of time, are used for the treatment and management of certain forms of DR TB. These are comprised of different drug classes including fluoroquinolones, injectable agents, and others including the newer drugs bedaquiline, linezolid and delamanid, and drug combinations are ideally prescribed according to drug susceptibility results for a given individual. Guidelines outlining potential treatment courses based upon drug resistance patterns are published regularly with the aim to simplify and streamline treatment to improve clinical outcomes.[218] DR TB can be grouped into different categories, including mono-resistant, poly-resistant, multidrug resistant (MDR), pre-extensively drug-resistant (pre-XDR) and extensively drug-resistant (XDR), dependent on the specific drugs to which an isolate is resistant. Mono- and poly-resistance are defined as resistance to one first-line drug and resistance to more than one first-line drug (other than both isoniazid and rifampin), respectively. MDR TB is defined as resistance to at least isoniazid and rifampicin, pre-XDR TB is defined as MDR TB disease with additional resistance to any fluoroquinolone, and XDR TB is defined as MDR TB disease with additional resistance to any fluoroquinolone and to at least one Group A second-line drug (i.e., levofloxacin, moxifloxacin, bedaquiline, and linezolid).[219]

Among all new TB cases from high-burden countries, approximately 3.6% are classified as MDR TB, and this proportion increases dramatically to 18% among individuals who have been previously treated for TB.[188] Although these proportions have stayed relatively stable across aggregated TB measures, country-specific trends are more diverse based upon the TB epidemic in their setting. For example, while the average annual rate of change of MDR TB in South Korea has decreased over the past decade, it has continued to increase over time in many countries in Eastern Europe.[188] The spread of XDR TB – the most drug-resistant form of TB – to over 100

countries is of grave concern.[188] As current treatments are extremely limited and expensive,[220] and with mortality rates ranging from 50-90%,[221] it has been deemed a public health crisis by the WHO.[188] While drug treatment cure rates for MDR and XDR TB have remained quite low at 12% and 6.8%, respectively, newer TB drugs including bedaquiline, linezolid, and delamanid have allowed for more feasible and shorter treatment options, resulting in reductions in treatment cost, and increases in treatment cure rates.[222]

TB epidemiology in South Africa

Worldwide, the TB burden is mainly fueled by transmission in high-incidence settings, such as Asia and sub-Saharan Africa.[223,224] Two-thirds of all new TB cases are found in just eight countries, one of which is South Africa.[189] South Africa has the highest per capita number of new TB cases globally.[224–226] TB was deemed a national emergency in South Africa in 1996, and the DOTS treatment program was implemented nationally.[227] Yet, prior to this, the combination of disorganized health services, no standard treatment courses, and the beginning of the HIV epidemic in South Africa led to high rates of HIV and MDR TB co-infection,[228] which remains a defining epidemiologic feature of the TB epidemic in this setting. Further, within the important mining industry in South Africa, miners are estimated to have one of the world's highest incidence rates at 3,000 per 100,000 persons annually.[229]

The first reports of DR TB were in the 1980s,[230] and although the national roll out of second-line drug treatments was prompt, delays in the start of treatment after diagnosis are still common. Even after the implementation of the Xpert MTB/RIF test, which provides rapid drug susceptibility test results for rifampicin allowing for earlier treatment initiation, delays in treatment initiation persist.[231] The number of reported cases of MDR TB has risen steadily since it was first reported in South Africa, with very large increases after 2010, likely due to improvements in case

detection.[232] KwaZulu Natal province in South Africa has one of the most challenging DR TB landscapes in the world, which had its first reported outbreak of XDR TB in 2005.[233] This outbreak highlighted not only the existence of community transmission of XDR TB rather than its development through unsuccessful treatment, but also a much higher local prevalence of MDR TB than previously thought.[233] After this outbreak was reported, it was determined that XDR TB had likely been present in South Africa over a decade prior.[234]

1.2.2 Progress towards tuberculosis elimination

Strategies to reduce the global TB burden

Strategies that are most relevant to the reduction in TB transmission in any setting include prompt diagnosis, appropriate treatment, and infection prevention.[235] Diagnosis of TB ideally should be paired with universal drug susceptibility testing in order to determine the most appropriate individual treatment regimen.[236] Rapid testing for drug resistance allows for both prompt diagnosis and appropriate treatment; however, rapid testing has been limited to rifampicin alone. Newer tests for a larger subset of TB drugs including second-line drugs are in development,[237] and these diagnostics are critical to reducing the global burden of DR TB. Delays in TB treatment, as a result of an infected individual not seeking care, laboratory or drug distribution delays, poor prescribing practices, or programmatic shutdowns are significantly associated with increased transmission as infected individuals may still be in contact with others.[238]

Development of drug resistance as a result of improper or insufficient treatment has highlighted the need for shorter and easier drug regimens for TB patients in order to prevent the continuation of drug resistance via this method. Long drug regimens are difficult to maintain, especially for DR TB, and cost of treatments remain a limiting factor to how far local TB programs

are able to invest into their treatment programs.[239] Although the vast majority of new TB cases can be treated with first-line drugs, it is essential that we continue to make progress in developing shorter treatment regimens for drug-susceptible TB, which remains a consistent reservoir for DR TB cases.[240] Further, latent TB infection acts as a reservoir for both drug-susceptible and DR TB; this means that preventative therapies are urgently required for latent DR TB infection, as well as diagnostics to identify individuals at greater risk for re-activation of TB disease.[240]

In order to reach the ambitious TB elimination targets set by the WHO, strategies to reduce TB transmission will need to become more creative and locally-targeted. Specifically, a better understanding of the local TB epidemiology through district health systems can provide a more granular perspective of local catalysts of TB transmission to guide community-level interventions.[241] Local TB epidemiology is closely related to the concept of active case finding, a strategy focused on testing specific areas or neighborhoods in a setting where there are likely to be more TB cases, which can lead to earlier detection and treatment of infected individuals.[242] Further, identifying areas that could potentially act as 'pockets of susceptibility' based upon age, occupation, or living conditions within a specific setting combined with active case finding can lead to more efficient use of community health resources.[241]

Potential secondary impacts of COVID-19 on TB control

Changes in social mixing patterns[243] and shifting resources towards COVID-19 have inevitably had negative repercussions in the control of other diseases such as TB.[244] On a global scale, COVID-19 has negatively impacted our healthcare systems and has the potential to severely disrupt services for TB, HIV, and malaria, the leading global killers among infectious diseases.[245,246] In particular, TB surveillance data indicate substantial negative effects of the pandemic with large reductions in case notifications, ranging from 20–78%.[247–254] In South Africa,

which has the highest per capita number of new TB cases globally,[224] case notifications decreased by 33% in early 2020 as compared to previous years.[255] Monthly notifications fell by > 50% in South Africa over the course of March – June 2020.[188] This pattern has precedent, with similar trends in TB case notifications seen in Hong Kong during the SARS epidemic.[256] With the complicated nature of TB disease including a long incubation period and latent disease,[257] reduced case notifications should not be considered a reflection of decreased incidence. Rather, decreased detection may lead to increased incidence and mortality, as individuals with undetected TB may continue spreading the disease while treatment is delayed.[258]

In a modeling analysis by the WHO, if the proportion of detected and treated individuals with TB were to fall by 25–50% over the course of three months (similar to trends described above), there may be up to 400,000 excess TB deaths in 2020 alone, which could push the total annual number of TB deaths up to 1.9 million, levels not observed since 2012.[259] Further, a 3-month lockdown with an extended 10-month period of reinstating TB services has been predicted to lead to at least 6 million additional cases from 2020–2025, with an additional 1.4 million deaths during this period.[246] Unfortunately, we have now seen some of these estimates come to fruition. There was a large drop in individuals reported as newly diagnosed with TB in 2020 – from 7.1 million in 2019 to 5.8 million in 2020.[260] There has also been a resultant increase in TB deaths with the best estimates reporting just over 1.5 million deaths, a total not observed since 2017.[260] The pandemic has also impacted access to treatment, with a 15% drop in DR TB treatment, a 21% drop in TB preventative treatment, and an overall drop spending for TB diagnostic, treatment, and preventative services (totaling $5.3 billion, which is less than half of what is needed).[260]

Social distancing and mask wearing policies may have an effect on TB transmission; however, the impact of these interventions are unlikely to outweigh those of longer periods of infectiousness, poor treatment outcomes, increased malnutrition, prolonged household TB

exposure, and increased rates of unemployment leading to higher levels of poverty.[261] Further, economic contractions as a result of the COVID-19 pandemic have the potential to affect both global TB response programs as well as individuals most at risk for contracting TB.[188] Methods to try and reduce the number of individuals infected with TB who remain undetected include more intensive active case finding approaches to target specific areas where cases are more likely going undetected, scaling up preventative treatment and contact tracing, as well as maintaining direct and uninterrupted diagnostic and treatment supply chains.[246]

1.3 Significance and Overview of Aims

Local public health programs have limited resources and determining which efforts will have the greatest benefit in terms of fewer COVID-19 cases, deaths, and hospitalizations is very difficult in a dynamic pandemic environment. In certain scenarios such as during levels of very high COVID-19 transmission, contact tracing may not be an efficient add-on to enhanced case investigations by local public health workers, yet these scenarios are not yet defined for specific settings. Further, exploring the impacts of both different levels and types of public health interventions within a specific setting has the potential to not only assess how well the pandemic could have been handled during the initial stages, but also to determine optimal timing of these interventions, which will be useful information as we work towards further reduction (and perhaps the endemicity) of COVID-19. A focused evaluation of local public health programs using modeling methods equipped to integrate the complexities of the testing, tracing, and COVID-19 disease processes has the potential to provide tailored programmatic goals for the greatest impact. In **Aim 1** of this dissertation, we utilized a network-based transmission model to determine the impact of feasible changes in specific steps in the contact tracing process in the state of Georgia.

It is crucial to have a better understanding of factors that drive disease transmission at the local level, taking into account the specific context whether that be a county-level contact tracing program or a university setting. Further, it is important to document transmission characteristics within the specific re-opening structure a university has taken to assess the overall effectiveness of current strategies, to build on future campus prevention strategies for epidemics. It is not yet known whether schools and universities have unique transmission characteristics: e.g., secondary attack rates, the extent of asymptomatic transmission, and contact patterns among students and faculty. Thus, it is unclear whether mitigation strategies applied in the community differ from those optimal for campuses. For example, whether further restrictions on group activities are warranted due to high numbers of close contacts, or more frequent testing requirements are necessary to address high levels of asymptomatic transmission. Estimation of transmission network characteristics in this setting is not only critical to informing re-opening strategies, but for maintaining safe learning environments as we slowly transition towards normalcy. In **Aim 2**, we constructed the contact tracing networks on the Emory University campus to explore network dynamics during the academic year.

Repercussions of COVID-19 mitigation strategies have already been observed for the control of other infectious diseases such as TB. Efforts to curb the COVID-19 pandemic and avoid setbacks in TB and DR TB control, specifically, require further studies to understand disease transmission dynamics and the secondary impacts of mitigation strategies, including how these strategies may need to vary by location and setting. The impact of mitigation strategies, such as national lockdowns, on TB incidence remains unknown. Important metrics to further understand the potential impact of mitigation strategies is the estimated number of undiagnosed DR TB cases and their spatial distribution. Quantifying changes in TB diagnoses and their geospatial

distribution after national lockdowns especially within a high-burden TB setting is needed to identify the impact of mitigation strategies on TB control, which will ultimately inform ongoing progress towards TB elimination. Identifying both the extent as well as the estimated locations of undetected DR TB cases has the potential to guide enhanced active case finding methods, as well as identify areas at greater risk of localized community transmission. In **Aim 3** of this dissertation, we examined trends in both the number and geospatial distribution of DR TB diagnoses in KwaZulu-Natal, South Africa and evaluated the potential extent of undiagnosed cases as a result of the COVID-19 national lockdowns.

1.4 Specific Aims

Aim 1: To determine the optimal combination of feasible interventions that can prevent the greatest proportion of COVID-19 transmission in Georgia.

Hypothesis: *We hypothesize that reducing time from positive test to index case interview to ≤ 2 days and eliciting information for ≥ 65% of close contacts will have the greatest impact on reducing transmission given the public health and clinical trade-offs among a set of defined feasible interventions (1–14 days to index case interview; 40–70% of close contacts elicited).*

Aim 2: To characterize transmission networks of COVID-19 at Emory University and determine the proportion of transmission epidemiologically linked to an asymptomatic index case.

Hypothesis: *We hypothesize that approximately 30% of cases reported on campus during the 2020–2021 school year are epidemiologically linked to an asymptomatic index case.*

Aim 3: To estimate the change in DR TB diagnosed cases and their spatial distribution after the COVID-19 pandemic lockdowns in KwaZulu-Natal province, South Africa.

Hypothesis: *We hypothesize that the number of diagnosed cases of DR TB will be 35% lower in the 12 months after pandemic shutdowns (April 2020), as compared to prior years. Neighborhoods with lower socioeconomic status will account for a greater proportion of cases than before the pandemic.*

1.5 Data Sources

Georgia Department of Public Health (GDPH)

The Georgia Department of Public Health (GDPH) COVID-19 surveillance and contact tracing data includes demographic, symptom, date, and home location information on cases and close contacts.

State Electronic Notifiable Disease Surveillance System (SendSS)

The State Electronic Notifiable Disease Surveillance System (SendSS) is an electronic database used for the capture and report of notifiable diseases in the state of Georgia. It allows for data input and tracking of individuals across the state, in order to monitor disease trends. Patient demographics, laboratory testing, and clinical information is captured, in addition to other information depending on the specific notifiable disease. Patients are uniquely identified using a 'Person Under Investigation' (PUI) ID.

Google/MTX

In response to the COVID-19 pandemic, the state of Georgia implemented a new contact tracing platform developed by Google/MTX in order to improve contact tracing efficiency.[262] This

is a web-based portal that allows for close contacts of diagnosed cases to be monitored via text by contact tracers, self-enroll as a close contact of a diagnosed case, and have their questions answered.

The GDPH databases to be utilized for this aim contain extensive information on diagnosed cases and their close contacts. Data elements utilized for this aim include demographics, location information (e.g., county of residence), date information (e.g., of interview, symptom onset, testing, hospital course), symptomaticity, and essential worker status. Further details on these data sources, variables used, and sample sizes are provided in **Appendix Table I-1.**

Online Analytical Statistical Information System (OASIS)

The Online Analytical Statistical Information System (OASIS) is a publicly available online platform comprised of tools to access GDPH's health data repository. The state's health data repository contains aggregated data on vital statistics, hospital visit and discharge information, behavioral risk factor surveillance, and other population-level data stratified by demographic characteristics such as age, race, and sex.

Emory University Contact Tracing Program

The Emory University Contact Tracing Program was created in response to the COVID-19 pandemic in preparation for the re-opening of the university in the Fall of 2020. The program utilizes a REDCap database to capture and store the information they gather through case investigation and contact tracing interviews for index cases and their reported close contacts.
This REDCap database contains extensive information on diagnosed cases and their reported close contacts. Data elements utilized for this aim include demographics, university affiliations,

location information, travel and close contact data, testing information, symptoms and risk factors, and dates of isolation and quarantine. Cases are uniquely identified with their Emory ID number. Further details on this data source, variables used, and sample sizes are provided in **Appendix Table I-2.**

Statistics South Africa

Statistics South Africa (Stats SA) collects population-level information through collection of the census in addition to many other country-wide surveys. Stats SA conducts over 300 different statistical releases annually. These data are publicly available for research use. This aim utilized sociodemographic and living condition information from the South African census, the Demographic and Health Survey, General Household Survey, and Living Conditions Survey. KwaZulu-Natal province data was exported by Stats SA and include detail to the census unit of main place, which are smaller spatial units within municipality, district, and province units. KwaZulu-Natal province consists of 10 districts, 43 municipalities, and 197 main places. The datasets acquired from Stats SA provided municipality-level information on population density, socioeconomic information, and general household information.

'The Role of Casual Contact and Migration in Extensively Drug-Resistant (XDR) TB Transmission in South Africa: a Geospatial, Genomic and Social Network Study' (CONTEXT)

'The Role of Casual Contact and Migration in XDR TB Transmission in South Africa: a Geospatial, Genomic and Social Network Study' (CONTEXT) (R01AI138646) is our group's current NIH-R01 prospective cohort study. The parent study aims to estimate the impact of casual contact and migration on XDR TB transmission in KwaZulu-Natal, South Africa. All culture-

confirmed DR TB patients diagnosed in KwaZulu-Natal province are eligible regardless of sex, age or vital status and are identified at the provincial TB reference laboratory weekly. Eligibility has been confirmed for *n* = 1,273 to date. DR TB cases will be geocoded based on the healthcare facility of diagnosis. From the CONTEXT study, DR TB patient demographics including age and sex, as well as comorbidity, occupation, and education information. Geocoded information including healthcare facility of diagnosis, home location, and places frequently visited will also be utilized in this analysis. Participants are uniquely identified with a Screening ID and, if eligible, a Study ID. Further details on these data sources, variables used, and sample sizes are provided in **Appendix Table I-3** and **Appendix Table I-4.**

Chapter 2: The balance between public health capacity and clinical capacity in the early stages of the COVID-19 pandemic in the state of Georgia: a modeling study

Abstract

Background

Local assessments of public health programs and their impact on healthcare strain during the COVID-19 pandemic are needed to inform decision making throughout the ongoing pandemic and in preparation for future disease outbreaks. We sought to assess the trade-offs between public health capacity and clinical capacity in the early stages of the COVID-19 pandemic in the state of Georgia.

Methods

We leveraged data from the Georgia Department of Public Health (GDPH) to parameterize a network-based mathematical model to study the relationship between contact tracing activities and hospital utilization. We represented the transmission and natural history of COVID-19 infection in Georgia from March 1st, 2020 to August 31st, 2020. We modeled two network contact structures (within household and community-level) within the full network using temporal exponential random graph model statistical frameworks. We estimated the impact of increasing the proportion of close contacts traced and reducing the time from index case diagnosis to case investigation interview on COVID-19 cases, deaths, and hospitalizations.

Results

We found that even with complete and immediate contact tracing, hospitals would remain over capacity for greater than a week during ICU census peaks. Complete and immediate contact tracing was able to avert 5% of infections and 4% of deaths and reduced the time during which ICU capacity was exceeded by 8 days. We found a greater impact for improvements to the speed

of tracing versus the completeness of tracing, with a 1-day lag negatively impacting outcomes to a greater degree than a reduction in the proportion of contacts traced by 20%.

Discussion

Overall, we found that in our modeled scenarios, any isolated or combined contact tracing intervention was unable to prevent the over-capacity of ICU beds in the state of Georgia. While contact tracing had a positive effect on outcomes, these effects were greatest shortly after index case diagnosis and declined thereafter before plateauing after approximately 1 week. Our results bring into question the utility of contact tracing programs in the setting of a widespread respiratory viral pandemic and highlight the importance of the use of multiple mitigation strategies and ensuring adequate clinical infrastructure in the context of emerging outbreaks and our preparation for the next pandemic.

Introduction

With over 79 million cases and 960,000 deaths in the United States as of March 2022, the COVID-19 pandemic has put a catastrophic strain on both our public health systems and clinical infrastructure.[1] With unprecedented hospital utilization in the initial waves of the pandemic, healthcare providers were forced to implement new frameworks around surge planning and adapt to the uncertainties of a novel infectious disease.[263–265] As with other infectious diseases, public health systems have implemented case investigation and contact tracing programs to prevent or relieve the strain placed on clinical capacity by halting transmission and new infections.[113,114] Like any other intervention strategy, contact tracing has its limitations. If transmission becomes too widespread in a community and potentially exposed cases cannot be identified prior to their becoming infectious, contact tracing becomes insufficient to reduce transmission. In turn, higher transmission levels may lead to strains on clinical capacity depending on the severity of disease.[118,119]

This balance between public health capacity and clinical capacity differs across settings, but there is typically an inverse relationship between public health staff workload and completeness and timeliness of contact tracing.[266] Local assessments of public health programs have described wide variation in local COVID-19 epidemiology in addition to large differences in a health department's ability to reach cases and elicit contacts; thus, comparisons between local health departments are difficult.[267] Careful assessment of local programs is needed to better inform decision making and implementation during the ongoing pandemic and preparation for future disease outbreaks.[268] It is important to determine whether or not a local public health program has the capacity to complete the majority of its case investigation and contact tracing responsibilities. Due to the diversity in programmatic approaches and little empirical evidence to inform best practices, it is

important to examine this at the local level to determine if resources may be better allocated to other mitigation strategies and clinical programs.[269]

While previous modeling studies aimed at providing guidance to public health programs have emphasized minimizing testing delays and optimizing tracing coverage, this advice is provided at the general level and lacks an assessment of the relationship to clinical utilization.[144] Further, the size and capacity of a local public health workforce (i.e., the number of staff and workload potential) should be considered when determining feasible and sustainable programmatic goals.[145,146] Even within the context of an effective vaccine, contact tracing will continue to be an indispensable tool for controlling the spread of COVID-19 amidst pandemic fatigue and new variants.[134,135,270] Thus, assessments and modeling studies of contact tracing programs at earlier stages in the pandemic with smaller caseloads may provide useful information as we move towards endemicity.

Local public health programs have limited resources and determining which efforts will have the greatest benefit in terms of fewer COVID-19 cases, deaths, and hospitalizations is challenging in a dynamic pandemic environment. During periods of very high COVID-19 transmission, contact tracing may not be an efficient add-on to enhanced case investigations by local public health workers. This may be especially true from a clinical capacity perspective, yet these scenarios are not well defined for specific settings. A focused evaluation of a local public health program using modeling methods equipped to integrate the complexities of the testing, tracing, and COVID-19 disease processes has the potential to identify programmatic goals with the greatest potential impact. In this study, we sought to assess the trade-offs between public health capacity and clinical capacity in the early stages of the COVID-19 pandemic in the state of Georgia. We

leveraged data from the Georgia Department of Public Health (GDPH) to parameterize a network-based mathematical model to study the relationship between contact tracing activities and hospital utilization.

Methods

We used a network-based model of infectious disease dynamics to represent the transmission and natural history of COVID-19 infection across the state of Georgia. The model was built and simulated using the EpiModel software platform.[271] This model represented individuals in Georgia with temporal exponential random graph models (TERGMs) that estimated and simulated dynamic contact networks based upon the formation and dissolution of both close (household) and casual (community-level) contacts.[272] We simulated individual scenarios from March 1st, 2020 to August 31st, 2020 (prior to subsequent waves) in daily time steps and classified individuals based upon age structure.

Network Structure

This model uniquely represented individuals in Georgia classified by age (represented as a continuous attribute), with initial distributions drawn from the empirical age distribution of Georgia estimated by US Census Bureau. The population on average was 37 years old. The approximately 10 million people who reside in Georgia were represented by a population of 100,000 individuals in the network simulations for computational efficiency; however, all summary model outputs are population standardized.

We modeled two network contact structures within the full network: a within-household network and community-level contact network (Figure 2.1). The same set of nodes (individuals) were used

for the full network, with differing connections (edges) between individuals based upon the distinct contact structures.

Among household-household contacts, individuals made repeated contacts with the other members in their household with a longer duration of contact. Individuals were assigned to a 'household' within the network to reach the average number of people per household in each county as estimated by the U.S. census (i.e., 2.7). The average daily community-community degree was 5 based upon reports of population contact patterns in the US during the COVID-19 pandemic (Table 2.1).[154] Both types of contacts were formed at random with respect to demographics.

We represented these networks using two multi-layer dynamic network approaches with TERGMs to simulate the interactions between household members over time, and ERGMs to simulate community-level contacts which were refreshed at every time step. Both approaches were fit to the network degree distributions of a household and a community. Models were estimated and simulated using standard MCMC-based fitting procedures[272,273], and then diagnosed by comparing the simulated network data against the input data points.

COVID-19 Transmission and Progression

This model represented COVID-19 transmission and disease processes via a modified SEIR framework (Figure 2.2). After infection, individuals in the network could stochastically transition from the susceptible to exposed compartment, followed by a transition into one of two infected pathways based upon presence or lack of symptoms. Following estimates from the Georgia Department of Public Health (GDPH), 57–81% of persons went through the symptomatic

infectious pathway, with the probability of symptoms dependent on age decile. Following prior modeling parameters, asymptomatic infected individuals had 50% the transmission probability compared to symptomatic infected individuals.[274]

For symptomatic individuals, there was a pre-symptomatic infectious stage followed by a clinical infectious stage. Contact rates were reduced for infected and symptomatic individuals, in addition to those hospitalized and in an intensive care unit (ICU). Infected individuals with symptoms may have had a mild or severe hospitalization course, represented by admissions to a hospital floor or an ICU, respectively.

Age-specific mortality rates were applied using general age-specific mortality data from OASIS for the state of Georgia, with an excess mortality factor due to COVID-19 approximated from the GDPH data. We calibrated the model to both daily case counts and daily death counts from the first month of the pandemic in Georgia (March 1st, 2020 to April 1st, 2020).

Intervention Scenarios

Control scenarios were fitted to observed daily case counts prior to the timing of each set of interventions, and these were compared to the simulations in which interventions were applied to reduce disease transmission. The flow from cases to eligible contacts for which interventions were applied is displayed in Figure 2.3. Further details regarding the rules dictating movement in the network model are described in the appendix. We modeled three intervention scenarios: increasing the fraction of traced contacts, decreasing the time from positive index test to interview date, and both of these interventions together.

Outcomes included the total number of COVID-19 cases, hospitalizations, and deaths. The intervention scenarios ran for the full six months. The fraction of traced contacts was varied from 25–100%. This intervention was implemented through a reduction in the number of contacts for a corresponding subset of the contacts in the network to represent the quarantine period for a fraction of traced contacts. Although close contacts could have been in any of the disease transmission and progression compartments, a larger proportion of contacts were represented by the S, E, and I (excluding those tested) compartments via defining the probability of tracing conditional on disease stage. A baseline lag in time to index case interview from positive test date was set at 2 days. Time to index case interview from positive test date was varied from 0–28 days. This intervention was implemented by the incorporation of a parameter that introduced a time lag prior to the quarantine period for the fraction of traced contacts by the corresponding number of days in which the index case interview is delayed. A baseline fraction of traced contacts was set at 60%. Combined increases in the fraction of traced contacts and decreases in the time to index case interview were assessed using fractions ranging from 25–100% with either a 1-day lag or no lag to index case interview. Intervention scenarios were applied on Day 35. For all intervention scenarios, we assumed that 80% of close contacts traced would successfully complete quarantine.[275]

In order to quantify the feasibility of trade-offs between public health and clinical capacity, various proxy measurements were captured during model simulations. To estimate local public health utilization and needs, the number of diagnosed cases and their eligible close contacts were quantified, corresponding to the eligible pool for case investigation and contact tracing, respectively. Clinical capacity was estimated by comparing the number of individuals in

hospitalized and ICU compartments in the disease transmission and progression framework to the total number of hospital and ICU beds in the state of Georgia.

Calibration, Simulation, and Analysis

The model was calibrated to observed cases and deaths in the first month of the outbreak (March 2020) prior to the timing of the interventions. Free parameters for model calibration were: daily screening rates (stratified by symptomatic status); the multiplier for COVID-19 mortality; and the probability of infection per contact.

Scenarios were simulated for a period of six months in daily time steps. The model was simulated 1000 times for each intervention scenario, and results were summarized with medians and 95% simulation intervals. Outcomes of the number and percent of infections and deaths averted, as well as the peak number of ICU admissions and length of time above ICU capacity were used to compare observed outcomes to simulated scenarios.

Results

Model calibration results are displayed in Figure 2.4. March 1st, 2020 represents Day 1 in the modeled scenarios. The empirical 7-day rolling average number of new cases diagnosed on April 1st was 522, compared to the fitted model of 520 (interquartile range [IQR]: 497, 539). The total incidence from this calibration which included both undiagnosed cases and false-negative cases (from imperfect PCR sensitivity) was 1327 (IQR: 1310, 1348). The empirical 7-day rolling average number of deaths on April 1st was 26, compared to the fitted model of 31 (IQR: 27, 34).

Table 2.2 displays the results of the three implemented interventions at Day 185. In the no-intervention scenario, the median cumulative incidence was 96550 (simulation interval [SI]: 96531, 96579) and the median cumulative mortality was 6571 (SI: 6554, 6596). Varying the proportion of traced contacts resulted in a percent of infections averted (PIA) ranging from 1% with 25% of contacts traced to 3.2% with 100% of contacts traced. There was no impact on the number of deaths averted for tracing only 25% of contacts. Tracing up to 80% or 100% of contacts averted 172 (SI: 118, 207) or 190 (SI: 164, 224) deaths, respectively. Regardless of the timing of when an index case was interviewed after a positive test, the PIA was 2.1% if contact tracing was performed, corresponding to approximately 2000 infections averted.

The number of infections averted, when put into the context of how many contacts were traced, can roughly estimate the 'number needed to trace' to avert 1 infection, or can be interpreted as the efficiency of contact tracing. The estimates for combined interventions are shown in Table 2.3, with the most efficient being the 100% traced with no lag scenario, where approximately 15 contacts would need to be traced to avert 1 infection. All scenarios in which there was no lag in tracing needed less than 20 contacts to be traced to avert 1 infection, while any of the scenarios with a 1-day lag needed 20 or more contacts to be traced to avert 1 infection.

With the combined increase in the fraction of traced contacts and reduction in time to index case interview, at 80% of contacts traced, reducing the time to interview from 1 to 0 days could avert almost 1000 infections and 82 deaths. This effect was magnified for contact tracing 100% contacts, with a similar reduction in reaching cases, over 1000 infections and 58 deaths could be averted. Even with only 25% contact tracing, immediately reaching index cases could avert over 300 cases compared with waiting 1 day. Transmission mainly occurred between household

contacts compared to community contacts (61% versus 39%) regardless of intervention scenario (Table 2.4).

The number and peak of ICU admissions over time are displayed in Figure 2.5 and Table 2.5. The dotted red line in Figure 2.5 represents the total ICU bed capacity in the state of Georgia. Under the no intervention scenario, the peak number of ICU admissions over capacity was 338 (SI: 330, 365) and the time over capacity was 19 days (SI: 18.5, 19.7). None of the interventions implemented were able to reduce the number of ICU admissions to below capacity; however, the time over capacity was affected by the various interventions. Increasing the proportion of traced contacts had an inverse dose-dependent response to peak number of ICU admissions over capacity. With 100% of contacts traced, the number of days over capacity could be reduced by 4 days, with 117 fewer ICU admissions at the peak.

Similar to the relationship between variation in time to index case interview and cumulative incidence, there was little impact on timing variation on the peak number of ICU admissions or time over capacity. Still, contact tracing at any point reduced the number of peak ICU admissions by at least 42, and the days over capacity by 1.5 days.

Combined interventions were able to reduce the peak number of ICU admissions by 211 and the time over capacity by 8 days in the 100% traced with no lag scenario. Approximately 100 peak ICU admissions could be averted with at least 50% contact tracing and no lag to index interview.

The number of eligible contacts differed across interventions varying the proportion traced and were similar across interventions solely varying the time to index case interview (Figure 2.6).

To better understand the impact of combined interventions, scenarios were plotted against outcome measures (Figure 2.7). There was a similar relationship between the combined intervention scenarios and cumulative incidence, with a greater impact of increases in the proportion traced on incidence at shorter lag times. The impact of increasing the proportion traced plateaued around days 10–14, resulting in minimal impacts of increasing the proportion traced on cumulative incidence beyond that point.

Similar overall patterns are observed for cumulative deaths and peak ICU admissions. There were sharp decreases in both outcomes if the proportion of contacts traced was increased shortly after an index case is diagnosed. The impact of these interventions plateaued around day 10 after index case diagnosis. Interestingly, the impact on cumulative deaths was similar given 100% or 80% of contacts traced, as well as for 60% or 50% of contacts traced, regardless of time lag. There were no differences in the impact of combined interventions on peak ICU admissions beyond day 5 after index case diagnosis.

Discussion

In this study, we modeled the impact of contact tracing interventions to determine the trade-offs between public health and clinical capacity. We found that even with complete and immediate contact tracing, hospitals would remain over ICU capacity for greater than a week. Complete and immediate contact tracing was able to avert 5% of infections and 4% of deaths and reduced the time over peak ICU capacity by 8 days, from 19 days to 11 days. While contact tracing had a positive effect on outcomes, we observed that these effects were greatest shortly after index case diagnosis, and that effects plateaued after approximately 1 week. Given this relatively modest

impact on infections and hospitalizations, our results emphasize the importance of ensuring adequate clinical infrastructure in the context of emerging outbreaks and our preparation for the next pandemic.

Previous studies have described that for airborne infections, contact tracing has to be far more efficient and rapid in order to have an impact.[117] Specifically, when the number of contacts cases have are heterogenous with little clustering among individuals, this necessitates a greater increase in the efficiency of contact tracing. Further, for airborne infections such as COVID-19, there may be a significant fraction of contacts that remain untraceable, which may make it impossible to achieve the desired reductions in incidence and hospitalizations, at which time additional control measures would be required for control. In our model, we theoretically captured all close contacts and targeted them for tracing and were still unable to avoid strained and overflowing ICUs.

We found a much greater impact of the speed of tracing versus the completeness of tracing, with a 1-day lag negatively impacting outcomes to a greater degree than a reduction in the proportion traced by 20%. This may have relevance when considering the prioritization of index cases to interview – prioritizing tracing for those individuals with many more contacts might help to reduce the healthcare burden to a greater degree than focusing efforts homogenously across all index cases. Similar findings emphasizing the importance of minimizing the delay to tracing have estimated up to 80% prevention of transmissions if tracing was able to occur immediately through the use of a digital contact tracing or app-based methods.[141]

It is important to note that we modeled contact tracing interventions apart from any other mitigation strategies such as effective vaccines, behavioral interventions, and lockdown policies. Other studies have shown that as an isolated intervention, contact tracing is unable to fully contain transmission at high levels, and should be implemented in conjunction with other measures.[138,276] Regardless, as a single intervention measure, it is still an effective tool for pandemic preparedness.[277] While contact tracing solely may not be able to control future waves of a pandemic, it does have the ability to reduce transmission and hospital admissions, as observed in our study and others.[278]

We found that combined contact tracing interventions had diminishing returns over time. These findings echo those of studies demonstrating that incremental increases in budgets for contact tracing programs have yielded diminishing returns in reducing disease prevalence.[120] In dense networks, where individuals have many contacts with their community and household, contact tracing typically has a low impact.[149] An important factor to consider is the primary contact structure that underlies disease transmission in a community, which can be done through empirical data analysis. We observed that transmission fractions of network layers did not differ across various intervention strategies, but this may not be the case in other settings. The majority of transmission in our scenarios occurred at the household level; however, we did not observe differential impacts on the fraction of transmission occurring within the household given varying contact tracing interventions. Thus, it may be important to prioritize household contacts in contact tracing protocols even if there is a delay between index case diagnosis and interview.

This study has important implications for resource allocation and outbreak preparedness. Contact tracing is a useful and necessary tool to reduce mortality and the burden on healthcare settings.[279]

However, in the case of a global pandemic, it is crucial to prioritize adequate clinical resources or have existing surge capacity units ready for use. Strengths of this analysis included its use of existing local surveillance data to inform model parameters, which make it more suited to provide locally targeted conclusions. Further, although these models and intervention scenarios were applied to the time period at the beginning of the pandemic, these results may be helpful in understanding the dynamic trade-offs within the context of other emerging infectious diseases, or within infection reduction or elimination programs.

There were several limitations to this study. First, we assumed homogenous age-mixing in our contact structures, which was unlikely and would have an impact on outcome measures given the greater risk for hospitalization and severe outcomes among the elderly population. Second, we did not consider contact tracing 'errors' in which elicited contacts were not truly contacts by definition. Third, we did not incorporate age- or time-stratified testing probabilities or an under-reporting factor, which was a noted limitation of incidence estimates at the beginning of the pandemic. Fourth, behavioral interventions such as stay-at-home orders and mask mandates were not incorporated into our model and would have impacted outcomes.

Overall, we found that in our modeled scenarios, either isolated or combined contact tracing interventions were unable to prevent an excess of critically ill patients above and beyond the capacity of ICU beds in the state of Georgia. Our findings have implications for the prioritization and preparation for future pandemics and outbreaks, in the context of allocating resources towards public health and clinical capacity. Specifically, increases in regional clinical capacity may be required as an adjunct to contact tracing activities to limit future outbreaks and their strain on local hospital systems.

Figure 2.1. Network model schematic. This model represented individuals within and across household and community network structures. Networks are comprised of household-household, community-community, and household-community contacts.

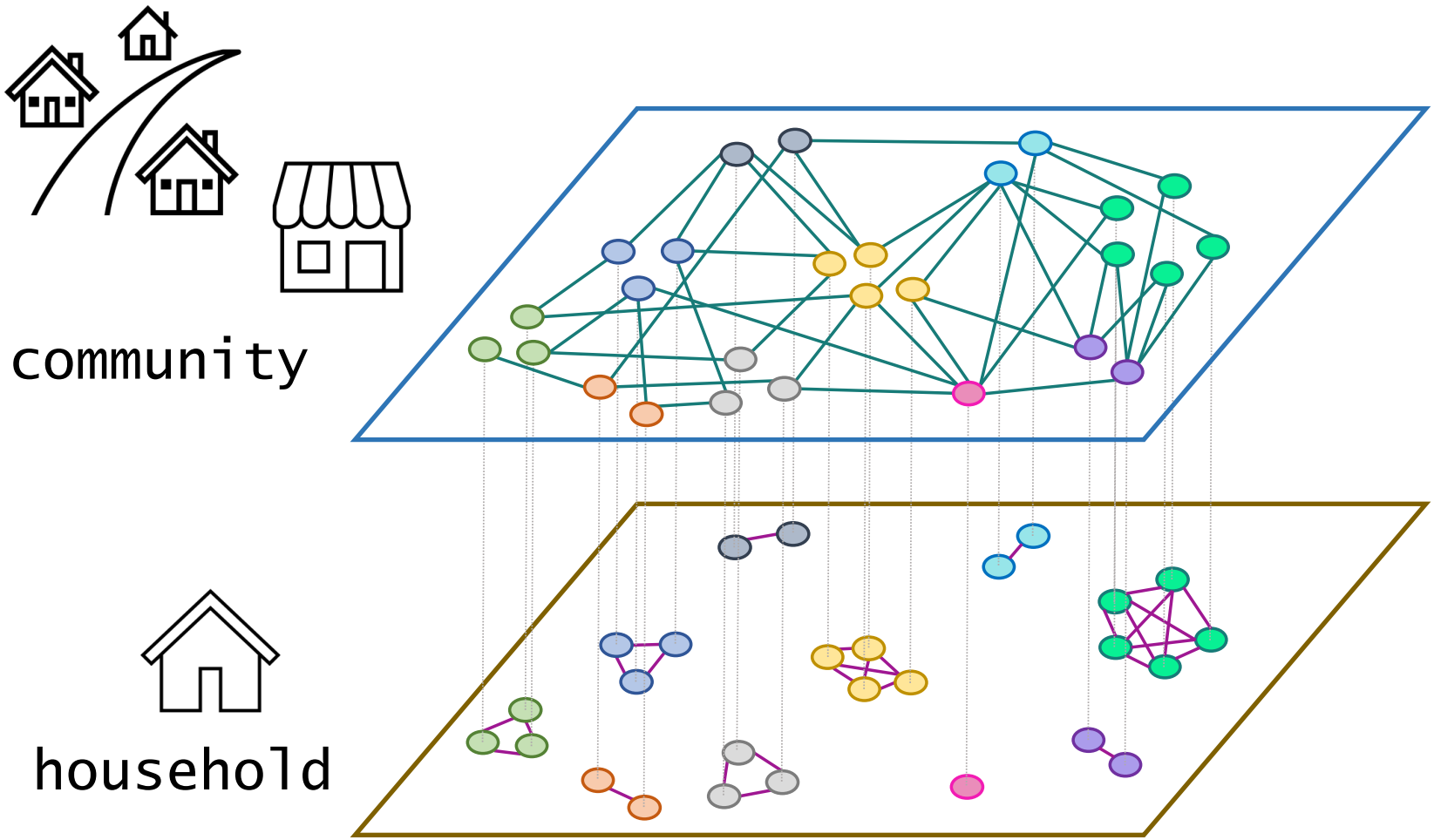


Figure 2.2. Model progression. COVID-19 transmission and disease progression processes were represented as transitions in a modified Susceptible-Exposed-Infected-Recovered compartmental framework.

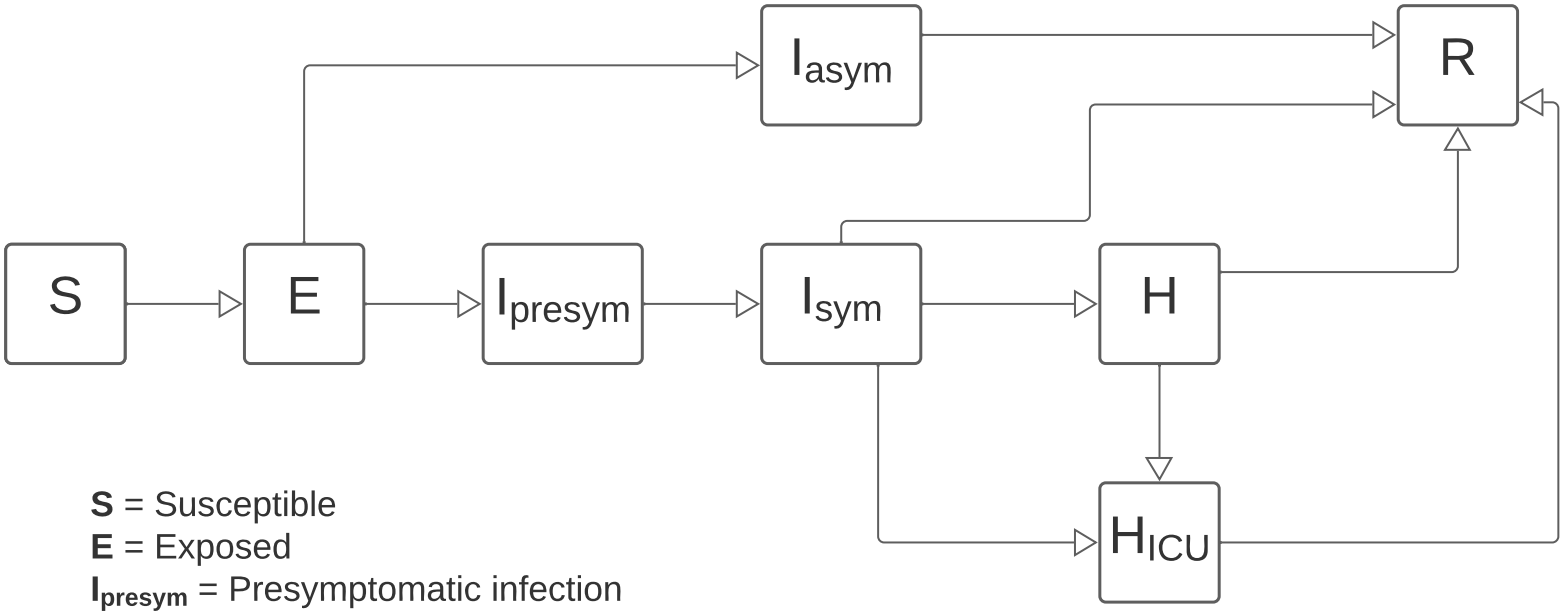


Table 2.1. Primary model parameters.

Parameter	Value - Georgia	Source
Populations		
Total population size	100,000	
Median age	36.7 years	US Census Bureau
Natural history & clinical		
Proportion symptomatic*	57.3, 64.2, 76.0, 80.0, 81.3, 81.4, 76.9, 72.3, 66.6	SendSS dataset
Proportion hospitalized given symptomatic infection*	6.0, 6.3, 8.1, 15.4, 20.7, 26.8, 35.7, 46.5, 53.9	SendSS dataset
Proportion needing intensive care given symptomatic infection*	1.8, 2.2, 2.0, 4.6, 7.5, 10.9, 17.8, 22.5, 20.0	SendSS dataset
Proportion recovered given symptomatic infection*	92.2, 91.5, 89.9, 80.0, 71.8, 62.3, 46.5, 31.0, 26.1	SendSS dataset
Proportion needing intensive care given hospitalization*	23.5, 26.0, 20.7, 22.7, 26.5, 28.9, 33.3, 32.7, 27.1	SendSS dataset
Duration of latent period	4 days	Davies, 2020[104]
Duration of preclinical infectious period	1.5 days	Davies, 2020
Duration of clinical infectious period prior to recovery	3.5 days	Davies, 2020
Duration of clinical infectious period prior to hospitalization	median 3 days (IQR 0,7)	SendSS dataset
Duration of clinical infectious period prior to intensive care	9.5 days	https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-guidance-management-patients.html
Duration of subclinical infectious period	5 days	Davies, 2020
Duration of hospitalization prior to recovery	median 4 days (IQR 2,7)	SendSS dataset
Duration of hospitalization prior to intensive care	2 days	Vekaria, 2021[280]
Duration of intensive care stay prior to recovery	median 5 days (IQR 2,11)	SendSS dataset
Natural mortality rate^	607.6, 29.6, 12.8, 21.6, 62.8, 116.1, 142.8, 186.5, 228.3, 300.4, 416.1, 600.4, 945.0, 1453.1, 1952.3, 2817.0, 4368.9, 7158.8, 15626.4	https://oasis.state.ga.us/oasis/webquery/qryMortality.aspx
COVID-related mortality multiplier	1300	Fitted
Transmission		
Transmission probability per contact	0.11	Kraay, 2021[281]; Fitted
Relative risk of asymptomatic individuals	0.5	Davies, 2020

Contact Patterns		
Household-Household Daily Mean Degree	2.7	https://www.census.gov/quickfacts/GA
Community-Community Daily Mean Degree	5	Feehan, 2021[154]
Testing & Quarantine		
PCR test sensitivity	0.8	Lopman et al., 2021[283]
Interventions		
Time lag to case investigation at baseline	2 days	Assumed
Proportion of contacts traced at baseline	0.6	Assumed

*Proportions displayed for following age groups: 0-10, 11-20, 21-30, 31-40, 41-50, 51-60, 61-70, 71-80, 80+
^Rates displayed for following age groups: <1, 1-4, 5-9, 10-14, 15-19, 20-24, 25-29, 30-34, 35-39, 40-44, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, 75-79, 80-84, 85+

Figure 2.3. Network model flow and contacts eligible for intervention. Overview of the identification of eligible contacts for intervention scenarios from all cases in the network.

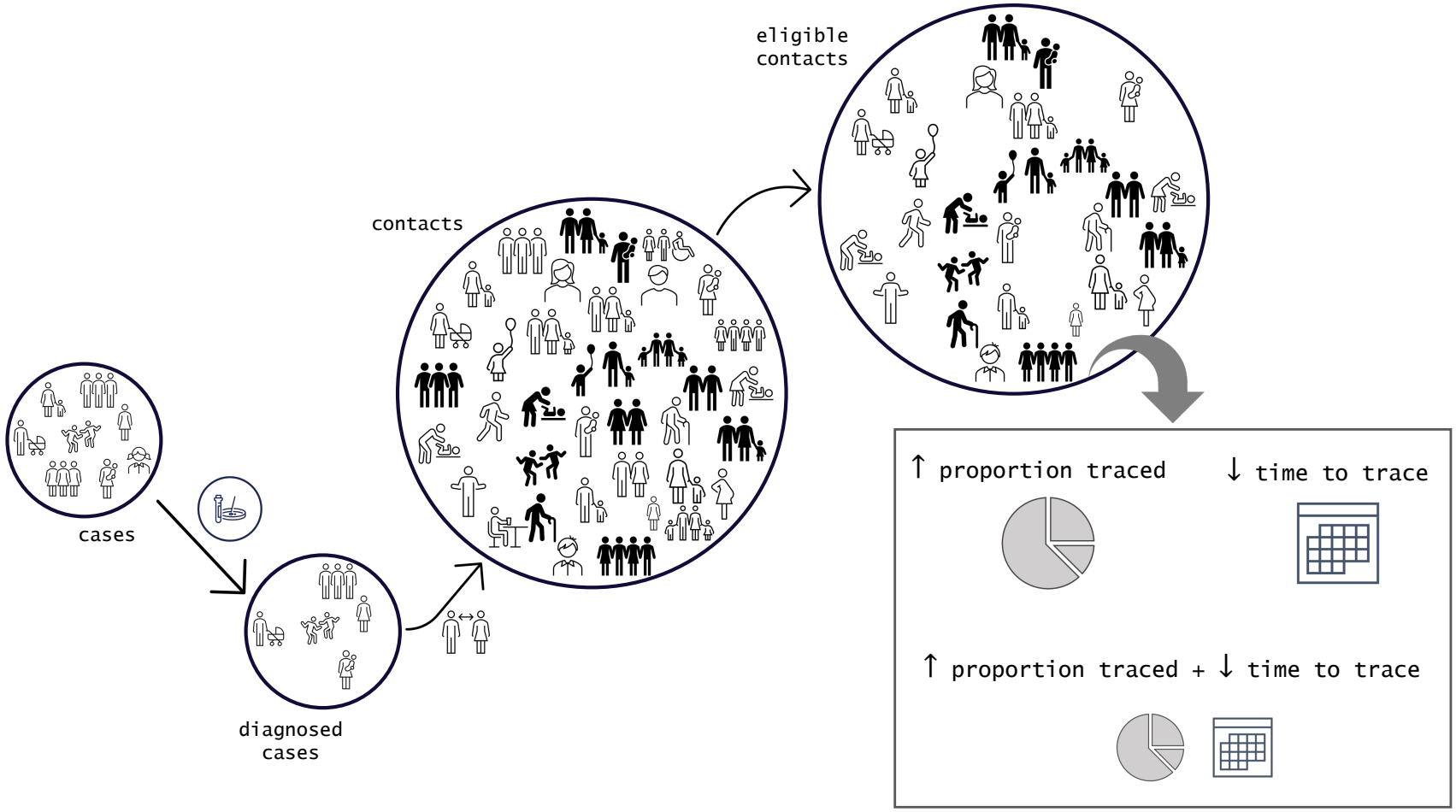


Figure 2.4. Model calibration. Network models were calibrated to (A) observed daily case counts and (B) observed daily death counts in the first month of the pandemic in Georgia.

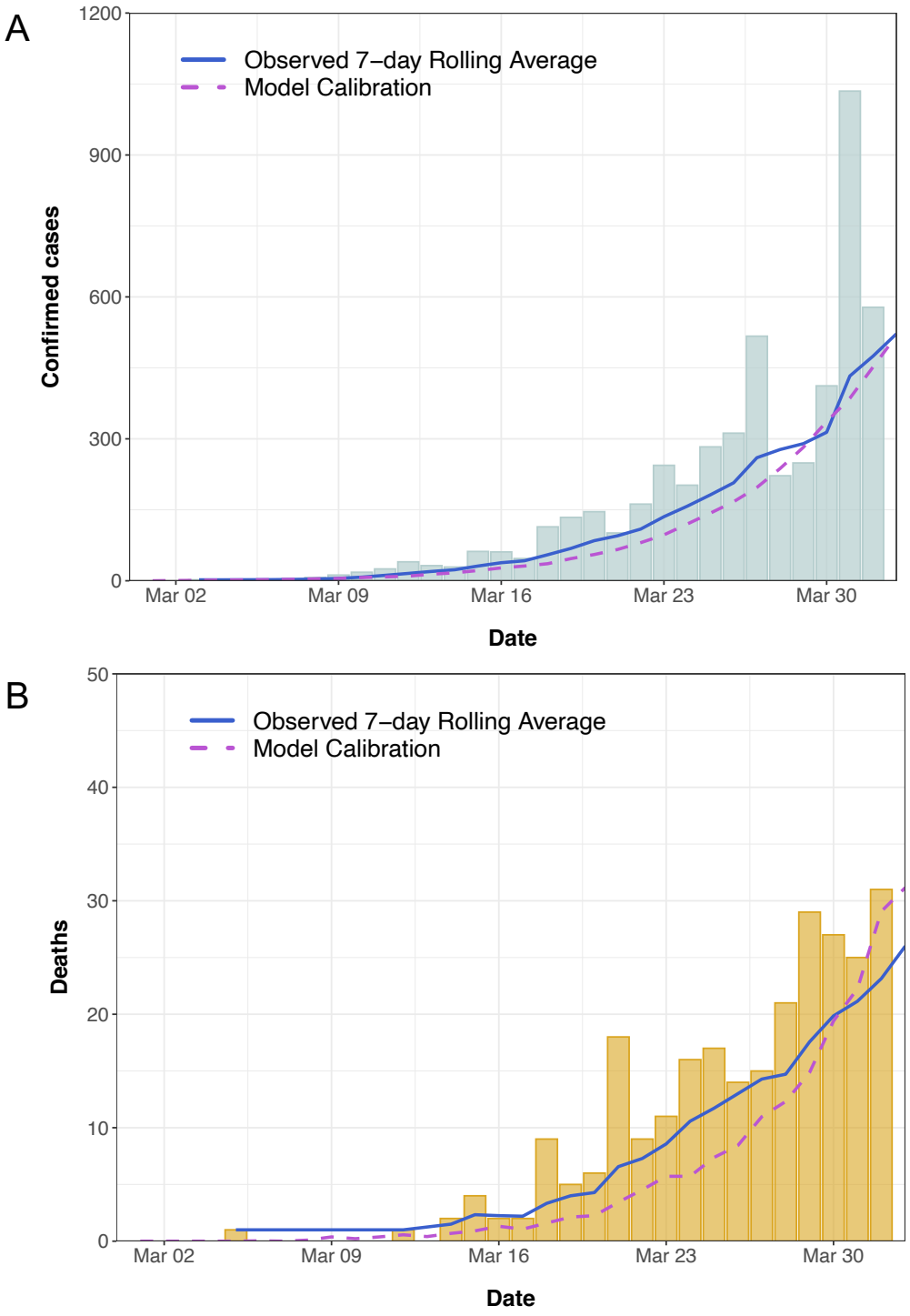


Table 2.2. Number and proportion of infections and deaths averted for intervention scenarios.

Scenario	Cumulative Incidence			Cumulative Mortality		
	Total	NIA	PIA	Total	NDA	PDA
	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)
No Intervention	96549.5 (96530.9, 96578.9)	–	–	6570.5 (6553.6, 6596.0)	–	–
Variation in Proportion of Traced Contacts[1]						
25%	95633.5 (95607.3, 95675.3)	945.5 (875.3, 951.9)	1.0 (0.9, 1.0)	6564.5 (6512.9, 6568.4)	14.5 (-5.9, 74.3)	0.2 (-0.1, 1.1)
50%	94862.0 (94786.4, 94898.9)	1716.0 (1646.9, 1777.6)	1.8 (1.7, 1.8)	6499.0 (6459.9, 6518.3)	80.0 (52.2, 119.1)	1.2 (0.8. 1.8)
60%	94477.0 (94448.4, 94594.6)	2025.0 (1959.3, 2117.6)	2.1 (2.0, 2.2)	6478.0 (6456.5, 6501.7)	86.0 (58.4, 132.9)	1.3 (0.9, 2.0)
80%	93990.5 (93889.0, 94067.4)	2550.0 (2484.3, 2669.1)	2.6 (2.6, 2.8)	6406.0 (6377.8, 6447.8)	172.0 (117.5, 206.5)	2.6 (1.8, 3.1)
100%	93437.0 (93312.8, 93523.6)	3131.0 (3023.2, 3250.3)	3.2 (3.1, 3.4)	6381.5 (6351.6, 6400.1)	189.5 (164.0, 233.9)	2.9 (2.5, 3.5)
Variation in Lag in Tracing[2]						
28-day	94550.5 (94498.9, 94652.5)	1984.5 (1899.6, 2058.8)	2.1 (2.0, 2.1)	6463.5 (6454.1, 6505.8)	104.0 (59.1, 130.6)	1.6 (0.9, 2.0)
14-day	94529.0 (94497.9, 94616.7)	2052.0 (1930.7, 2064.6)	2.1 (2.0, 2.1)	6467.0 (6444.9, 6495.3)	87.5 (64.7, 144.7)	1.3 (1.0, 2.2)
10-day	94482.0 (94428.2, 94566.6)	2037.0 (1988.3, 2126.7)	2.1 (2.1, 2.2)	6475.5 (6455.7, 6507.4)	93.0 (60.5, 125.9)	1.4 (0.9, 1.9)
5-day	94548.0 (94499.2, 94608.1)	2012.5 (1945.8, 2055.8)	2.1 (2.0, 2.1)	6452.0 (6442.0, 6515.3)	121.0 (49.3, 143.1)	1.8 (0.7, 2.2)
2-day	94506.5 (94434.2, 94557.2)	2010.0 (1990.2, 2128.3)	2.1 (2.1, 2.2)	6472.5 (6454.9, 6508.7)	99.5 (59.0, 127.0)	1.5 (0.9, 1.9)
0-day	94528.0 (94467.3, 94604.1)	2024.5 (1951.0, 2087.4)	2.1 (2.0, 2.2)	6450.5 (6432.3, 6486.0)	151.5 (78.2, 153.1)	2.3 (1.2, 2.3)
Combined Variation in Proportion and Lag in Tracing						
25% and 1-day	95434.5 (95411.2, 95485.0)	1100.0 (1067.4, 1146.2)	1.1 (1.1, 1.2)	6546.0 (6508.3, 6561.3)	29.5 (12.2, 67.7)	0.4 (0.2, 1.0)
25% and no lag	95116.5 (95089.5, 95156.9)	1441.5 (1392.9, 1470.6)	1.5 (1.4,1.5)	6522.0 (6484.9, 6538.1)	77.0 (29.9, 96.7)	1.2 (0.4, 1.5)
50% and 1-day	94401.5 (94334.8, 94445.0)	2166.0 (2098.8, 2228.2)	2.2 (2.2, 2.3)	6460.0 (6437.3, 6486.9)	96.5 (79.5, 145.9)	1.5 (1.2, 2.2)
50% and no lag	93913.0 (93824.3, 93971.6)	2643.5 (2580.6, 2733.3)	2.7 (2.7, 2.8)	6427.5 (6397.3, 6454.7)	143.5 (114.3, 183.3)	2.2 (1.7, 2.8)
80% and 1-day	93486.5 (93364.5, 93539.9)	3058.5 (3014.8, 3190.6)	3.2 (3.1, 3.3)	6385.0 (6358.9, 6405.6)	183.5 (158.1, 227.0)	2.8 (2.4, 3.4)
80% and no lag	92576.0 (92526.0, 92706.0)	3960.5 (3846.8, 4031.1)	4.1 (4.0, 4.2)	6321.5 (6287.9, 6351.9)	265.5 (219.5, 290.2)	4.1 (3.3, 4.4)
100% and 1-day	92842.0 (92698.4, 92904.5)	3721.0 (3648.2, 3858.7)	3.9 (3.8, 4.0)	6354.5 (6337.6, 6380.9)	224.0 (182.1, 248.9)	3.4 (2.8, 3.8)
100% and no lag	91743.0 (91628.0, 91820.3)	4825.0 (4728.0, 4933.5)	5.0 (4.9, 5.1)	6297.5 (6265.2, 6319.7)	282.0 (249.9, 314.7)	4.3 (3.8, 4.8)

[1]A baseline lag in time to index case interview from positive test date was set at 2 days.

[2]A baseline fraction of traced contacts was set at 60%.

Abbreviations: SI, simulation interval; NIA, number of infections averted; PIA, percent of infections averted; NDA, number of deaths averted; PDA, percent of deaths averted.

Table 2.3. Number needed to trace for intervention scenarios.

	Number Needed to Trace to Prevent 1 Infection
Variation in Proportion of Traced Contacts	
25%	29.7
50%	28.2
60%	27.3
80%	25.9
100%	23.9
Variation in Lag in Tracing	
28-day	27.6
14-day	26.7
10-day	27.2
5-day	27.4
2-day	27.5
0-day	27.2
Combined Variation in Proportion and Lag in Tracing	
25% and 1-day	25.5
25% and no lag	19.3
50% and 1-day	22.4
50% and no lag	18.2
80% and 1-day	21.4
80% and no lag	16.5
100% and 1-day	20.0
100% and no lag	15.4

Table 2.4. Transmission fractions across network layers for intervention scenarios.

Scenario	Total	Household Layer		Community Layer	
	Cumulative Incidence	Cumulative Incidence	Proportion of Total	Cumulative Incidence	Proportion of Total
	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)	Median (95% SI)
No Intervention	96549.5 (96530.9, 96578.9)	58916.0 (58867.2, 58974.4)	61.0 (60.1, 61.1)	37653.0 (37581.9, 37686.3)	39.1 (38.9, 39.0)
Variation in Proportion of Traced Contacts[1]					
25%	95633.5 (95607.3, 95675.3)	58425.5 (58354.6, 58474.5)	61.1 (61.0, 61.1)	37225.5 (37175.0, 37278.5)	38.9 (38.9, 39.0)
50%	94862.0 (94786.4, 94898.9)	57964.0 (57855.8, 58005.4)	61.1 (61.0, 61.1)	36927.0 (36854.4, 36969.7)	38.9 (38.9, 39.0)
60%	94477.0 (94448.4, 94594.6)	57752.0 (57705.6, 57832.4)	61.1 (61.1, 61.2)	36730.0 (36678.5, 36816.6)	38.9 (38.8, 38.9)
80%	93990.5 (93889.0, 94067.4)	57486.5 (57442.6, 57577.8)	61.2 (61.1, 61.3)	36454.5 (36394.8, 36541.2)	38.8 (38.7, 38.9)
100%	93437.0 (93312.8, 93523.6)	57189.0 (57118.7, 57283.6)	61.2 (61.2, 61.3)	36238.5 (36149.4, 36284.7)	38.8 (38.7, 38.8)
Variation in Lag in Tracing[2]					
28-day	94550.5 (94498.9, 94652.5)	57764.5 (57724.3, 57854.7)	61.1 (61.0, 61.2)	36774.5 (36730.9, 36841.6)	38.9 (38.8, 38.9)
14-day	94529.0 (94497.9, 94616.7)	57767.0 (57739.7, 57852.5)	61.1 (61.1, 61.2)	36771.5 (36714.5, 36807.9)	38.9 (38.8, 38.9)
10-day	94482.0 (94428.2, 94566.6)	57678.0 (57638.6, 57777.4)	61.1 (61.0, 61.1)	36798.5 (36732.2, 36846.6)	38.9 (38.9, 39.0)
5-day	94548.0 (94499.2, 94608.1)	57836.5 (57779.4, 57904.9)	61.2 (61.1, 61.2)	36717.5 (36654.8, 36768.2)	38.8 (38.8, 38.9)
2-day	94506.5 (94434.2, 94557.2)	57771.5 (57688.2, 57820.4)	61.1 (61.1, 61.2)	36707.5 (36677.1, 36805.7)	38.9 (38.8, 38.9)
0-day	94528.0 (94467.3, 94604.1)	57806.5 (57713.8, 57874.4)	61.1 (61.1, 61.2)	38742.0 (36676.3, 36806.9)	38.9 (38.8, 38.9)
Combined Variation in Proportion and Lag in Tracing					
25% and 1-day	95434.5 (95411.2, 95485.0)	58305.0 (58279.8, 58404.3)	61.1 (61.1, 61.2)	37119.5 (37041.7, 37170.5)	38.9 (38.8. 38.9)
25% and no lag	95116.5 (95089.5, 95156.9)	58109.5 (58041.9, 58141.2)	61.1 (61.0, 61.1)	37053.0 (36980.3, 37082.9)	38.9 (38.9, 39.0)
50% and 1-day	94401.5 (94334.8, 94445.0)	57711.0 (57663.4, 57778.3)	61.2 (61.1, 61.2)	36668.0 (36621.3, 36719.8)	38.8 (38.8, 38.9)
50% and no lag	93913.0 (93824.3, 93971.6)	57422.5 (57347.3, 57471.2)	61.2 (61.1, 61.2)	36509.0 (36433.2, 36544.2)	38.8 (38.8, 38.9)
80% and 1-day	93486.5 (93364.5, 93539.9)	57100.5 (57034.9, 57196.3)	61.1 (61.1, 61.2)	36328.0 (36271.8, 36401.5)	38.9 (38.8, 38.9)
80% and no lag	92576.0 (92526.0, 92706.0)	56600.0 (56563.1, 56731.6)	61.1 (61.1, 61.2)	35940.5 (35930.6, 36006.7)	38.9 (38.8, 38.9)
100% and 1-day	92842.0 (92698.4, 92904.5)	56775.5 (56703.0, 56842.6)	61.2 (61.1, 61.2)	36009.0 (35949.4, 36107.8)	38.8 (38.8, 38.9)
100% and no lag	91743.0 (91628.0, 91820.3)	56067.5 (56009.5, 56174.7)	61.1 (61.1, 61.2)	35637.5 (35581.2, 35682.8)	38.9 (38.8, 38.9)

[1]A baseline lag in time to index case interview from positive test date was set at 2 days.

[2]A baseline fraction of traced contacts was set at 60%.

Abbreviations: SI, simulation interval.

Figure 2.5. ICU admissions over time for intervention scenarios. Number of individuals admitted to an intensive care unit (ICU). Time over peak ICU capacity levels is displayed as inset.

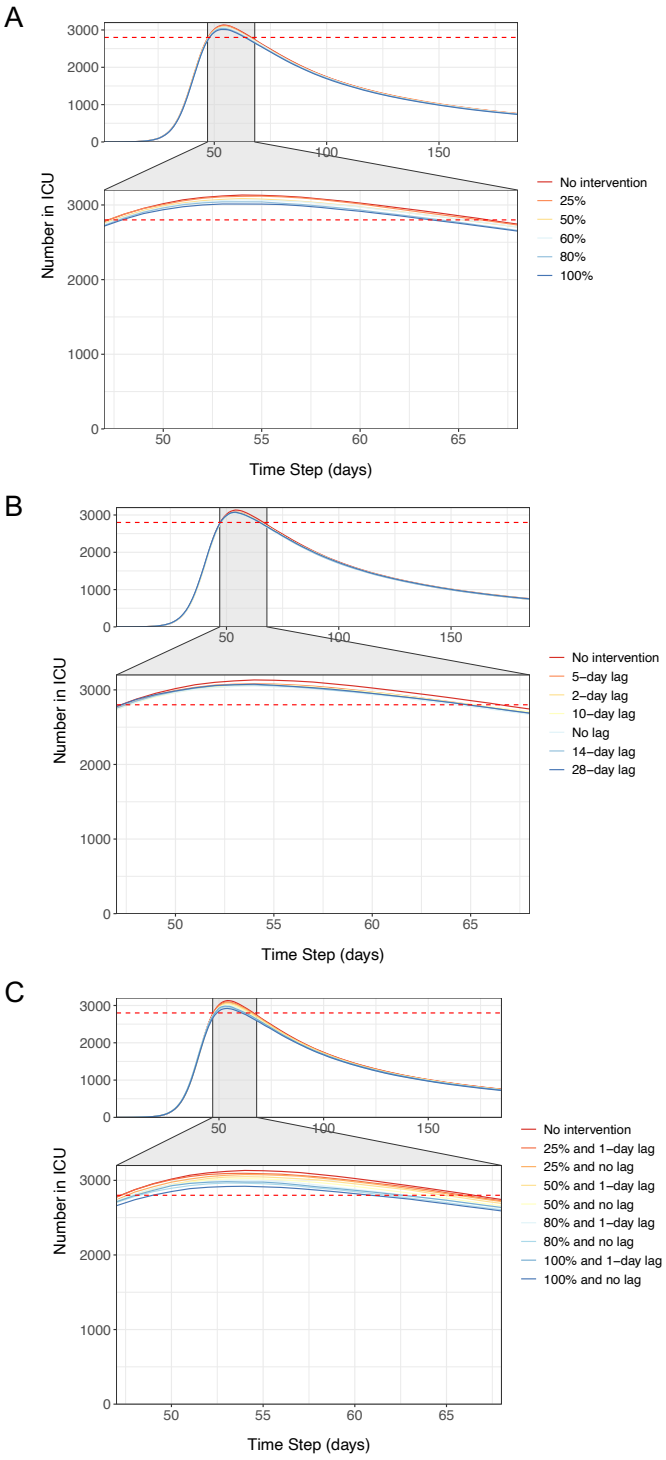


Table 2.5. Number and length of time over ICU capacity by intervention scenario.

Scenario	Peak number of ICU admissions over capacity	Total number of days over capacity
	Median (95% SI)	**Median (95% SI)**
No Intervention	337.5 (329.8, 365.3)	19.0 (18.5, 19.7)
Variation in Proportion of Traced Contacts[1]		
25%	334.5 (316.1, 347.4)	19.0 (18.4, 19.4)
50%	283.5 (274.8, 315.2)	17.0 (17.0, 18.3)
60%	277.5 (261.8, 302.4)	17.0 (16.7, 18.3)
80%	259.0 (237.3, 277.3)	17.0 (15.5, 17.0)
100%	220.5 (209.2, 251.8)	15.0 (15.0, 16.2)
Variation in Lag in Tracing[2]		
28-day	270.5 (266.5, 304.7)	17.5 (16.9, 18.2)
14-day	271.0 (260.7, 299.5)	17.5 (16.4, 18.0)
10-day	277.0 (265.1, 298.4)	17.0 (16.8, 18.1)
5-day	296.0 (276.9, 311.3)	17.5 (17.0, 18.0)
2-day	286.0 (267.9, 299.8)	17.0 (16.7, 17.9)
0-day	274.5 (242.7, 281.0)	17.0 (16.1, 17.3)
Combined Variation in Proportion and Lag in Tracing		
25% and 1-day	311.5 (292.4, 325.1)	18.0 (18.0, 19.0)
25% and no lag	292.5 (271.1, 309.5)	18.0 (17.2, 18.7)
50% and 1-day	261.0 (247.6, 277.8)	17.0 (16.2, 17.5)
50% and no lag	237.0 (211.8, 262.1)	16.0 (15.2, 16.9)
80% and 1-day	232.5 (194.9, 240.2)	15.0 (14.1, 16.0)
80% and no lag	179.5 (151.6, 198.9)	13.0 (12.2, 14.3)
100% and 1-day	200.5 (184.2, 219.3)	14.5 (13.8, 15.4)
100% and no lag	126.0 (117.1, 157.4)	11.0 (10.6, 12.8)

[1]A baseline lag in time to index case interview from positive test date was set at 2 days.
[2]A baseline fraction of traced contacts was set at 60%.
Abbreviations: SI, simulation interval.

Figure 2.6. Eligible contacts for contact tracing by intervention scenario. Number of individuals identified as contacts and who were eligible for contact tracing over time.

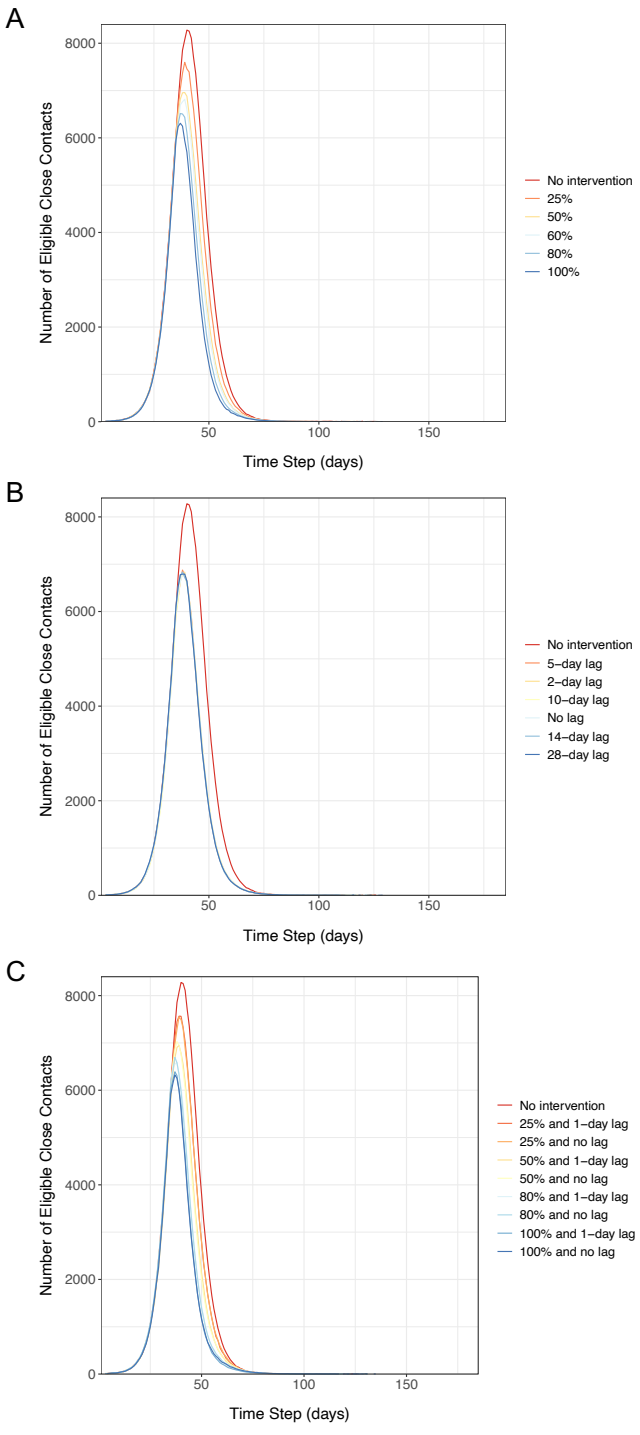
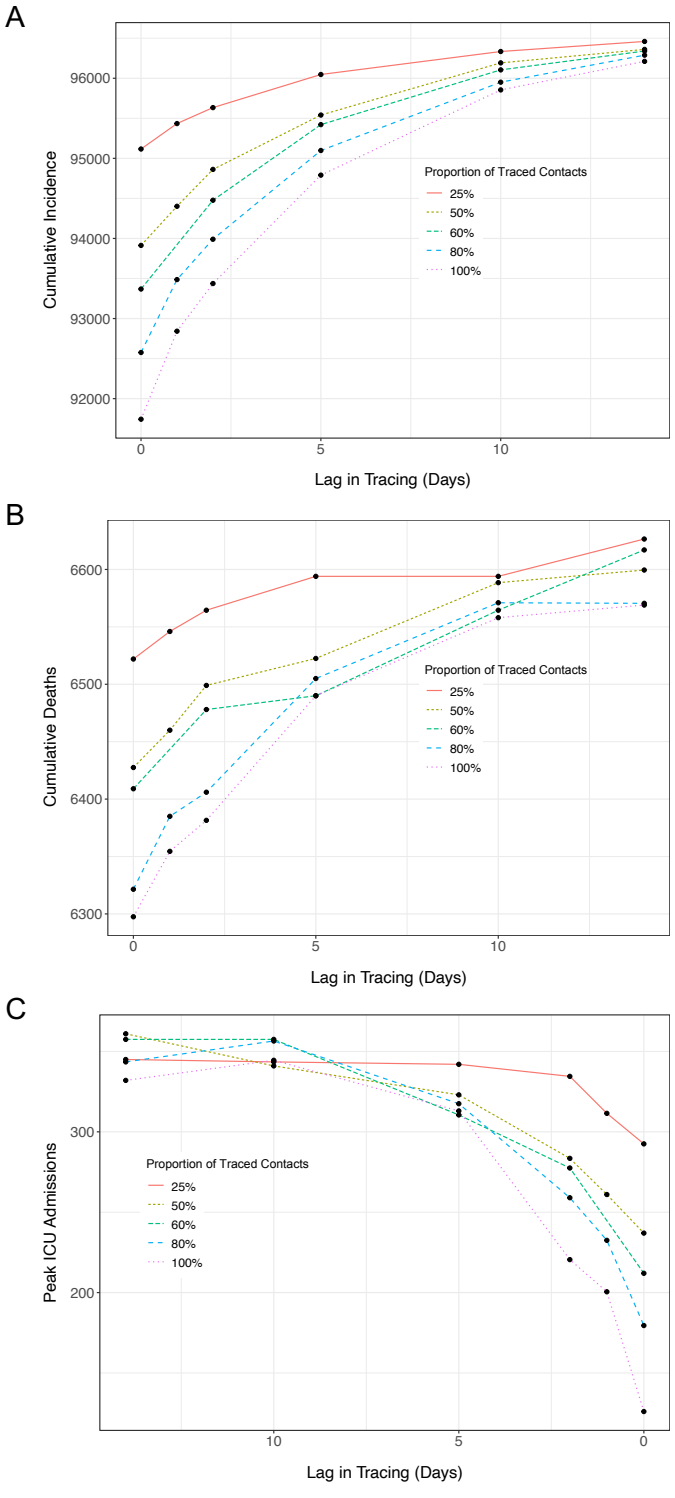


Figure 2.7. Relationship between combined interventions and outcomes. (A) Cumulative incidence, (B) cumulative deaths, and (C) number of intensive care unit (ICU) admissions over peak capacity and the relationship to proportion traced and lag in tracing.



Chapter 3: The application of social network analysis to examine COVID-19 contact tracing networks in a university setting

Abstract

Background

Despite the importance of underlying network structures in the spread of respiratory infectious diseases such as COVID-19, there are limited data on contact patterns relevant for the spread of disease in university settings. We constructed COVID-19 contact tracing networks within a university community to examine the role of individual characteristics and network structures on transmission during the 2020-2021 school year.

Methods

We used individual-level exposure histories collected through case investigation and contact tracing interviews performed by the Emory University contact tracing program during the hybrid Fall 2020 semester to construct contact tracing networks. Networks were visualized, and global network statistics and secondary attack rates (SAR) were estimated. We conducted a bias analysis using exponential random graph models (ERGMs) to simulate complete networks with imputed missing cases based on observed characteristics.

Results

During the Fall 2020 semester, we identified 441 COVID-19 cases, 1121 close contacts, and 1206 links between individuals. Most cases were female (62%), off-campus students (49%), and symptomatic (82%). The mean degree of the network was 2.9, and the maximum path length was 8. The overall SAR was 9.7, and contacts of symptomatic cases had a higher SAR compared to contacts of asymptomatic cases (11.8 vs. 4.9). Networks were minimally clustered with the highest levels of clustering observed in September (k=0.05). We found that bias analysis

assumptions including random sampling and sampling based on symptomaticity were inconsistent with the observed network.

Conclusions

In this assessment of contact tracing network structure and transmission characteristics of COVID-19 on the Emory University campus during the Fall 2020 semester, we found minimal clustering, a low proportion of asymptomatic cases, higher SAR among contacts of symptomatic cases, and observed that it was unlikely that symptomatic cases were oversampled in our observed network. Our findings suggest that university campuses have unique transmission characteristics, even in the context of a hybrid learning environment in which social interactions and contacts may be attenuated.

Introduction

The COVID-19 pandemic has had a severe global health impact, resulting in over 380 million cases and 5 million deaths to date.[1] The causative infectious agent, SARS-CoV-2, is transmitted via the respiratory route and spreads through both close and casual contacts.[284–286] Universities are unique locations from a social mixing perspective, as shared classrooms, dormitories, laboratories, and other campus spaces (e.g., dining halls, fitness centers, etc.) allow for both close and casual connections between students, faculty, and staff.[171,172] Given this diversity of settings, transmission risk of SARS-CoV-2 may be heterogenous across a university community. The heterogeneity of these interactions and social mixing patterns within a campus community complicate the dynamics of respiratory disease transmission; however, a better understanding of the network structures in this setting can provide insight into what factors may help drive the spread of infection.

Although several studies have documented social mixing patterns with respect to the spread of infectious diseases in the general population,[174–177] few have focused on examining patterns in school settings.[178,179] Universities have been described as 'small-world networks',[183] which are networks in which any two individuals can be connected through only a small number of other people. These networks are further characterized by having 'hubs', or certain individuals in the network who have a very high number of contacts that connect many other individuals in the network. Among studies conducted at the university-level,[180] both high and low enrollment courses have been identified as powerful connectors of students within a university, in that they make both a large number of connections as well as act as a unique connection between students.[182] Further, certain types of students (e.g., those in highly populated majors or double-

majors) act as unique connectors across university networks.[182] There are scarce data extending these school-level contact networks to infectious disease transmission networks.

Advances in individual electronic sensors and modeling analyses have made it possible to construct and estimate social network structures relevant for the transmission of respiratory diseases.[184] Modeling studies incorporating social network structure have found that infectious diseases have the potential to spread quickly in small-world networks, as would be found in universities. However, context-specific network structure, such a subtle differences in the number or type of contacts, can influence both the speed and extent of disease transmission.[185] Given the importance of underlying network structures to infectious disease transmission dynamics, combined with the lack of availability of individual-level contact pattern and disease data within a university setting, further empirical studies are needed to better estimate contact structures in dynamic infectious disease models.[187]

Universities are also likely to have unique transmission characteristics for respiratory pathogens. A closer look at social network structures, risk factors for infection, and potentially under-surveilled groups will be critical to develop a comprehensive understanding of transmission dynamics and contact structures in this setting that will enable the design of improved campus prevention strategies for future epidemics. Information from individual-level datasets including contact tracing programs can provide estimates on secondary attack rates, assess risk factors for infection, and allow for documentation of chains of transmission.[287] The aim of this study was to construct a COVID-19 contact tracing network within a university community in order to examine the importance of individual characteristics and network structures. We utilized individual-level exposure histories collected through case investigation and contact tracing interviews to construct

and assess the social networks of COVID-19 cases and their contacts on a medium-sized, private university in the U.S. during the 2020-2021 school year.

Methods

Data Source

Data for this analysis came from the Emory University Contact Tracing Program. The Emory University Contact Tracing Program was created in response to the COVID-19 pandemic in preparation for the re-opening of the university in the Fall of 2020. The program utilizes a REDCap database to capture and store the information they gather through case investigation and contact tracing interviews for index cases and their reported close contacts. The database contains extensive information on diagnosed cases and their reported close contacts. Information collected via interviews included demographics, university affiliations, location information, travel and close contact data, testing information, symptoms and risk factors, and dates of isolation and quarantine.

Study Population

The study population for this analysis included all confirmed COVID-19 cases and their elicited close contacts during the Fall 2020 semester (August 17, 2020–December 19, 2020). Emory University had a hybrid-learning environment during this time period.

Definitions

A confirmed case was defined as an individual who had a positive COVID-19 test results from any University source, including saliva RT-PCR and nasopharyngeal RT-PCR test performed at testing sites on the university campus. A confirmed close contact was an individual who was

reported by an index case to have been within six feet of an infected person for ≥15 minutes during two days before illness onset (or positive specimen collection for asymptomatic cases) until the isolation date of the infected person, regardless of mask usage.

Network Structure

To define the contract tracing network structure, we created edge and node lists to construct the empirical contact tracing networks on the Emory University campus during the Fall 2020 semester. The edge list was a record of the directed nominations of contacts by cases in the network. These relationships were determined via manual review of index case interview notes taken by case investigators to identify all elicited close contacts for each index case. The node list was a compilation of all of the individuals in the network (i.e., index cases and elicited close contacts) along with their corresponding attributes (e.g., sex, race, symptomaticity, university affiliation, month of test date, and county of residence).

Known clusters and outbreaks

There were a number of known clusters and outbreaks that occurred at Emory University during the Fall 2020 semester. A dichotomous variable was created for all index cases and close contacts known to be affiliated with a cluster or outbreak as determined by the contact tracing program and the university cluster investigation team via weekly review of index case investigation interview notes. Stratification of certain analyses was performed using this indicator as isolated clusters and outbreaks may inherently have different global network statistics compared to the full empirical network.

Statistical Analysis

The empirical contact tracing network was built and visualized with the 'igraph' package in R.[288] Demographic, clinical, and network characteristics were analyzed using the statnet suite of R packages.[289] Global network statistics were estimated for the empirical network and were stratified by month of index case test date. Calculated global network statistics included are listed below and displayed in Figure 3.1:

- *degree distribution*: number of direct connections an individual to others in the network
- *path length:* the number of connections that separate any two nodes in the network
- *degree centrality*: measure of the 'connectedness' of an individual in the network to other individuals
- *betweenness centrality*: measure of the proportion of the paths between other nodes that pass through an individual node
- *clustering coefficient:* measure of the degree to which individuals tend to cluster together (when two nodes connect to a third)

Secondary attack rates were estimated for the observed network and networks stratified by month.

Bias Analyses

A bias analysis was performed on the empirical network via sampling methods to estimate the full (unobserved) network. Although sampled networks do not necessarily contain all possible nodes and edges compared to the true, complete network (in which all cases had been detected and all close contacts had been elicited), inferences about the complete network are still able to be made

given certain assumptions about cases included and excluded in the sampled network regarding their transmission potential.[290] An important violation of these assumptions may include exclusion of very highly connected cases; however, as testing protocols were implemented and enforced throughout Emory's re-opening, we assumed that cases sampled and cases excluded are not systematically different with regard to their transmission potential.

We used exponential random graph models (ERGMs) to simulate complete networks with imputed missing cases based on information from the observed network including demographic, symptom, month of test date, and affiliation covariates to estimate the propensity of nodes to create edges in the network.[291] These models were modeled using the ergm R package.[292,293] The size of the full, unobserved network was estimated based upon local seroprevalence estimates[294], in addition to testing protocols and aggregated adherence data collected by the university for students, faculty, and staff throughout the Fall 2020 semester (Table 3.1). For each scenario, we simulated 1,000 complete contact tracing networks. We assumed a complete network size of 1,200 for our analyses. The missing network data scenarios tested were: 1) cases missing at random; and 2) asymptomatic cases are more likely to be missing from the observed network. For each modeled network, we sampled a similar number of cases (n = 450) as the observed network (Figure 3.2). We aimed to examine the scenarios and their similarity to the observed network. Quantiles of degree distribution were compared between observed and modeled networks, and 2-sided p-values were calculated using a modified Kolmogorov-Smirnov test calculated using boot-strapping techniques.[295–297]

All analyses were performed in R version 4.1.2 (Vienna, Austria). This study was approved by the Emory University IRB.

Results

During the Fall 2020 semester, Emory University identified 441 COVID-19 cases. The majority (49%) of cases were off-campus students, followed by faculty and staff (40%) and on-campus students (11%) (Table 3.2). Less than half (38%) of cases were male, and most (82%) were symptomatic. Almost one-third (28%) of cases were between 17-22 years of age, with one-quarter of cases falling into the 23-28 years of age group. Approximately half of cases (46%) lived in DeKalb County. The largest proportion of cases were diagnosed in December (39%) and November (31%).

The observed contact tracing networks and their global network statistics stratified by month of index case diagnosis are displayed in Figure 3.2 and Table 3.3. The number of both cases and contacts increased over time, from 15 cases and 34 contacts in August to 174 cases and 424 contacts in December. The number of connections between nodes in the network (edges) was 1,206 in the full Fall 2020 network. There were 43 (9.7%) cases with no links (degree = 0). The number of edges similarly increased by month, from 35 in August to 439 in December. The maximum path length between two nodes was 8. The highest levels of clustering occurred in September (clustering coefficient = 0.05) followed by November (clustering coefficient = 0.03). Across all months, November displayed the highest degree, longest path length, and largest betweenness centrality measures across the stratified monthly contact tracing networks. There were cases involved in a cluster investigation by the university from September to October, with the proportion of nodes involved in a cluster investigation increasing over time from 5% of the network in September, to 7% of the network in October, to 16% of the network in November.

Degree distributions are displayed in Figure 3.3. In the Fall 2020 contact tracing network, each case had an average of 2.9 contacts (mean network degree), with the highest mean degree in October (3.4) followed by September (3.2). The maximum degree of the full network was 20, which was observed in both October and November. The median degree of the Fall 2020 network was 2, with 1 and 4 degrees as the 25^{th} and 75^{th} percentiles, respectively. Mean degree tables stratified by index case characteristics are further detailed in the **Chapter 3 Technical Appendix**.

The proportion of cases with a specified number of close contacts was calculated and is displayed in Figure 3.4. From September to December, approximately half of all cases had two or fewer close contacts. Over 10% of all cases in the Fall 2020 network had ≥6 contacts. In contrast, almost one-third of cases associated with a “known” cluster investigation had greater than five or greater close contacts.

Secondary attack rates (SAR) differed across month and between symptomatic and asymptomatic cases (Table 3.5). The overall SAR for the Fall 2020 semester was 9.7, and monthly SAR ranged from 3.4 in October to 14.2 in November. When stratifying by symptomaticity of the index case, the SAR was greater among contacts of symptomatic cases in comparison to that among contacts of asymptomatic cases. During the Fall 2020 semester, the SAR among contacts of symptomatic cases was 11.8, and among contacts of asymptomatic cases was 4.9. Among all close contacts that converted into a case, 16% (8/50) were epidemiologically linked to an asymptomatic case.

Our bias analysis assumption that cases were sampled randomly from the complete network was inconsistent with our observed network (Table 3.6 and Figure 3.5A). Models with a mean degree

of 5 under this scenario could reproduce the 25th percentile and median of the observed degree distribution (1 and 2 degrees, respectively). However, models with a mean degree of 8 were required to reproduce the 75th percentile of the observed degree distribution (4 degrees). P-values suggested that none of the randomly sampled models were consistent with the observed network.

Sampling cases differentially by symptomaticity did not produce different results based upon the proportion of symptomatic cases (Table 3.6 and Figure 3.5B). Results for this assumption were similar to those for the randomly sampled network with a mean degree of 5. P-values suggested that none of our modeled networks were consistent with the observed network, likely due to the inability of the modeled networks to capture the highly connected individuals in our observed network.

Discussion

In this study, we constructed the contact tracing networks of COVID-19 on the Emory University campus to examine network structures and assess the importance of risk factors for transmission on a university campus. Contact tracing networks were minimally clustered, suggesting either a high amount of missing data from the network, or immediate discontinuation of transmission propagation through the work of the contact tracing program in reaching cases and contacts, or self-imposed isolation and quarantine by individuals. As observed through our bias analyses, missingness in our observed contact tracing network was unlikely to have been random, and it may have been possible that we oversampled more highly connected individuals via the university contact tracing protocols and cluster investigations performed throughout the semester. The individual-level exposure information captured for this analysis allowed for key network structures and characteristics to be described for this unique population and helps set the groundwork for

future transmission network studies within a university population.

Asymptomatic cases comprised less than 20% of index cases during the Fall 2020 semester, which is lower than published estimates that have described estimates around 35-40%.[41] The frequency of asymptomatic infection was a motivating factor for one of our bias analysis scenarios. SAR were substantially greater among contacts of symptomatic cases compared to among contacts of asymptomatic cases. This finding is consistent with several other studies, including household contact studies that have observed a limited role of asymptomatic index cases in household transmission.[298] This may suggest a similarly limited role of asymptomatic cases on university campuses for transmission in this setting.

The mean degree for on-campus students was greater than that for both off-campus students and faculty/staff, which may highlight the more connected nature of undergraduate university students. Similarly, the mean degree was the highest for the youngest age group (17-22 years), again emphasizing the differences in individual social network size across age groups. Interestingly, mean degree decreased for the age groups spanning 23-40 years of age, and subsequently increased for individuals >40 years old. This may reflect differences in life events that occur across ages, such as transitions to home ownership or parenthood. Our findings are consistent with general trends in social network size across the life span.[299] Mean degree was highest during the middle of the semester (October), which may suggest extracurricular activities or other opportunities for contact were more prevalent during this time.

It is important to consider the impact of the hybrid nature of Emory's campus during the Fall 2020 semester, in which most classes were remote, with mainly undergraduates living on campus in

single dormitory rooms (no roommates). This may have had an impact on their mean degree estimates as well as the clustering coefficients calculated for the networks, in that our observed estimates may be attenuated compared to what would be seen in a more typical university setting. Clustering has been a common observation among university networks, thus our finding of minimal clustering for cases and close contacts was unexpected. Recent work has reported that non-student resident populations near a university setting restricted their movement patterns more so than residents of neighboring counties, which may have also contributed to our findings.[300]

While none of the bias analysis models were able to fully explain the observed network, this may suggest that other scenarios we did not test may help to better explain observed network distributions. For example, although testing protocols were taken into account when estimating the full size of the network, we did not assess whether different testing protocols would have helped to explain the full network. While we assumed that symptomatic individuals were oversampled in our observed network, we could have also assumed that individuals with more rigorous testing protocols were oversampled in our network. This could have been implemented by undersampling on-campus students (with or without off-campus students). Interestingly, we found similar results for modeled networks in which either 60% or 40% of cases were symptomatic. This is the opposite of what we had hypothesized, in which symptomatic cases were preferentially sampled based upon their higher testing rates as asymptomatic cases may not know they are infected, and thus may never get tested. This apparent discrepancy may indicate that standard testing protocols, even at infrequent intervals, may be enough to capture asymptomatic cases. Moreover, the university population may be more inclined to perform screening tests regularly. To capture the more highly connected individuals in our network, it may also be

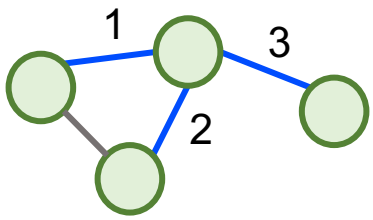
important to test whether a super-spreading factor may help to explain the observed network – that is, whether or not there was a factor strongly related to having a high degree in a minority of cases.

There are several limitations to this work. First, due to the self-reported nature of close contact elicitation, close contacts are likely missing from the observed network due to recall or social desireability biases. Second, we calculated the SAR only among Emory-affiliated contacts as testing information was not available for individuals outside of Emory. As a result, these estimates may be impacted for contacts of symptomatic and/or asymptomatic cases. Third, the university campus used for these analyses is a heterogenous population, and although we aimed to capture some of this through our bias analyses, we were likely unable to account for all major sources of bias. Fourth, we recognize the population and environment of our setting does not reflect that of many university campuses, so network and transmission characteristics described here may be limited in their generalizability to other university settings.

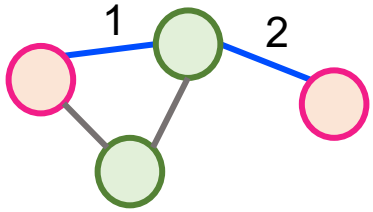
In this assessment of contact tracing network structure and transmission characteristics of COVID-19 on the Emory University campus during the Fall 2020 semester, we found minimal clustering, a low proportion of asymptomatic cases, higher SAR among contacts of symptomatic cases, and observed that it was unlikely that symptomatic cases were oversampled in our observed network. Our findings suggest that university campuses have unique transmission characteristics, even in the context of a hybrid learning environment in which social interactions and contacts may be attenuated. These results build further upon the work that has been done examining contact structures on university campuses, and how these structures may affect transmission of respiratory infections. Future work may apply these and other methods to

university campuses to better inform targeted prevention strategies in preparation for future outbreaks.

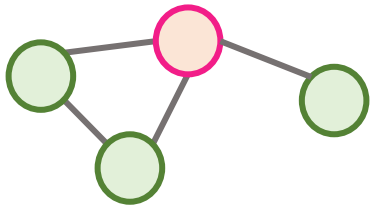
Figure 3.1. Visualization of global network statistics calculated for all networks. Visualizations for global network statistics including degree, path length, degree centrality, betweenness, and clustering.



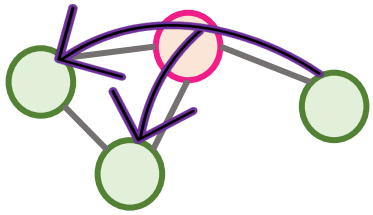
degree



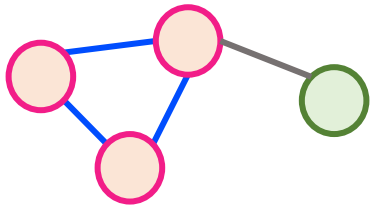
path length



degree centrality



betweenness



clustering

Figure 3.2. Depiction of network model sampling for bias analyses. Full unobserved networks were simulated and networks were sampled given tested scenarios for a similar number of observed cases.

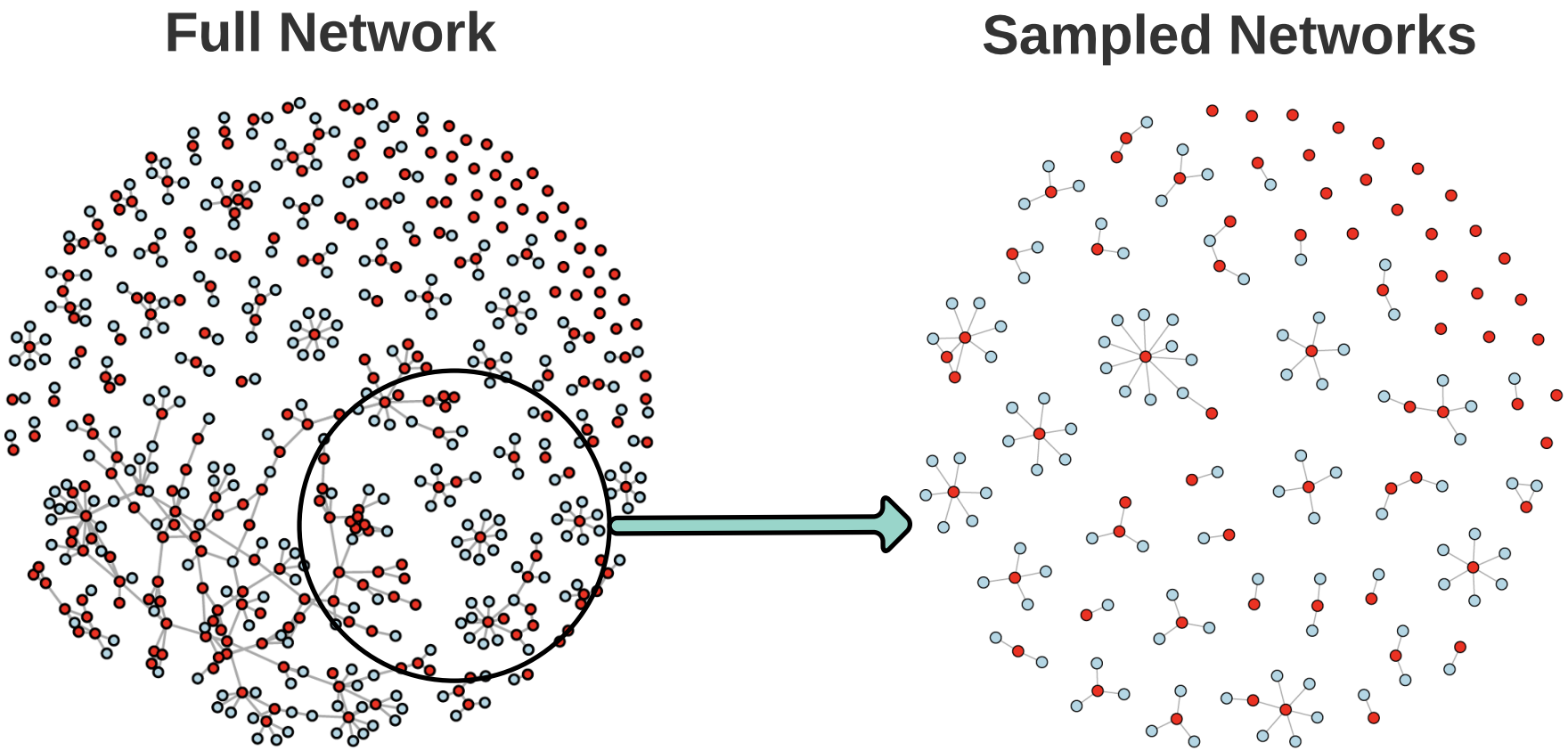


Table 3.1. Testing protocols implemented by Emory University for on- and off-campus students, faculty, and staff throughout the Fall 2020 semester.

	2020				
	August	**September**	**October**	**November**	**December**
Students - On Campus	Testing required before return to campus. Follow-up testing in late August.	Testing once a week.	Testing once a week.	Testing once a week. Transition to saliva-based collection begins November 16 and fully in-place by November 25.	Testing once a week.
Students - Off Campus	Testing required before return to campus.	Testing required before return to campus.	Testing required before return to campus.	Testing required before return to campus.	Testing required before return to campus.
Faculty/Staff	Testing required before return to campus.	Testing required before return to campus.	Testing required before return to campus.	Testing required before return to campus.	Testing required before return to campus.

Table 3.2. Characteristics of index cases during the Fall 2020 semester at Emory University (N = 441).

	N (%)
Characteristics	
Affiliation	
On-Campus Student	48 (11)
Off-Campus Student	215 (49)
Faculty/Staff	176 (40)
Male	166 (38)
Symptomatic	362 (82)
Headache	252 (57)
Fatigue	234 (53)
Cough	218 (49)
Loss of taste/smell	135 (31)
Fever	75 (17)
Shortness of breath	64 (15)
Age group	
17-22 years	122 (28)
23-28 years	111 (25)
29-40 years	99 (22)
>40 years	104 (24)
Race	
Black	11 (26)
White	239 (54)
Asian	55 (12)
Other	
Non-Hispanic/Latino	381 (86)
County	
DeKalb	201 (46)
Fulton	83 (19)
Gwinnett	39 (9)
Month of test	
August	15 (3)
September	50 (11)
October	63 (14)
November	139 (31)
December	174 (39)

Figure 3.2. Empirical contact tracing networks at Emory University during the Fall 2020 semester. Contact tracing networks stratified by month of index case diagnosis from August to December. Cases and contacts involved in a cluster investigation are indicated.

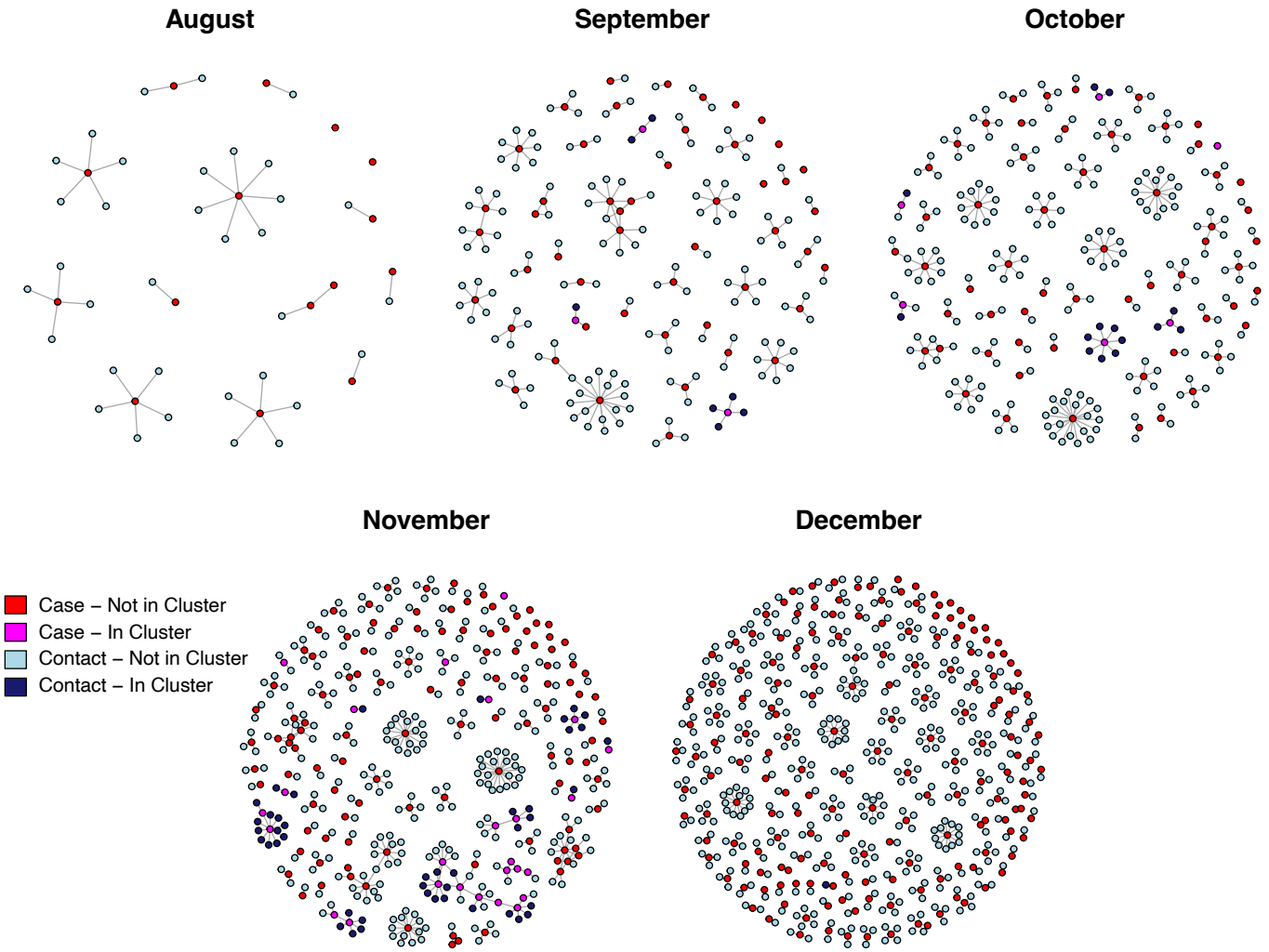


Table 3.3. Global network statistics of empirical contact tracing networks.

	Fall 2020	August	September	October	November	December
Number of nodes	1,562	49	188	274	453	598
Number of cases	441	15	50	63	139	174
Number of contacts	1,121	34	138	211	314	424
Number of edges	1,206	35	153	216	371	439
Median degree (IQR)	2 (1,4)	1 (1,4.5)	2.5 (1,4)	3 (1,4)	2 (1,4)	2 (1,4)
Mean degree	2.9	2.4	3.2	3.4	3.0	2.5
Maximum degree	20	7	17	20	20	12
Median shortest path length (IQR)	2 (1,2)	2 (1,2)	2 (1,2)	2 (1,2)	2 (2,3)	2 (1,2)
Minimum path length	1	1	1	1	1	1
Maximum path length	8	2	4	4	8	4
Maximum betweenness centrality	20	1	12	3	20	3
Clustering coefficient	0.02	0.0	0.05	0.01	0.03	0.01

Abbreviations: IQR, interquartile range.

Figure 3.3. Degree distribution of empirical contact tracing networks. Contact tracing network degree distributions stratified by month of index case diagnosis.

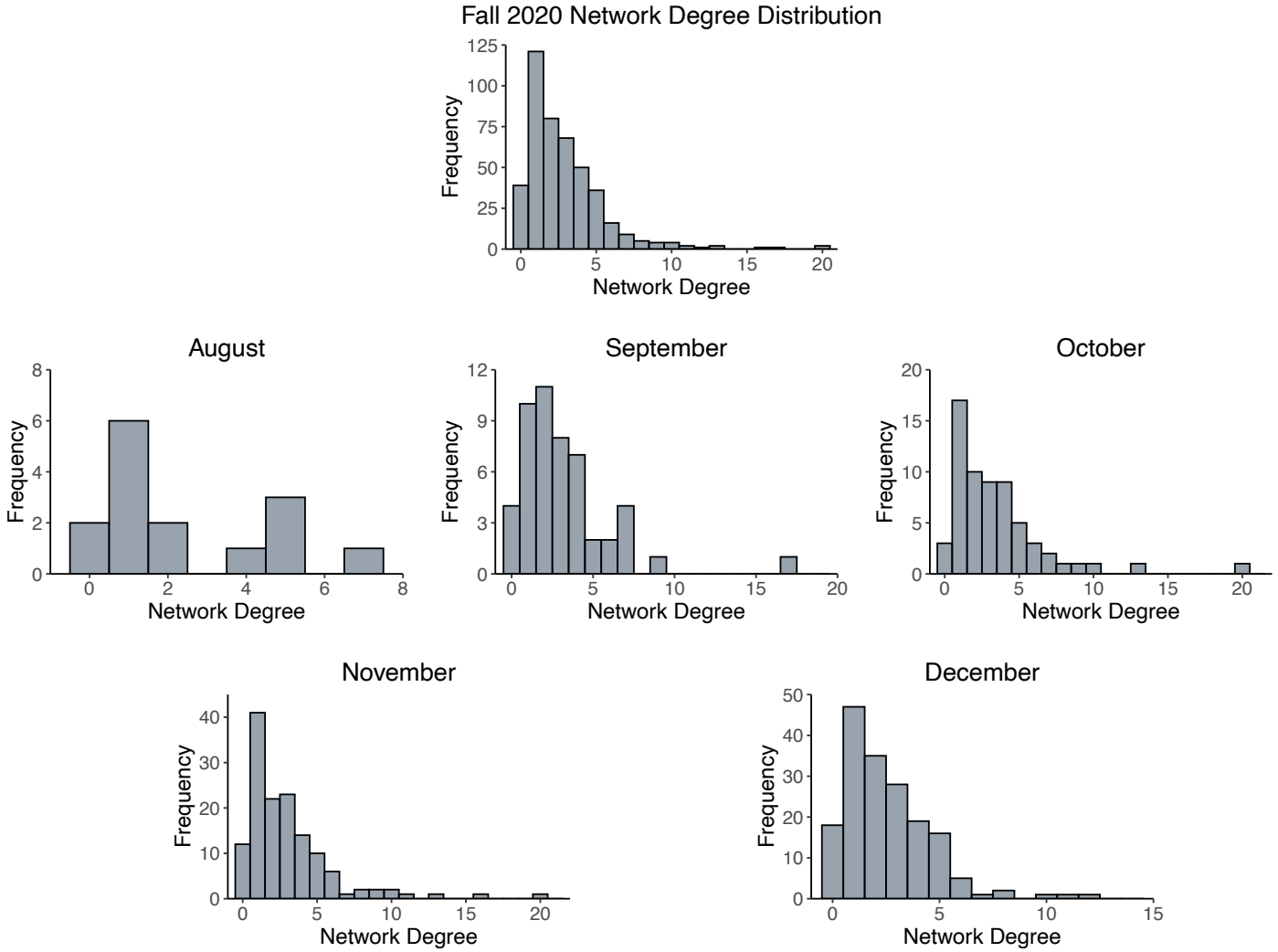


Figure 3.4. Distribution of the proportion of cases with certain number of contacts. Distributions stratified by month of index case diagnosis for the number of close contacts reported by index cases.

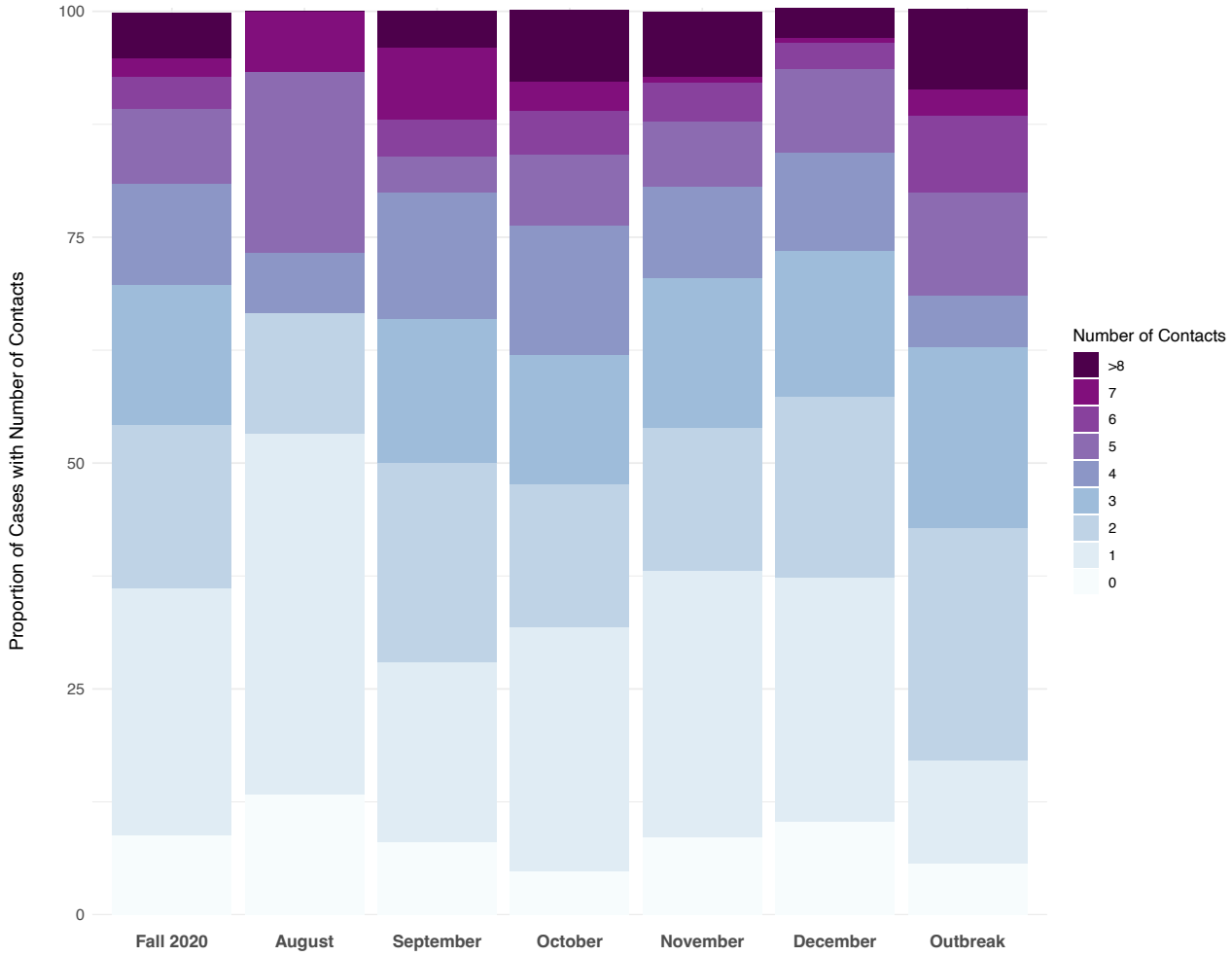


Table 3.5. Secondary attack rates stratified by symptomaticity of index case and index case test date month.

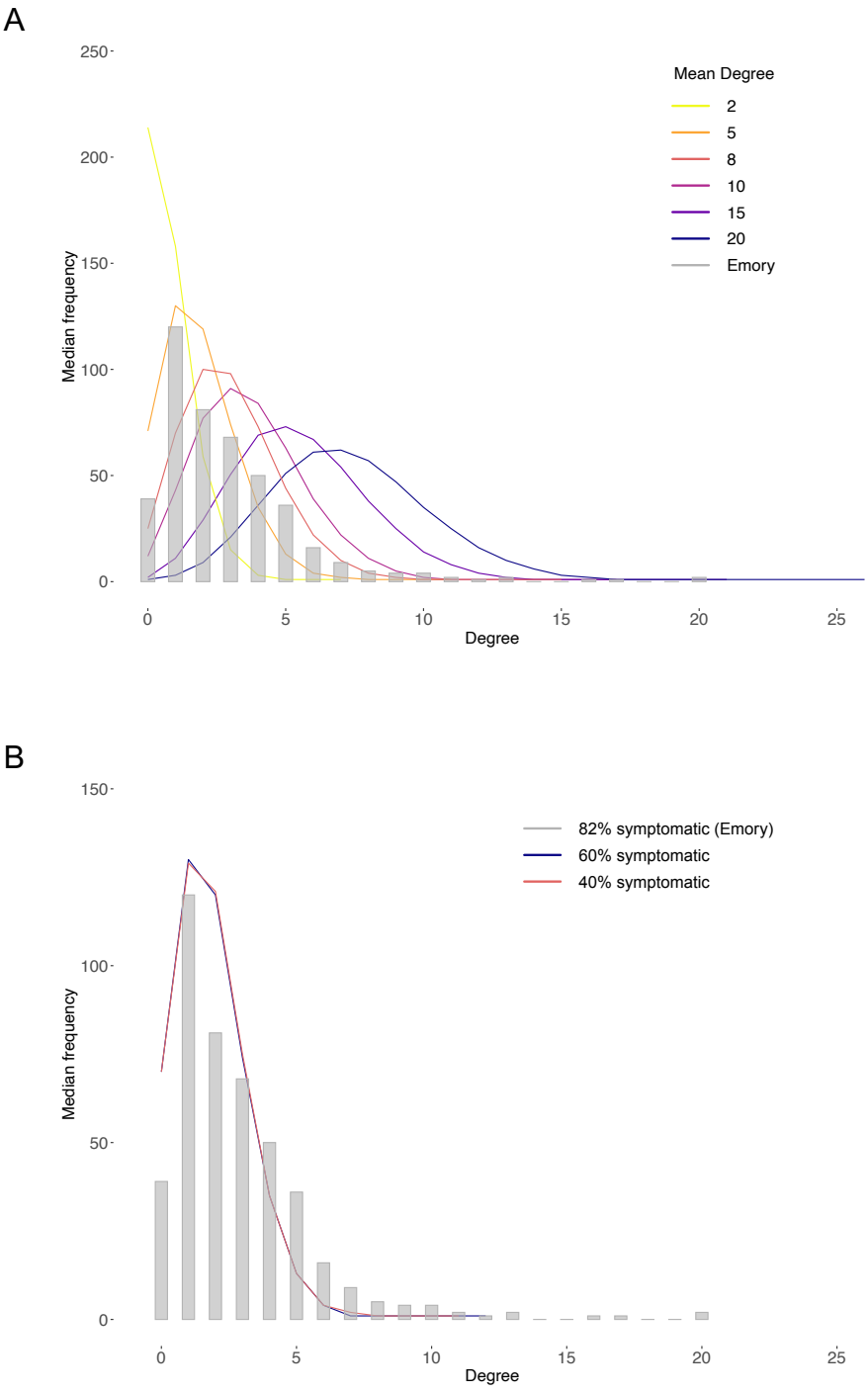
	Fall 2020	August	September	October	November	December
Proportion of cases that were symptomatic	82.1	86.7	82.0	81.0	80.6	83.3
Proportion of cases that were asymptomatic	17.9	13.3	18.0	19.0	19.4	16.7
Number of contacts	518	9	93	89	210	118
Number of cases among contacts	50	1	8	3	30	8
Overall secondary attack rate	**9.7**	**11.1**	**8.6**	**3.4**	**14.2**	**6.8**
Number of symptomatic cases	362	13	41	51	112	145
Number of contacts	356	8	61	62	144	82
Number of cases among contacts	42	1	7	3	24	7
SAR for symptomatic cases	**11.8**	**12.5**	**11.5**	**4.8**	**16.7**	**8.5**
Number of asymptomatic cases	79	2	9	12	27	29
Number of contacts	162	1	32	27	66	36
Number of cases among contacts	8	0	1	0	6	1
SAR for asymptomatic cases	**4.9**	**0.0**	**2.6**	**0.0**	**9.1**	**2.8**

All calculations were performed among Emory-affiliated close contacts.
There was N = 1 Emory-affiliated close contact that was elicited in two separate months.
There were N = 2 cases that were counted twice as they were elicited as a contact in one month and converted into an index case in the following month (1 case in both September and October and 1 case in October and November).
Abbreviations: SAR, secondary attack rate.

Table 3.6. Target statistics for observed and modeled networks.

Scenario	Degree Distribution			p-value
	25th Percentile	Median	75th Percentile	
Observed Network Target Statistics	1	2	4	
Random sampling				
2 degrees	0 (0–0)	1 (1–1)	1 (1–1)	0 (0–0)
5 degrees	1 (1–1)	2 (2–2)	3 (3–3)	0 (0–0.001)
8 degrees	2 (2–2)	3 (3–3)	4 (4–4)	0.001 (0–0.002)
10 degrees	2 (2–2)	4 (3–4)	5 (5–5)	0.002 (0.001–0.003)
15 degrees	4 (4–4)	5 (5–5)	7 (7–7)	0.001 (0–0.002)
20 degrees	5 (5–5)	7 (7–7)	9 (9–9)	0 (0–0)
Cases preferentially sampled by symptomaticity				
40/60 symptomatic/asymptomatic	1 (1–1)	2 (2–2)	3 (3–3)	0 (0–0.001)
60/40 symptomatic/asymptomatic	1 (1–1)	2 (2–2)	3 (3–3)	0 (0–0.001)

Figure 3.5. Degree distributions of observed and modeled networks. Median frequencies of mean degrees for observed and modeled networks for (A) randomly sampled cases and (B) cases sampled based upon symptomaticity.



Chapter 4: The impact of COVID-19 national lockdowns on drug-resistant tuberculosis in KwaZulu-Natal, South Africa: a spatial analysis

Abstract

Background

Observed declines in case notifications for tuberculosis (TB) associated with the COVID-19 pandemic are not yet well understood. Quantifying changes in TB diagnoses and their spatial distribution throughout the pandemic is needed to identify the impact of COVID-19 mitigation strategies on TB control. We sought to understand the impact of COVID-19 mitigation strategies on drug-resistant (DR) TB cases in KwaZulu-Natal, South Africa. Here we describe changes in the number, spatial distribution, and neighborhood characteristics of DR TB cases before and after the COVID-19 national lockdowns.

Methods

We collected individual-level information on drug-resistant (DR) TB cases from a prospective cohort study of all culture-confirmed DR TB patients diagnosed in KwaZulu-Natal province. We utilized two populations: 1) the provincial population (all DR TB patients in the province) and 2) the enrolled cohort population (those who fell into the eThekwini Cohort catchment area) which is a subset of the provincial population. Population-level demographic information and census data came from Statistics South Africa. Time periods before and after the pandemic national lockdowns were defined by the date of the lockdown announcement on March 26th, 2020. Individuals were stratified based upon their laboratory sample collection date. We examined patient characteristics and assessed spatial patterning of cases using spatial log relative-risk surface maps. To examine spatial predictors of DR TB incidence, we used Bayesian conditional autoregressive models accounting for spatial autocorrelation.

Results

Among the provincial population, there were 405 cases diagnosed prior to the COVID-19 national lockdowns and 288 after the lockdowns (29% decrease). Similarly, among the enrolled cohort, there were 95 cases diagnosed prior to the COVID-19 national lockdowns and 74 diagnosed after the lockdowns (22% decrease). Compared to cases diagnosed before the COVID-19 lockdowns, cases diagnosed after were less likely to have any source of fuel for heating (73% vs. 48%; p-value = 0.001) and were less likely to have either piped water (62% vs. 84%; p-value = 0.001) or a flush toilet (39% vs. 57%; p-value = 0.021). Across the province, there were two regions (one in the center of the province and one in the southern region) that had significantly greater relative risks for DR TB after the lockdowns.

Conclusions

We found a reduction in the number of diagnosed DR TB cases after the COVID-19 pandemic lockdowns in KwaZulu-Natal, South Africa, and observed that cases diagnosed after the lockdowns had worse living conditions, fewer household resources, and had more adults living in their household compared to before the pandemic. This work sheds light on the impacts of COVID-19 mitigation strategies on TB control in the context of reductions in both case notifications and diagnoses observed globally.

Introduction

Tuberculosis (TB) has been a leading cause of infectious disease morbidity and mortality worldwide for the past decade. Approximately 10 million individuals fell ill with TB in 2019, with 1.4 million deaths, including over 200,000 deaths among people with HIV.[188] The COVID-19 pandemic has significantly impacted rates of TB diagnosis, with an 18% decline in the number of cases in 2020 compared to 2019. There are large gaps between the number diagnosed and the number estimated to have developed active TB in 2020 (5.8 million versus 10 million).[260] With the prolonged nature of TB infection and disease,[257] reduced case notifications should not be considered a reflection of decreased incidence. Importantly, there has been a recorded increase in TB deaths to over 1.5 million, bringing the total back up to the level observed in 2017[260] – an observation that corroborates an increase in cases.

Disruptions in health care services for TB and other infectious diseases due to the COVID-19 pandemic have led to fewer available staff and laboratory tests.[301–305] Patients have also reported hesitance and unwillingness to visit health care facilities out of fear of contracting COVID-19 in these locations.[306,307] Further, longer periods of infectiousness, poor treatment outcomes, increased malnutrition, prolonged household TB exposure, and increased rates of unemployment leading to higher levels of poverty have all been described as potential consequences of the pandemic.[261,308] Concurrently, common COVID-19 mitigation strategies such as social distancing and mask wearing policies may have had beneficial effects by reducing the transmission of respiratory pathogens such as TB.[309,310] Restrictions on mobility and indoor gatherings likely decreased interaction between individuals. Moreover, the use of masks by individuals and use of ventilation and air purifying systems by businesses may have had beneficial impacts through reducing airborne transmission.

Although many COVID-19 mitigation strategies such as national lockdowns, mask mandates, and reductions in indoor capacity of public spaces were implemented at the national or subnational level, the impacts of these mitigation strategies is unlikely to have been homogenous across all populations.[311,312] Differential impacts may exist due to individual differences in education, employment (essential versus non-essential workers), public transportation use, and household structure and size.[313,314] Although it may not be possible to determine the exact drivers of observed declines in case notifications and their implications for broader TB control efforts, available data may be able to improve our understanding of the impact of the COVID-19 pandemic on the incidence and distribution of TB.

Quantifying changes in TB diagnoses and their spatial distribution as a result of the COVID-19 pandemic, especially within a high-burden TB setting, is needed to identify the impact of mitigation strategies on TB control. Such efforts will ultimately inform ongoing progress towards TB elimination. In this study, we sought to understand the impact of COVID-19 mitigation strategies on drug-resistant (DR) TB cases in KwaZulu-Natal province, South Africa. Leveraging data from a prospective cohort study of TB patients and the South African census, we describe and compare observed and expected changes in the number, spatial distribution, and neighborhood characteristics of DR TB cases before and after the COVID-19 national lockdowns. We hypothesized that fewer TB cases would be observed after the initiation of national lockdowns, and that cases observed in the period after the lockdowns would be in areas of lower income with poor living conditions.

Methods

Data Sources

Population-level demographic information and census data (e.g., population density, employment and education levels, and living conditions) were collected from Statistics South Africa (Stats SA). All variables were collected at the level of the census unit of main place and local municipality, which are both smaller spatial units within district and province units. KwaZulu-Natal province consists of 10 districts, 54 municipalities, and 197 main places.

Individual-level information on drug-resistant (DR) TB cases was collected from a prospective cohort study: 'The Role of Casual Contact and Migration in XDR TB Transmission in South Africa: a Geospatial, Genomic and Social Network Study' (CONTEXT) (R01AI138646). The parent study aims to estimate the impact of casual contact and migration on XDR TB transmission in KwaZulu-Natal, South Africa. All culture-confirmed DR TB patients diagnosed in KwaZulu-Natal province were eligible regardless of sex, age or vital status and were identified at the provincial TB reference laboratory weekly. DR TB cases were geocoded based on the healthcare facility of diagnosis to both main place and local municipality spatial areas.

From the CONTEXT study, we utilized two populations: 1) the provincial population (defined as all culture-confirmed DR TB patients above) and 2) the enrolled cohort population (those who fell into the eThekwini Cohort catchment area) which is a subset of the provincial population. From the time of study initiation (December 2018) until June 2020, the catchment area consisted of the eThekwini district municipality. Due to reductions in study enrollment during the COVID-19 pandemic, the catchment area was expanded to include the eThekwini, iLembe, Ugu, and uMgungundlovu district municipalities as of June 2020 (Figure 4.1).

Age was captured for individuals in the provincial population, while the enrolled cohort underwent in-depth interviews that captured extensive information on their demographics, HIV status, comorbidities, living conditions, places frequently visited, and home locations. **Appendix Table I-4**. displays further detail on the spatial and individual variables used in this analysis. Location information captured residences, overnight visits, and daily locations. Specific questions to prompt recall of these locations during the interview included the following:

> *Residences: 'Please tell me about where you stay right now?' 'Is there any other place that you stayed for more than 1 month in the past 2 years?'*
> *Overnight visits: 'Were there any places where you spent the night at least 5 times in the past two years?'*
> *Daily locations: 'Where did you regularly go during the daytime and evenings on weekdays and weekends? Regularly means that you visited a place for at least 2 hours most weeks.'*

Definitions

The definition of DR TB used by the CONTEXT study was a set of laboratory results documenting resistance to at least one second-line drug or drug class. Time periods before and after the pandemic national lockdowns were defined by the date of the lockdown announcement on March 26th, 2020. Individuals were stratified into either time period based upon their laboratory sample collection date. Date ranges for the provincial population were October 4th, 2018–March 25th, 2020 (539 days) and April 2nd, 2020–February 1st, 2022 (671 days) for before and after the national lockdowns, respectively. Date ranges for the enrolled cohort were October 4th, 2018–March 19th, 2020 (533 days) and April 6th, 2020–May 31st, 2021 (421 days) for before and after the national lockdowns, respectively.

Outcomes

The primary outcomes of this analysis were the frequency and spatial distribution of DR TB diagnosed cases before and after national lockdowns. Secondary outcomes included differences in both individual- and spatial-level characteristics of DR TB cases before and after pandemic lockdowns. Incidence of DR TB was calculated using the number of cases per spatial unit divided by the full population of the corresponding spatial unit, multiplied by 100,000 persons.

Statistical Analysis

Descriptive statistics (absolute frequencies or medians with interquartile ranges [IQR]) were used to describe patient characteristics prior to and after the pandemic lockdowns. Comparisons were performed using the Chi-square and Kruskal-Wallis test for categorical and continuous variables, respectively, with $p<0.05$ considered statistically significant.

To assess spatial patterning of cases across the two time periods before and after lockdowns, spatial log relative-risk (RR) surface maps were created for DR TB cases comparing healthcare facility locations of diagnosis across time periods. Under the assumption that the population at-risk remained mainly unchanged over time, kernel density estimations of case locations were calculated and compared. An adaptive log RR bandwidth was used to improve estimation accuracy by accounting for greater uncertainty in areas with fewer cases with greater smoothing.[315] Scalar smoothing bandwidths for kernel density estimates were calculated using the geometric mean of case counts. The ratio of densities for cases before and after COVID-19 lockdowns created a continuous estimate of RR which was then mapped. Areas with statistically significantly increased or decreased DR TB RRs were detected and highlighted by calculating

tolerance contour lines at a threshold of p<0.05.[316] For the enrolled cohort map, we limited the spatial area to only those local municipalities with cases detected to compute stable estimates. As there were no cases diagnosed in the outlying local municipalities, edge effects resulted in unstable estimates.

We utilized Bayesian conditional autoregressive models to estimate the relationship of spatial characteristics with local DR TB incidence for the enrolled cohort. The number of new DR TB cases was modeled as Poisson random variables. The natural log of the Poisson distribution mean was divided by the natural log of the population at risk to estimate the per capita incidence rate. Local municipality characteristics (flush toilet connected to sewage, ownership of stove, ownership of motor car, access to internet, electricity for lighting), X_{ni}, were modeled as fixed effects over each geographical census unit i. Neighborhood characteristics were publicly accessible and came from the South African census for each census unit. A non-spatially correlated random effect, ϵ_i, was included and fitted to a Gaussian distribution. Spatial dependence was incorporated into the model through a random effect, α_i, and accounted for the effects of spatial proximity via a conditional autoregressive prior distribution with neighbors defining the prior mean (weighted average of neighboring random effects) and variance (itself following an inverse gamma distribution). The model was run for local municipality units i = 1 to 18, for which at least one DR TB case was diagnosed during the study period. A geographic neighborhood matrix was constructed using the 'poly2nb' function from the 'spdep' packaged in R. Neighbors were defined as spatial units with any shared boundary point ('queen' criterion).

For $n + 1$ regression coefficients β_n and intercept β_0, non-informative prior distributions were chosen resulting in estimates similar to maximum likelihood estimates. For model estimates,

samples were drawn from posterior distributions utilizing Markov Chain Monte Carlo methods and the model was run for 200,000 iterations with 20,000 warm-up samples. Model convergence was checked via Gelman-Rubin statistics, inspection of trace plots, plots of residuals and of the spatial distribution of differences between predicted and observed cases of DR TB.

Model fit was examined via the deviance information criterion (DIC) statistic for the models to determine the benefit of accounting for spatial dependence as a random effect (i.e., including α_i). We plotted credible intervals for fixed effect parameters and evaluated the spatial pattern of residuals to check for residual clustering.

Statistical, geospatial, and modeling analyses were performed using a combination of functions in the 'spdep', 'sparr', 'spatstat', 'CARBayes', and 'geoR' packages in R version 4.1.2 (Vienna, Austria). Base-layer maps were created and scaled using the R package 'ggmap'.[317]

Results

During October 2018–February 2022, there were 693 DR TB cases diagnosed in the provincial population. Throughout October 2018–May 2021, there were 169 cases eligible for the enrolled cohort. Among the provincial population, there were 405 cases diagnosed prior to the COVID-19 national lockdowns and 288 after the lockdowns, corresponding to a 29% decrease. Similarly, among the enrolled cohort, there were 95 cases diagnosed prior to the COVID-19 national lockdowns and 74 diagnosed after the lockdowns, corresponding to a 22% decrease.

The median age of DR TB cases in the provincial population was 35 years (IQR = 28,43). Median age did not significantly differ between time periods (prior = 35 years [IQR = 27,42]; post = 35

years [IQR = 28,44]; p-value = 0.307). Characteristics of the enrolled cohort population are displayed in Tables 4.1A–E. Median age of DR TB cases prior to the lockdowns was 36 years (IQR = 30,44), and after the lockdowns was 34 years (IQR = 28,42; p-value=0.141). Distribution of sex, marital status, employment and education of cases was similar across the two time periods. The median number of adults living in a household that completed ≥5 years of school was significantly greater after the lockdowns (3; IQR = 1,4) compared to before the lockdowns (2; IQR = 1,3) (p-value = 0.016). Compared to cases diagnosed before the COVID-19 lockdowns, cases diagnosed after were more likely to use wood for cooking (45% vs. 26%; p-value = 0.01), less likely to have any source of fuel for heating (73% vs. 48%; p-value = 0.001), and were less likely to have either piped water (62% vs. 84%; p-value = 0.001) or a flush toilet (39% vs. 57%; p-value = 0.021) in their household. While almost all (98%) of cases diagnosed before the lockdowns owned a telephone, this proportion decreased to 81% after the lockdowns (p-value <0.001). Almost all cases diagnosed prior to the lockdowns had been tested for HIV at some point before (97%), and this proportion decreased to 82% for cases diagnosed after the lockdowns (p-value = 0.001).

Figure 4.2 displays dot plot maps for the healthcare facilities of diagnosis for cases in the (A) the provincial population and (B) the enrolled cohort. Most cases were diagnosed near or around Durban, the largest city in the KwaZulu-Natal province. Incidence rates per 100,000 persons for local municipalities differed across time period for both the provincial population and enrolled cohort (Figure 4.3). In the provincial population, Hlabisa and uMlazi in the northeastern region of the province had the highest incidence rates at 16.7 and 12.1 cases per 100,000 persons prior to the lockdowns. Incidence rates were more dispersed after the lockdowns, with 3 local municipalities (Hibiscus Coast, Msinga, and Umtshezi) that had incidence rates greater than 6

cases per 100,000. In the enrolled cohort area, eThekwini and Ndwedwe had the highest incidence rates prior to the lockdowns (2.3 and 2.1 cases per 100,000, respectively). Similar to the provincial population, incidence rates were more dispersed after the lockdowns, with 3 local municipalities (Hibiscus Coast, Maphumulo, and Ndwedwe) that had incidence rates greater than 2 cases per 100,000.

Differences in incidence were quantified using a relative-risk surface comparing the period after the lockdowns to the period before the lockdowns (Figure 4.4). Across the province, there were two regions (one approximately in the center of the province, and one in the southern region) that had significantly greater relative risks for DR TB after the lockdowns. These regions correspond to the local municipalities of Umtshezi, Msinga, Umvoti, and the area around the Umzimkhulu and Umzumbe border. In the enrolled cohort space, the northeastern and southwestern regions had significantly greater relative risks for DR TB. The regions at greatest risk corresponded to the local municipalities of Maphumulo, Ndwedwe, and Vulamehlo.

Posterior distributions from Bayesian CAR model fixed parameters are displayed in Figure 4.5, with credible intervals indicated by vertical lines. Before pandemic lockdowns, there was an inverse relationship between DR TB incidence and having electricity for lightning, and a positive correlation between incidence and having access to the internet or owning a stove. After pandemic lockdowns, posterior distributions were generally not as wide compared to those before the lockdowns. After the lockdowns, there was an inverse relationship between DR TB incidence and having a flush toilet connected to sewage and having electricity for lighting. Similarly to before pandemic lockdowns, there was a positive association between DR TB incidence and the ownership of a stove.

We examined the characteristics of residences, overnight visit locations, and daily visit locations reported by DR TB cases in the enrolled cohort. There were no differences in the number of overnight visit or daily visit locations between before and after the lockdowns; however, there was a shift in the distribution of residences reported which decreased in number after the COVID-19 lockdowns (Figure 4.6) (p-value = 0.07). The proportion of individuals who stated they moved to their residence as it was their childhood home was 19% prior to the lockdowns, and 35% after the lockdowns (Figure 4.7). For overnight visit locations, there was an increase in individuals stating they visited these locations after the lockdowns compared to before for work (11% vs. 0%) and to visit an intimate partner (22% vs. 12%) (Figure 4.8).

There was a 10% increase in the proportion of individuals reporting a private home as a daily visit location after the lockdowns compared to before (Figure 4.9). Further, the number of people they interacted with in these daily visit locations decreased after the lockdowns with 84% of cases after the lockdowns reporting 0-4 close contacts compared to before the lockdowns in which 66% of cases reported 0-4 close contacts.

Discussion

In this study, we combined data from a cohort study of DR TB patients and census information to explore differences in the number and spatial distribution of diagnosed DR TB cases before and after the COVID-19 national lockdowns in KwaZulu-Natal, South Africa. We observed a 29% reduction in the number of DR TB cases diagnosed in the province during the two-year period after the COVID-19 lockdowns compared to the year and a half prior to the lockdowns. Although the catchment area for the enrolled population was expanded shortly after the COVID-19

pandemic, we observed a reduction of 22% in the number of DR TB cases diagnosed during the period after the lockdowns compared to before the lockdowns. We found further individual-level and spatial-level differences between cases diagnosed prior to versus after the COVID-19 lockdowns, with cases diagnosed after the lockdowns associated with worse living conditions and a greater number of people living in their households. Our results shed light on the impacts of COVID-19 mitigation strategies on TB control.

We observed a reduction in DR TB diagnoses across the time periods before and after the COVID-19 national lockdowns. To examine the potential drivers of this reduction, we assessed location information reported by participants. Characteristics of and reported interactions within locations visited by DR TB cases in the enrolled cohort differed before and after the COVID-19 lockdowns. In general, cases after the lockdowns reported visiting locations consistent with more limited movement such as a private home, work, or an intimate partner's home. Close interactions with others also decreased after the lockdowns. These findings are broadly consistent with differences in mobility patterns described after global COVID-19 lockdowns.[318] At the same time, studies have shown that although mobility to work locations dramatically decreased early in the pandemic for high-income countries, this was not necessarily the case in low- to middle-income countries.[319] These findings, in conjunction with the individual-level characteristics of DR TB cases after the pandemic, suggest that those looking for or traveling for work after pandemic lockdowns may be at higher at risk for infection. Although we observed an overall decline in incidence, this decrease was likely heterogeneous. Perhaps a larger portion of individuals may have been at decreased risk as a result of staying at home and interacting with fewer individuals, while a minority of individuals were at greater risk as a result of their movement or mobility patterns after the pandemic lockdowns. Further, this decrease may have been observed if household

transmission (versus community transmission) became the main contributor to new infections after the pandemic lockdowns due to the finite threshold of potential transmissions within a household setting.

There were many individual and household characteristics reported by DR TB patients in the enrolled cohort that differed significantly after the national lockdowns. Changes in these household characteristics across time periods were also observed at the spatial level. Cases diagnosed after the lockdowns were less likely to have owned a telephone or have a flush toilet or piped water, the majority did not have any source of fuel for heat, and almost half of individuals used wood for cooking. Further, DR TB cases reported significantly more adults living in their household compared to cases prior to the lockdowns. These results are important in that they highlight the importance of households and social networks in South Africa. An analysis of mobility and living arrangements in South Africa during the pandemic emphasized the 'translocality' of South African adults, characterized by an attachment to their childhood homes to which many returned during the lockdowns.[320] This notion is consistent with our findings, in which we observed a greater proportion of DR TB cases after pandemic lockdowns reporting the reason they moved to their primary residence was because it was a childhood home. Further, during the lockdowns, households were found to become more 'stretched' or 'extended' due to the absorption of dependent kin networks as a result of job loss or poverty.[320] We observed a similar increase in the number of adults in the household after the lockdowns.

Areas were identified to have a greater risk of DR TB after the COVID-19 lockdowns in both the provincial population and enrolled cohort in the central and southern regions of the KwaZulu-Natal. Roughly, these regions correspond to the district of Ugu, and area around the borders of

uThukela, uMzinyathi, and uMgungundlovu districts. There is limited literature on specific directional migration patterns across South Africa during the pandemic, and existing data are unable to determine explicit patterns across district municipalities other than that clustered municipalities (based upon mobile phone tracking) were in general not located spatially closer to one another.[321] Thus, increases in incidence in local municipalities outside of the more urban regions of the province may be explained by clustering due to a factor other than spatial proximity.

This study has several limitations. First, within the enrolled cohort dataset, interviews with participants were substantial and took a considerable amount of time to complete. Therefore, biases associated with respondent fatigue such as recall bias, answering “Don’t know” more often, and providing less detail in their answers are likely. Further, as many of the questions specifically regarding location information was in the context of locations spanning the previous two years, there is also the potential for recall bias with respect to these responses. Second, this work was not meant to determine a causal relationship between COVID-19 lockdowns and DR TB incidence but rather aimed to examine the relationship of the lockdown time periods to frequency and spatial patterns in DR TB diagnoses. Further work could apply causal inference methods to better understand the relationship between lockdown levels and TB incidence.

In conclusion, we found a reduction in the number of diagnosed DR TB cases after the COVID-19 pandemic lockdowns in KwaZulu-Natal, South Africa, and observed that cases diagnosed after the lockdowns had worse living conditions, fewer household resources, and more adults living in their household compared to before the pandemic. This work provides valuable insight into the transmission dynamics of DR TB and helps to refine the need for further study of these regions and the impacts of COVID-19 mitigation strategies on TB control. Prevention strategies such as

targeted active case finding and allocation of resources to at-risk geographic regions may be implemented in areas identified to be at higher risk for DR TB after the COVID-19 lockdowns.

Figure 4.1. Map of provincial population and enrolled cohort population spatial boundaries. Lines represent boundaries for the provincial population area (black), and enrolled cohort population catchment area initially (blue) and after its expansion (purple).

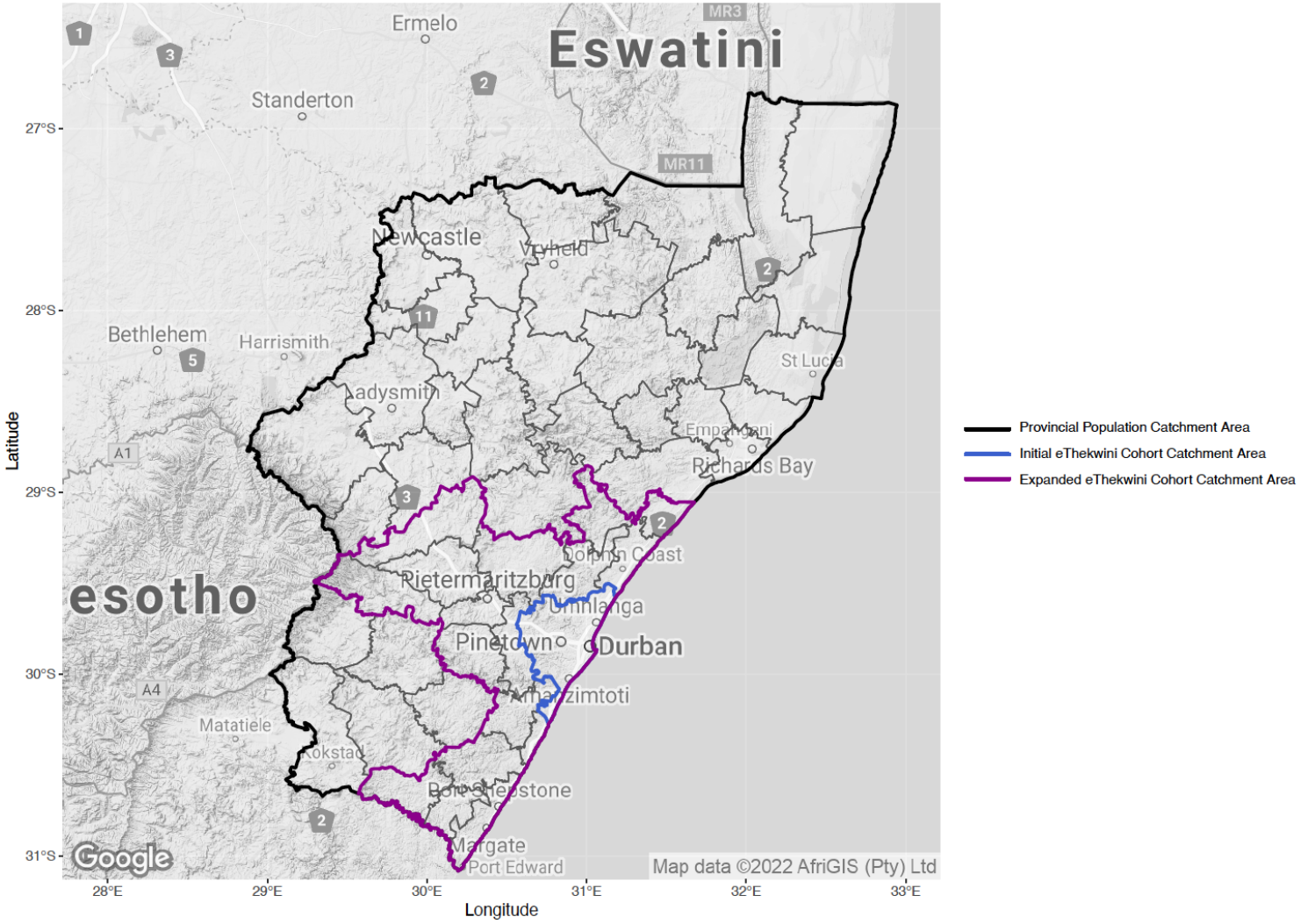


Table 4.1. Descriptive tables for enrolled cohort characteristics.

Table 4.1A. Sociodemographic characteristics of participants.

	Total N = 169	Prior to COVID lockdowns N = 95	Post COVID lockdowns N = 74	p value
Age (median, IQR)	35 (29, 43)	36 (30, 44)	34 (28, 42)	0.141
Male	92 (54)	53 (56)	39 (53)	0.698
Marital Status				0.839
Single	130 (77)	76 (80)	54 (73)	
Cohabitating/Married	28 (17)	16 (17)	12 (16)	
Divorced/Separated	1 (1)	1 (1)	0 (0)	
Widowed	4 (2)	2 (2)	2 (3)	
Currently Employed	47 (28)	29 (31)	18 (24)	0.316
Employed in past two years	19 (11)	10 (11)	9 (12)	0.840
Highest Educational Level				0.856
No formal schooling	5 (3)	3 (3)	2 (3)	
Primary school	22 (13)	12 (13)	10 (14)	
Secondary school, but not Matric	90 (53)	56 (59)	34 (46)	
Matric	33 (20)	17 (18)	16 (22)	
University or other higher degree	10 (6)	6 (6)	4 (5)	
Adults Living in Household (median, IQR)	3 (2, 5)	3 (2, 4)	4 (2, 6)	0.085
Unemployed Adults in Household (median, IQR)	1 (1, 2)	1 (1, 2)	2 (1, 3)	0.315
Total Monthly Household Income (median, IQR)	2,100 (1,500, 3,300)	2,500 (1,500, 3,500)	2,000 (1,300, 3,000)	0.251
Household Members Supported by Income (median, IQR)	4 (3, 5)	4 (3, 5)	–	
Fully Supported (median, IQR)	5 (3, 7)	5 (3, 6)	5 (3, 7)	0.742
Partially Supported (median, IQR)	0 (0, 1)	0 (0, 2)	0 (0, 1)	0.332
Adults in Household that completed ≥5 yrs school	2 (1, 3)	2 (1, 3)	3 (1, 4)	0.016
School-aged children in household	86 (51)	47 (49)	39 (53)	0.700
Children currently in school	82 (49)	45 (47)	37 (50)	0.700
Death of Child <5 in household in past year	2 (1)	1 (1)	1 (1)	–

Numbers presented are reported as N (%) unless otherwise stated.
Abbreviations: IQR, interquartile range.

Table 4.1B. Residences, overnight visits, and daily visits reported by participants.

	Total N = 169	Prior to COVID lockdowns N = 95	Post COVID lockdowns N = 74	p value
Number of residences reported (median, IQR)	1 (1, 1)	1 (1, 2)	1 (1, 1)	0.017
Number of daily visits reported (median, IQR)	2 (2, 3)	3 (2, 3)	2 (2, 3)	0.193
Number of overnight visits reported (median, IQR)	1 (1, 2)	1 (1, 2)	1 (1, 1)	0.290

Abbreviations: IQR, interquartile range.

Table 4.1C. Household characteristics of participants.

	Total N = 169	Prior to COVID lockdowns N = 95	Post COVID lockdowns N = 74	p value
Electricity in Household	150 (89)	88 (93)	62 (84)	0.064
Fuel for Cooking				
Electricity	149 (88)	87 (92)	62 (84)	0.107
Gas	28 (17)	18 (19)	10 (14)	0.390
Paraffin	32 (19)	18 (19)	14 (19)	–
Wood	58 (34)	25 (26)	33 (45)	0.010
Coal	4 (2)	3 (3)	1 (1)	0.372
Fuel for Lighting				
Electricity	150 (89)	88 (93)	62 (84)	0.064
Paraffin	11 (7)	6 (6)	5 (7)	0.793
Candles	93 (55)	48 (51)	45 (61)	0.196
Solar	1 (1)	1 (1)	0 (0)	0.390
Fuel for Heating				
Electricity	48 (28)	41 (43)	7 (9)	<0.0001
Paraffin	1 (1)	1 (1)	0 (0)	0.390
Wood	11 (7)	7 (7)	4 (5)	0.592
Coal	1 (1)	1 (1)	0 (0)	0.390
None	100 (59)	46 (48)	54 (73)	0.001
Piped Water in Household	126 (75)	80 (84)	46 (62)	0.001
Flush Toilet in Household	83 (49)	54 (57)	29 (39)	0.021
Type of Home				0.270
Brick/concrete house on private land	115 (68)	62 (65)	53 (72)	
Dwelling made of traditional materials	6 (4)	4 (4)	2 (3)	
Townhouse or semi-detached house	1 (1)	1 (1)	0 (0)	
Flat or apartment	5 (3)	5 (5)	0 (0)	
Flat/room on another property (in a backyard)	4 (2)	3 (3)	2 (3)	
Dwelling in Informal Settlement	28 (17)	19 (20)	9 (12)	
At least 1 car for Household	21 (12)	10 (11)	11 (15)	0.441
Radio	120 (71)	69 (73)	51 (69)	0.570
TV	127 (75)	70 (74)	57 (77)	0.655
Telephone	153 (91)	93 (98)	60 (81)	<0.001

Refrigerator	132 (78)	76 (80)	56 (76)	0.533

Numbers presented are reported as N (%) unless otherwise stated.

Table 4.1D. Tobacco, dagga, and alcohol use of participants.

	Total N = 169	Prior to COVID lockdowns N = 95	Post COVID lockdowns N = 74	p value
Smoked ≥100 cigarettes in lifetime	51 (30)	30 (32)	21 (28)	0.576
Smoked cigarettes in past 6 months	36 (21)	20 (21)	16 (22)	0.876
Cigarettes smoked daily				0.063
0-1	3 (2)	2 (2)	1 (1)	
2-10	26 (15)	14 (15)	12 (16)	
11-20	4 (2)	2 (2)	12 (16)	
>20	3 (2)	2 (2)	1 (1)	
Smoke cigarettes				0.343
Every day	28 (17)	15 (16)	13 (18)	
Some days	4 (2)	1 (1)	3 (4)	
Not at all	4 (2)	4 (4)	0 (0)	
Smoking indoors in home	14 (8)	9 (9)	5 (7)	0.638
Smoke dagga in past 2 years	25 (15)	13 (14)	12 (16)	0.718
Smoke dagga				0.389
Almost everyday	19 (11)	9 (9)	10 (14)	
A few days per week	4 (2)	3 (3)	1 (1)	
A few days per month	1 (1)	1 (1)	0 (0)	
A few days per year	1 (1)	0 (0)	1 (1)	
Alcohol use				0.081
Never	108 (64)	52 (55)	28 (38)	
Monthly or less	20 (12)	11 (12)	2 (3)	
2 to 4 times a month	19 (11)	14 (15)	1 (1)	
2 to 3 times a week	8 (5)	5 (5)	1 (1)	
Alcoholic drinks/day				0.347
None	108 (64)	60 (63)	48 (65)	
1 to 2 drinks	10 (6)	8 (8)	2 (3)	
3 to 5 drinks	17 (10)	12 (13)	5 (7)	
6 or more drinks	15 (9)	9 (9)	6 (8)	
≥6 drinks on occasion				0.083
Never	123 (73)	71 (75)	52 (70)	
Less than monthly	7 (4)	7 (8)	0 (0)	

Monthly	15 (9)	6 (6)	9 (12)
Weekly	6 (4)	5 (5)	1 (1)

Numbers presented are reported as N (%) unless otherwise stated.

Table 4.1E. Co-morbidities and HIV status of participants.

	Total N = 169	Prior to COVID lockdowns N = 95	Post COVID lockdowns N = 74	p value
Ever diagnosed with diabetes	7 (4)	3 (3)	4 (5)	0.505
Ever diagnosed with cancer	2 (1)	1 (1)	1 (2)	0.589
Ever tested for HIV	153 (91)	92 (97)	61 (82)	0.001
Currently on ARVs	96 (57)	57 (60)	39 (53)	0.363
Aggregated HIV Result				
Negative	47 (28)	27 (28)	20 (27)	0.886
Positive	105 (62)	64 (67)	41 (55)	0.112

Numbers presented are reported as N (%) unless otherwise stated.
Abbreviations: ARVs, antiretrovirals.

Figure 4.2 Drug-resistant tuberculosis cases diagnosed in the (A) provincial population and (B) enrolled cohort areas. Cases diagnosed prior to the lockdowns are denoted as circles, and those diagnosed after lockdowns are denoted as X's. Local municipality regions are outlined in gray.

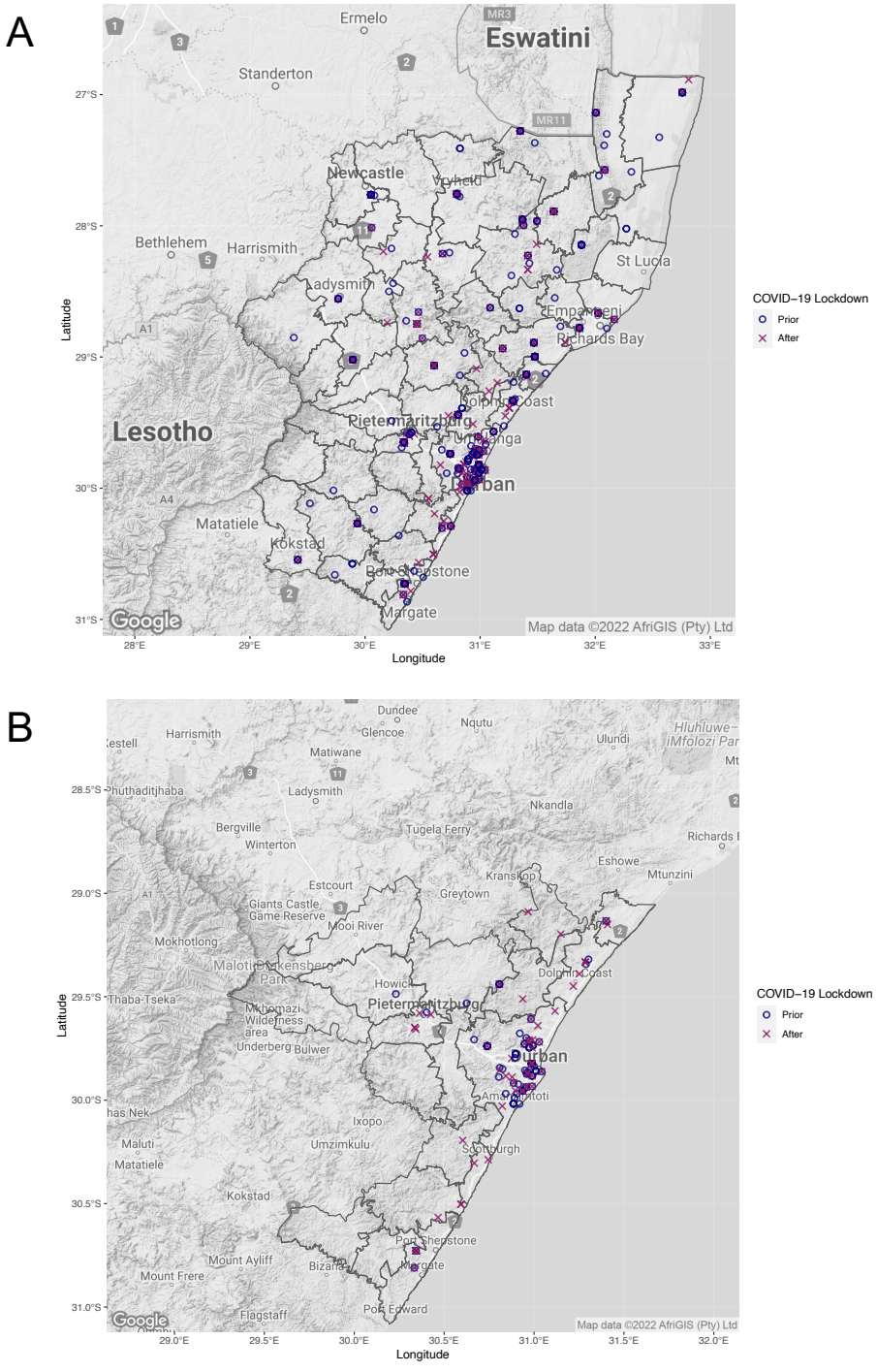
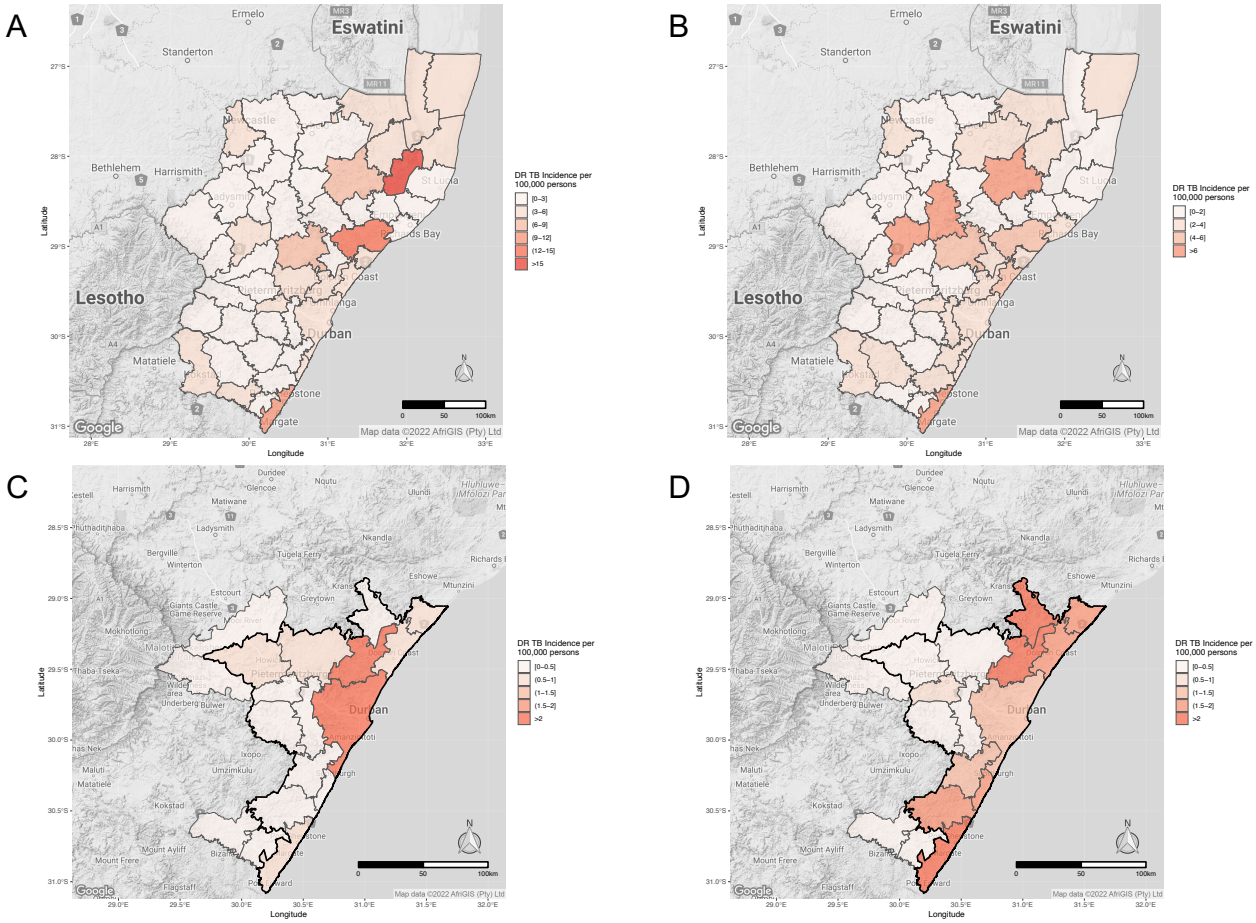


Figure 4.3 Choropleth maps of drug-resistant tuberculosis incidence. Incidence rates for the provincial population (A) prior to and (B) after the COVID-19 national lockdowns and for the enrolled cohort (C) prior to and (D) after the COVID-19 national lockdowns. Local municipality regions are outlined in gray.



In (C) and (D), the thick black line indicates the spatial area in which at least one case was diagnosed either before or after the lockdowns. This smaller spatial region was used for subsequent analyses to compute stable estimates.

Figure 4.4. Risk-ratio surface maps. Maps are shown for the (A) provincial population and (B) enrolled cohort areas. Areas with significantly higher relative risk for drug-resistant tuberculosis after the lockdowns are highlighted with contour lines.

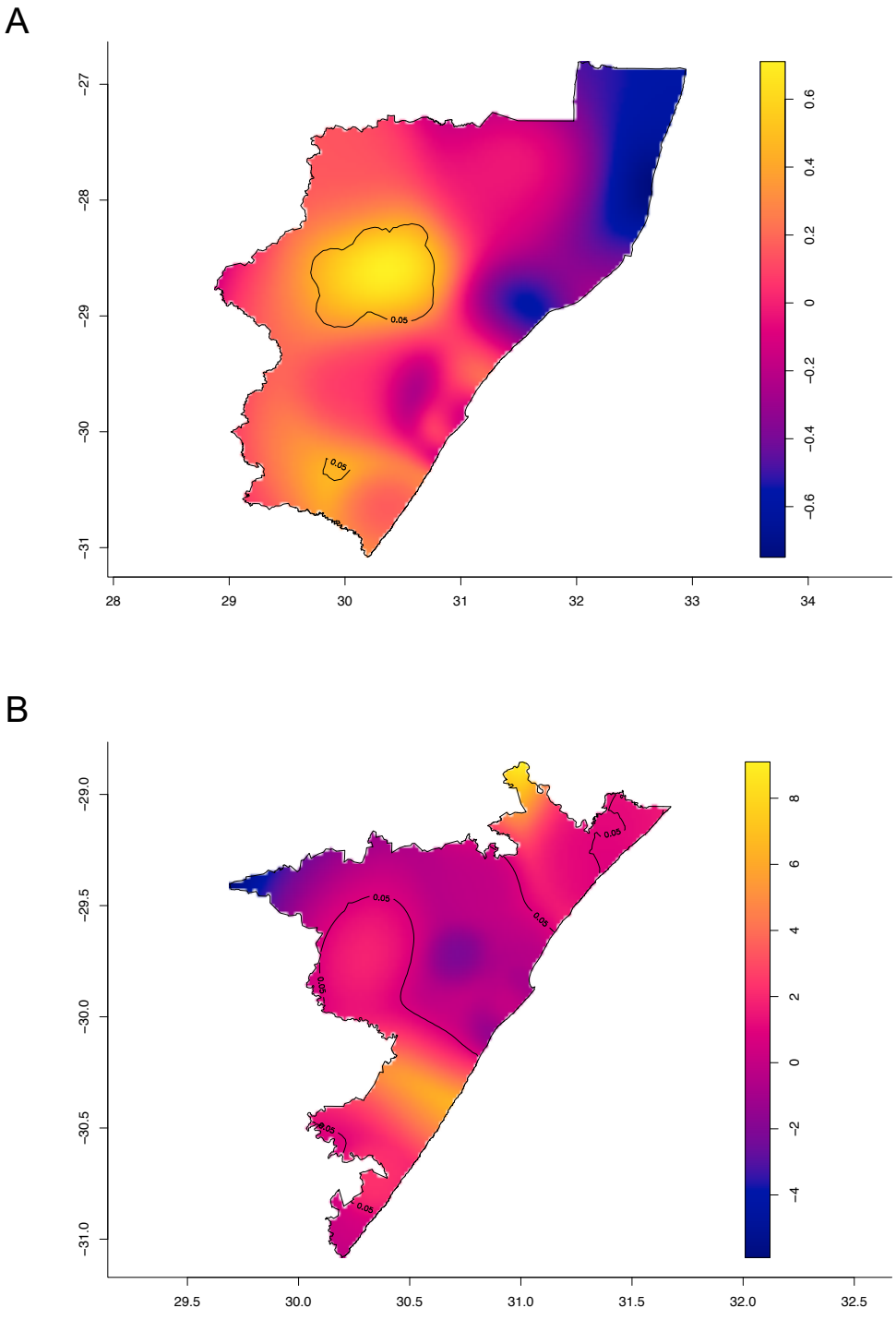


Figure 4.5. Posterior distributions of fixed parameters from Bayesian autocorrelated regression models. Distributions from (A) before and (B) after the pandemic lockdowns are displayed. Fixed parameters from top to bottom are: flush toilet connected to sewage; ownership of a stove; ownership of a car; access to internet; and electricity for lighting.

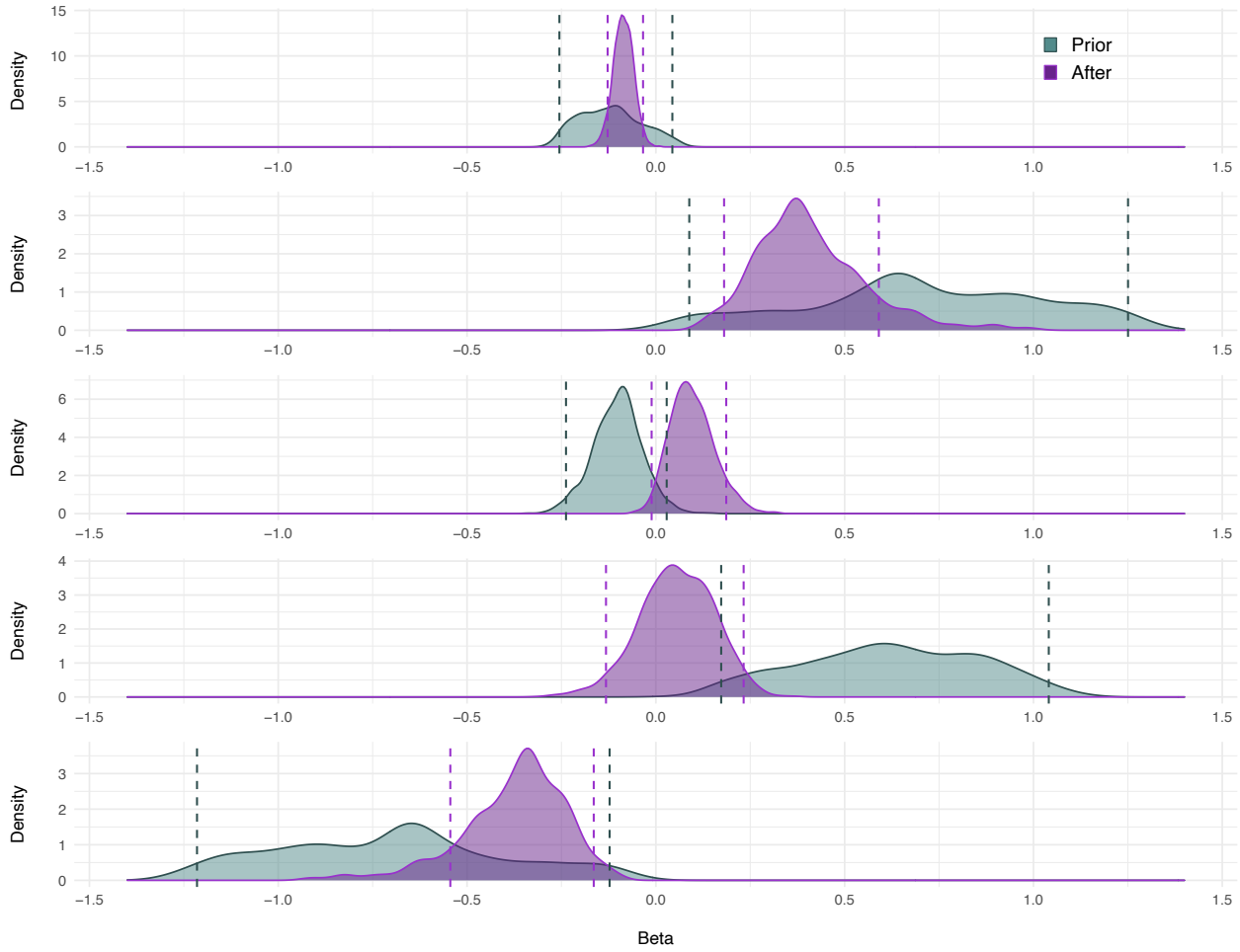


Figure 4.6. Number of locations reported by enrolled cohort participants. Number of (A) residences, (B) overnight visit locations, and (C) daily visit locations for individuals diagnosed before and after COVID-19 pandemic lockdowns.

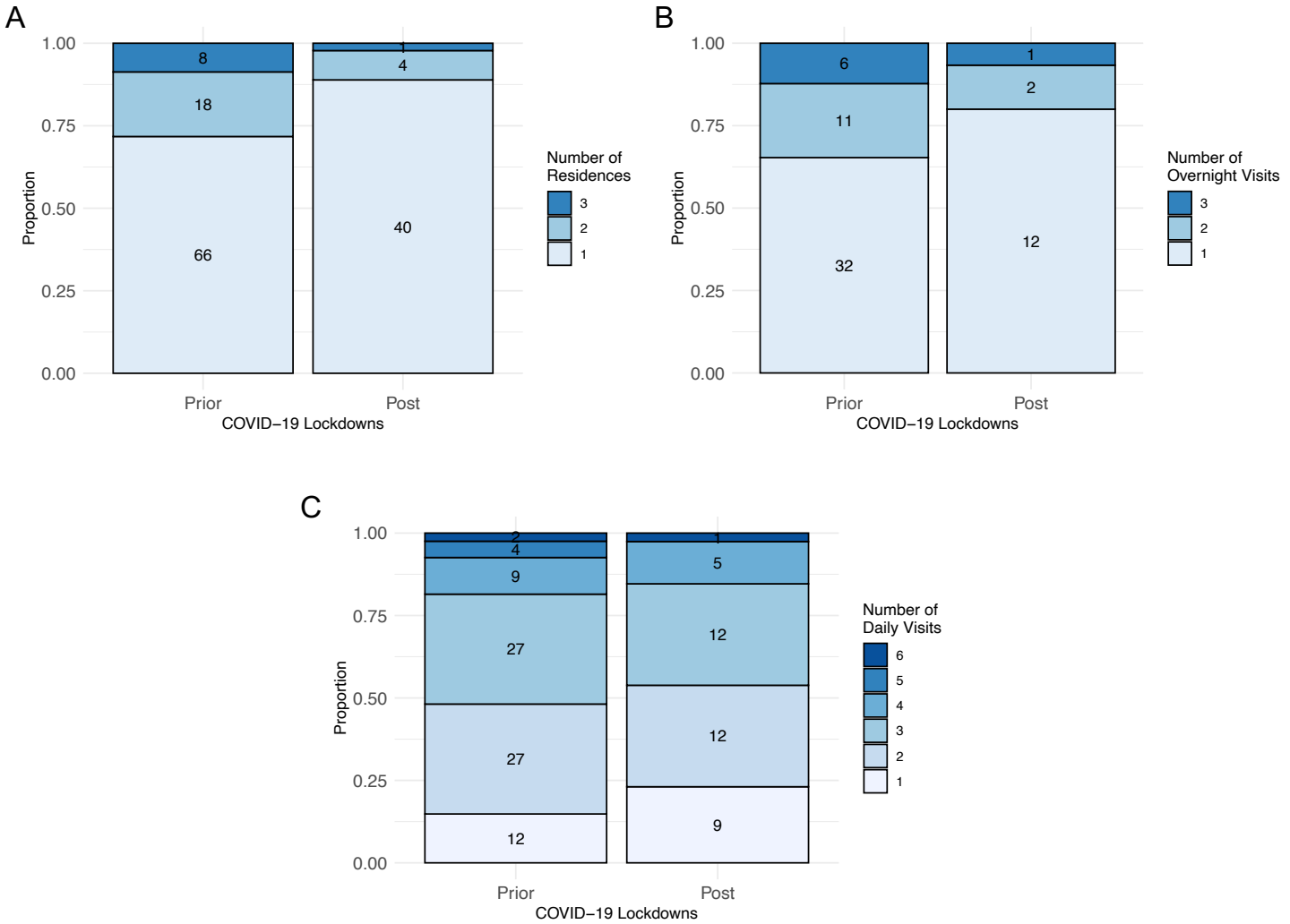


Figure 4.7. Characteristics of residence locations reported by enrolled cohort participants. Distribution of (A) the reason why individuals moved to their residence location and (B) which district their residence locations were located in for individuals diagnosed before and after COVID-19 pandemic lockdowns.

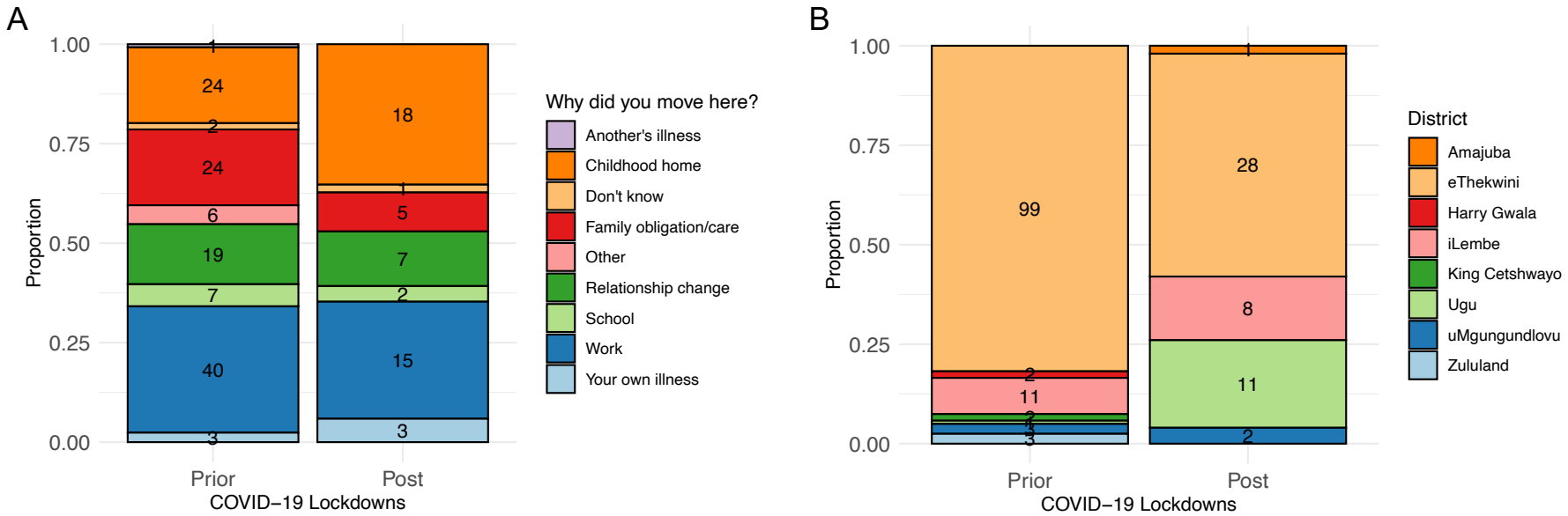


Figure 4.8. Characteristics of overnight visit locations reported by enrolled cohort participants. Distribution of (A) the reason for visiting the overnight visit location, (B) the number of nights spent per visit, (C) the number of people, (D) the number of people interacted with, and (E) which district their overnight visit locations were located in for individuals diagnosed before and after COVID-19 pandemic lockdowns.

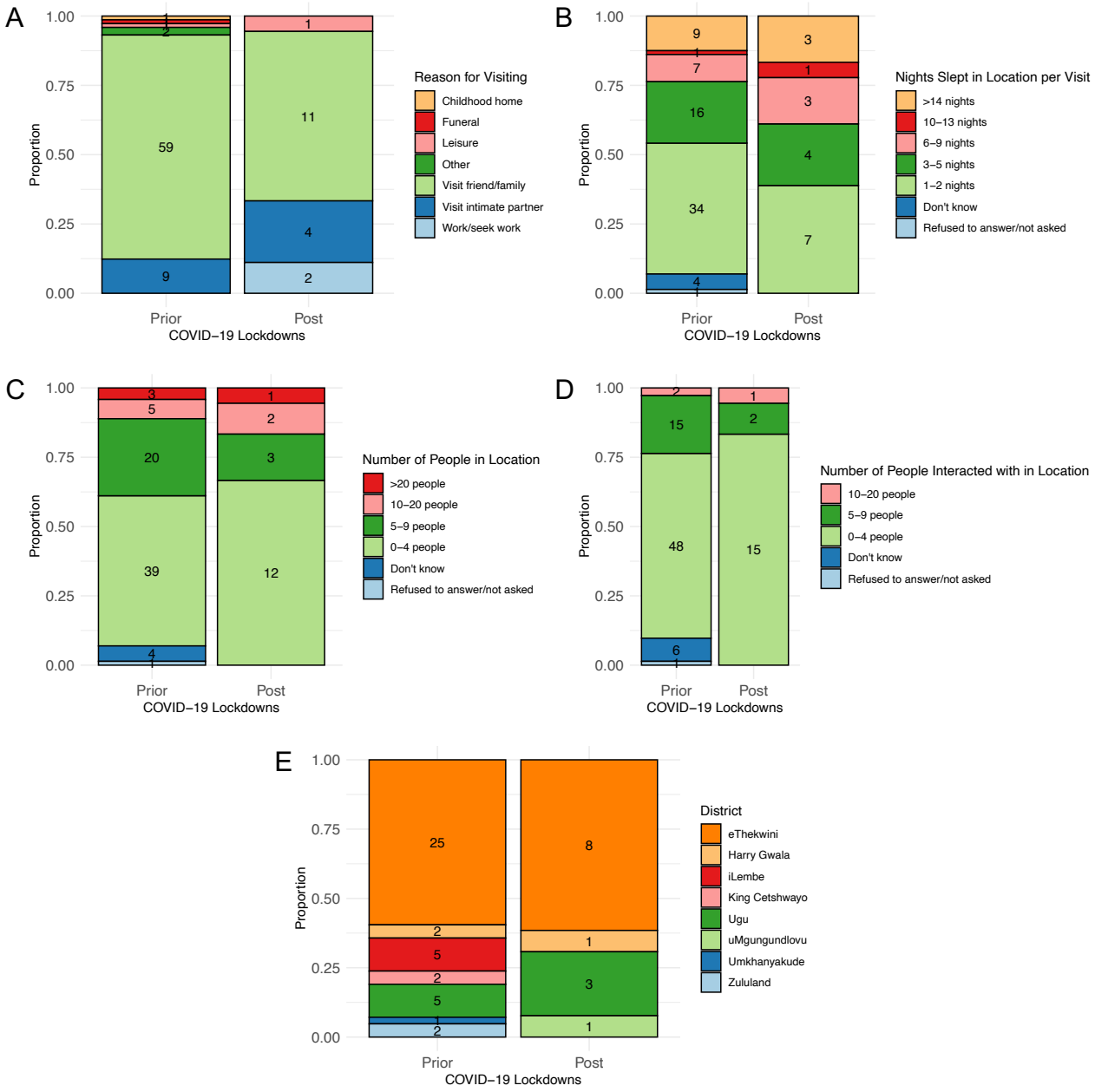
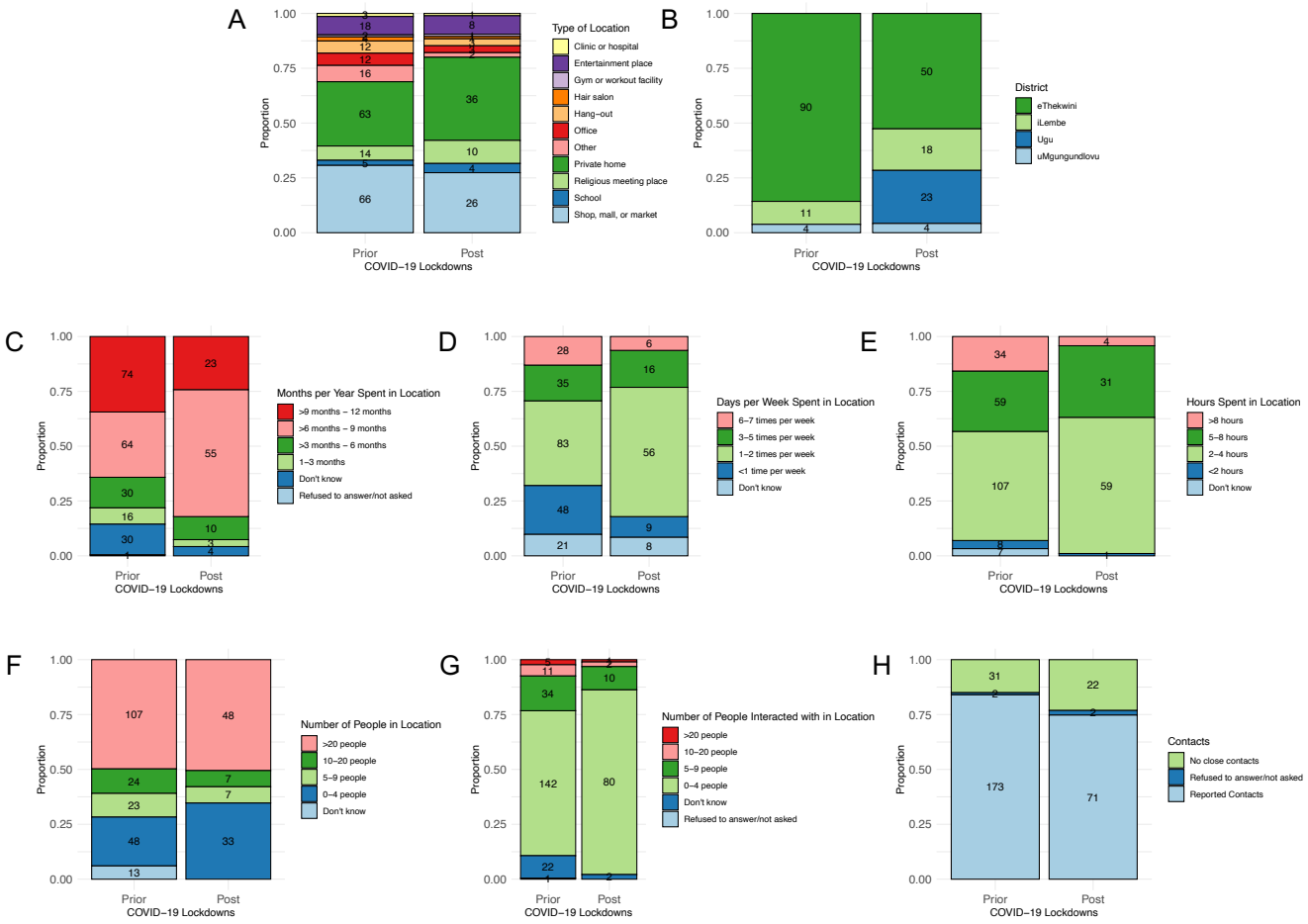


Figure 4.9. Characteristics of daily visit locations reported by enrolled cohort participants. Distribution of (A) the type of location for daily visit locations, (B) which district their daily visit locations were located in, (C) the months per year spent in the location, (D) the days per week spent in the location, (E) the number of hours spent in the location, (F) the number of people, (G) the number of people interacted with, and (H) whether contacts were reported for individuals diagnosed before and after COVID-19 pandemic lockdowns.



Chapter 5: Public Health Implications and Future Directions

There remain gaps in our understanding around how nationally implemented COVID-19 mitigation strategies such as contact tracing and social distancing impact transmission dynamics on a local scale, such as at the state level or on a university campus. Unique settings such as university communities likely have different respiratory disease transmission dynamics due to differences in their underlying social network structures.[171,172] Further, widespread mitigation strategies for COVID-19 impact other disease control programs and these myriad effects have yet to be fully understood. To address these gaps, the overarching goal of this dissertation was to explore local transmission dynamics of COVID-19 and the secondary impacts of COVID-19 on both pandemic spread and DR TB control.

Review of Major Findings

In Chapter 2, we assessed trade-offs between public health capacity and clinical capacity in the early stages of the COVID-19 pandemic in the state of Georgia. Considering the utility of contact tracing as a mitigation strategy for many other infectious diseases[106,109,111], we hypothesized that reducing the time to index case interview to ≤ 2 days and eliciting ≥ 65% of close contacts from index cases would have the greatest impact on transmission and reducing strain on the healthcare system. We found that while all contact tracing intervention scenarios reduced the number of infections, deaths, and ICU admissions, even with complete and immediate contact tracing, hospitals would remain over capacity for greater than a week. Importantly, the speed of contact tracing seemed to play a larger role in impacting outcomes compared to the completeness of contact tracing.

In Chapter 3, we constructed the contact tracing networks for COVID-19 cases and their reported close contacts on the Emory University campus during the Fall 2020 semester. Given the unique nature of a university community, with shared classrooms, dormitories, laboratories, or other campus spaces, the heterogeneity of interactions and social mixing patterns may result in unique transmission characteristics. With the importance of asymptomatic transmission emphasized throughout the beginning of the pandemic[38–41], we hypothesized that approximately 30% of secondary cases reported on campus would be epidemiologically linked to an asymptomatic index case. We found that contact tracing networks were minimally clustered, with SAR higher among contacts of symptomatic cases compared to contacts of asymptomatic cases. Among all contacts that converted into an index case, 16% were epidemiologically linked to an asymptomatic index case. Further, in subsequent bias analyses, our results suggest that it was unlikely that many asymptomatic cases were missing from the observed network, likely due to standard testing protocols.

In Chapter 4, we compared the number, spatial distribution, and individual- and spatial-level characteristics of DR TB diagnosed before and after the national pandemic lockdowns cases to better understand their impact on TB control in KwaZulu-Natal, South Africa. The simultaneous observation of reduced case notifications and diagnoses paired with increased TB mortality to levels not observed since 2017 suggest complicated interactions between different drivers of transmission.[260] We hypothesized that the number of diagnosed DR TB cases would be 35% lower in the period after the pandemic lockdowns compared to the period before, and that neighborhoods with lower socioeconomic status would account for a greater proportion of cases observed. We observed a 29% reduction in DR TB cases across the province after the COVID-19 lockdowns, and a 22% decrease observed in local municipalities surrounding the major urban

city of Durban. Importantly, the cases observed after the pandemic lockdowns reported worse living conditions, fewer household resources, and more individuals living in their households than before the pandemic lockdowns.

Strengths and Limitations

There were several strengths and limitations of this dissertation. A major strength of the analyses presented in this dissertation was its use of individual-level datasets as inputs for making estimations. In Chapter 2, this allowed our network model to be uniquely parameterized to the state of Georgia through the use of the statewide notifiable disease surveillance system database. In Chapter 3, we had case investigation interview notes and systematic follow-up of reported close contacts which allowed for us to identify individual links between the cases and contacts in our networks. In Chapter 4, extensive interviews with DR TB patients allowed for the collection of granular information on their demographics, their living conditions, and their movement patterns. Other strengths included the range of epidemiologic methods applied throughout this dissertation, spanning infectious disease mathematical modeling and spatial statistics. We implemented contact tracing interventions via the modification of contact rates for individuals in our network model for Chapter 2. An exponential random graph model framework was used for the simulation of networks in Chapter 2, as well as to explore potential bias in our observed networks in Chapter 3. Techniques accounting for spatial autocorrelation, an important consideration in the context of an airborne-transmitted infectious disease, were used to examine patterns correlates of DR TB incidence in Chapter 4.

Main limitations of this dissertation include the common biases that come with data collected through interviewing methods. In all aims of this dissertation, individual-level information was

collected through case investigation, contact tracing, or study-specific interviews. These include interviewee fatigue, recall bias, social desirability bias, and interviewer bias. Further, the extent of these biases likely differs across individuals in each aim, depending on the timing of their interview in relation to their diagnostic test date. Other limitations include the assumptions made for analyses performed in this dissertation, including homogenous age-mixing for individuals in the network model in Chapter 2, the restriction to Emory-affiliated close contacts in SAR estimates in Chapter 3, and the requirement of Bayesian methods for the selection of pre-defined prior distributions in Chapter 4.

Relevance and Public Health Impact

The results of this dissertation provide support for the implementation of mitigation strategies for COVID-19 at the local level and highlight important considerations for the use of and secondary impacts of globally applied prevention strategies aimed at one disease.

At the state-level, we found a much greater impact of the speed of tracing versus the completeness of tracing, which provides support for the potential use of app-based methods or digital contact tracing.[322] Prioritization schemes outlining which index cases to complete interviews for may also help to reduce the burden on both public health and clinical capacity if index cases who have a higher number of close contacts are chosen to be interviewed first. It is important to note that contact tracing, an incredibly useful non-pharmaceutical intervention, is typically not suitable as an isolated intervention strategy in the setting of an emerging infectious disease, especially one that is airborne-transmitted. The probability of having ‘untraceable’ contacts given the potential opportunities for casual contacts in various settings in which air is shared is much greater, and present an almost impossible barrier to successful contact tracing

without the use of technology such as proximity sensors.[179] Lastly, contact tracing interventions have diminishing returns over time. These findings imply that thoughtful and careful consideration of the efficiency and capacity of a local public health program must be taken before making decisions around resource allocation for outbreak epidemic planning. If contact tracing cannot be performed quickly and thoroughly, resources may be better allocated to additional mitigation strategies or clinical capacity. At the university-level, we found that the contact tracing network did not represent a 'small-world' network but was minimally clustered with very few chains of transmission. These results may imply that in the setting of a hybrid learning environment, what is often described as a highly connected network is considerably disrupted. This empirical data differs from what has been described in modeling studies on the impact of hybrid learning environments on epidemic control, which have previously shown that only completely virtual learning environments had the ability to prevent spread.[183] Testing protocols in addition to the work of the contact tracing program on the Emory University campus seemed to have successfully prevented major transmission events during the Fall 2020 semester.

Taking into account the various ways in which the pandemic may have affected TB incidence, there were likely trade-offs between the impact of healthcare disruptions leading to interruptions in TB services versus mask mandates and social distancing preventing airborne disease transmission.[302,309,310] These trade-offs were unlikely to have been experienced equally by the population, although many of these disruptions and mitigation strategies were occurring at the national or subnational level. The implications from results of Chapter 4 of this dissertation include the importance of the different risks for TB infection experienced by various groups of individuals based upon certain characteristics (such as employment and education), and how these risks may have increased or decreased after the COVID-19 lockdowns (due to lack of employment or

housing instability). Shifts in these risks, depending on the size of the groups involved, may result in observed overall reduced case notification and incidence estimates. Areas identified in the spatial analyses of this dissertation that had a higher risk of DR TB may be potential regions to focus active case finding methods on, or areas in which localized community transmission may be occurring throughout pandemic lockdowns.

Future Directions

This dissertation contributes to the groundwork of future studies.

1. **Examining the impact of age-targeted contact tracing interventions on the morbidity and mortality of elderly individuals.** Contact tracing interventions may have differential impacts on different age groups. Stratification of the network model by age and implementing contact tracing interventions by targeting specific age groups may result in further reductions in peak ICU numbers and length of time above capacity. This work would be possible given the existing model infrastructure built for this dissertation.
2. **Testing alternative hypotheses for missing cases in the university network.** This work would include examining the importance of a superspreading factor on the observed network, as well as testing the impact of different testing protocols on the propensity of cases being observed in the network. The existing model infrastructure created for this dissertation would be able to incorporate these different sampling methods.
3. **Assessing movement patterns of DR TB cases prior to and after the pandemic lockdowns.** Specific movement patterns and the timing of movement of individuals before and after the pandemic lockdowns would provide further insight into the impact of COVID-19 mitigation strategies on TB control. Geocoded locations for residence locations, overnight visit locations, daily visit locations, and public transportation routes are currently

being collected by the parent prospective cohort study for Chapter 4 of this dissertation, thus mobility patterns can be more thoroughly analyzed at the end of the data collection period.

Appendix I. Data Sources

Appendix Table I-7. Data source description, date ranges, variables used, and sample sizes for chapter 1.

Data Source	Description	Date Range	Variables	Estimated Sample Size	URL/Source
SendSS	Electronic database used for the capture and report of notifiable diseases in the state of Georgia	01/01/2020 – 12/31/2020	age, sex, race, ethnicity, county of residence, date information (symptom onset, testing, interview, admission and discharge), symptoms, comorbidities, essential worker status details, relevant exposure details, hospitalization course (ICU admission, intubation), mortality (date and cause)	>500,000 cases in GA; ~50,000 cases in Fulton County	https://sendss.state.ga.us/
MTX	Web-based portal implemented in the state of Georgia in response to the pandemic that allows for close contacts of diagnosed cases to be monitored via text by contact tracers and self-enroll as a close contact of a diagnosed case	01/01/2020 – 12/31/2020	age, sex, race, ethnicity, monitoring dates, essential worker status, symptoms, testing dates, zip code	~15,000	Shared via OneDrive file by Juliana Prieto at FCBOH on 03/02/2021
OASIS	Aggregated data from GDPH's health data repository	2020	age, race, ethnicity, sex, mortality, hospital discharge, and emergency room visits	N/A	https://oasis.state.ga.us/

Appendix Table I-1. Data source description, date ranges, variables used, and sample sizes for chapter 2.

Data Source	Description	Date Range	Variables	Estimated Sample Size	URL/Source
Emory University Contact Tracing Program	REDCap database to capture and store information gathered via case investigation and contact tracing interviews for index cases and their reported close contacts	06/01/2020 – 06/30/2021	age, sex, race, ethnicity, university affiliation, clinician and/or research status, location information (work and residence locations), use of public transportation, travel locations (48 hours prior to and since symptom onset), contacts (number of household and close contacts), testing information (type, date, result, location), symptoms, co-morbidities, dates of isolation and quarantine	>1,300 index cases; ~2,000 close contacts	Data exported from Emory Contact Tracing Program project at https://redcap.emory.edu/

Appendix Table I-2. Data source description, date ranges, variables used, and sample sizes for chapter 3.

Data Source	Description	Date Range	Variables	Estimated Sample Size	URL/Source
Statistics South Africa	Stats SA is the national statistical service of the country and conducts over 300 different statistical releases annually	2011 – 2018	South African Census (2011); Demographic and Health Survey (2016); General Household Survey (2018); Living Conditions Survey (2014)	N/A	http://www.statssa.gov.za/?page_id=3955; https://microdata.worldbank.org/index.php/catalog
CONTEXT Study	REDCap database to capture and store information gathered from provincial TB reference laboratories, in-depth participant interviews, and location geocoding	01/2018 – 12/2021	age, sex, employment status and occupation, educational attainment, number of adults and/or dependents in household, income, household characteristics (type, electricity and fuel usage, access to piped water and flush toilet), smoking status, symptoms, history of TB disease (dates and results of testing and drug-susceptibility testing and previous and current treatments), potential exposures (mine or healthcare worker, incarceration), risk factors (diabetes, cancer, HIV), healthcare facility of diagnosis, home location, places frequently visited	>680 enrolled in provincial population; ~220 enrolled in eThekwini cohort	Data exported from CONTEXT project at https://redcap.emory.edu/
Oxford COVID-19 Government Response Tracker (OxCGRT)	Collection of systematic information on policy measures that governments have taken to tackle COVID-19	01/2020-present	Stringency index	N/A	https://www.bsg.ox.ac.uk/research/research-projects/covid-19-government-response-tracker

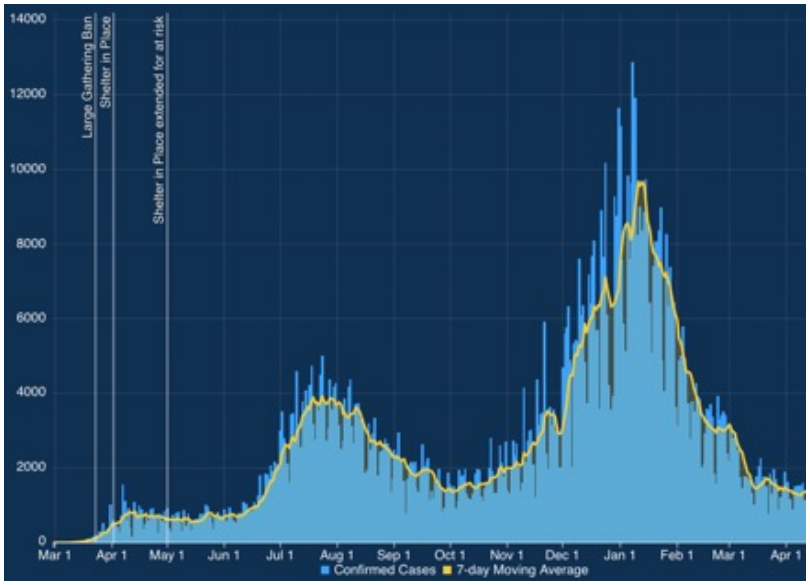
Appendix Table I-3. Variables and characteristics at the individual level and spatial level for chapter 3.

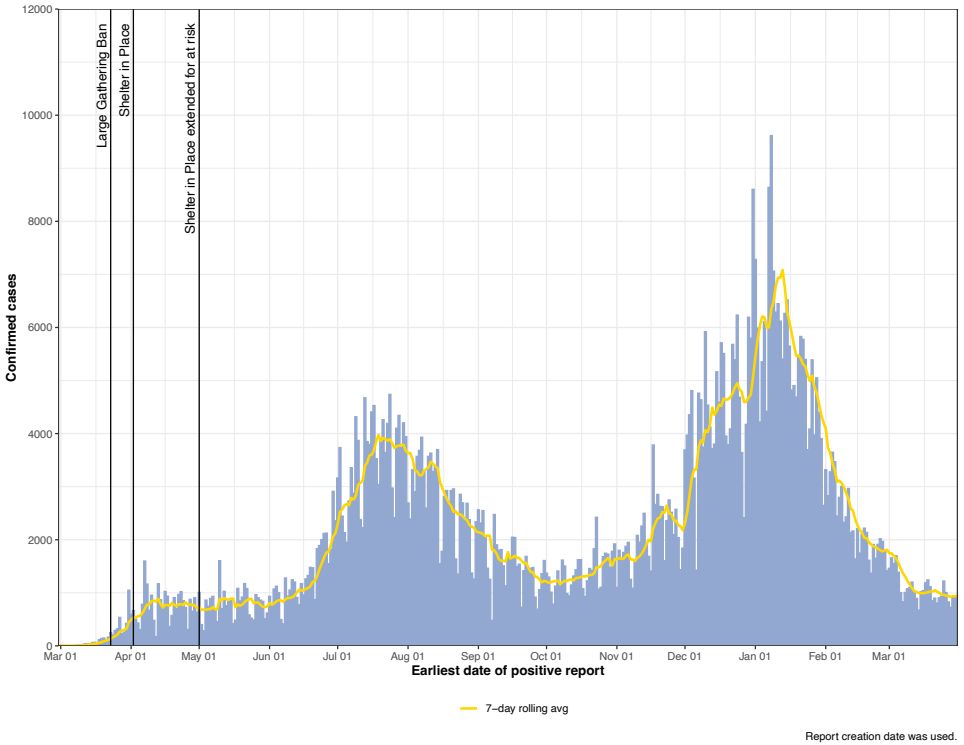
	Individual-level (Source: CONTEXT Study)		Spatial-level (Source: Stats SA)	
Variable/Characteristic	**Provincial Population**	**Enrolled Cohort**	**Main-place Level**	**Municipal Level**
Age	X	X	X	X
Sex	X	X	X	X
Marital Status		X	X	X
Employment		X		
Educational Level		X	X	X
Adults in Household		X		
Household Size*		X	X	X
Household Income		X	X	X
Death of Child in Household		X		
Electricity in Household^		X	X	X
Fuel for Cooking		X	X	X
Fuel for Lighting		X	X	X
Fuel for Heating		X	X	X
Piped Water in Household		X	X	X
Flush Toilet in Household		X	X	X
Type of Home		X	X	X
Car Ownership		X	X	X
Radio		X	X	X
TV		X	X	X
Telephone		X	X	X
Refrigerator		X	X	X
Tobacco use		X		
Dagga use		X		
Alcohol use		X		
Cough symptoms		X		
Exposure histories		X		
Co-morbidities		X		
HIV results		X		
Location Variables[#]		X		
Healthcare Facility of Diagnosis	X	X		

*Interview question (F20 CRF) asks how many household members are supported by household income.
^From Stats SA, percentage of population with electricity in household is estimated using percentage who use electricity for lighting.
[#]Residence locations, daily visit locations, overnight visit locations.

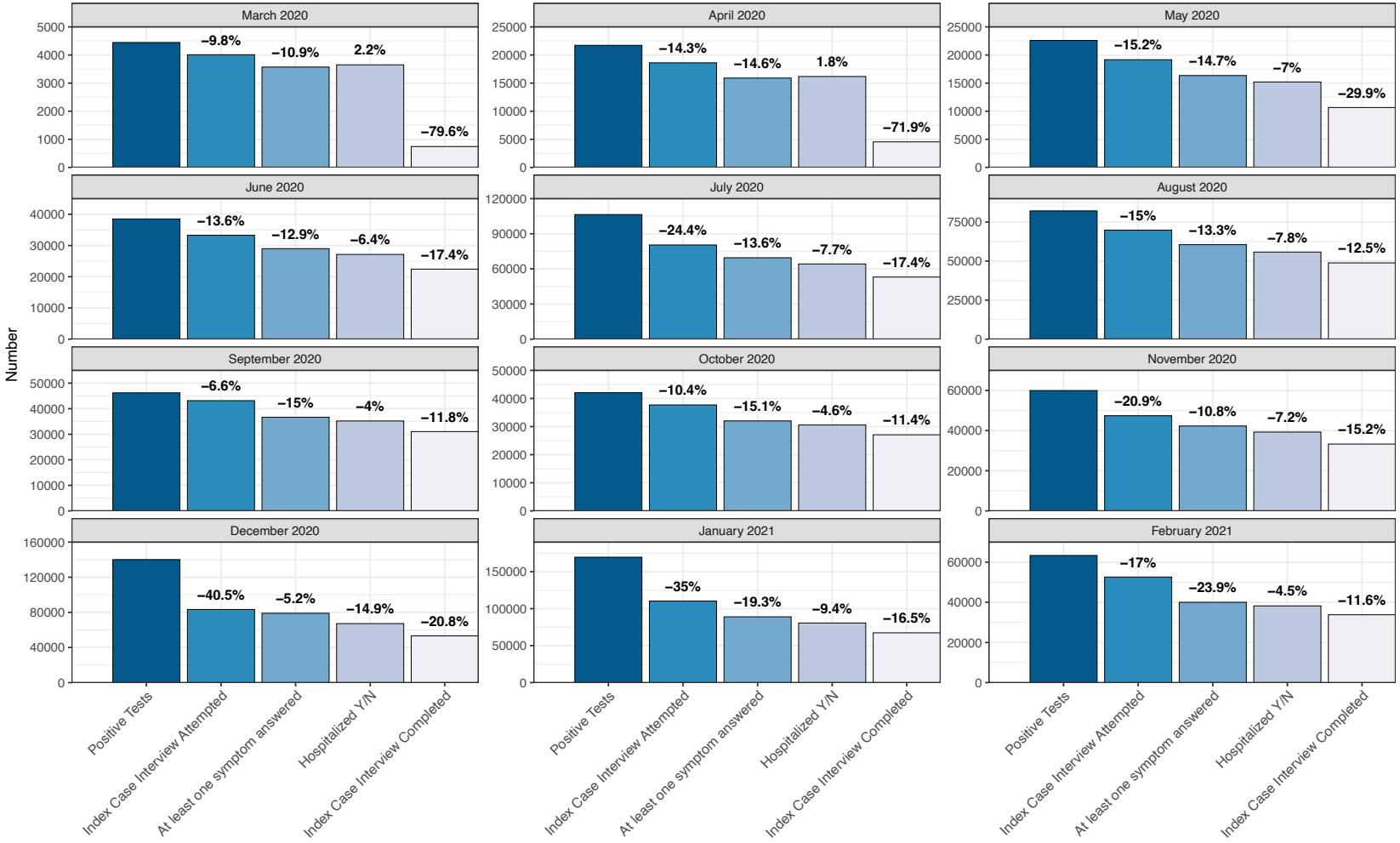
Appendix II. Chapter 2 Technical Appendix

Appendix Figure II-1. Epi curves for the state of Georgia were re-created using Georgia Department of Public Health data.

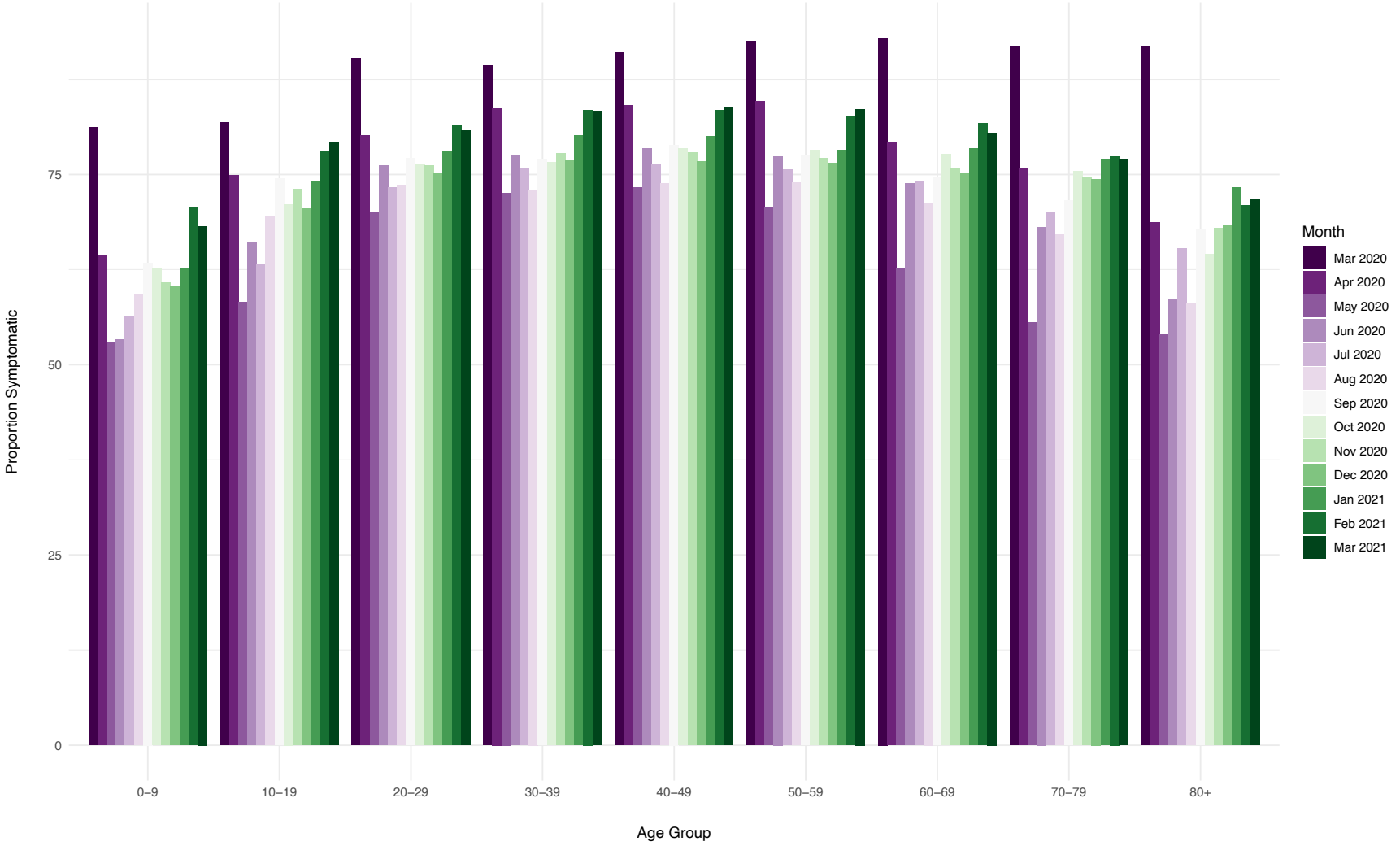




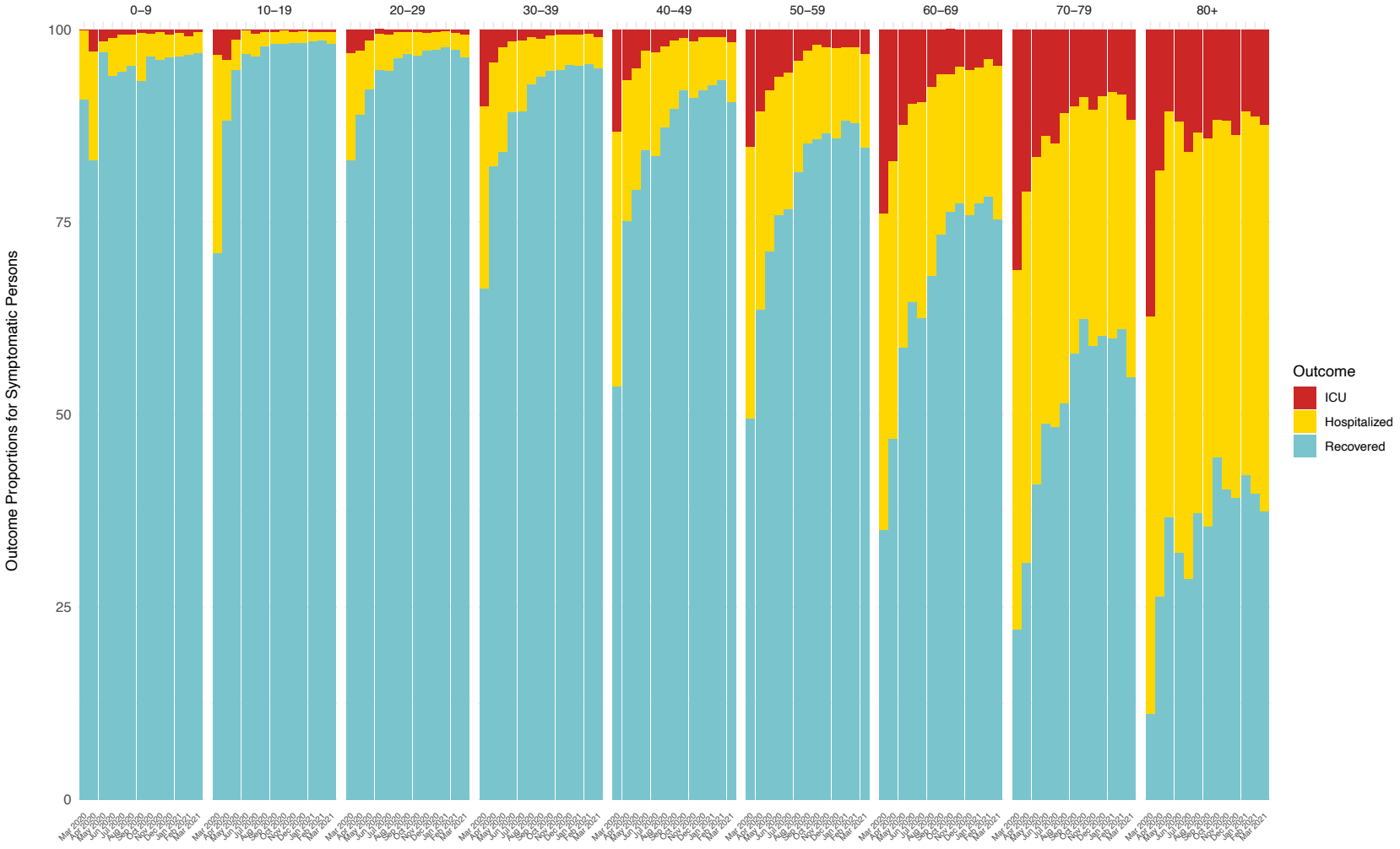
Appendix Figure II-2. Cascade diagrams for case investigation processes stratified by month from March 2020-February 2021 estimated from Georgia Department of Public Health data.



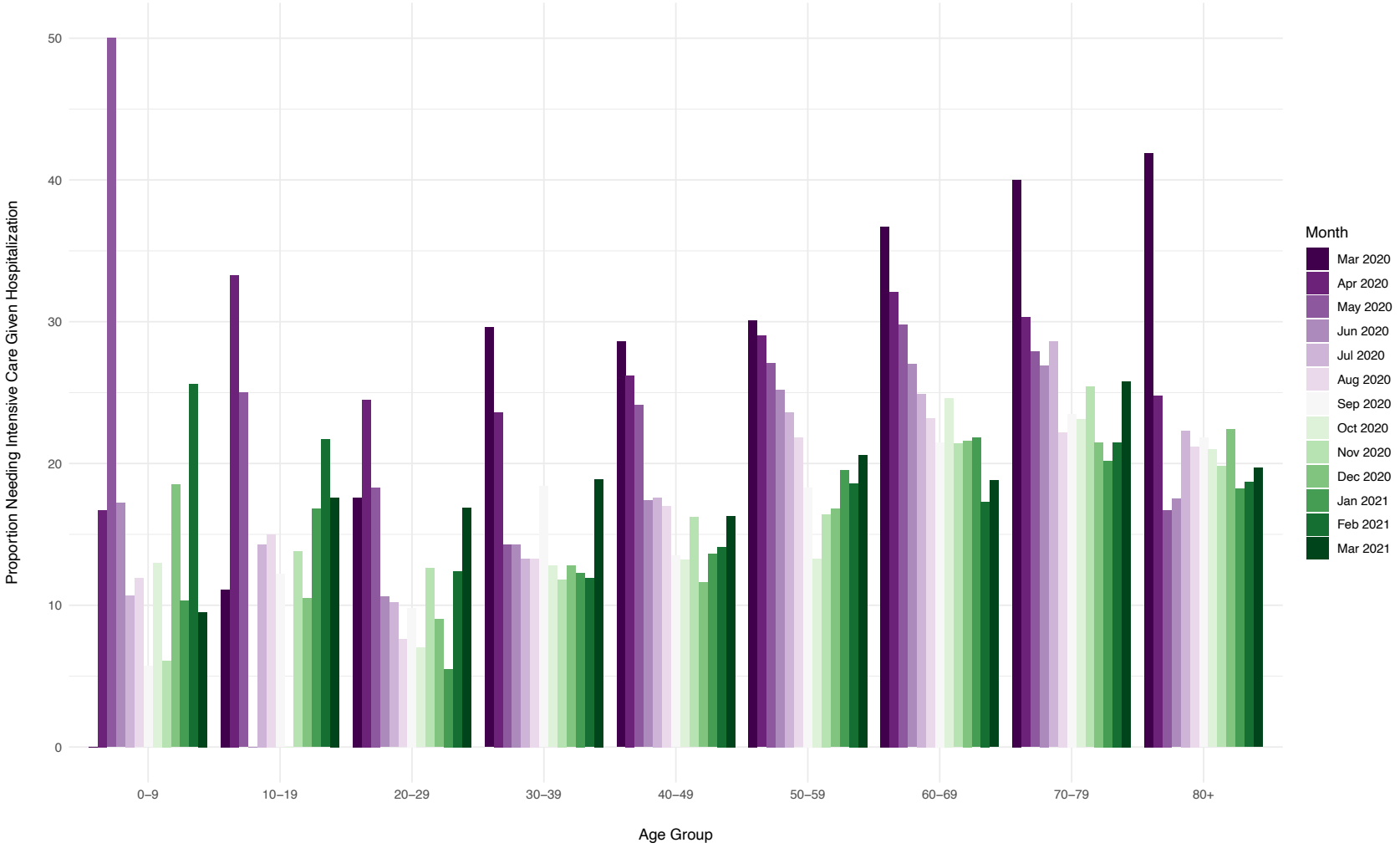
Appendix Figure II-3. Distribution of the proportion of symptomatic individuals across time from March 2020-March 2021 stratified by age decile estimated from Georgia Department of Public Health data.



Appendix Figure II-4. Distribution of the proportion of individuals who were recovered, admitted to the hospital, or admitted to the intensive care unit across time from March 2020-March 2021 stratified by age decile estimated from Georgia Department of Public Health data.



Appendix Figure II-5. Distribution of the proportion of individuals needing intensive care hospitalization across time from March 2020-March 2021 stratified by age decile estimated from Georgia Department of Public Health data.



Exponential Random Graph Models

The relationships between the nodes in our network were represented by a set of conditional logit equations. The probability that an edge will form between time t and $t+1$ given its non-existence at time t was represented by the following:

$$logit\left[P\left(Y_{ij,t+1}=1\middle|Y_{ij,t}^{C}\right)\right]=\theta'\,\partial\left(g(y)\right)$$

where time, t, was simulated in discrete time steps in days, $Y_{ij,t+1}$ represented the connection formed between nodes i and j between time t and $t+1$, $Y_{ij,t}^{C}$ represented the rest of the network, θ represented the vector of parameters in the model, and $g(y)$ represented the vector of network statistics corresponding to each contact network structure described in the table above. The probability that an edge dissolved between time t and $t+1$ given its existence at time t was represented by the following:

$$logit\left[P\left(Y_{ij,t+1}=0\middle|Y_{ij,t}^{C}\right)\right]=\theta'\,\partial\left(g(y)\right)$$

where variables were analogous to those in the formation formula, except for $Y_{ij,t+1}$, which represented the dissolved connection between nodes i and j between time t and $t+1$.

Network Model Conditions

The following conditions were coded for network model interventions:

Pool of eligible cases: Individuals within the ‘a’, ‘ip’, or ‘ic’ compartments at time *t*

Cases identified for case investigation: Were diagnosed via a screening or diagnostic test before time *t*

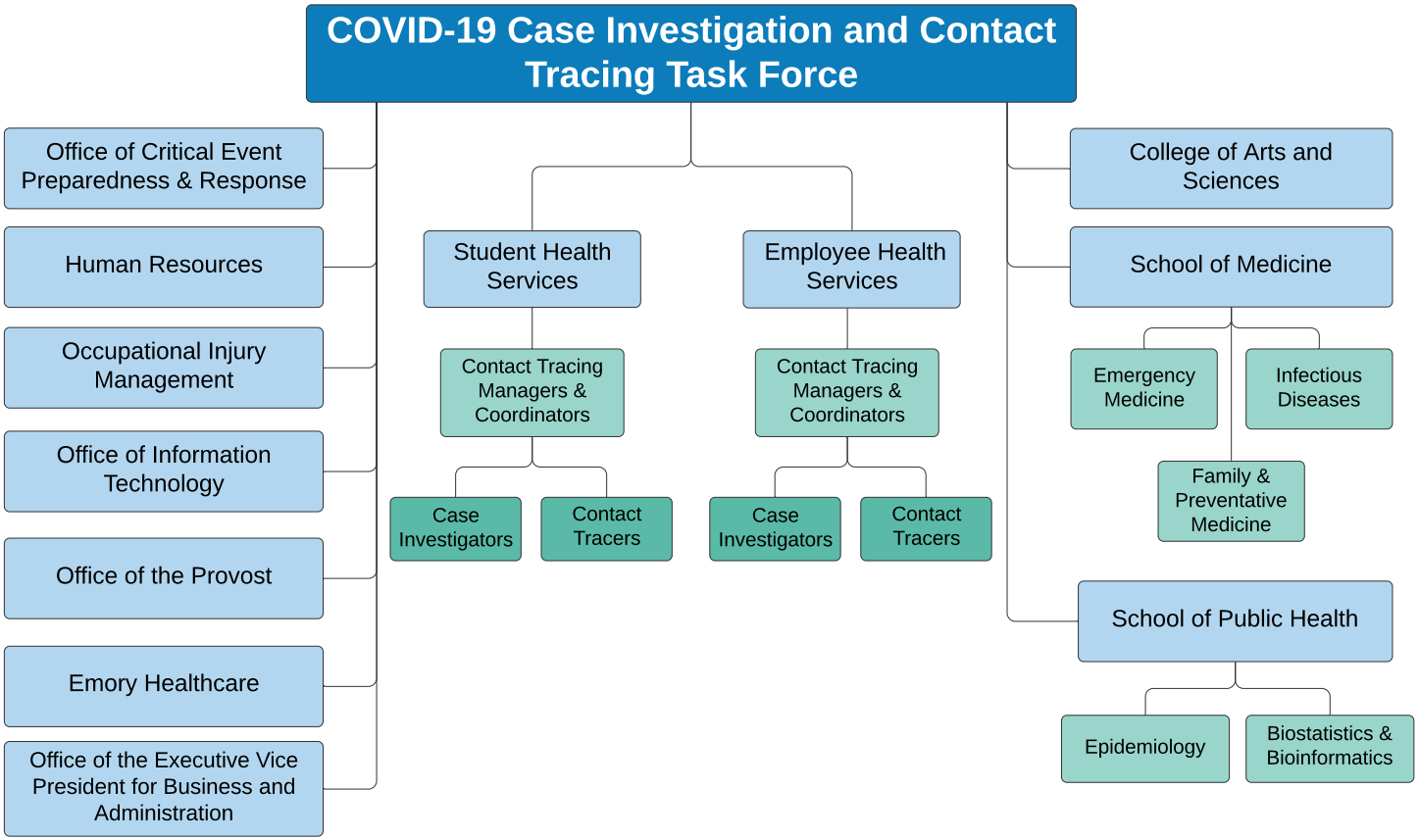
Close contacts of cases identified for case investigation: Retrieved from cumulative discordant edgelist for within household and community layer contact networks

Eligible contacts for contact tracing: Within appropriate time range as defined by the Georgia Department of Public Health in 2020 (close contact within 48 hours prior to

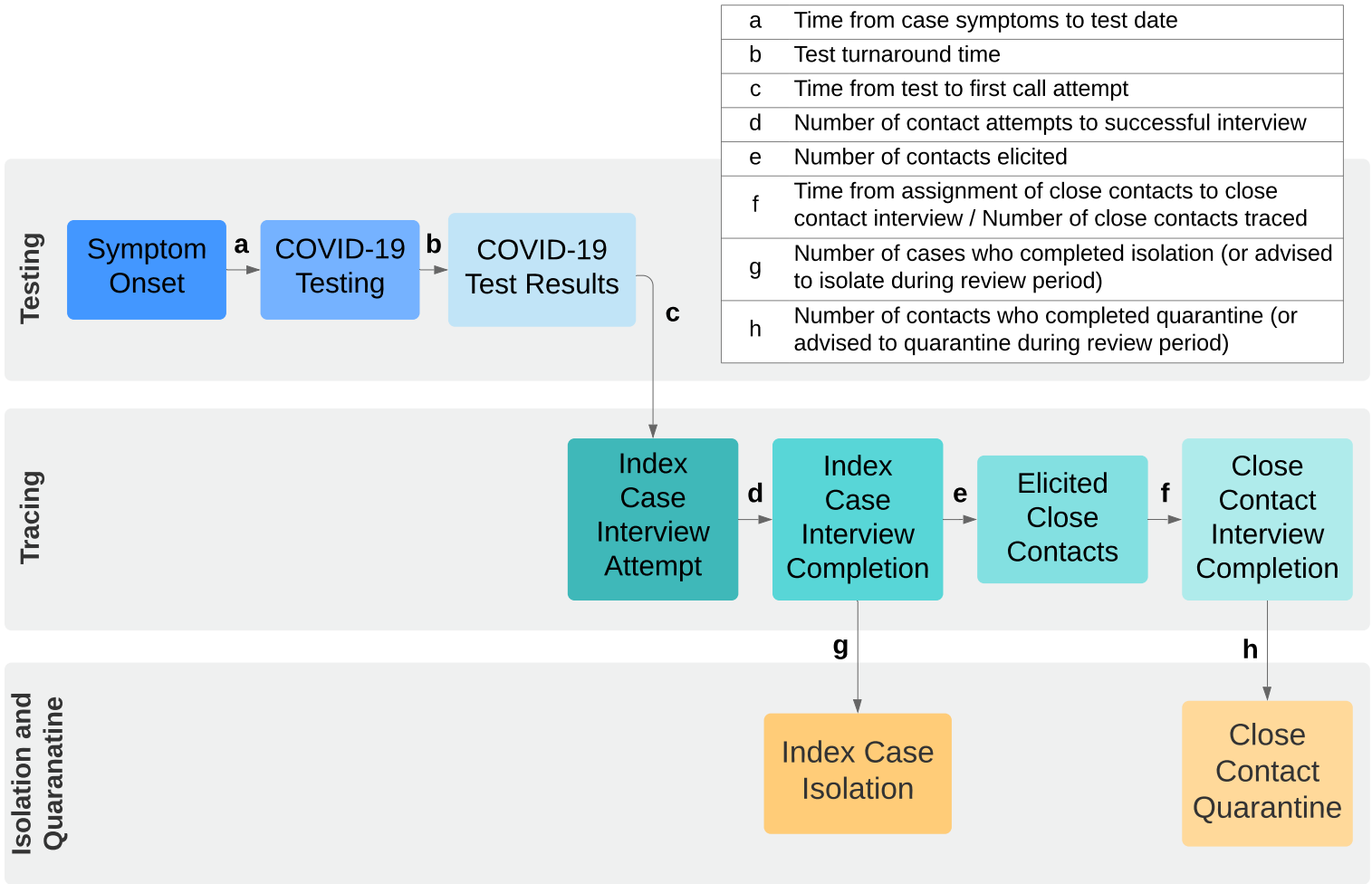
symptom onset or positive test to 10 days after symptom onset or time of symptom resolution [whichever is longer] or positive test)

Appendix III. Chapter 3 Technical Appendix

Appendix Figure III-1. Structure of the Emory University contact tracing program during the 2020-2021 school year at Emory University.



Appendix Figure III-2. Visualization of the testing, tracing, and isolation and quarantine processes of the Emory contact tracing program during the 2020-2021 school year.



a	Time from case symptoms to test date
b	Test turnaround time
c	Time from test to first call attempt
d	Number of contact attempts to successful interview
e	Number of contacts elicited
f	Time from assignment of close contacts to close contact interview / Number of close contacts traced
g	Number of cases who completed isolation (or advised to isolate during review period)
h	Number of contacts who completed quarantine (or advised to quarantine during review period)

Bias analysis model framework

The network models used in the bias analyses were used to simulate networks of COVID-19 cases and their close contacts. In our models, each case in the network was assigned specific clinical and demographic attributes according to pre-defined distributions. Each attribute is represented by a 'nodefactor' term in the network model. This allowed the number of links to vary by an individual's attributes. We defined target statistics for the number of edges attributed to a case with a given set of attributes in the network. We used data collected by the Emory University contact tracing program to estimate all attributes and their target statistics. The attributes assigned to each case influence the number of other individuals that case is connected to in the network.

Full network size estimates

To simulate full networks, we needed to make assumptions about the true size of the network. We estimated the denominators for individuals by affiliation (i.e., on-campus students, off-campus students, and faculty/staff) using university-estimated counts as well as aggregated compliance measure statistics used by the university to track the number of on-campus students required to test weekly. We also took into account the rigor of testing requirements for each affiliation, and how that would impact the potential number of missing cases (Table 1).

Population denominators

Student body (on-campus) = 1,570

Student body (off-campus) = 9,868

Faculty/staff = 8,442

Seroprevalence estimate = 8.6% (6.3%-11.8%)[294]

Assumptions for each population given testing protocols

Student body (on-campus): Very unlikely to have many missed cases. Used seroprevalence estimate / 2

Student body (off-campus): Unlikely to have many missed cases. Used seroprevalence estimate / 2

Faculty/staff: Very likely to have many missed cases. Used seroprevalence estimate / 1

Estimated number of cases: (1,570 x 0.043) + (9,868 x 0.043) + (8,442 x 0.086) = 1,218 cases

For our primary analysis, we estimated a total number of COVID-19 cases at n = 1,200.

Demographic and Clinical measures

We categorized mean degree tables based on symptomaticity, university affiliation, gender, age group, race, ethnicity, month of index case test, county, and housing (for students). Models with target statistics specified for every level of each attribute did not easily converge, so we reduced the number of target statistics to the distributions for: symptomaticity, month of index case test, and the joint distribution for university affiliation and housing. Using these target statistics, we simulated full transmission networks from each model.

Appendix Tables III-1. Number, percent, and mean degree of individuals based upon characteristics including symptomaticity, affiliation, housing, gender, age group, race, ethnicity, month of index case diagnosis, and county.

Symptomatic	No. (%)	Mean Degree
Yes	362 (82)	2.9
No	79 (18)	3.0

Affiliation	No. (%)	Mean Degree

Student	263 (60)	3.0
Faculty/Staff	176 (40)	2.8

Student Housing	No. (%)	Mean Degree
On-Campus	48 (18)	3.8
Off-Campus	215 (82)	2.8

Gender	No. (%)	Mean Degree
Male	166 (38)	3.2
Female	271 (61)	2.7

Age Group	No. (%)	Mean Degree
17-22 years	122 (28)	3.5
23-28 years	111 (25)	2.5
29-40 years	99 (22)	2.5
>40 years	104 (24)	3.0

Race	No. (%)	Mean Degree
Black	113 (26)	2.9
White	239 (54)	3.0
Asian	55 (12)	2.6

Ethnicity	No. (%)	Mean Degree
Non-Hispanic/Latino	381 (86)	3.0
Hispanic/Latino	30 (7)	2.9

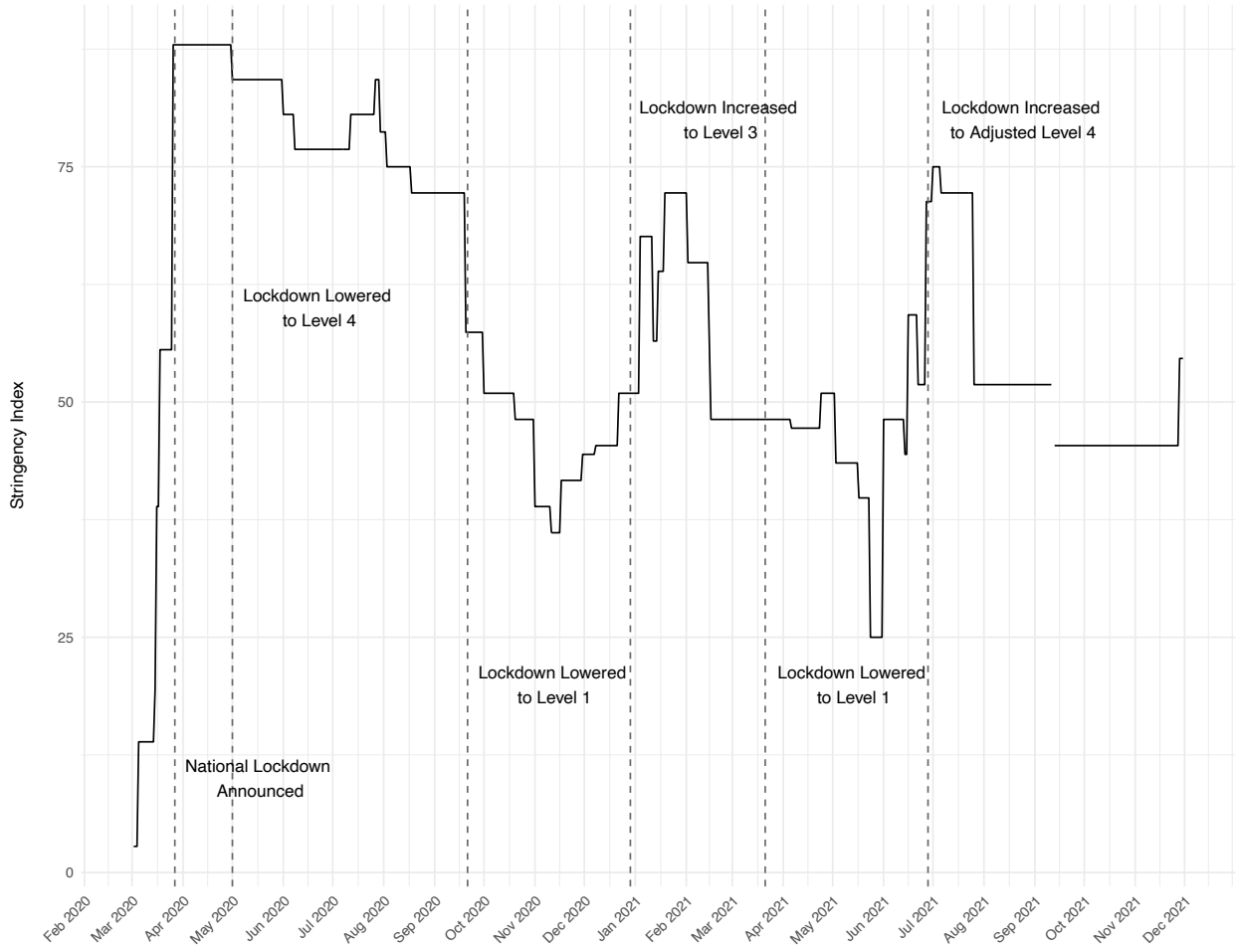
Month	No. (%)	Mean Degree
August	15 (3)	2.4
September	50 (11)	3.2
October	63 (14)	3.4
November	139 (31)	3.0
December	174 (39)	2.5

County	No. (%)	Mean Degree
DeKalb	201 (46)	2.9
Fulton	83 (19)	2.3
Gwinnett	39 (9)	3.7
Cobb	16 (4)	2.2
Rockdale	7 (2)	2.6
Henry	6 (1)	2.3

Affiliation + Housing	No. (%)	Mean Degree
On-Campus Student	48 (11)	3.8
Off-Campus Student	215 (49)	2.8
Faculty/Staff	176 (40)	2.8

Appendix IV. Chapter 4 Technical Appendix

Appendix Figure IV-1. Timeline of lockdowns with the estimated stringency index for South Africa from February 2020-December 2021.



Bayesian spatial conditional autoregressive models

Spatial CAR models were run for cases in the enrolled cohort. Local municipality characteristics were leveraged for use as covariates in the models. Number of DR TB cases were aggregated over spatial units before and after COVID-19 national lockdowns.

The CAR distribution smoothes data according to an adjacency structure given by a neighborhood matrix that specifies neighbors as units sharing a boundary.[323] The CAR distribution is as follows:

$$u_i|\boldsymbol{u}_{-\boldsymbol{i}} \sim N\left(\bar{u}_{\delta_i}, \frac{\sigma_u^2}{n_{\delta_i}}\right)$$

Where $\bar{u}_{\delta_i} = n_{\delta_i}^{-1} \sum_{j \epsilon \delta_i} u_j$, and δ_i and n_{δ_i} represent the set of neighbors and number of neighbors of area i, respectively.

Models were fit using the following structure:

$$Number\ of\ cases \sim offset(\log(population\ count)) + \beta_0 + \beta_n X_{ni} + u_i + v_i$$

Where X_{ni} were neighborhood characteristics of the local municipality unit, $X_{(n+1)ij}$ was the number of diagnosed DR TB cases in the spatial units that shared a border with the index census unit, u_i was a spatially correlated random effect, and v_i was a non-spatially correlated random effect.

Final models were chosen based upon optimizing DIC values across the two time periods.

Fixed effect variables for each model are listed below:

Model 1: Flush toilet connected to sewage, weekly refuse removal, electricity for lighting

Model 2: Flush toilet connected to sewage, owns stove, owns motor car, access to internet, electricity for lighting

Model 3: Formal dwellings, female headed household, tribal settlement, average household size

Model 4: Flush toilet connected to sewage, electricity for lighting, formal dwellings, tribal settlement, female headed household

Model 5: Flush toilet connected to sewage, owns stove, electricity for lighting, female headed house

Model 6: Flush toilet connected to sewage, owns stove, electricity for lighting, access to internet

Appendix Table IV-1. Estimated deviance information criterion for Bayesian autocorrelated models for drug-resistant tuberculosis cases diagnosed before and after COVID-19 pandemic lockdowns.

	Before lockdowns	**After lockdowns**
	DIC	
Model 1	45.89	66.00
Model 2	42.17	52.23
Model 3	51.61	56.03
Model 4	47.32	58.40
Model 5	47.36	58.05
Model 6	40.87	54.82

References

1. Dong E, Du H, Gardner L. An interactive web-based dashboard to track COVID-19 in real time. *Lancet Infect Dis*. 2020;20(5):533-534. doi:10.1016/S1473-3099(20)30120-1
2. Li Q, Guan X, Wu P, et al. Early Transmission Dynamics in Wuhan, China, of Novel Coronavirus–Infected Pneumonia. *N Engl J Med*. 2020;382(13):1199-1207. doi:10.1056/nejmoa2001316
3. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. *Lancet*. 2020;395(10223):507-513. doi:10.1016/S0140-6736(20)30211-7
4. Zhu N, Zhang D, Wang W, et al. A Novel Coronavirus from Patients with Pneumonia in China, 2019. *N Engl J Med*. 2020;382(8):727-733. doi:10.1056/nejmoa2001017
5. Chen S, Yang J, Yang W, Wang C, Bärnighausen T. COVID-19 control in China during mass population movements at New Year. *Lancet*. 2020;395(10226):764-766. doi:10.1016/S0140-6736(20)30421-9
6. Announcement of Wuhan Headquarters for Prevention and Control of Pneumonia Outbreak of Novel Coronavirus Infection (No. 1)_Local Government_Chinese Government Network. Accessed January 31, 2021. http://www.gov.cn/xinwen/2020-01/23/content_5471751.htm
7. Coronavirus Travel Restrictions: Here Are the Airlines, Countries - Bloomberg. Accessed January 31, 2021. https://www.bloomberg.com/news/articles/2020-02-02/coronavirus-these-countries-airlines-restrict-travel-to-china
8. Statement on the second meeting of the International Health Regulations (2005) Emergency Committee regarding the outbreak of novel coronavirus (2019-nCoV).

Accessed January 31, 2021. https://www.who.int/news/item/30-01-2020-statement-on-the-second-meeting-of-the-international-health-regulations-(2005)-emergency-committee-regarding-the-outbreak-of-novel-coronavirus-(2019-ncov)

9. Baraniuk C. What the Diamond Princess taught the world about covid-19. *BMJ*. 2020;369. doi:10.1136/bmj.m1632
10. Sekizuka T, Itokawa K, Kageyama T, et al. Haplotype Networks of SARS-CoV-2 Infections in the Diamond Princess Cruise Ship Outbreak. *Proc Natl Acad Sci U S A*. 2020;117(33):20198-20201. doi:10.1073/PNAS.2006824117
11. Coronavirus Disease (COVID-19) Situation Reports. Accessed January 31, 2021. https://www.who.int/emergencies/diseases/novel-coronavirus-2019/situation-reports
12. WHO Timeline - COVID-19. Accessed January 31, 2021. https://www.who.int/news/item/27-04-2020-who-timeline---covid-19
13. Chu DK, Akl EA, Duda S, et al. Physical distancing, face masks, and eye protection to prevent person-to-person transmission of SARS-CoV-2 and COVID-19: a systematic review and meta-analysis. *Lancet*. 2020;395(10242):1973-1987. doi:10.1016/S0140-6736(20)31142-9
14. Lewis D. Is the coronavirus airborne? Experts can't agree. *Nature*. 2020;580(7802):175. doi:10.1038/d41586-020-00974-w
15. Tang S, Mao Y, Jones RM, et al. Aerosol transmission of SARS-CoV-2? Evidence, prevention and control. *Environ Int*. 2020;144:106039. doi:10.1016/j.envint.2020.106039
16. Bourouiba L. Turbulent Gas Clouds and Respiratory Pathogen Emissions Potential Implications for Reducing Transmission of COVID-19. *Number*. 2020;323:1837. doi:10.1001/jama.2020.4756
17. Setti L, Passarini F, De Gennaro G, et al. Airborne Transmission Route of COVID-19:

Why 2 Meters/6 Feet of Inter-Personal Distance Could Not Be Enough. *Int J Environ Res Public Heal*. 2020;17. doi:10.3390/ijerph17082932

18. Liu Y, Ning Z, Chen Y, et al. Aerodynamic analysis of SARS-CoV-2 in two Wuhan hospitals. *Nature*. 2020;582(7813):557-560. doi:10.1038/s41586-020-2271-3
19. de Man P, Paltansing S, Ong DSY, Vaessen N, van Nielen G, Koeleman JGM. Outbreak of Coronavirus Disease 2019 (COVID-19) in a Nursing Home Associated With Aerosol Transmission as a Result of Inadequate Ventilation. *Clin Infect Dis*. Published online August 28, 2020. doi:10.1093/cid/ciaa1270
20. Li Y, Qian H, Hang J, et al. Evidence for probable aerosol transmission of SARS-CoV-2 in a poorly ventilated restaurant. *medRxiv*. Published online April 22, 2020:2020.04.16.20067728. doi:10.1101/2020.04.16.20067728
21. van Doremalen N, Bushmaker T, Morris DH, et al. Aerosol and Surface Stability of SARS-CoV-2 as Compared with SARS-CoV-1. *N Engl J Med*. 2020;382(16):1564-1567. doi:10.1056/nejmc2004973
22. Kang M, Wei J, Yuan J, et al. Probable Evidence of Fecal Aerosol Transmission of SARS-CoV-2 in a High-Rise Building. *Ann Intern Med*. 2020;173(12):974-980. doi:10.7326/M20-0928
23. Somsen GA, van Rijn C, Kooij S, Bem RA, Bonn D. Small droplet aerosols in poorly ventilated spaces and SARS-CoV-2 transmission. *Lancet Respir Med*. 2020;8(7):658-659. doi:10.1016/S2213-2600(20)30245-9
24. Azimi P, Keshavarz Z, Laurent JGC, Stephens BR, Allen JG. Mechanistic transmission modeling of COVID-19 on the diamond princess cruise ship demonstrates the importance of aerosol transmission. *medRxiv*. Published online July 15, 2020:2020.07.13.20153049. doi:10.1101/2020.07.13.20153049

25. Lelieveld J, Helleis F, Borrmann S, et al. Model Calculations of Aerosol Transmission and Infection Risk of COVID-19 in Indoor Environments. *Int J Environ Res Public Health*. 2020;17(21):8114. doi:10.3390/ijerph17218114

26. Morawska L, Milton DK. It Is Time to Address Airborne Transmission of Coronavirus Disease 2019 (COVID-19). *Clin Infect Dis*. 2020;71(9):2311-2313. doi:10.1093/cid/ciaa939

27. Scientific Brief: SARS-CoV-2 and Potential Airborne Transmission | CDC. Published October 5, 2020. Accessed February 3, 2021. https://www.cdc.gov/coronavirus/2019-ncov/more/scientific-brief-sars-cov-2.html

28. Flaxman S, Mishra S, Gandy A, et al. Estimating the effects of non-pharmaceutical interventions on COVID-19 in Europe. *Nature*. 2020;584(7820):257-261. doi:10.1038/s41586-020-2405-7

29. Wells CR, Sah P, Moghadas SM, et al. Impact of international travel and border control measures on the global spread of the novel 2019 coronavirus outbreak. *Proc Natl Acad Sci U S A*. 2020;117(13):7504-7509. doi:10.1073/pnas.2002616117

30. Chinazzi M, Davis JT, Ajelli M, et al. The effect of travel restrictions on the spread of the 2019 novel coronavirus (COVID-19) outbreak. *Science (80-)*. 2020;368(6489):395-400. doi:10.1126/science.aba9757

31. Keeling MJ, Hollingsworth TD, Read JM. Efficacy of contact tracing for the containment of the 2019 novel coronavirus (COVID-19). *J Epidemiol Community Health*. Published online 2020:861-866. doi:10.1136/jech-2020-214051

32. Gollust SE, Nagler RH, Fowler EF. The emergence of COVID-19 in the US: A public health and political communication crisis. *J Health Polit Policy Law*. 2020;45(6):967-981. doi:10.1215/03616878-8641506

33. Abrams EM, Greenhawt M. Risk Communication During COVID-19. *J Allergy Clin Immunol Pract*. 2020;8(6):1791-1794. doi:10.1016/j.jaip.2020.04.012

34. Jeong E, Hagose M, Jung H, Ki M, Flahault A. Understanding south Korea's response to the COVID-19 outbreak: A real-time analysis. *Int J Environ Res Public Health*. 2020;17(24):1-18. doi:10.3390/ijerph17249571

35. Lessons learned from Taiwan and South Korea's tech-enabled COVID-19 communications. Accessed April 26, 2021. https://www.brookings.edu/techstream/lessons-learned-from-taiwan-and-south-koreas-tech-enabled-covid-19-communications/

36. Barari S, Caria S, Davola A, et al. Evaluating COVID-19 public health messaging in Italy: Self-reported compliance and growing mental health concerns. *medRxiv*. Published online April 5, 2020:2020.03.27.20042820. doi:10.1101/2020.03.27.20042820

37. He X, Lau EHY, Wu P, et al. Temporal dynamics in viral shedding and transmissibility of COVID-19. *Nat Med*. 2020;26(5):672-675. doi:10.1038/s41591-020-0869-5

38. Bai Y, Yao L, Wei T, et al. Presumed Asymptomatic Carrier Transmission of COVID-19. *JAMA*. 2020;323(14):1406-1407. doi:10.1001/jama.2020.2565

39. Kronbichler A, Kresse D, Yoon S, Lee KH, Effenberger M, Shin J Il. Asymptomatic patients as a source of COVID-19 infections: A systematic review and meta-analysis. *Int J Infect Dis*. 2020;98:180-186. doi:10.1016/j.ijid.2020.06.052

40. Wei WE, Li Z, Chiew CJ, Yong SE, Toh MP, Lee VJ. Presymptomatic Transmission of SARS-CoV-2 — Singapore, January 23–March 16, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(14):411-415. doi:10.15585/mmwr.mm6914e1

41. Oran DP, Topol EJ. Prevalence of Asymptomatic SARS-CoV-2 Infection : A Narrative Review. *Ann Intern Med*. 2020;173(5):362-367. doi:10.7326/M20-3012

42. Lauer SA, Grantz KH, Bi Q, et al. The incubation period of coronavirus disease 2019 (CoVID-19) from publicly reported confirmed cases: Estimation and application. *Ann Intern Med*. 2020;172(9):577-582. doi:10.7326/M20-0504

43. Sanche S, Lin YT, Xu C, Romero-Severson E, Hengartner N, Ke R. High Contagiousness and Rapid Spread of Severe Acute Respiratory Syndrome Coronavirus 2. *Emerg Infect Dis*. 2020;26(7):1470-1477. doi:10.3201/eid2607.200282

44. Bi Q, Wu Y, Mei S, et al. Epidemiology and transmission of COVID-19 in 391 cases and 1286 of their close contacts in Shenzhen, China: a retrospective cohort study. *Lancet Infect Dis*. 2020;20(8):911-919. doi:10.1016/S1473-3099(20)30287-5

45. Guan W, Ni Z, Hu Y, et al. Clinical Characteristics of Coronavirus Disease 2019 in China. *N Engl J Med*. 2020;382(18):1708-1720. doi:10.1056/nejmoa2002032

46. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, Transmission, Diagnosis, and Treatment of Coronavirus Disease 2019 (COVID-19): A Review. *JAMA - J Am Med Assoc*. 2020;324(8):782-793. doi:10.1001/jama.2020.12839

47. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting Characteristics, Comorbidities, and Outcomes among 5700 Patients Hospitalized with COVID-19 in the New York City Area. *JAMA - J Am Med Assoc*. 2020;323(20):2052-2059. doi:10.1001/jama.2020.6775

48. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ*. 2020;369:m1985. doi:10.1136/bmj.m1985

49. Dawson P, Rabold EM, Laws RL, et al. Loss of Taste and Smell as Distinguishing Symptoms of Coronavirus Disease 2019. *Clin Infect Dis*. 2020;48(Xx Xxxx):18-21. doi:10.1093/cid/ciaa799

50. Mao R, Qiu Y, He JS, et al. Manifestations and prognosis of gastrointestinal and liver

involvement in patients with COVID-19: a systematic review and meta-analysis. *Lancet Gastroenterol Hepatol*. 2020;5(7):667-678. doi:10.1016/S2468-1253(20)30126-6

51. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. doi:10.1016/S0140-6736(20)30183-5
52. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. doi:10.1016/S2213-2600(20)30079-5
53. Myers LC, Parodi SM, Escobar GJ, Liu VX. Characteristics of Hospitalized Adults With COVID-19 in an Integrated Health Care System in California. *JAMA - J Am Med Assoc*. 2020;323(21):2195-2198. doi:10.1001/jama.2020.0757
54. Trentini F, Marziano V, Guzzetta G, et al. Healthcare strain and intensive care during the COVID-19 outbreak in the Lombardy region: A retrospective observational study on 43,538 hospitalized patients. *medRxiv*. Published online 2020:1-25. doi:10.1101/2020.11.06.20149690
55. Argenziano MG, Bruce SL, Slater CL, et al. Characterization and clinical course of 1000 patients with coronavirus disease 2019 in New York: Retrospective case series. *BMJ*. 2020;369. doi:10.1136/bmj.m1996
56. Wang Y, Liu Y, Struthers J, Lian M. Spatiotemporal Characteristics of the COVID-19 Epidemic in the United States. *Clin Infect Dis*. 2020;(May):1-9. doi:10.1093/cid/ciaa934
57. Bialek S, Bowen V, Chow N, et al. Geographic Differences in COVID-19 Cases , Deaths , and Incidence — United States, February 12-April7, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69:1-7. doi:10.15585

58. Fauver JR, Petrone ME, Hodcroft EB, et al. Coast-to-Coast Spread of SARS-CoV-2 during the Early Epidemic in the United States. *Cell*. 2020;181(5):990-996.e5. doi:10.1016/j.cell.2020.04.021

59. Schuchat A. Public Health Response to the Initiation and Spread of Pandemic COVID-19 in the United States, February 24–April 21, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(18):551-556. doi:10.4324/9781003141402-16

60. Clouston SAP, Natale G, Link BG. Socioeconomic inequalities in the spread of coronavirus-19 in the United States: A examination of the emergence of social inequalities. *Soc Sci Med*. 2021;268(November 2020):113554. doi:10.1016/j.socscimed.2020.113554

61. Cheng MP, Papenburg J, Desjardins M, et al. Diagnostic Testing for Severe Acute Respiratory Syndrome-Related Coronavirus 2: A Narrative Review. *Ann Intern Med*. 2020;172(11):726-734. doi:10.7326/M20-1301

62. Wang CJ, Ng CY, Brook RH. Response to COVID-19 in Taiwan: Big Data Analytics, New Technology, and Proactive Testing. *JAMA - J Am Med Assoc*. 2020;323(14):1341-1342. doi:10.1001/jama.2020.3151

63. Diseases KS of I, Diseases KS of PI, Epidemiology KS of, Therapy KS for A, Prevention KS for HIC and, Prevention KC for DC and. Report on the Epidemiological Features of Coronavirus Disease 2019 (COVID-19) Outbreak in the Republic of Korea from January 19 to March 2, 2020. *J Korean Med Sci*. 2020;35(10):e112-e112. doi:10.3346/jkms.2020.35.e112

64. Wu SL, Mertens AN, Crider YS, et al. Substantial underestimation of SARS-CoV-2 infection in the United States. *Nat Commun*. 2020;11(1). doi:10.1038/s41467-020-18272-4

65. Omori R, Mizumoto K, Chowell G. Changes in testing rates could mask the novel coronavirus disease (COVID-19) growth rate. *Int J Infect Dis*. 2020;94:116-118. doi:10.1016/j.ijid.2020.04.021

66. Pearce N, Vandenbroucke JP, VanderWeele TJ, Greenland S. Accurate Statistics on COVID-19 Are Essential for Policy Guidance and Decisions. *Am J Public Health*. 2020;110(7):949-951. doi:10.2105/AJPH.2020.305708

67. Pitzer VE, Chitwood M, Havumaki J, et al. The impact of changes in diagnostic testing practices on estimates of COVID-19 transmission in the United States. *medRxiv*. Published online 2020. doi:10.1101/2020.04.20.20073338

68. Greene DN, Jackson ML, Hillyard DR, Delgado JC, Schmidt RL. Decreasing median age of COVID-19 cases in the United States—Changing epidemiology or changing surveillance? *PLoS One*. 2020;15(10):1-7. doi:10.1371/journal.pone.0240783

69. Boehmer T, DeVies J, Caruso E, et al. Changing Age Distribution of the COVID-19 Pandemic — United States, May–August 2020. *Morb Mortal Wkly Rep*. 2020;69(39):1404-1409.

70. Pei S, Kandula S, Shaman J. Differential effects of intervention timing on COVID-19 spread in the United States. *Sci Adv*. 2020;6:1-9. doi:10.1101/2020.05.15.20103655

71. White ER, Hébert-Dufresne L. State-level variation of initial COVID-19 dynamics in the United States. *PLoS One*. 2020;15(10 OCTOBER):1-13. doi:10.1371/journal.pone.0240648

72. Grossman G, Kim S, Rexer JM, Thirumurthy H. Political partisanship influences behavioral responses to governors' recommendations for COVID-19 prevention in the United States. *Proc Natl Acad Sci U S A*. 2020;117(39):24144-24153. doi:10.1073/pnas.2007835117

73. Wellenius GA, Vispute S, Espinosa V, et al. Impacts of US State-Level Social Distancing Policies on Population Mobility and COVID-19 Case Growth During the First Wave of the Pandemic. *arXiv*. Published online April 21, 2020. Accessed January 30, 2021. http://arxiv.org/abs/2004.10172

74. Yehya N, Venkataramani A, Harhay MO. Statewide Interventions and Covid-19 Mortality in the United States: An Observational Study. *Clin Infect Dis*. 2020;ciaa923. https://doi.org/10.1093/cid/ciaa923

75. Miller IF, Becker AD, Grenfell BT, Metcalf CJE. Disease and healthcare burden of COVID-19 in the United States. *Nat Med*. 2020;26(8):1212-1217. doi:10.1038/s41591-020-0952-y

76. Ross J, Diaz CM, Starrels JL. The Disproportionate Burden of COVID-19 for Immigrants in the Bronx, New York. *JAMA Intern Med*. 2020;180(8):1043-1044. doi:10.1056/nejmp1808020

77. Kakani P, Chandra A, Mullainathan S, Obermeyer Z. Allocation of COVID-19 Relief Funding to Disproportionately Black Counties. *JAMA - J Am Med Assoc*. 2020;324(10):1000-1003. doi:10.1001/jama.2020.15301

78. Clark E, Fredricksid K, Woc-Colburn L, Bottazzi ME, Weatherheadid J. Disproportionate impact of the COVID-19 pandemic on immigrant communities in the United States. *PLoS Negl Trop Dis*. 2020;14(7):1-9. doi:10.1371/journal.pntd.0008484

79. Dyer O. Covid-19: Black people and other minorities are hardest hit in US. *BMJ*. 2020;369:1-2. doi:10.1136/bmj.m1483

80. Rossen LM, Branum AM, Ahmad FB, Sutton P, Anderson RN. Excess Deaths Associated with COVID-19, by Age and Race and Ethnicity — United States, January 26–October 3, 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(42):1522-1527.

doi:10.15585/mmwr.mm6942e2

81. Ridenhour B, Kowalik JM, Shay DK. Unraveling R0: Considerations for public health applications. *Am J Public Health*. 2018;108:S445-S454. doi:10.2105/AJPH.2013.301704

82. Dushoff J, Park SW. Speed and strength of an epidemic intervention. *Proc R Soc B Biol Sci*. 2021;288(1947):20201556. doi:10.1098/rspb.2020.1556

83. Heffernan JM, Smith RJ, Wahl LM. Perspectives on the basic reproductive ratio. *J R Soc Interface*. 2005;2(4):281-293. doi:10.1098/rsif.2005.0042

84. Liu Y, Gayle AA, Wilder-Smith A, Rocklöv J. The reproductive number of COVID-19 is higher compared to SARS coronavirus. *J Travel Med*. 2020;27(2):1-4. doi:10.1093/jtm/taaa021

85. Zhuang Z, Zhao S, Lin Q, et al. Preliminary estimates of the reproduction number of the coronavirus disease (COVID-19) outbreak in Republic of Korea and Italy by 5 March 2020. *Int J Infect Dis*. 2020;95:308-310. doi:10.1016/j.ijid.2020.04.044

86. Zhang S, Diao MY, Yu W, Pei L, Lin Z, Chen D. Estimation of the reproductive number of novel coronavirus (COVID-19) and the probable outbreak size on the Diamond Princess cruise ship: A data-driven analysis. *Int J Infect Dis*. 2020;93:201-204. doi:10.1016/j.ijid.2020.02.033

87. Gostic KM, McGough L, Baskerville EB, et al. Practical considerations for measuring the effective reproductive number, Rt. *PLoS Comput Biol*. 2020;16(12):1-21. doi:10.1371/journal.pcbi.1008409

88. Xiao Y, Tang B, Wu J, Cheke RA, Tang S. Linking key intervention timing to rapid decline of the COVID-19 effective reproductive number to quantify lessons from mainland China. *Int J Infect Dis*. 2020;97:296-298. doi:10.1016/j.ijid.2020.06.030

89. Halloran M. Secondary Attack Rate. In: *Encyclopedia of Biostatistics*. ; 2005.

doi:10.1002/0470011815.b2a04049

90. Fung HF, Martinez L, Alarid-Escudero F, et al. The household secondary attack rate of SARS-CoV-2: A rapid review. *Clin Infect Dis*. Published online October 12, 2020:ciaa1558. doi:10.1093/cid/ciaa1558

91. Jing QL, Liu MJ, Zhang Z Bin, et al. Household secondary attack rate of COVID-19 and associated determinants in Guangzhou, China: a retrospective cohort study. *Lancet Infect Dis*. 2020;20(10):1141-1150. doi:10.1016/S1473-3099(20)30471-0

92. Lewis NM, Chu VT, Ye D, et al. Household Transmission of SARS-CoV-2 in the United States. *Clin Infect Dis*. Published online August 16, 2020. doi:10.1093/cid/ciaa1166

93. Grijalva CG, Rolfes MA, Zhu Y, et al. Transmission of SARS-COV-2 Infections in Households — Tennessee and Wisconsin, April–September 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(44). doi:10.15585/mmwr.mm6944e1

94. Liu Y, Eggo RM, Kucharski AJ. Secondary attack rate and superspreading events for SARS-CoV-2. *Lancet*. 2020;395(10227):e47. doi:10.1016/S0140-6736(20)30462-1

95. Bell D, Nicoll A, Fukuda K, et al. Nonpharmaceutical interventions for pandemic influenza, international measures. *Emerg Infect Dis*. 2006;12(1):81-87. doi:10.3201/eid1201.051370

96. Markel H, Lipman HB, Navarro JA, et al. Nonpharmaceutical interventions implemented by US cities during the 1918-1919 influenza pandemic. *J Am Med Assoc*. 2007;298(6):644-654. doi:10.1001/jama.298.6.644

97. Caley P, Philp DJ, McCracken K. Quantifying social distancing arising from pandemic influenza. *J R Soc Interface*. 2008;5(23):631-639. doi:10.1098/rsif.2007.1197

98. Ali ST, Wang L, Lau EHY, et al. Serial interval of SARS-CoV-2 was shortened over time by nonpharmaceutical interventions. *Science (80-)*. 2020;369(6507):1106-1109. doi:10.1126/science.abc9004

99. Pan A, Liu L, Wang C, et al. Association of Public Health Interventions with the Epidemiology of the COVID-19 Outbreak in Wuhan, China. *JAMA - J Am Med Assoc*. 2020;323(19):1915-1923. doi:10.1001/jama.2020.6130

100. Tian H, Liu Y, Li Y, et al. An investigation of transmission control measures during the first 50 days of the COVID-19 epidemic in China. *Science (80-)*. 2020;368(6491):638-642. doi:10.1126/science.abb6105

101. Chen S, Li Q, Gao S, Kang Y, Shi X. State-specific Projection of COVID-19 Infection in the United States and Evaluation of Three Major Control Measures. *medRxiv*. Published online 2020. doi:10.1101/2020.02.18.20024414

102. Prague M, Wittkop L, Collin A, et al. Population modeling of early COVID-19 epidemic dynamics in French regions and estimation of the lockdown impact on infection rate. *medRxiv*. Published online July 13, 2020:2020.04.21.20073536. doi:10.1101/2020.04.21.20073536

103. Hsiang S, Allen D, Annan-Phan S, et al. The effect of large-scale anti-contagion policies on the COVID-19 pandemic. *Nature*. 2020;584(7820):262-267. doi:10.1038/s41586-020-2404-8

104. Davies NG, Kucharski AJ, Eggo RM, et al. Effects of non-pharmaceutical interventions on COVID-19 cases, deaths, and demand for hospital services in the UK: a modelling study. *Lancet Public Heal*. 2020;5(7):e375-e385. doi:10.1016/S2468-2667(20)30133-X

105. Honein MA, Christie A, Rose DA, et al. Summary of Guidance for Public Health Strategies to Address High Levels of Community Transmission of SARS-CoV-2 and Related Deaths, December 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(49):1860-1867. doi:10.15585/mmwr.mm6949e2

106. Ospina JE, Orcau À, Millet J-P, Sánchez F, Casals M, Caylà JA. Community health

workers improve contact tracing among immigrants with tuberculosis in Barcelona. *BMC Public Health*. 2012;12(1):158. doi:10.1186/1471-2458-12-158

107. Mandal P, Craxton R, Chalmers JD, et al. Contact tracing in pulmonary and non-pulmonary tuberculosis. *QJM An Int J Med*. 2012;105(8):741-747. doi:10.1093/qjmed/hcs045

108. Carré H, Boman J, Österlund A, Gärdén B, Nylander E. Improved contact tracing for Chlamydia trachomatis with experienced tracers, tracing for one year back in time and interviewing by phone in remote areas. *Sex Transm Infect*. 2008;84(3):239-242. doi:10.1136/sti.2007.028068

109. Rothenberg RB, McElroy PD, Wilce MA, Muth SQ. Contact tracing: Comparing the approaches for sexually transmitted diseases and tuberculosis. *Int J Tuberc Lung Dis*. 2003;7(12 SUPPL. 3):342-348.

110. James L, Shindo N, Cutter J, Ma S, Chew SK. Public health measures implemented during the SARS outbreak in Singapore, 2003. *Public Health*. 2006;120(1):20-26. doi:10.1016/j.puhe.2005.10.005

111. Greiner AL, Angelo KM, McCollum AM, Mirkovic K, Arthur R, Angulo FJ. Addressing contact tracing challenges-critical to halting Ebola virus disease transmission. *Int J Infect Dis*. 2015;41:53-55. doi:10.1016/j.ijid.2015.10.025

112. CDC. COVID-19: When to Quarantine | CDC. Accessed February 15, 2021. https://www.cdc.gov/coronavirus/2019-ncov/if-you-are-sick/quarantine.html

113. Kwok KO, Tang A, Wei VWI, Park WH, Yeoh EK, Riley S. Epidemic Models of Contact Tracing: Systematic Review of Transmission Studies of Severe Acute Respiratory Syndrome and Middle East Respiratory Syndrome. *Comput Struct Biotechnol J*. 2019;17:186-194. doi:10.1016/j.csbj.2019.01.003

114. Peak CM, Childs LM, Grad YH, Buckee CO. Comparing nonpharmaceutical interventions for containing emerging epidemics. *Proc Natl Acad Sci U S A*. 2017;114(15):4023-4028. doi:10.1073/pnas.1616438114

115. Fine P, Eames K, Heymann DL. “Herd immunity”: A rough guide. *Clin Infect Dis*. 2011;52(7):911-916. doi:10.1093/cid/cir007

116. Klinkenberg D, Fraser C, Heesterbeek H. The Effectiveness of Contact Tracing in Emerging Epidemics. doi:10.1371/journal.pone.0000012

117. Eames KTD, Keeling MJ. Contact tracing and disease control. *Proc R Soc B Biol Sci*. 2003;270(1533):2565-2571. doi:10.1098/rspb.2003.2554

118. Fraser C, Riley S, Anderson RM, Ferguson NM. Factors that make an infectious disease outbreak controllable. *Proc Natl Acad Sci U S A*. 2004;101(16):6146-6151. doi:10.1073/pnas.0307506101

119. Dhillon RS, Srikrishna D. When is contact tracing not enough to stop an outbreak? *Lancet Infect Dis*. 2018;18(12):1302-1304. doi:10.1016/S1473-3099(18)30656-X

120. Armbruster B, Brandeau ML. Contact tracing to control infectious disease: When enough is enough. *Health Care Manag Sci*. 2007;10(4):341-355. doi:10.1007/s10729-007-9027-6

121. Kaplan EH, Craft DL, Wein LM. Emergency response to a smallpox attack: The case for mass vaccination. *Proc Natl Acad Sci U S A*. 2002;99(16):10935-10940. doi:10.1073/pnas.162282799

122. Megnin-Viggars O, Carter P, Melendez-Torres GJ, Weston D, Rubin GJ. Facilitators and barriers to engagement with contact tracing during infectious disease outbreaks: A rapid review of the evidence. Soundy A, ed. *PLoS One*. 2020;15(10):e0241473. doi:10.1371/journal.pone.0241473

123. Holder S. Why Are Americans So Uneasy About Contact Tracing? - Bloomberg.

Published 2020. Accessed February 15, 2021. https://www.bloomberg.com/news/articles/2020-08-12/why-are-americans-so-uneasy-about-contact-tracing

124. Fear Fuels COVID-19 Contact Tracing Scams | Federal Communications Commission. Accessed February 15, 2021. https://www.fcc.gov/fear-fuels-covid-19-contact-tracing-scams

125. Stone W. Public Health Workers Threatened Over Coronavirus Contact Tracing : Shots - Health News - NPR. Published 2020. Accessed February 15, 2021. https://www.npr.org/sections/health-shots/2020/06/03/868566600/local-public-health-workers-report-hostile-threats-and-fears-about-contact-traci

126. Mooney G. “A Menace to the Public Health” — Contact Tracing and the Limits of Persuasion. *N Engl J Med*. 2020;383(19):1806-1808. doi:10.1056/nejmp2021887

127. Association AP. *Building Community Trust to Improve Participation in COVID-19 Testing and Contact Tracing*.; 2020. Accessed February 15, 2021. https://www.hsph.harvard.edu/horp/discrimination-in-america/

128. Khazan O. Is Contact Tracing Working in the U.S.? - The Atlantic. Published 2020. Accessed February 15, 2021. https://www.theatlantic.com/politics/archive/2020/08/contact-tracing-hr-6666-working-us/615637/

129. Althoff KN, Coburn SB, Nash D. Contact Tracing: Essential to the Public Health Response and Our Understanding of the Epidemiology of Coronavirus Disease 2019. *Clin Infect Dis*. 2020;71(8):1960-1961. doi:10.1093/cid/ciaa757

130. Cheng HY, Jian SW, Liu DP, Ng TC, Huang WT, Lin HH. Contact Tracing Assessment of COVID-19 Transmission Dynamics in Taiwan and Risk at Different Exposure Periods

before and after Symptom Onset. *JAMA Intern Med*. 2020;180(9):1156-1163. doi:10.1001/jamainternmed.2020.2020

131. Eichner M. Case Isolation and Contact Tracing Can Prevent the Spread of Smallpox. *Am J Epidemiol*. 2003;158(2):118-128. doi:10.1093/aje/kwg104

132. Fenner F, Henderson DA, Arita I, Jezek Z, Ladnyi ID. *Smallpox and Its Eradication*. World Health Organization; 1988.

133. Saurabh S, Prateek S. Role of contact tracing in containing the 2014 Ebola outbreak: A review. *Afr Health Sci*. 2017;17(1):225-236. doi:10.4314/ahs.v17i1.28

134. MacIntyre CR. Case isolation, contact tracing, and physical distancing are pillars of COVID-19 pandemic control, not optional choices. *Lancet Infect Dis*. 2020;20(10):1105-1106. doi:10.1016/S1473-3099(20)30512-0

135. Simmons-Duffin S. U.S. Contact Tracing Workforce Grows To Meet Rising Coronavirus Cases : Shots - Health News : NPR. Published 2020. Accessed February 15, 2021. https://www.npr.org/sections/health-shots/2020/12/23/949580432/for-overwhelmed-and-burnt-out-covid-19-contact-tracers-help-is-hopefully-coming

136. Garnett GP, Cousens S, Ballett TB, Steketee R, Walker N. Mathematical models in the evaluation of health programmes. *Lancet*. 2011;378:515-540. doi:10.1016/S0140

137. Juneau C-E, Briand A-S, Pueyo T, Collazzo P, Potvin L. Effective Contact Tracing for COVID-19: A Systematic Review. *medRxiv*. 2020;(July):2020.07.23.20160234. https://doi.org/10.1101/2020.07.23.20160234

138. Malheiro R, Figueiredo AL, Magalhães JP, et al. Effectiveness of contact tracing and quarantine on reducing COVID-19 transmission: a retrospective cohort study. *Public Health*. 2020;189:54-59. doi:10.1016/j.puhe.2020.09.012

139. Aleta A, Martín-Corral D, Pastore y Piontti A, et al. Modelling the impact of testing,

contact tracing and household quarantine on second waves of COVID-19. *Nat Hum Behav*. Published online 2020. doi:10.1038/s41562-020-0931-9

140. Hellewell J, Abbott S, Gimma A, et al. Feasibility of controlling COVID-19 outbreaks by isolation of cases and contacts. *Lancet Glob Heal*. 2020;8(4):e488-e496. doi:10.1016/S2214-109X(20)30074-7

141. Kretzschmar ME, Rozhnova G, Bootsma MCJ, van Boven M, van de Wijgert JHHM, Bonten MJM. Impact of delays on effectiveness of contact tracing strategies for COVID-19: a modelling study. *Lancet Public Heal*. 2020;5(8):e452-e459. doi:10.1016/S2468-2667(20)30157-2

142. Ferretti L, Wymant C, Kendall M, et al. Quantifying SARS-CoV-2 transmission suggests epidemic control with digital contact tracing. *Science (80-)*. 2020;368(6491):0-8. doi:10.1126/science.abb6936

143. Peak CM, Kahn R, Grad YH, et al. Individual quarantine versus active monitoring of contacts for the mitigation of COVID-19: a modelling study. *Lancet Infect Dis*. 2020;20(9):1025-1033. doi:10.1016/S1473-3099(20)30361-3

144. Chiu WA, Fischer R, Ndeffo-Mbah ML. State-level needs for social distancing and contact tracing to contain COVID-19 in the United States. *Nat Hum Behav*. 2020;4(10):1080-1090. doi:10.1038/s41562-020-00969-7

145. Clark E, Chiao EY, Amirian ES. Why Contact Tracing Efforts Have Failed to Curb Coronavirus Disease 2019 (COVID-19) Transmission in Much of the United States. *Clin Infect Dis*. Published online August 6, 2020. doi:10.1093/cid/ciaa1155

146. Worden L, Wannier R, Blumberg S, Ge AY, Rutherford GW, Porco TC. Estimation of effects of contact tracing and mask adoption on COVID-19 transmission in San Francisco: a modeling study. *medRxiv*. Published online June 11,

2020:2020.06.09.20125831. doi:10.1101/2020.06.09.20125831

147. Chen S, Robinson P, Janies D, Dulin M. Four challenges associated with current mathematical modeling paradigm of infectious diseases and call for a shift. *Open Forum Infect Dis*. 2020;7(8):3-4. doi:10.1093/ofid/ofaa333

148. Ludwig A, Berthiaume P, Orpana H, et al. Assessing the impact of varying levels of case detection and contact tracing on COVID-19 transmission in Canada during lifting of restrictive closures using a dynamic compartmental model. *Canada Commun Dis Rep*. 2020;46(1112):409-421. doi:10.14745/ccdr.v46i1112a08

149. Kiss IZ, Green DM, Kao RR. Disease contact tracing in random and clustered networks. doi:10.1098/rspb.2005.3092

150. Sturniolo S, Waites W, Colbourn T, Manheim D, Panovska-Griffiths J. Testing, tracing and isolation in compartmental models. *medRxiv*. Published online 2020:2020.05.14.20101808. doi:10.1101/2020.05.14.20101808

151. Eubank S, Guclu H, Kumar VSA, et al. Modelling disease outbreaks in realistic urban social networks. *Nature*. 2004;429(6988):180-184. doi:10.1038/nature02541

152. Mishra S, Fisman DN, Boily M-C. The ABC of terms used in mathematical models of infectious diseases. doi:10.1136/jech.2009.097113

153. Jewell NP, Lewnard JA, Jewell BL. Predictive Mathematical Models of the COVID-19 Pandemic: Underlying Principles and Value of Projections. *JAMA - J Am Med Assoc*. 2020;323(19):1893-1894. doi:10.1001/jama.2020.6585

154. Feehan DM, Mahmud AS. Quantifying population contact patterns in the United States during the COVID-19 pandemic. *Nat Commun*. 2021;12(1):1-9. doi:10.1038/s41467-021-20990-2

155. Sparks SRJ, Aspinall WP, Brooks-Pollock E, et al. A novel approach for evaluating

contact patterns and risk mitigation strategies for COVID-19 in English primary schools with application of structured expert judgement. *medRxiv*. Published online 2020. doi:10.1101/2020.08.13.20170068

156. Yamana T, Pei S, Kandula S, Shaman J. Projection of COVID-19 cases and deaths in the US as individual states re-open May 4, 2020. *medRxiv*. Published online May 13, 2020:2020.05.04.20090670. doi:10.1101/2020.05.04.20090670
157. Which states are reopening and closing again after coronavirus shutdown - Washington Post. Accessed February 15, 2021. https://www.washingtonpost.com/graphics/2020/national/states-reopening-coronavirus-map/
158. Karatayev VA, Anand M, Bauch CT. Local lockdowns outperform global lockdown on the far side of the COVID-19 epidemic curve. *Proc Natl Acad Sci U S A*. 2020;117(39):24575-24580. doi:10.1073/pnas.2014385117
159. Head JR, Andrejko K, Cheng Q, et al. The effect of school closures and reopening strategies on COVID-19 infection dynamics in the San Francisco Bay Area: a cross-sectional survey and modeling analysis. *medRxiv*. 2020;1(510):2020.08.06.20169797. doi:10.1101/2020.08.06.20169797
160. Yamey G, Walensky RP. Covid-19: Re-opening universities is high risk. *BMJ*. 2020;370:20-21. doi:10.1136/bmj.m3365
161. Paltiel AD, Zheng A, Walensky RP. Assessment of SARS-CoV-2 Screening Strategies to Permit the Safe Reopening of College Campuses in the United States. *JAMA Netw open*. 2020;3(7):e2016818. doi:10.1001/jamanetworkopen.2020.16818
162. Leidner AJ, Barry V, Bowen VB, et al. Opening of Large Institutions of Higher Education and County-Level COVID-19 Incidence — United States, July 6–September 17, 2020.

MMWR Morb Mortal Wkly Rep. 2021;70(1):14-19. doi:10.15585/mmwr.mm7001a4

163. Cheng SY, Wang CJ, Shen ACT, Chang SC. How to Safely Reopen Colleges and Universities During COVID-19: Experiences From Taiwan. *Ann Intern Med*. 2020;173(8):638-641. doi:10.7326/M20-2927

164. Yoon Y, Kim KR, Park H, Kim S, Kim YJ. Stepwise School Opening and an Impact on the Epidemiology of COVID-19 in the Children. *J Korean Med Sci*. 2020;35(46). doi:10.3346/JKMS.2020.35.E414

165. Gressman PT, Peck JR. Simulating COVID-19 in a university environment. *Math Biosci*. 2020;328:1-16.

166. Panovska-Griffiths J, Kerr CC, Stuart RM, et al. Determining the optimal strategy for reopening schools, the impact of test and trace interventions, and the risk of occurrence of a second COVID-19 epidemic wave in the UK: a modelling study. *Lancet Child Adolesc Heal*. 2020;4(11):817-827. doi:10.1016/S2352-4642(20)30250-9

167. Christley RM, Pinchbeck GL, Bowers RG, et al. Infection in social networks: Using network analysis to identify high-risk individuals. *Am J Epidemiol*. 2005;162(10):1024-1031. doi:10.1093/aje/kwi308

168. Block P, Hoffman M, Raabe IJ, et al. Social network-based distancing strategies to flatten the COVID-19 curve in a post-lockdown world. *Nat Hum Behav*. 2020;4(6):588-596. doi:10.1038/s41562-020-0898-6

169. Ball F, Britton T, Sirl D. A network with tunable clustering, degree correlation and degree distribution, and an epidemic thereon. *J Math Biol*. 2013;66(4-5):979-1019. doi:10.1007/s00285-012-0609-7

170. Glass RJ, Glass LM, Beyeler WE, Min HJ. Targeted social distancing design for pandemic influenza. *Emerg Infect Dis*. 2006;12(11):1671-1681.

doi:10.3201/eid1211.060255

171. Breiger RL. The Duality of Persons and Groups. *Soc Forces*. 1974;53(2):181. doi:10.2307/2576011

172. Borgatti SP, Everett MG. Network analysis of 2-mode data. *Soc Networks*. 1997;19(3):243-269. doi:10.1016/S0378-8733(96)00301-2

173. Vang KE, Krow-Lucal ER, James AE, et al. Participation in Fraternity and Sorority Activities and the Spread of COVID-19 Among Residential University Communities — Arkansas, August 21–September 5, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(1):20-23. doi:10.15585/mmwr.mm7001a5

174. Mossong J, Hens N, Jit M, et al. Social contacts and mixing patterns relevant to the spread of infectious diseases. *PLoS Med*. 2008;5(3):0381-0391. doi:10.1371/journal.pmed.0050074

175. Hens N, Goeyvaerts N, Aerts M, Shkedy Z, Van Damme P, Beutels P. Mining social mixing patterns for infectious disease models based on a two-day population survey in Belgium. *BMC Infect Dis*. 2009;9:1-18. doi:10.1186/1471-2334-9-5

176. Wallinga J, Teunis P, Kretzschmar M. Using data on social contacts to estimate age-specific transmission parameters for respiratory-spread infectious agents. *Am J Epidemiol*. 2006;164(10):936-944. doi:10.1093/aje/kwj317

177. Johnstone-Robertson SP, Mark D, Morrow C, et al. Social mixing patterns within a South African township community: Implications for respiratory disease transmission and control. *Am J Epidemiol*. 2011;174(11):1246-1255. doi:10.1093/aje/kwr251

178. Glass LM, Glass RJ. Social contact networks for the spread of pandemic influenza in children and teenagers. *BMC Public Health*. 2008;8:1-15. doi:10.1186/1471-2458-8-61

179. Grantz KH, Cummings DAT, Zimmer S, et al. Age-specific social mixing of school-aged

children in a US setting using proximity detecting sensors and contact surveys. *Sci Rep*. 2021;11(1):1-11. doi:10.1038/s41598-021-81673-y

180. Edmunds WJ, Kafatos G, Wallinga J, Mossong JR. Mixing patterns and the spread of close-contact infectious diseases. *Emerg Themes Epidemiol*. 2006;3:1-8. doi:10.1186/1742-7622-3-10

181. Feld SL, Grofman B. Variation in class size, the class size paradox, and some consequences for students. *Res High Educ*. 1977;6(3):215-222. doi:10.1007/BF00991287

182. Israel U, Koester BP, McKay TA. Campus Connections: Student and Course Networks in Higher Education. *Innov High Educ*. 2020;45(2):135-151. doi:10.1007/s10755-019-09497-3

183. Weeden KA, Cornwell B. The Small-World Network of College Classes: Implications for Epidemic Spread on a University Campus. Published online 2020. doi:10.15195/v7.a9

184. Salathé M, Kazandjieva M, Lee JW, Levis P, Feldman MW, Jones JH. A high-resolution human contact network for infectious disease transmission. *Proc Natl Acad Sci U S A*. 2010;107(51):22020-22025. doi:10.1073/pnas.1009094108

185. Watts DJ, Strogatz SH. Collective dynamics of 'small-world' networks. *Nature*. 1998;393(4):440-442. https://www.ncbi.nlm.nih.gov/pubmed/9623998

186. Read JM, Eames KTD, Edmunds WJ. Dynamic social networks and the implications for the spread of infectious disease. *J R Soc Interface*. 2008;5(26):1001-1007. doi:10.1098/rsif.2008.0013

187. Halloran ME. Invited commentary: Challenges of using contact data to understand acute respiratory disease transmission. *Am J Epidemiol*. 2006;164(10):945-946. doi:10.1093/aje/kwj318

188. *Global Tuberculosis Report 2020*. World Health Organization; 2020.

189. Tuberculosis Fact Sheet. Accessed February 20, 2021. https://www.who.int/news-room/fact-sheets/detail/tuberculosis

190. Hargreaves JR, Boccia D, Evans CA, Adato M, Petticrew M, Porter JDH. The social determinants of tuberculosis: from evidence to action. *Am J Public Health*. 2011;101(4):654-662. doi:10.2105/AJPH.2010.199505

191. Lönnroth K, Jaramillo E, Williams BG, Dye C, Raviglione M. Drivers of tuberculosis epidemics: The role of risk factors and social determinants. *Soc Sci Med*. 2009;68(12):2240-2246. doi:10.1016/j.socscimed.2009.03.041

192. Floyd K, Glaziou P, Houben RMGJ, Sumner T, White RG, Raviglione M. Global tuberculosis targets and milestones set for 2016-2035: Definition and rationale. *Int J Tuberc Lung Dis*. 2018;22(7):723-730. doi:10.5588/ijtld.17.0835

193. Yates TA, Tanser F, Abubakar I. Plan Beta for tuberculosis: It's time to think seriously about poorly ventilated congregate settings. *Int J Tuberc Lung Dis*. 2016;20(1):5-10. doi:10.5588/ijtld.15.0494

194. Nardell EA, Dharmadhikari A. Turning off the spigot: Reducing drug-resistant tuberculosis transmission in resource-limited settings. *Int J Tuberc Lung Dis*. 2010;14(10):1233-1243.

195. Matteelli A, Rendon A, Tiberi S, et al. Tuberculosis elimination: Where are we now? *Eur Respir Rev*. 2018;27(148):1-15. doi:10.1183/16000617.0035-2018

196. Murray JF, Schraufnagel DE, Hopewell PC. Treatment of tuberculosis: A historical perspective. *Ann Am Thorac Soc*. 2015;12(12):1749-1759. doi:10.1513/AnnalsATS.201509-632PS

197. Martini M, Gazzaniga V, Behzadifar M, Bragazzi NL, Barberis I. The history of tuberculosis: The social role of sanatoria for the treatment of tuberculosis in Italy between

the end of the 19 th century and the middle of the 20 th. *J Prev Med Hyg*. 2018;59(4):E323-E327. doi:10.15167/2421-4248/jpmh2018.59.4.1103

198. Murray JF. A century of tuberculosis. *Am J Respir Crit Care Med*. 2004;169(11):1181-1186. doi:10.1164/rccm.200402-140oe
199. Colditz GA, Brewer TF, Berkey CS, et al. Efficacy of BCG Vaccine in the Prevention of Tuberculosis: Meta-analysis of the Published Literature. *JAMA J Am Med Assoc*. 1994;271(9):698-702. doi:10.1001/jama.1994.03510330076038
200. Brewer TF. Preventing Tuberculosis with Bacillus Calmette-Guérin Vaccine: A Meta-Analysis of the Literature. *Clin Infect Dis*. 2000;31(Supplement_3):S64-S67. doi:10.1086/314072
201. Trunz BB, Fine P, Dye C. Effect of BCG vaccination on childhood tuberculous meningitis and miliary tuberculosis worldwide: a meta-analysis and assessment of cost-effectiveness. *Lancet*. 2006;367(9517):1173-1180. doi:10.1016/S0140-6736(06)68507-3
202. Pooransingh S, Sakhamuri S. Need for BCG vaccination to prevent TB in high-incidence countries and populations. *Emerg Infect Dis*. 2020;26(3):624-625. doi:10.3201/eid2603.191232
203. Chakraborty S, Rhee KY. Tuberculosis drug development: History and evolution of the mechanism-based paradigm. *Cold Spring Harb Perspect Med*. 2015;5(8):1-11. doi:10.1101/cshperspect.a021147
204. Li Y, Sun F, Zhang W. Bedaquiline and delamanid in the treatment of multidrug-resistant tuberculosis: Promising but challenging. *Drug Dev Res*. 2019;80(1):98-105. doi:10.1002/ddr.21498
205. Conradie F, Diacon AH, Ngubane N, et al. Treatment of Highly Drug-Resistant Pulmonary Tuberculosis. *N Engl J Med*. 2020;382(10):893-902. doi:10.1056/NEJMoa1901814

206. Mohr E, Ferlazzo G, Hewison C, De Azevedo V, Isaakidis P. Bedaquiline and delamanid in combination for treatment of drug-resistant tuberculosis. *Lancet Infect Dis*. 2019;19(5):470. doi:10.1016/S1473-3099(19)30168-9

207. Churchyard G, Kim P, Shah NS, et al. What We Know about Tuberculosis Transmission: An Overview. *J Infect Dis*. 2017;216(Suppl 6):S629-S635. doi:10.1093/infdis/jix362

208. Turner RD, Bothamley GH. Cough and the transmission of tuberculosis. *J Infect Dis*. 2015;211(9):1367-1372. doi:10.1093/infdis/jiu625

209. Heemskerk D, Caws M, Marais B, Farrar J. *Tuberculosis in Adults and Children*. Springer; 2015. Accessed February 21, 2021. http://www.springer.com/series/10138

210. Kiazyk S, Ball T. Latent tuberculosis infection: An overview. *Canada Commun Dis Rep*. 2017;43(3/4):62-66. doi:10.14745/ccdr.v43i34a01

211. Getahun H, Matteelli A, Chaisson RE, Raviglione M. Latent *Mycobacterium tuberculosis* Infection. Campion EW, ed. *N Engl J Med*. 2015;372(22):2127-2135. doi:10.1056/NEJMra1405427

212. Chaw L, Chien LC, Wong J, Takahashi K, Koh D, Lin RT. Global trends and gaps in research related to latent tuberculosis infection. *BMC Public Health*. 2020;20(1):352. doi:10.1186/s12889-020-8419-0

213. Cox HS, Morrow M, Deutschmann PW. Long term efficacy of DOTS regimens for tuberculosis: Systematic review. *BMJ*. 2008;336(7642):484-487. doi:10.1136/bmj.39463.640787.BE

214. Crofton J, Mitchison DA. Streptomycin resistance in pulmonary tuberculosis. *Br Med J*. 1948;2(4588):1009-1015. doi:10.1136/bmj.2.4588.1009

215. Cohn ML, Middlebrook G, Russell WF. *Combined Drug Treatment of Tuberculosis: Prevention of Emergence of Mutant Populations of Tubercle Bacilli Resistant to Both*

Streptomycin and Isoniazid in Vitro.

216. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *Am Rev Respir Dis*. 1986;133(3):423-430. doi:10.1164/arrd.1986.133.3.423
217. Zignol M, Dean AS, Falzon D, et al. Twenty Years of Global Surveillance of Antituberculosis-Drug Resistance. *N Engl J Med*. 2016;375(11):1081-1089. doi:10.1056/NEJMsr1512438
218. Nahid P, Mase SR, Migliori GB, et al. Treatment of drug-resistant tuberculosis an official ATS/CDC/ERS/IDSA clinical practice guideline. *Am J Respir Crit Care Med*. 2019;200(10):E93-E142. doi:10.1164/rccm.201909-1874ST
219. WHO announces updated definitions of extensively drug-resistant tuberculosis. Accessed March 1, 2021. https://www.who.int/news/item/27-01-2021-who-announces-updated-definitions-of-extensively-drug-resistant-tuberculosis
220. Master I, Furin J. Access to new drugs and the global drug-resistant TB crisis: A case series from KwaZulu-Natal, South Africa. *Int J Tuberc Lung Dis*. 2016;20(7):985-987. doi:10.5588/ijtld.15.0905
221. Pietersen E, Ignatius E, Streicher EM, et al. Long-term outcomes of patients with extensively drug-resistant tuberculosis in South Africa: A cohort study. *Lancet*. 2014;383(9924):1230-1239. doi:10.1016/S0140-6736(13)62675-6
222. Gandhi NR, Brust JCM, Sarita Shah N. A new era for treatment of drug-resistant tuberculosis. *Eur Respir J*. 2018;52(4). doi:10.1183/13993003.01350-2018
223. Auld SC, Shah NS, Cohen T, Martinson NA, Gandhi NR. Where is tuberculosis transmission happening? Insights from the literature, new tools to study transmission and implications for the elimination of tuberculosis. *Respirology*. 2018;23(9):807-817.

doi:10.1111/resp.13333

224. Dye C, Glaziou P, Floyd K, Raviglione M. Prospects for tuberculosis elimination. *Annu Rev Public Health*. 2013;34:271-286. doi:10.1146/annurev-publhealth-031912-114431

225. Glaziou P, Floyd K, Raviglione MC. Global Epidemiology of Tuberculosis. *Semin Respir Crit Care Med*. 2018;39(3):271-285. doi:10.1055/s-0038-1651492

226. Centis R, D'Ambrosio L, Zumla A, Migliori GB. Shifting from tuberculosis control to elimination: Where are we? What are the variables and limitations? Is it achievable? *Int J Infect Dis*. 2017;56:30-33. doi:10.1016/j.ijid.2016.11.416

227. Weyer K. Case study: South Africa. *Bull World Health Organ*. 2007;85(5):391-392. doi:10.2471/06.036004

228. WHO | Tuberculosis control in South Africa. *WHO*. Published online 2014.

229. Vynnycky E, Sumner T, Fielding KL, et al. Tuberculosis control in South African gold mines: Mathematical modeling of a trial of community-wide isoniazid preventive therapy. *Am J Epidemiol*. 2015;181(8):619-632. doi:10.1093/aje/kwu320

230. Weyer K, Kleeberg HH. Primary and acquired drug resistance in adult black patients with tuberculosis in South Africa: results of a continuous national drug resistance surveillance programme involvement. *Tuber Lung Dis*. 1992;73(2):106-112. doi:10.1016/0962-8479(92)90064-Q

231. Cox H, Dickson-Hall L, Ndjeka N, et al. Delays and loss to follow-up before treatment of drug-resistant tuberculosis following implementation of Xpert MTB/RIF in South Africa: A retrospective cohort study. *PLoS Med*. 2017;14(2). doi:10.1371/journal.pmed.1002238

232. Cox H, Dickson-Hall L, Jassat W, et al. Drug-resistant tuberculosis in South Africa: History, progress and opportunities for achieving universal access to diagnosis and effective treatment. *South African Heal Rev 2017*. Published online 2017:157-167.

233. Gandhi NR, Moll A, Sturm AW, et al. Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis and HIV in a rural area of South Africa. *Lancet*. 2006;368(9547):1575-1580. doi:10.1016/S0140-6736(06)69573-1

234. Symons G, Shean K, Pietersen E, et al. A historical review of XDR tuberculosis in the Western Cape province of South Africa - PubMed. *S Afr Med J*. 2011;101(9):636-638. Accessed February 28, 2021. https://pubmed.ncbi.nlm.nih.gov/21920174/

235. WHO | WHO policy on TB infection control in health-care facilities, congregate settings and households. Accessed February 27, 2021. https://www.who.int/tb/publications/tb-facilities-policy/en/

236. Uplekar M, Weil D, Lonnroth K, et al. WHO's new end TB strategy. *Lancet*. 2015;385(9979):1799-1801. doi:10.1016/S0140-6736(15)60570-0

237. Xie YL, Chakravorty S, Armstrong DT, et al. Evaluation of a Rapid Molecular Drug-Susceptibility Test for Tuberculosis. *N Engl J Med*. 2017;377(11):1043-1054. doi:10.1056/NEJMoa1614915

238. Melsew YA, Doan TN, Gambhir M, Cheng AC, McBryde E, Trauer JM. Risk factors for infectiousness of patients with tuberculosis: A systematic review and meta-analysis. *Epidemiol Infect*. 2018;146(3):345-353. doi:10.1017/S0950268817003041

239. Dye C, Williams BG, Espinal MA, Raviglione MC. Erasing the world's slow stain: Strategies to beat multidrug-resistant tuberculosis. *Science (80-)*. 2002;295(5562):2042-2046. doi:10.1126/science.1063814

240. Kendall EA, Sahu S, Pai M, et al. What will it take to eliminate drug-resistant tuberculosis? *Int J Tuberc Lung Dis*. 2019;23(5):535-546. doi:10.5588/ijtld.18.0217

241. Dowdy DW, Azman AS, Kendall EA, Mathema B. Transforming the Fight Against Tuberculosis: Targeting Catalysts of Transmission. *Clin Infect Dis*. 2014;59(8):1123-1129.

doi:10.1093/cid/ciu506

242. Yuen CM, Amanullah F, Dharmadhikari A, et al. Turning off the tap: Stopping tuberculosis transmission through active case-finding and prompt effective treatment. *Lancet*. 2015;386(10010):2334-2343. doi:10.1016/S0140-6736(15)00322-0

243. Zhang J, Litvinova M, Liang Y, et al. Changes in contact patterns shape the dynamics of the COVID-19 outbreak in China. *Science (80-)*. 2020;368(6498):1481-1486. doi:10.1126/science.abb8001

244. Togun T, Kampmann B, Stoker NG, Lipman M. Anticipating the impact of the COVID-19 pandemic on TB patients and TB control programmes. *Ann Clin Microbiol Antimicrob*. 2020;19(1):1-6. doi:10.1186/s12941-020-00363-1

245. Hogan AB, Jewell BL, Sherrard-Smith E, et al. Potential impact of the COVID-19 pandemic on HIV, tuberculosis, and malaria in low-income and middle-income countries: a modelling study. *Lancet Glob Heal*. 2020;8(9):e1132-e1141. doi:10.1016/S2214-109X(20)30288-6

246. Stop TB partnership. The Potential Impact of the Covid-19 Response on Tuberculosis in High-Burden Countries: a Modelling Analysis. *Dev by Stop TB Partnersh Collab with Imp Coll Avenir Heal Johns Hopkins Univ USAID*. Published online 2020:1-7. http://www.stoptb.org/assets/documents/news/Modeling Report_1 May 2020_FINAL.pdf

247. Lui Q, Lu P, Shen Y, et al. Collateral Impact of the COVID-19 Pandemic on Tuberculosis. *Clin Infect Dis*. 2020;ciaa1289. doi:10.0193

248. Kwak N, Hwang S, Yim J. Effect of COVID-19 on Tuberculosis Notification, South Korea. 2020;26(10):2506-2508.

249. Komiya K, Yamasue M, Takahashi O, Hiramatsu K, Kadota J, Kato S. The COVID-19 Pandemic and the True Incidence of Tuberculosis in Japan. *J Infect*. 2020;81:e24-e25.

doi:10.1016

250. Adewole OO. Impact of COVID-19 on TB care: experiences of a treatment centre in Nigeria. *Int J Tuberc Lung Dis*. 2020;Epub:0-4.

251. Fei H, Yinyin X, Hui C, et al. The impact of the COVID-19 epidemic on tuberculosis control in China. *Lancet Reg Heal - West Pacific*. 2020;3:100032. doi:10.1016/j.lanwpc.2020.100032

252. Jain VK, Iyengar KP, Samy DA, Vaishya R. Tuberculosis in the era of COVID-19 in India. *Diabetes Metab Syndr Clin Res Rev*. 2020;14(5):1439-1443. doi:10.1016/j.dsx.2020.07.034

253. Kadota JL, Reza TF, Nalugwa T, et al. Impact of shelter-in-place on TB case notifications and mortality during the COVID-19 pandemic. *Int J Tuberc Lung Dis*. 2020;24(11):1212-1214. doi:10.5588/ijtld.20.0626

254. Louie JK, Reid M, Stella J, et al. A decrease in tuberculosis evaluations and diagnoses during the COVID-19 pandemic. *Int J Tuberc Lung Dis*. 2020;24(8):860-862. doi:10.5588/ijtld.20.0364

255. Ismail N, Moultrie H. Impact of COVID-19 intervention on TB testing in South Africa. *Natl Inst Commun Dis Cent Tuberc*. 2020;10 May 202(May):1-7. https://www.nicd.ac.za/wp-content/uploads/2020/05/Impact-of-Covid-19-interventions-on-TB-testing-in-South-Africa-10-May-2020.pdf

256. Ichikawa M, Nakahara S, Wakai S, Chang HJ, Huang N. Lowered tuberculosis notifications and deterred health care seeking during the sars epidemic in Hong Kong. *Am J Public Health*. 2005;95(6):933-934. doi:10.2105/AJPH.2004.046763

257. Vynnycky E, Fine PEM. Lifetime risks, incubation period, and serial interval of tuberculosis. *Am J Epidemiol*. 2000;152(3):247-263. doi:10.1093/aje/152.3.247

258. Dookie N, Padayatchi N, Naidoo K. Tuberculosis Elimination in the Era of Coronavirus Disease 2019 (COVID-19): A Moving Target. *Clin Infect Dis*. 2020;2019(Xx):1-2. doi:10.1093/cid/ciaa1400

259. Glaziou P. Predicted impact of the COVID-19 pandemic on global tuberculosis deaths in 2020. *medRxiv*. 2020;66. doi:10.1101/2020.04.28.20079582

260. *Global Tuberculosis Report 2021*. World Health Organization; 2021.

261. Report of the UN Secretary-General. *Progress towards the Achievement of Global Tuberculosis Targets and Implementation of the Political Declaration of the High-Level Meeting of the General Assembly on the Fight against Tuberculosis*.; 2020. Accessed February 28, 2021. https://undocs.org/en/A/75/236

262. Atlanta – The Georgia Department of Publ | Georgia Department of Public Health. Accessed May 21, 2021. https://dph.georgia.gov/press-releases/2020-05-12/atlanta-georgia-department-publ

263. Weissman GE, Crane-Droesch A, Chivers C, et al. Locally informed simulation to predict hospital capacity needs during the covid-19 pandemic. *Ann Intern Med*. 2020;173(1):21-28. doi:10.7326/M20-1260/SUPPL_FILE/M20-1260_SUPPLEMENT.PDF

264. Griffin KM, Karas MG, Ivascu NS, Lief L. Hospital preparedness for COVID-19: A practical guide from a critical care perspective. *Am J Respir Crit Care Med*. 2020;201(11):1337-1344. doi:10.1164/RCCM.202004-1037CP/SUPPL_FILE/DISCLOSURES.PDF

265. Cavallo JJ, Donoho DA, Forman HP. Hospital Capacity and Operations in the Coronavirus Disease 2019 (COVID-19) Pandemic—Planning for the Nth Patient. *JAMA Heal Forum*. 2020;1(3):e200345-e200345. doi:10.1001/JAMAHEALTHFORUM.2020.0345

266. Spencer KD, Chung CL, Stargel A, et al. COVID-19 Case Investigation and Contact Tracing Efforts from Health Departments — United States, June 25–July 24, 2020. *MMWR Morb Mortal Wkly Rep*. 2021;70(3):83-87. doi:10.15585/MMWR.MM7003A3

267. Lash RR, Moonan PK, Byers BL, et al. COVID-19 Case Investigation and Contact Tracing in the US, 2020. *JAMA Netw open*. 2021;4(6):e2115850. doi:10.1001/jamanetworkopen.2021.15850

268. Ruebush E, Fraser MR, Poulin A, Allen M, Lane JT, Blumenstock JS. COVID-19 case investigation and contact tracing: Early lessons learned and future opportunities. *J Public Heal Manag Pract*. 2021;27:S87-S97. doi:10.1097/PHH.0000000000001290

269. Hossain AD, Jarolimova J, Elnaiem A, Huang CX, Richterman A, Ivers LC. Effectiveness of contact tracing in the control of infectious diseases: a systematic review. *Lancet Public Heal*. Published online February 16, 2022. doi:10.1016/S2468-2667(22)00001-9

270. Taylor MM, Spencer KD, Henry M;, Walke T. COVID-19 Contact Tracing as an Enduringly Important Public Health Tool. *JAMA Heal Forum*. 2021;2(3):e210189-e210189. doi:10.1001/JAMAHEALTHFORUM.2021.0189

271. Jenness SM, Goodreau SM, Morris M. Epimodel: An R package for mathematical modeling of infectious disease over networks. *J Stat Softw*. 2018;84. doi:10.18637/jss.v084.i08

272. Krivitsky PN, Handcock MS. A separable model for dynamic networks. *J R Stat Soc Ser B Stat Methodol*. 2014;76(1):29-46. doi:10.1111/rssb.12014

273. Xue L, Jing S, Miller JC, et al. A data-driven network model for the emerging COVID-19 epidemics in Wuhan, Toronto and Italy. *Math Biosci*. 2020;326:108391. doi:10.1016/J.MBS.2020.108391

274. Ferguson NM, Laydon D, Nedjati-Gilani G, et al. Report 13: Estimating the number of

infections and the impact of non-pharmaceutical interventions on COVID-19 in 11 European countries. *Imp Coll COVID-19 Response Team*. 2020;(March). https://doi.org/10.25561/77482.

275. Czeisler M, Howard ME, Robbins R, et al. Early public adherence with and support for stay-at-home COVID-19 mitigation strategies despite adverse life impact: a transnational cross-sectional survey study in the United States and Australia. *BMC Public Health*. 2021;21(1):1-16. doi:10.1186/S12889-021-10410-X/TABLES/8
276. Vecino-Ortiz AI, Congote JV, Bedoya SZ, Cucunuba ZM. Impact of contact tracing on COVID-19 mortality: An impact evaluation using surveillance data from Colombia. *PLoS One*. 2021;16(3):e0246987. doi:10.1371/JOURNAL.PONE.0246987
277. Fetzer T, Graeber T. Measuring the scientific effectiveness of contact tracing: Evidence from a natural experiment. *Proc Natl Acad Sci U S A*. 2021;118(33). doi:10.1073/PNAS.2100814118/SUPPL_FILE/PNAS.2100814118.SAPP.PDF
278. Willem L, Abrams S, Libin PJK, et al. The impact of contact tracing and household bubbles on deconfinement strategies for COVID-19. *Nat Commun 2021 121*. 2021;12(1):1-9. doi:10.1038/s41467-021-21747-7
279. Yalaman A, Basbug G, Elgin C, Galvani AP. Cross-country evidence on the association between contact tracing and COVID-19 case fatality rates. *Sci Reports 2021 111*. 2021;11(1):1-6. doi:10.1038/s41598-020-78760-x
280. Vekaria B, Overton C, Wiśniowski A, et al. Hospital length of stay for COVID-19 patients: Data-driven methods for forward planning. *BMC Infect Dis*. 2021;21(1):1-15. doi:10.1186/S12879-021-06371-6/TABLES/2
281. Kraay A, Nelson K, Zhao C, Weitz J, Lopman B. Modeling serological testing to inform relaxation of social distancing for COVID-19 control. *medRxiv Prepr Serv Heal Sci*.

Published online 2020:1-20. doi:10.1101/2020.04.24.20078576

282. Jenness SM, Willebrand KS, Malik AA, Lopman BA, Omer SB. Dynamic Network Strategies for SARS-CoV-2 Control on a Cruise Ship. *medRxiv*. Published online 2020:2020.08.26.20182766. http://medrxiv.org/content/early/2020/10/06/2020.08.26.20182766.abstract

283. Lopman B, Liu CY, Le Guillou A, et al. A modeling study to inform screening and testing interventions for the control of SARS-CoV-2 on university campuses. *Sci Rep*. 2021;11(1):5900. doi:10.1038/s41598-021-85252-z

284. Wendelboe AM, Hudgens MG, Poole C, Van Rie A. Estimating the role of casual contact from the community in transmission of Bordetella pertussis to young infants. *Emerg Themes Epidemiol*. 2007;4(1):1-7. doi:10.1186/1742-7622-4-15/TABLES/3

285. Auld SC, Sarita Shah N, Mathema B, et al. Extensively drug-resistant tuberculosis in South Africa: genomic evidence supporting transmission in communities. *Eur Respir J*. 2018;52(4):1800246. doi:10.1183/13993003.00246-2018

286. Shen Y, Xu W, Li C, et al. A Cluster of Novel Coronavirus Disease 2019 Infections Indicating Person-to-Person Transmission Among Casual Contacts From Social Gatherings: An Outbreak Case-Contact Investigation. *Open Forum Infect Dis*. 2020;7(6). doi:10.1093/OFID/OFAA231

287. Paireau J, Mailles A, Eisenhauer C, et al. Early chains of transmission of COVID-19 in France, January to March 2020. *Euro Surveill*. 2022;27(6). doi:10.2807/1560-7917.ES.2022.27.6.2001953

288. Csardi G, Nepusz T. The igraph software package for complex network research. *InterJournal*. Published online 2006:1695.

289. Handcock MS, Hunter DR, Butts CT, Goodreau SM, Morris M. statnet: Software tools for

the representation, visualization, analysis and simulation of network data. *J Stat Softw*. 2008;24(1):1548. doi:10.18637/jss.v024.i01

290. Bliss CA, Danforth CM, Dodds PS. Estimation of global network statistics from incomplete data. *PLoS One*. 2014;9(10):108471. doi:10.1371/journal.pone.0108471
291. Nelson KN, Gandhi NR, Mathema B, et al. Modeling missing cases and transmission links in networks of extensively drug-resistant tuberculosis in KwaZulu-Natal, South Africa. *Am J Epidemiol*. 2020;189(7):735-745. doi:10.1093/aje/kwaa028
292. Handcock MS, Hunter DR, Butts CT, Goodreau SM, Krivitsky PN, Morris M. ergm: Fit, Simulate and Diagnose Exponential-Family Models for Networks. Published online 2020. https://cran.r-project.org/package=ergm
293. Hunter DR, Handcock MS, Butts CT, Goodreau SM, Morris M. ergm: A package to fit, simulate and diagnose exponential-family models for networks. *J Stat Softw*. 2008;24(3):nihpa54860. doi:10.18637/jss.v024.i03
294. Chamberlain AT, Toomey KE, Bradley H, et al. Cumulative Incidence of SARS-CoV-2 Infections Among Adults in Georgia, United States, August to December 2020. *J Infect Dis*. 2021;(December 2020):1-8. doi:10.1093/infdis/jiab522
295. Hall P, Härdle W, Simar L. On the inconsistency of bootstrap distribution estimators. *Comput Stat Data Anal*. 1993;16(1):11-18. doi:10.1016/0167-9473(93)90241-K
296. Janssen A. Two-sample goodness-of-fit tests when ties are present. *J Stat Plan Inference*. 1994;39(3):399-424. doi:10.1016/0378-3758(94)90095-7
297. Abadie A. Bootstrap Tests for Distributional Treatment Effects in Instrumental Variable Models. *http://dx.doi.org/101198/016214502753479419*. 2011;97(457):284-292. doi:10.1198/016214502753479419
298. Madewell ZJ, Yang Y, Longini IM, Halloran ME, Dean NE. Household Transmission of

SARS-CoV-2: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2020;3(12):e2031756-e2031756. doi:10.1001/JAMANETWORKOPEN.2020.31756

299. Wrzus C, Hänel M, Wagner J, Neyer FJ. Social network changes and life events across the life span: A meta-analysis. *Psychol Bull*. 2013;139(1):53-80. doi:10.1037/A0028601
300. Bharti N, Lambert B, Exten C, Faust C, Ferrari M, Robinson A. Large university with high COVID-19 incidence is not associated with excess cases in non-student population. *Sci Reports 2022 121*. 2022;12(1):1-7. doi:10.1038/s41598-022-07155-x
301. Malik AA, Safdar N, Chandir S, et al. Tuberculosis control and care in the era of COVID-19. *Health Policy Plan*. 2020;35(8):1130-1132. doi:10.1093/HEAPOL/CZAA109
302. Dlangalala T, Musekiwa A, Brits A, et al. Evidence of TB Services at Primary Healthcare Level during COVID-19: A Scoping Review. *Diagnostics 2021, Vol 11, Page 2221*. 2021;11(12):2221. doi:10.3390/DIAGNOSTICS11122221
303. World Health Organization. *Pulse Survey on Continuity of Essential Health Services during the COVID-19 Pandemic*. World Health Organization; 2020. https://apps.who.int/iris/bitstream/handle/10665/334048/WHO-2019-nCoV-EHS_continuity-survey-2020.1-eng.pdf
304. Stop TB Partnership. The impact of COVID-19 on the TB epidemic: A community perspective. Published online 2020:1-65. http://www.stoptb.org/assets/documents/resources/publications/acsm/Civil Society Report on TB and COVID.pdf
305. Khan MS, Rego S, Rajal JB, et al. Mitigating the impact of COVID-19 on tuberculosis and HIV services: A cross-sectional survey of 669 health professionals in 64 low and middle-income countries. *PLoS One*. 2021;16(2 February 2021):1-12. doi:10.1371/journal.pone.0244936

306. Meyerowitz-Katz G, Bhatt S, Ratmann O, et al. Is the cure really worse than the disease? The health impacts of lockdowns during COVID-19. *BMJ Glob Heal*. 2021;6(8):e006653. doi:10.1136/BMJGH-2021-006653

307. Fuady A, Houweling TAJ, Richardus JH. COVID-19 and Tuberculosis-Related Catastrophic Costs. *Am J Trop Med Hyg*. 2021;104(2):436. doi:10.4269/AJTMH.20-1125

308. McQuaid CF, Vassall A, Cohen T, Fiekert K, White RG. The impact of COVID-19 on TB: A review of the data. *Int J Tuberc Lung Dis*. 2021;25(6):436-446. doi:10.5588/ijtld.21.0148

309. Vanden Driessche K, Mahlobo PZ, Venter R, et al. Face masks in the post-COVID-19 era: a silver lining for the damaged tuberculosis public health response? *Lancet Respir Med*. 2021;9(4):340-342. doi:10.1016/S2213-2600(21)00020-5

310. Teo A, Ong C, Hsu L. COVID-19 and TB: a progression-regression conundrum. *Int J Tuberc Lung Dis*. 2021;25(6):421-423. doi:10.5588/IJTLD.21.0219

311. Maddock J, Parsons S, Di Gessa G, et al. Inequalities in healthcare disruptions during the Covid-19 pandemic: Evidence from 12 UK population-based longitudinal studies. *medRxiv*. Published online 2021. https://doi.org/10.1101/2021.06.08.21258546

312. Hrynick TA, Ripoll Lorenzo S, Carter SE. COVID-19 response: mitigating negative impacts on other areas of health. *BMJ Glob Heal*. 2021;6(4):e004110. doi:10.1136/BMJGH-2020-004110

313. Palm M, Sturrock SL, Howell NA, Farber S, Widener MJ. The uneven impacts of avoiding public transit on riders' access to healthcare during COVID-19. *J Transp Heal*. 2021;22:101112. doi:10.1016/J.JTH.2021.101112

314. Knipper M, Sedas AC, Keshavjee S, et al. The need for protecting and enhancing TB health policies and services for forcibly displaced and migrant populations during the

ongoing COVID-19 pandemic. *Int J Infect Dis*. 2021;113:S22-S27. doi:10.1016/J.IJID.2021.03.047

315. Davies TM, Hazelton ML. Adaptive kernel estimation of spatial relative risk. *Stat Med*. 2010;29(23):2423-2437. doi:10.1002/SIM.3995
316. Hazelton ML, Davies TM. Inference Based on Kernel Estimates of the Relative Risk Function in Geographical Epidemiology. *Biometrical J*. 2009;51(1):98-109. doi:10.1002/BIMJ.200810495
317. Kahle D, Wickham H. ggmap: Spatial Visualization with ggplot2. *R J*. 2013;5(1):144-161.
318. Askitas N, Tatsiramos K, Verheyden B. Lockdown Strategies, Mobility Patterns and COVID-19. *SSRN Electron J*. Published online November 17, 2020. doi:10.2139/SSRN.3619687
319. Bargain O, Aminjonov U. Poverty and COVID-19 in Africa and Latin America. *World Dev*. 2021;142:105422. doi:10.1016/J.WORLDDEV.2021.105422
320. Posel D, Casale D. Moving during times of crisis: Migration, living arrangements and COVID-19 in South Africa. *Sci African*. 2021;13. doi:10.1016/J.SCIAF.2021.E00926
321. Potgieter A, Fabris-Rotelli IN, Kimmie Z, et al. Modelling representative population mobility for COVID-19 spatial transmission in South Africa. Published online June 8, 2021. doi:10.20944/preprints202106.0211.v1
322. Colizza V, Grill E, Mikolajczyk R, et al. Time to evaluate COVID-19 contact-tracing apps. *Nat Med 2021 273*. 2021;27(3):361-362. doi:10.1038/s41591-021-01236-6
323. Moraga P. Small area disease risk estimation and visualization using R. *R J*. 2018;10(1):495-506. doi:10.32614/RJ-2018-036