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Transmission, control, and mortality of infectious diseases in vulnerable populations: norovirus and SARS-CoV-2 in long-term care facilities and the wider community

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Transmission, control, and mortality of infectious diseases in vulnerable populations: norovirus and SARS-CoV-2 in long-term care facilities and the wider community

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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 in Philosophy

in Epidemiology

2022

Abstract

Transmission, control, and mortality of infectious diseases in vulnerable populations: norovirus and SARS-CoV-2 in long-term care facilities and the wider community

By Carly Adams

The burden of norovirus and COVID-19 in long-term care facilities (LTCFs) is substantial, and the COVID-19 pandemic is an urgent threat to public health in both LTCFs and the wider community. This research aimed to inform data-driven norovirus and COVID-19 outbreak prevention and control in LTCFs, and to examine trends in COVID-19 case fatality in the general population.

In **Aim 1**, we conducted a systematic review and meta-analysis to assess associations between norovirus outbreak control measures and outbreak outcomes in hospitals and LTCFs globally. We used regression analyses stratified by setting (hospital/LTCF) to compare the size and duration of outbreaks in which control measures were reported to be implemented to those in which they were not. Control measures were associated with smaller and shorter outbreaks in hospitals but larger and longer outbreaks in LTCFs. In LTCFs, control measures were likely implemented in response to larger and longer outbreaks, rather than causing them.

In **Aim 2**, we examined SARS-CoV-2 transmission in Fulton County, Georgia LTCFs from March 2020 to September 2021. We estimated the time-varying reproduction number, R(t), and used linear mixed regression models to examine its association with LTCF role (resident or staff) and vaccination status. Transmission declined rapidly after vaccines were first distributed to LTCFs (December 2020) and remained low until September 2021. Staff-cases were substantially more infectious than resident-cases. Results suggest that infection prevention and control measures improved over time, and that staff are driving SARS-CoV-2 transmission in LTCFs.

In **Aim 3**, we used multivariable logistic regression, adjusted for age and other individual-level characteristics, to examine associations between report month and mortality among COVID-19 cases in Georgia from March 2, 2020 to March 31, 2021. After adjusting for factors associated with COVID-19 death, we observed lower mortality risk from November 2020 to March 2021 compared to August 2020, suggesting that improved clinical management may have contributed to improved survival.

Through this research, we can inform data-driven guidelines for the prevention and control of norovirus and COVID-19 outbreaks in LTCFs. Moreover, we can gain a better understanding of COVID-19 mortality risk among cases in the general population.

Transmission, control, and mortality of infectious diseases in vulnerable populations: norovirus and SARS-CoV-2 in long-term care facilities and the wider community

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Acknowledgements

First, I would like to thank my dissertation committee for their guidance and support over the past five years. Not only have they provided me with valuable direction and feedback on my dissertation, but they have also shown tremendous patience and understanding as I shifted the focus of my aims not once, but twice, in response to the COVID-19 pandemic. To Ben, I am not sure I can accurately convey my gratitude for the guidance and support you have provided over the years. I'm grateful for your always thoughtful and timely feedback, innovative ideas, insightful career advice, and encouragement to take breaks when needed (as you said many times, the work will still be there when you come back). To Allison, thank you for facilitating communications with external partners and for helping me to keep the bigger picture in mind by always encouraging me to think about the larger implications of our results. To Scott, thank you for not only providing your expertise on long-term care facilities, but also for the opportunities to work on other COVID-19 research projects (COPE and COPING), which were tremendous learning opportunities for me. To Aron, I appreciate your willingness to always provide your expert knowledge on norovirus and COVID-19, and for your continued support of my dissertation even when busy responding to the COVID-19 pandemic. And to Jon, thank you for all of your methodological support and for taking complex methods and describing them in a way that is understandable, and for allowing me to maintain connections with my alma mater (go blue!).

Second, to my amazing cohort of PhD students, I would not have made it through coursework, qualifying exams, and dissertation work without you. I'm grateful for your support and friendship. And to the Lopman Lab Group, for creating a collaborative work environment and making the dissertation process less lonely.

This dissertation is dedicated to my family. To my parents for being my biggest champions and instilling in me a strong work ethic, while reminding me to not stress about the small things and to always remember what's really important. Thank you for your unwavering support throughout all of my endeavors. To my siblings, for being amazing role models, both in childhood and adulthood, and for always being there to provide advice or just to lend a listening ear. To my husband, Pierre, for being my rock over the past nine years. Not only would this dissertation not have been possible without you, but I would not be the person I am today without your unwavering love and support. And to my son, Noah, for being my constant companion during the final months of my dissertation and for bringing us so much joy in just the few months you've been with us.

Finally, to the Georgia Department of Public Health, Fulton County Board of Health, and all members of the Emory COVID-19 Response Collaborative, thank you for the opportunity to work with you on this dissertation and for your dedication to the COVID-19 response.

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CHAPTER 1: BACKGROUND

1.1 Infectious disease outbreaks in long-term care facilities

Infectious disease outbreaks are common in U.S. long-term care facilities (LTCFs).[1,2] Pathogens can be introduced into LTCFs by staff, visitors, and newly admitted residents, and can spread rapidly among residents once introduced.[2] LTCFs, which include skilled nursing facilities (SNFs, also called nursing homes) and assisted living facilities (ALFs), are healthcare facilities that provide a variety of services, including both medical and personal care, to people who are unable to live independently.[3] Both SNFs and ALFs provide residents with 24-hour supervision and assistance with daily care (e.g., personal care, meals, and medication management), however SNFs typically provide a higher level of care with a greater focus on medical care.[4] SNFs are federally regulated by the Centers for Medicare and Medicaid Services (CMS),[5] whereas ALFs are regulated by state governments, with regulations varying greatly by state.[6]

LTCFs often have frequent staffing shortages and inadequate infection prevention and control (IPC) programs. Even prior to the COVID-19 pandemic, the majority of SNFs had insufficient numbers of registered nurses and relied on certified nursing assistants (CNAs), who typically have minimal training and earn low wages, to provide the majority of care.[7,8] Since the COVID-19 pandemic, these staffing shortages have only worsened.[9] Moreover, SNF staff commonly hold second jobs, often working in multiple LTCFs, which can facilitate disease transmission between facilities.[8,10] Furthermore, IPC deficiencies are common in LTCFs. In the most recent CMS report of SNF deficiencies (2013 – 2017), the most common type of deficiencies cited were IPC deficiencies, with 82% of all SNFs being cited for an IPC deficiency in one or more years during the survey period.[11] Cited deficiencies

included improper hand hygiene and failure to implement outbreak control measures, such as isolating sick residents or using personal protective equipment (PPE). Taken together, staffing shortages and IPC deficiencies highlight the vulnerability of LTCFs to infectious disease outbreaks.

Infectious disease outbreaks are common in LTCFs, and can cause substantial morbidity and mortality among residents.[12,13] The shared living environment and dependence of residents on staff for personal and/or medical care leads to prolonged and frequent contact among individuals in this setting, leading to an increased risk of infection among LTCF residents and staff. With most infections, LTCF residents, who are generally older adults with underlying chronic medical conditions, are at higher risk of severe illness and death. More than 88% of U.S. nursing home residents are 65 years of age and older, and nearly 90% have at least one underlying physical and/or mental/cognitive condition.[12,13] Moreover, the proportion of LTCF residents with underlying conditions and the average number of underlying conditions per resident is increasing, suggesting an increasingly sicker population.[13]

With nearly 2.5 million people in the U.S. currently living in a LTCF,[14] a number that is projected to nearly double by 2030 due to an aging population,[15,16] there is an urgent need for effective IPC measures in this setting. In particular, targeted control measures for norovirus and Coronavirus Disease 2019 (COVID-19) outbreaks are urgently needed.

1.2 Norovirus outbreaks in long-term care facilities

Norovirus is a leading cause of sporadic cases and outbreaks of acute gastroenteritis in the U.S. and globally.[17,18] In the U.S. and other high-income countries, the majority of norovirus

outbreaks occur in healthcare facilities, including hospitals and LTCFs. However, unlike other high-income countries, where roughly equal numbers of norovirus outbreaks are reported in hospitals and LTCFs,[19] the majority (61%) of all norovirus outbreaks in the U.S. occur in LTCFs.[20]

Norovirus is a highly transmissible virus that causes acute gastroenteritis, the most common symptoms of which are diarrhea, vomiting, nausea, and stomach pain.[21] There are multiple strains of norovirus, with new variants emerging every few years,[22] so infection with norovirus evokes only limited immunity.[23] Moreover, duration of immunity is short-lived,[24] so reinfection with the same strain is possible. Norovirus is spread primarily through the fecal-oral route, either by direct person-to-person transmission or fecally contaminated food or water.[25] In U.S. LTCFs, the vast majority (90%) of norovirus outbreaks are spread via person-to-person transmission.[20]

While norovirus gastroenteritis is generally mild and self-limiting, older LTCF residents are at greater risk for severe outcomes, including prolonged symptoms, hospitalization, and death.[3,14,26,27] Norovirus outbreaks are common in LTCFs,[20] and are associated with increased hospitalization and mortality.[26-31] Because there is currently no vaccine or specific antiviral therapy available to prevent or treat norovirus infection, rapid implementation of control measures is the mainstay for curtailing transmission.[32] Guidelines for the prevention and control of norovirus gastroenteritis outbreaks in U.S. healthcare settings, including LTCFs, are provided by the Centers for Disease Control and Prevention (CDC), as advised by the Healthcare Infection Control Practices Advisory Committee (HICPAC).[33,34] These guidelines are based on a systematic review of published material conducted by the CDC and HICPAC in 2011 that aimed to evaluate the evidence on preventing and controlling norovirus gastroenteritis outbreaks in healthcare settings. Recommendations include, but

are not limited, to the following: 1) placing patients with norovirus gastroenteritis on contact precautions, 2) actively promoting adherence to hand hygiene among residents, staff, and visitors, 3) closing wards to new admissions or transfers, 4) increasing the frequency of cleaning and disinfection, and 5) excluding ill staff from work for a minimum of 48 hours after resolution of symptoms.[34] However, the evidence base for the effectiveness of these guidelines in minimizing norovirus transmission in healthcare facilities is limited.[30,34]

1.3 The COVID-19 pandemic

In early January 2020, Chinese health authorities first confirmed that a cluster of cases of pneumonia in Wuhan, China was associated with a novel coronavirus disease, COVID-19, caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2).[35] SARS-CoV-2 is primarily transmitted by exposure to infectious respiratory fluids, including respiratory droplets and aerosolized particles. Symptoms of COVID-19 typically appear 2-14 days after exposure and often include fatigue, fever, cough, shortness of breath, and loss of taste and smell, although a wide range of symptoms have been reported.[36,37] Approximately 16% of infections are asymptomatic.[38]

SARS-CoV-2 has now spread worldwide, causing a global pandemic and immense morbidity and mortality.[39] In the U.S., the first detection of SARS-CoV-2 was reported on January 20, 2020 in Washington State.[40] Since then, SARS-CoV-2 has been detected in all 50 states, causing more than 78 million cases of COVID-19 and a staggering 935,000 COVID-19 deaths as of February 2022, making the U.S. the leading country in cumulative numbers of COVID-19 cases and deaths worldwide.[39]

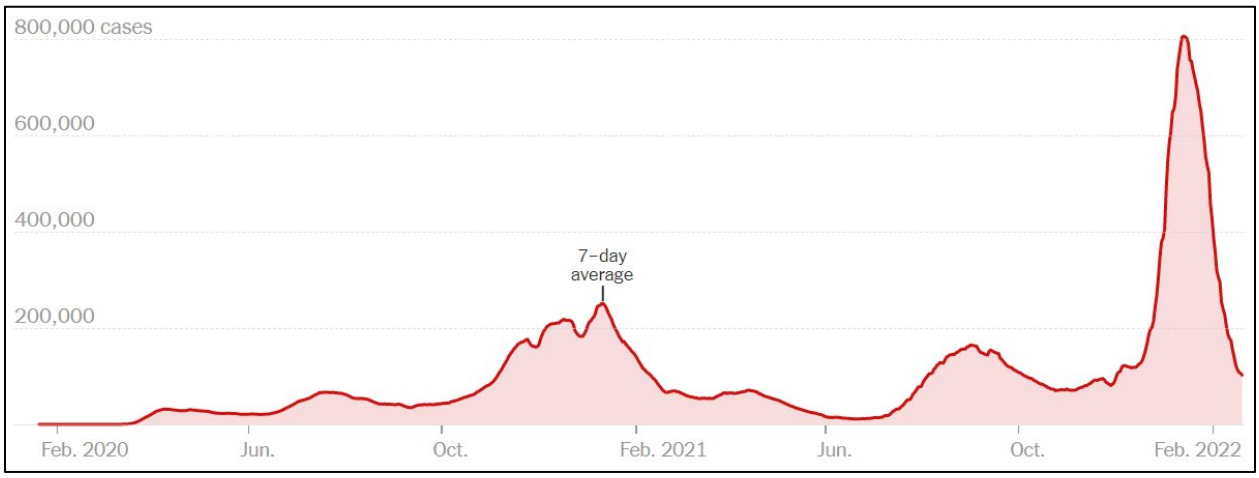
In response to the pandemic, states began implementing various community mitigation measures in March 2020, including stay-at-home orders, school and workplace closures, cancellation of public events, restrictions on public gatherings, and mask mandates.[41] At the height of these restrictions, in late March and early April 2020, more than 310 million Americans were under stay-at-home orders.[42] Most states began reopening again in early May 2020, allowing certain businesses to reopen and services to resume with proper safety measures in place. As of October 2021, all stay-at-home orders have been lifted, but other restrictions, such as indoor mask mandates and limits on social gatherings, remain in place in some areas. These restrictions vary widely by state, county and even city, and are regularly updated as the COVID-19 situation evolves.[41]

The rapid development of effective vaccines against SARS-CoV-2 was an unprecedented scientific achievement. As early as January 2020, plans to develop SARS-CoV-2 vaccines had already begun.[43] In the U.S., the Department of Health and Human Services started a program called “Operation Warp Speed”, which allocated funds for vaccine research and development and even purchased allotments of vaccines prior to knowing whether any would be successful.[44] In under a year, multiple SARS-CoV-2 vaccines were developed, and by December 2020, vaccines were already being distributed to healthcare workers and LTCF residents in the U.S.[43,45] As of November 2021, vaccines are widely available in the U.S. to all individuals 5 years and older.[46] There are currently three COVID-19 vaccines authorized for use in the U.S.: Pfizer-BioNTech, Moderna, and Johnson and Johnson’s Janssen, all of which are highly effective at preventing serious illness and death due to COVID-19.[47]

Despite extreme measures to limit the spread of SARS-CoV-2, including the rapid development of effective vaccines, the U.S. has experienced several waves of cases (i.e.,

surges in cases followed by declines). A large wave of cases followed the winter holidays in 2020-21, and another wave followed introduction of the Delta variant, a more contagious SARS-CoV-2 variant, in late summer 2021 (Figure 1-1).[48,49] The largest wave, however, occurred most recently from December to February 2022 following introduction of the Omicron variant, which is more contagious than both the original virus and the Delta variant.[50]

Figure 1-1. Reported cases of COVID-19 in the U.S. by report date as of February 21, 2022[49]



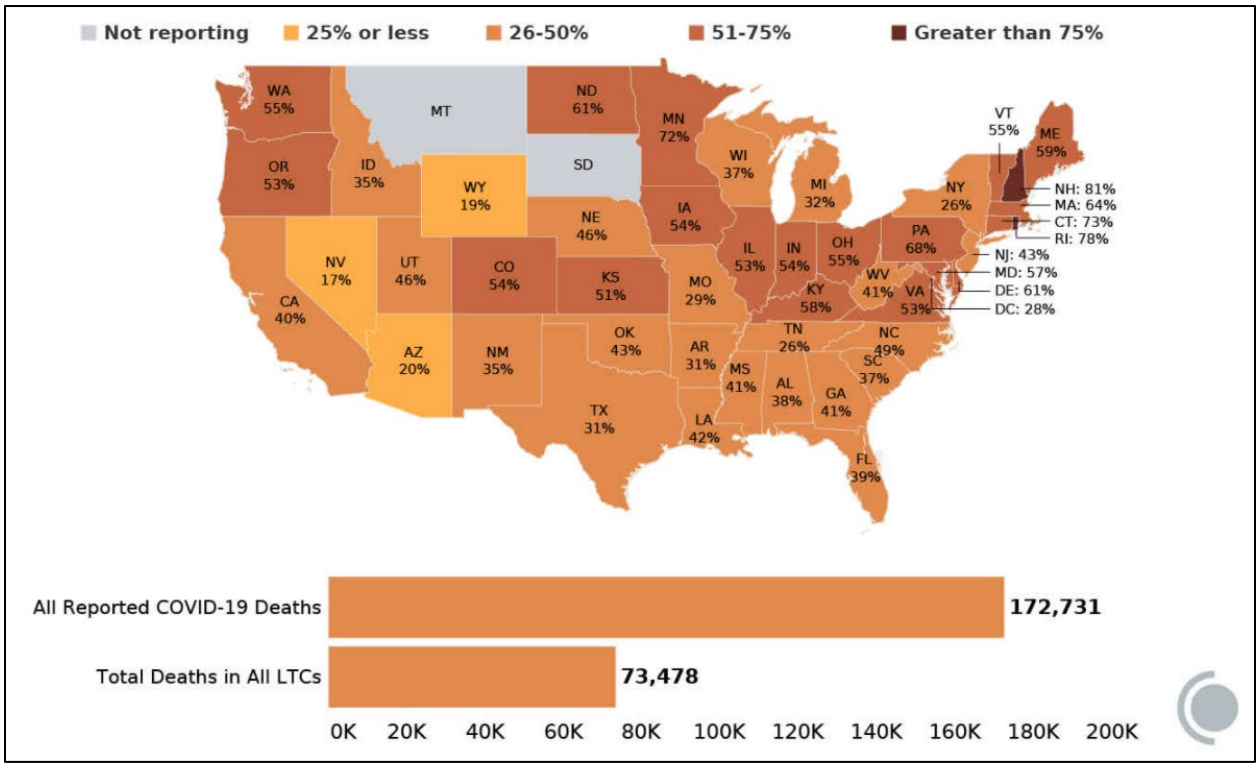
Source: The New York Times

1.3.1 COVID-19 in long-term care facilities

The first major COVID-19 outbreak in the U.S. occurred in a LTCF in Kirkland, Washington in late February 2020. The outbreak spread rapidly throughout the facility, infecting a third of the residents and resulting in 35 deaths (a 33.7% case fatality ratio) among residents in just over two weeks.[51] Since then, LTCF residents and staff throughout the U.S. have been disproportionately affected by COVID-19. As of October 2021, outbreaks have been

reported in nearly all 15,600 skilled nursing facilities in the U.S., resulting in more than 1.3 million confirmed cases and nearly 140,000 confirmed deaths among residents and staff.[52,53] Despite accounting for <1% of the total U.S. population,[54] more than 43% of reported COVID-19 deaths in the U.S. occurred in LTCFs by the end of August 2020, with even higher percentages reported in some states (Figure 1-2).[55] By March 2021, it was estimated that nearly 1 in 12 U.S. LTCF residents had died from COVID-19.[56]

Figure 1-2. Percentage of all U.S. COVID-19 deaths occurring in long-term care facilities through August 27, 2020[55]

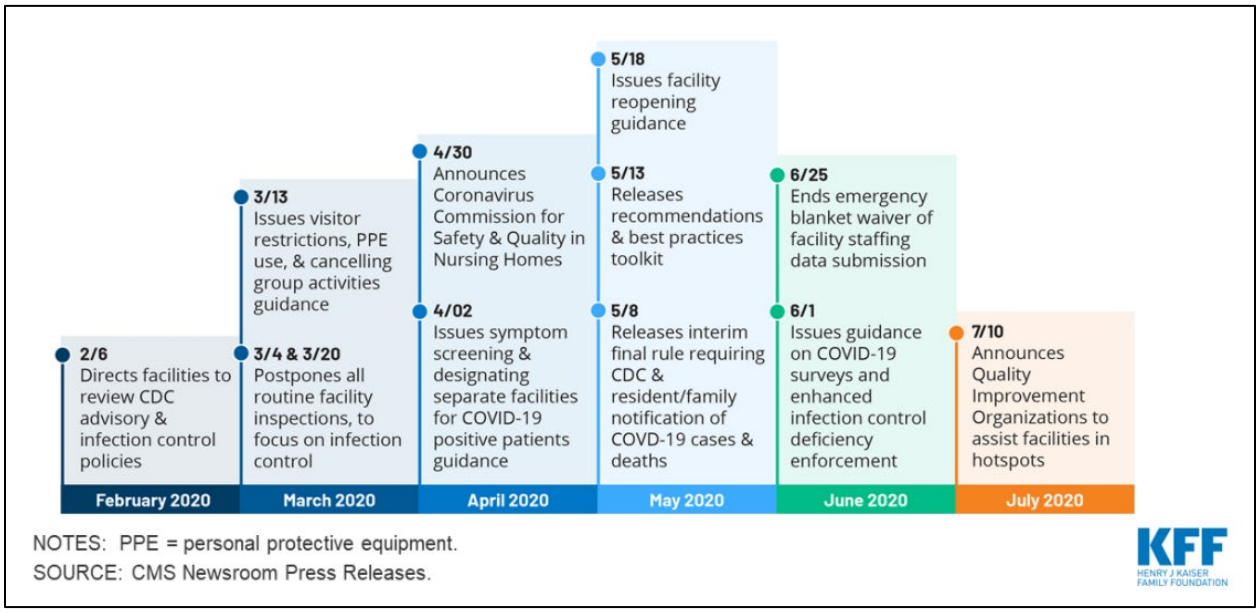


Source: The COVID Tracking Project at The Atlantic

In response to the pandemic, CMS released a series of guidance and other policy actions to limit SARS-CoV-2 transmission in LTCFs (Figure 1-3).[57] On March 13, 2020, CMS began requiring facilities to restrict all visitors except for compassionate care circumstances and to

cancel all communal dining and group activities.[58] As a result, residents were largely confined to their rooms and unable to receive visitors. On May 18, 2020, CMS released reopening guidance, which included guidance for relaxing restrictions using a phased approach.[59] A number of factors were to be considered by LTCFs when deciding whether to relax restrictions, including levels of community transmission, staffing levels, access to testing, access to PPE, and whether any new COVID-19 cases had been reported in the facility. Most facilities did not begin relaxing restrictions until much later in the pandemic in March 2021, after vaccines became widely available to LTCF residents and staff and case counts in LTCFs began to rapidly decline.[60]

Figure 1-3. Key CMS nursing home COVID-19 guidance and actions[57]

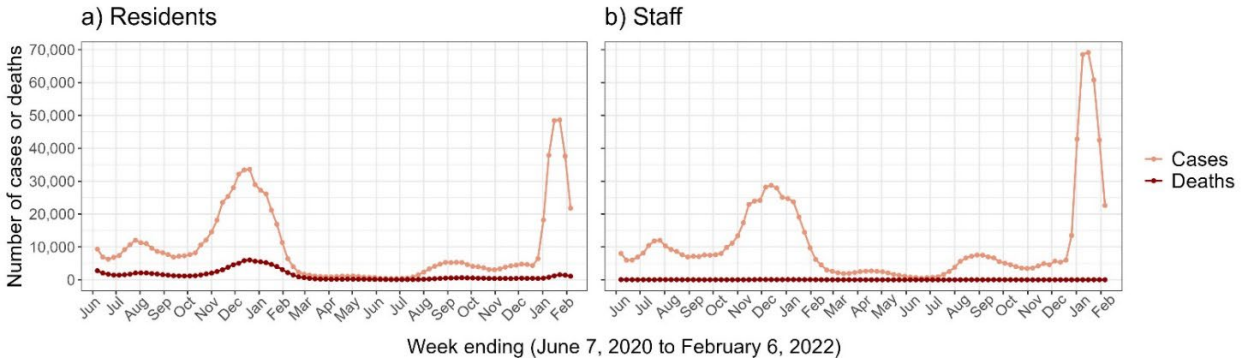


Source: The Henry J Kaiser Family Foundation (KFF)

Despite the extreme measures to limit SARS-CoV-2 transmission in LTCFs, COVID-19 case and death counts in LTCFs remained high in 2020 and early 2021.[52] Staff still had to enter and leave, and new residents were still being admitted,[52] remaining possible sources

of SARS-CoV-2 introduction. Furthermore, staff often work in multiple facilities, further increasing the risk of SARS-CoV-2 introduction.[10,61,62] Once introduced into a facility, SARS-CoV-2 can spread rapidly, infecting both LTCF residents and the staff who care for them.[63,64] After COVID-19 vaccines were first distributed to U.S. LTCFs in December 2020,[65] case counts among LTCF residents and staff declined sharply.[52] However, nationwide, LTCF case counts increased again from July to September 2021 and December 2021 to January 2022, corresponding to the waves of community cases caused by the Delta and Omicron variants, respectively.[48] Because staff continue to interact with the community, and over 15% of staff nationwide remain unvaccinated as of February 2022,[66] COVID-19 remains a threat to LTCFs.

Figure 1-4. Number of COVID-19 cases and deaths by report week for long-term care facility residents and staff in the United States: June 7, 2020 to February 6, 2022



Data source: CMS COVID-19 Nursing Home Data[52]

1.3.2 The time-varying reproduction number, R(t)

While studies have examined risk factors for susceptibility to SARS-CoV-2 infection in LTCFs,[67-69] an understanding of risk factors for SARS-CoV-2 transmission is lacking.

Examining SARS-CoV-2 transmissibility can lead to a better understanding of the impact of policy changes on SARS-CoV-2 transmission in LTCFs, and lead to more informed IPC measures that target individuals who are contributing the most to transmission. However, because transmission is not directly observed, it is difficult to study. Unlike disease outcomes, such as test results, symptoms, and fatalities, which can be directly observed, transmission of SARS-CoV-2 between individuals can only be inferred using epidemiologic methods.

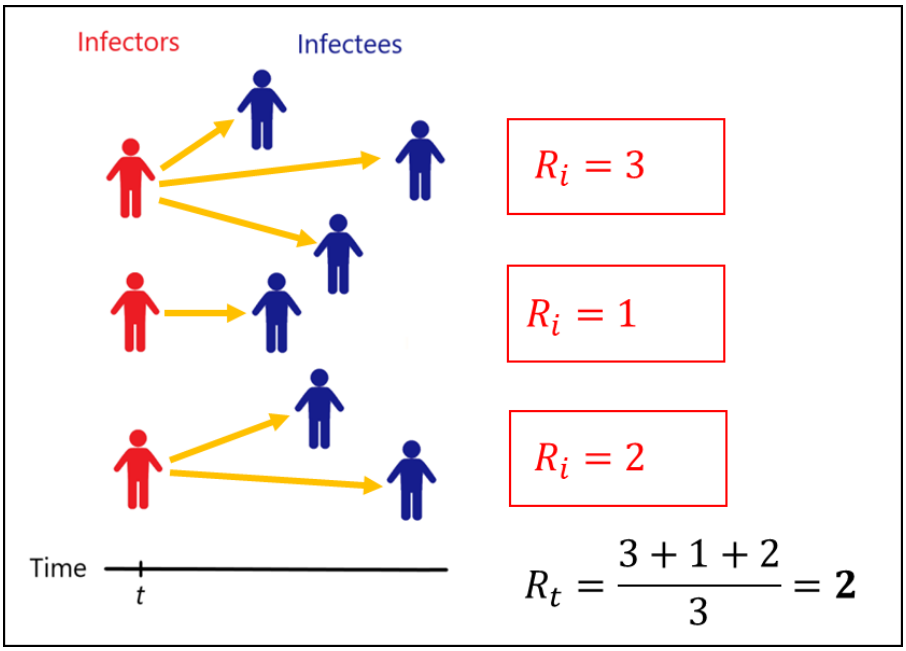
One measure that can be used to quantify SARS-CoV-2 transmissibility is the time-varying reproduction number, R(t), which is the average number of secondary cases generated by a single infectious case at time *t*, where *t* often represents the date of symptom onset. R(t) is calculated by taking the average of the individual reproduction numbers, R_i, defined as the number of secondary cases generated by a single infectious case, for all cases with symptom onset at time *t*. A R(t) of 1 signifies the extinction threshold, below which each infectious individual, on average, infects less than one other individual and the outbreak cannot be maintained. R(t) differs from the more commonly known basic reproduction number, R_0, and effective reproduction number, R_E, in that R_0 and R_E are the average R_i for all cases in a population, whereas R(t) is the average R_i for all cases at a specific time point (Table 1-1). In Figure 1-5, the R(t) calculation for a hypothetical outbreak of 9 cases is shown. Three cases have symptom onset at time *t* (infectors) and each infects 3, 1 and 2 cases (infectees), respectively, resulting in a R(t) of 2.

Table 1-1. Reproduction number definitions

Reproduction number	**Definition**

Individual reproduction number, R_i	Number of secondary cases generated by a single infectious case.
Time-varying reproduction number, R(t)	Average number of secondary cases generated by a single infectious case with symptom onset at time *t*.
Basic reproduction number, R_0	Average number of secondary cases generated by a single infectious case in a population that is entirely immune.
Effective reproduction number, R_E	Average number of secondary cases generated by a single infectious case in a population that has some level of immunity.

Figure 1-5. Calculation of the time-varying reproduction number, R(t)

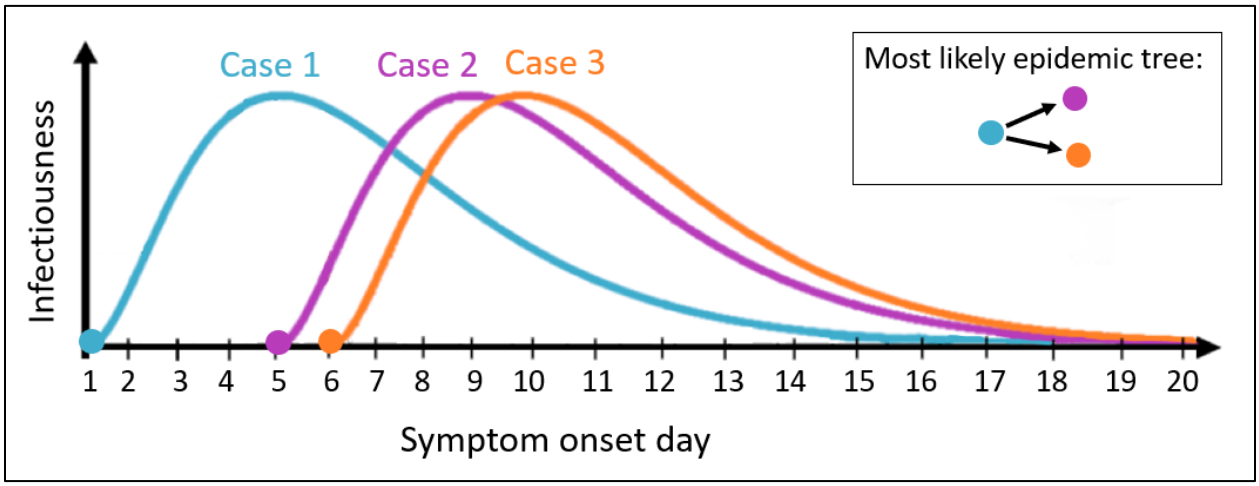


R(t) can be estimated using a method originally developed by Wallinga and Teunis that uses dates of symptom onset for all cases involved in an outbreak and the probability distribution of the serial interval, defined as the time between symptom onset in a primary case (infector) and a secondary case (infectee), to estimate the probability of transmission between any pair of cases.[70,71] If the serial interval for two cases in an outbreak is approximately equal to the mean serial interval, it is highly probable that the case with earlier symptom onset infected the case with later symptom onset. Conversely, if the serial interval for two cases is much larger or smaller than the mean serial interval, the probability of transmission is much lower. These probabilities are used to construct epidemic trees, from which R(t) can be estimated. A large number (e.g., 1,000) of epidemic trees can be simulated, from which the average R(t) estimates and 95% confidence intervals can be calculated. The Wallinga-Teunis method assumes that cases cannot infect other cases with the same or earlier symptom onset dates, and that outbreaks are complete, such that no cases are missing and there is no ongoing transmission.

The Wallinga-Teunis method is illustrated in Figure 1-6, which shows a hypothetical outbreak of three cases with a gamma distributed serial interval. The mean serial interval is 4 days, meaning that the most likely infector of a case with symptom onset on day *t* is a case with symptom onset on day *t* - 4. In other words, a case with symptom onset at time *t* - 4 was at their peak infectiousness when they came into contact with a case with symptom onset at time *t*. In Figure 1-6, Case 1 (symptom onset = day 1) is the most likely infector of Case 2 (symptom onset = day 5) because they were at their peak infectiousness when they came into contact with Case 2. Moreover, Case 1 is the only case with symptom onset prior to Case 2, so the probability that Case 1 infected Case 2 is 100%. Case 3 (symptom onset = day 6) could have been infected by either Case 1 or Case 2. However, given the serial

intervals (4 days for Case 1 and 1 day for Case 2) it is much more likely that Case 1 infected Case 3. From the most likely epidemic tree, we can calculate the R_i for Case 1, Case 2, and Case 3 as 2, 0 and 0, respectively. Furthermore, because there is only one case on each symptom onset day, we can calculate R(t) for days 1, 5, and 6 as 2, 0 and 0, respectively.

Figure 1-6. Serial interval probability distributions for three cases[a] in an outbreak with the most likely epidemic tree[b] shown



[a] Dots illustrate symptom onset days.

[b] Arrows in epidemic tree illustrate transmission.

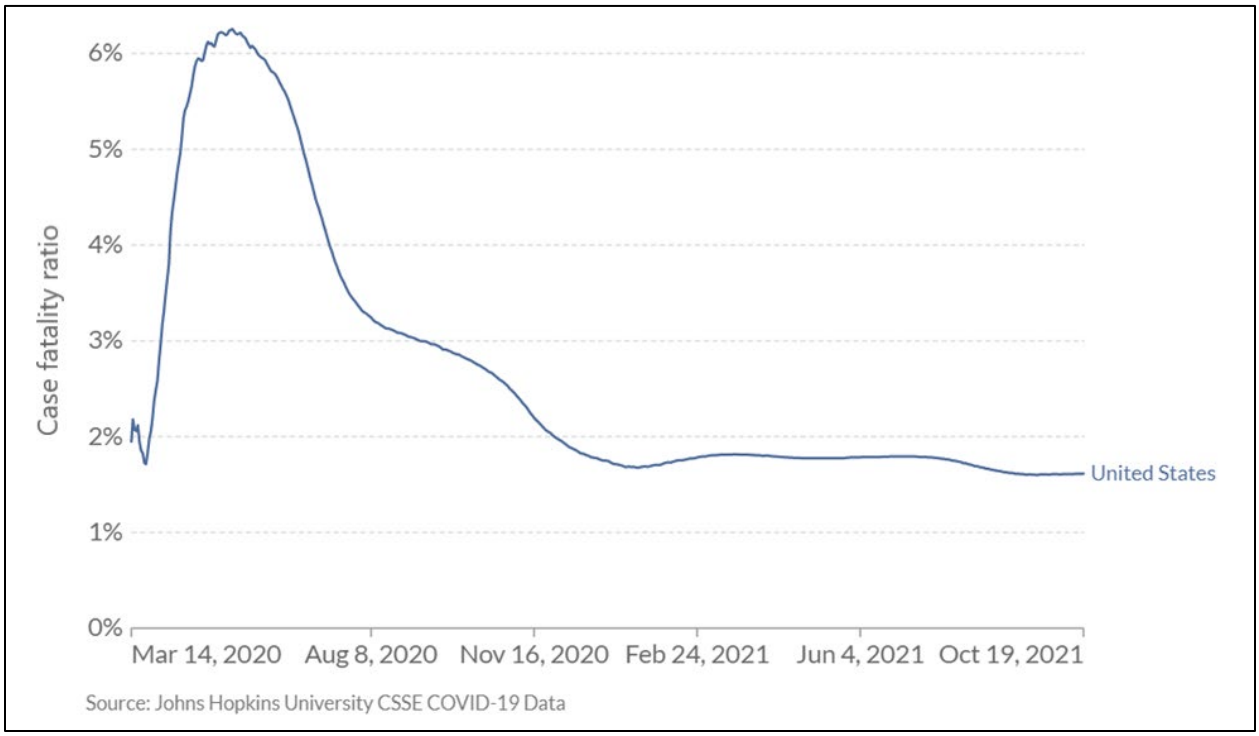
1.3.3 COVID-19 mortality in the general population

Although LTCFs experienced a disproportionate burden of COVID-19, there was also substantial morbidity and mortality in the general population.[72] Since the beginning of the pandemic, COVID-19 has been in the top seven leading causes of death in the U.S., even becoming the leading cause of death in December 2020 and early 2021.[73] While U.S. case counts have followed complex patterns, the crude case fatality ratio (CFR), or the proportion

of identified cases who died, declined between May 2020 and January 2021 (Figure 1-7),[74] possibly due to improved clinical management, such as the use of remdesivir,[75] dexamethasone,[76,77] and monoclonal antibody treatment.[78,79]

However, the CFR is a complex measure that is affected by several different factors. First, a changing case mix may explain changes in the CFR. In the first few months of the pandemic, the average age of COVID-19 cases in the U.S. decreased[80] and the proportion of cases occurring in LTCFs declined,[65] and both older age[81-83] and being institutionalized[84,85] are associated with increased risk of COVID-19 death, which may explain early declines in the CFR. Second, safe and effective COVID-19 vaccines, which first became available in the U.S. in December 2020 to vulnerable individuals,[86] along with increases in partial immunity from prior infection as the pandemic progressed, may also have contributed to declines in the CFR. Third, more widespread testing beginning in spring/summer 2020, which led to an increased detection of less severe cases, most certainly contributed to early declines.[87] More recently, however, an increase in the availability of self-tests has likely led to a decrease in case reporting and therefore an increase in the CFR.[88] Finally, inconsistent reporting of cases across the country, including varying definitions of a confirmed vs. probable cases, has impacted the CFR in ways that are difficult to determine.[89] Because a better understanding of trends in the CFR, and reasons for these trends, can lead to improvements in case fatality in the future, a detailed examination of the CFR is needed.

Figure 1-7. United States COVID-19 case fatality ratio (CFR) for confirmed deaths and cases: March 14, 2020 to October 19, 2021[74]



Source: Our World in Data

1.4 Summary

Taken together, the disproportionate burden of norovirus and COVID-19 morbidity and mortality in LTCFs, and the high fatality rates from COVID-19 in the general population, highlight the need for detailed analyses of norovirus outbreak control measures and SARS-CoV-2 transmission in LTCFs and trends in COVID-19 case fatality in the general population. These analyses could lead to more data-driven norovirus and SARS-CoV-2 infection prevention and control measures in LTCFs and improved COVID-19 case management in the general population.

CHAPTER 2: STUDY RATIONALE AND SPECIFIC AIMS

2.1 Study rationale

Given the high incidence of infectious disease outbreaks in LTCFs, and the increased risk of severe infections among residents, there is an urgent need for targeted, evidence-based measures to control infectious disease outbreaks in this setting. Moreover, given the staggering number of COVID-19 deaths reported in the U.S., there is a need to examine trends in the CFR in the general population and risk factors for COVID-19 mortality among cases.

As described in Chapter 1, norovirus outbreaks are common in LTCFs,[29] and while there are detailed guidelines available for LTCFs on how to control outbreaks,[34] the evidence for the effectiveness of norovirus outbreak control measures in this setting is lacking. Quantifying the effectiveness of control measures on reducing the size and duration of norovirus outbreaks could lead to more informed outbreak control measures for LTCFs.

Moreover, the COVID-19 pandemic has highlighted the vulnerability of LTCFs to emerging infectious disease outbreaks. A disproportionate number of COVID-19 cases and deaths in the U.S. have occurred among LTCF residents and staff.[52,53,55] As long as SARS-CoV-2 continues to circulate in the community, LTCFs remain at-risk for SARS-CoV-2 introductions and COVID-19 outbreaks. By examining trends in the transmissibility of SARS-CoV-2, along with individual risk factors associated with increased case infectiousness, more targeted SARS-CoV-2 intervention measures can be implemented in LTCFs.

Lastly, the general population in the U.S. has also experienced staggering numbers of COVID-19 cases and deaths.[72] However, there is evidence that the CFR has declined since the beginning of the pandemic.[74] Examining trends in the CFR and possible explanations for

these trends can lead to a better understanding of mortality risk among cases and how this risk can be minimized.

The primary goals of this research are to inform data-driven guidelines for the prevention and control of norovirus and COVID-19 outbreaks in LTCFs and to examine possible explanations for trends in COVID-19 case fatality in the general population. In Aim 1, we examine published reports of norovirus outbreaks in healthcare facilities, including LTCFs, to quantify associations between the reported implementation of control measures and outbreak size, duration, and attack rates. In Aim 2, we examine temporal changes in the SARS-CoV-2 time-varying reproduction number, R(t), and associations between individual case characteristics and R(t) in LTCFs. In Aim 3, we examine temporal trends in the SARS-CoV-2 CFR in the general population, adjusted for age, race, and other individual-level characteristics, to determine if improved case management may have contributed to declines in the CFR. Through examining outbreak control measures and transmission patterns in LTCFs and case fatality in the general population, we can inform outbreak control measure recommendations in LTCFs and improve our understanding of COVID-19 case fatality in the community.

2.2 Specific aims overview

Aim 1: Assess the evidence from published literature to quantify the effectiveness of existing norovirus outbreak control measures in healthcare facilities.

This analysis will consist of a systematic review of published norovirus outbreak reports in healthcare facilities (LTCFs and hospitals) globally and a meta-analysis to quantify associations between the reported implementation of norovirus outbreak control measures

and outbreak outcomes. This will be an update of a previous systematic review from 2009, in which authors found no evidence that implementing infection control measures affected norovirus outbreak duration or attack rates in enclosed and semi-enclosed settings.[30]

Exposures of interest will include the reported implementation of any control measures and the reported implementation of individual control measures. If the implementation of control measures (any or individual) is mentioned in the paper, outbreaks will be classified as having had control measures implemented. Otherwise, outbreaks will be classified as having not had control measures implemented. Outcomes of interest will include: 1) outbreak duration, 2) outbreak attack rates, and 3) outbreak case counts.

Meta-regression mixed effects models will be used to assess associations between the reported implementation of any and individual control measures and all outcome variables. Log-linear, linear, and negative binomial models will be used to examine associations between control measures and outbreak duration, attack rates, and case counts, respectively.

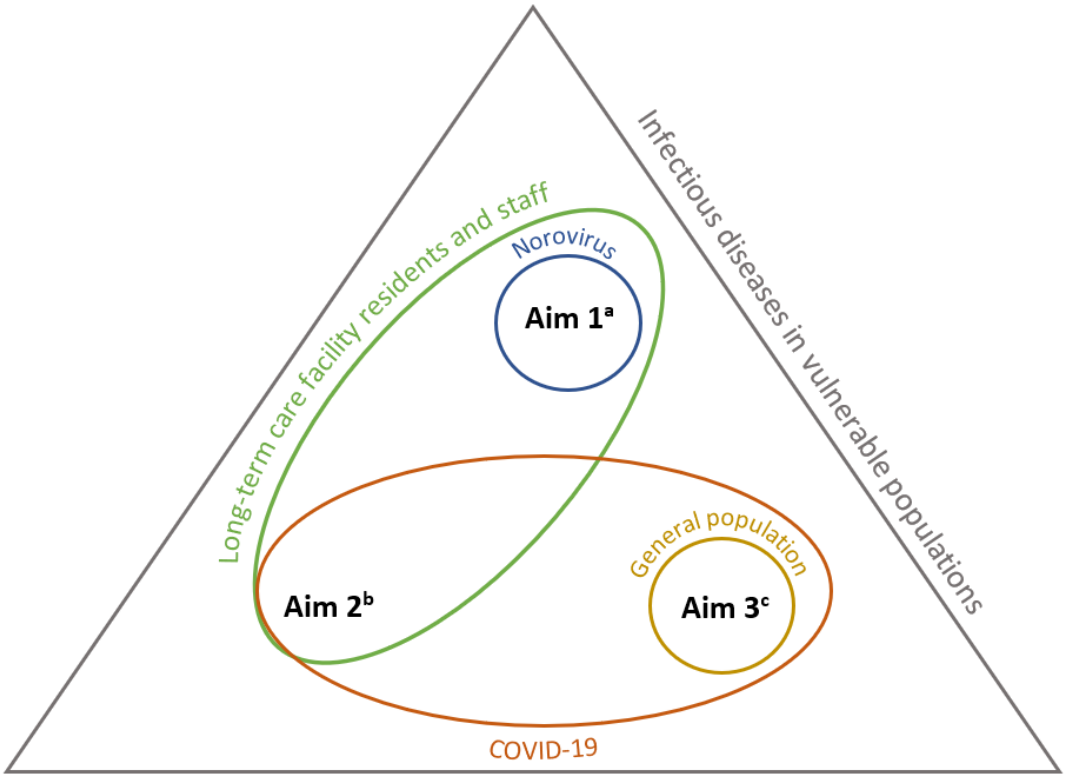
Aim 2: Characterize temporal changes in SARS-CoV-2 transmission and individual-level risk factors for case infectiousness in long-term care facility outbreaks.

Individual-level COVID-19 data from the Georgia Department of Public Health (GDPH) COVID-19 Surveillance Dataset, restricted to cases associated with Fulton County LTCFs, will be used to achieve this aim. SARS-CoV-2 transmissibility in Fulton County LTCFs will be quantified by the time-varying reproduction number, R(t), which will be calculated using the Wallinga-Teunis method. Linear mixed regression models will be used to examine associations between time and individual case characteristics (vaccination status, resident or staff, and disease severity) and R(t).

Aim 3: Examine temporal trends in COVID-19 case fatality in Georgia, USA, and determine the extent to which trends can be explained by shifts in case demographics and setting as opposed to improved survival.

Individual-level COVID-19 surveillance data from the Georgia Department of Public Health (GDPH) will be used to achieve this aim. Multivariable logistic regression models, adjusted for age and other individual-level characteristics, will be used to examine associations between report month and COVID-19 mortality among confirmed and probable COVID-19 cases and hospitalized cases in Georgia.

Figure 2-1. Diagram illustrating the focus of dissertation aims



[a] Aim 1 focuses on norovirus cases in healthcare facilities, including hospitals and long-term care facilities (LTCFs), among both patients/residents and staff.

[b] Aim 2 focuses on COVID-19 cases in LTCFs among both residents and staff.

[c] Aim 3 focuses on COVID-19 deaths in the general population, including LTCF residents and staff.

CHAPTER 3: DATA SOURCES

3.1 Published outbreak reports

The analysis for Aim 1 used data from norovirus outbreak reports in the published literature. PubMed/MEDLINE, Embase (Elsevier), Scopus (Elsevier), and gray literature sources (CDC Stacks, World Health Organization [WHO] Institutional Repository for Information Sharing [IRIS], and the National Technical Reports Library [NTRL]) were searched for papers describing healthcare-associated norovirus outbreaks globally that were published August 2008 to July 2019. Extracted data were merged with data from a previous systematic review by Harris et al. (2009),[30] which included information from norovirus outbreak reports published prior to August 2008. Methods will be described more fully in Chapter 4.

3.2 GDPH COVID-19 surveillance data

GDPH COVID-19 surveillance datasets, including the COVID-19 Surveillance, Facility, Vaccine Breakthrough Dashboard, and Testing Datasets (described in detail below), were available through the Emory COVID-19 Response Collaborative (ECRC), an initiative established within the Emory Rollins School of Public Health for approved Emory investigators to assist GDPH in analyses pertinent to understanding and characterizing the COVID-19 pandemic in Georgia. Through this initiative, a Memorandum of Agreement and Business Associates Agreement were established to govern COVID-19-related data sharing between GDPH and Emory-approved investigators.

3.2.1 COVID-19 Surveillance Dataset

Analyses for Aims 2 and 3 used data from the GDPH COVID-19 Surveillance Dataset, which includes information on all persons being investigated for COVID-19 in the state of Georgia. The dataset for Aim 2 was restricted to cases from Fulton County, GA, whereas the dataset for Aim 3 included statewide cases. The GDPH COVID-19 Surveillance Dataset was available through the State Electronic Notifiable Disease Surveillance System (SendSS), a web-based database for capturing and reporting notifiable diseases in Georgia.[90] Cases were identified through clinical evaluations, contact tracing, routine surveillance, positive lab reports, and other sources, and could be lab-confirmed, probable, or suspect cases of COVID-19. Individual-level information was available for cases, including demographic information (age and gender), severity of disease (hospitalization and/or death from COVID-19), and important dates (onset, report, and specimen collection dates). A description of variables that were used for Aims 2 and/or 3 can be found in Table 3-1.

Table 3-1. Description of variables in the Georgia Department of Public Health (GDPH) COVID-19 Surveillance Dataset

Variable	**Description**
QARESONSEID	Unique identifier for each Person Under Investigation (PUI) for COVID-19
Case definition	Case definition assigned to PUI: Confirmed; Probable; Suspect; Not A Case; Pending
Age	Age of PUI (in years) at time of initial diagnosis as a case
Date of birth	Date of birth of PUI; used to determine age if missing

Gender	Gender of PUI: Male; Female; Unknown; Other
Race	Race of PUI: American Indian/Native Alaskan; Asian; Black; Native Hawaiian/Pacific Islander; White; Other; Unknown
Ethnicity	Ethnicity of PUI: Hispanic/Latino, Non-Hispanic/Latino; Not specified
Current county	County where PUI was at the time of initial report
County of residence	County where PUI usually resided at the time of exposure/infection
Address	Street address where PUI usually resided at the time of exposure/infection; used to determine long-term care facility (LTCF) role (resident or staff)
Institutionalized	PUI was institutionalized in a LTCF at the time of specimen collection or at any time within 30 days prior: Yes or No; used to determine LTCF role
Healthcare worker	PUI worked in a healthcare setting: Yes or No; used to determine LTCF role
Report date	Date of initial PUI creation
First positive specimen collection date	Date of specimen collection associated with the first positive result from any test type
Symptom onset date	Date of symptom onset
Hospitalization	PUI was hospitalized at any time during illness: Yes or No
COVID-19 death	PUI died as a result of COVID-19 infection (cause of death or significant contributor to death)
Vaccination	PUI received a COVID-19 vaccine: Yes or No

Reinfection	PUI was suspected of having been reinfected (>90 days between positive specimen collection dates)
Outbreak ID	Outbreak identifier for the outbreak in which the PUI was involved; used by the Fulton County Board of Health to enter unique facility identifiers for PUIs associated with LTCFs
Exposed to QARESPONSEID	Unique identifier(s) for other PUI(s) in the dataset with whom the PUI had a known exposure

3.2.2 COVID-19 Facility Dataset

The analysis for Aim 3 used data from the GDPH COVID-19 Facility Dataset, which included information on facilities, including LTCFs, with which COVID-19 cases in the GDPH COVID-19 Surveillance Dataset were associated. This dataset was also available through SendSS. Information on the type of facility (e.g., LTCF), facility name, facility address, and unique facility identifiers for facilities with which cases were associated, along with unique case identifiers so that data could be merged with the COVID-19 Surveillance Dataset, were included. However, not all LTCF-associated cases were included in this dataset, and facility name was a free text field, often resulting in multiple facility identifiers being created for the same facility. Therefore, this dataset was used in combination with other variables in the COVID-19 Surveillance Dataset to identify LTCF-associated cases, but not to link LTCF-associated cases to individual facilities.

3.2.3 COVID-19 Vaccine Breakthrough Dashboard Dataset

The analysis for Aim 2 used data from the GDPH COVID-19 Vaccine Breakthrough Dashboard Dataset, which was provided by the Fulton County Board of Health (FCBOH).

Data were restricted to Fulton County LTCF cases. This dataset was used to determine vaccination status of cases in the analysis. The following variables were used: 1) vaccination status (fully vaccinated, partially vaccinated, or unknown), 2) date of last vaccine dose, 3) vaccine manufacturer (Pfizer-BioNTech, Moderna, or Johnson and Johnson's Janssen), and 4) unique case identifiers to link the data with the COVID-19 Surveillance Dataset.

3.2.4 COVID-19 Testing Dataset

The analysis for Aim 3 used data from the GDPH COVID-19 Testing Dataset. This dataset included information on the reported numbers of total and positive COVID-19 reverse-transcription polymerase chain reaction (RT-PCR) tests in Georgia by county and collection date. Data were used to examine trends in COVID-19 testing.

3.3 Publicly available data

3.3.1 COVID-19 Reported Patient Impact and Hospital Capacity by State Timeseries dataset

The analysis for Aim 3 used data from the COVID-19 Reported Patient Impact and Hospital Capacity by State Timeseries dataset from the U.S. Department of Health and Human Services.[91] This dataset provided state-aggregated data for hospital utilization in a timeseries format dating back to January 1, 2020. Information on the numbers of inpatient beds (total, occupied, and occupied by COVID-19 patients) and adult intensive care unit (ICU) beds (total, occupied, and occupied by COVID-19 patients) by state and date were available. Data were used to examine trends in COVID-19 hospital occupancy rates.

3.3.2 U.S. Census Bureau dataset

The analysis for Aim 3 used 2010 census data from the U.S. Census Bureau.[92] These data, in combination with rural-urban continuum codes from the U.S. Department of Agriculture,[93] were used to categorize cases as residing in metro-urban, nonmetro-urban or nonmetro-rural areas.

Table 3-2. Summary of datasets used for Aims 1-3

Analysis	**Dataset(s) used**
Aim 1	• Norovirus outbreak reports from the published literature
Aim 2	• GDPH COVID-19 Surveillance Dataset • GDPH COVID-19 Vaccine Breakthrough Dashboard Dataset
Aim 3	• GDPH COVID-19 Surveillance Dataset • GDPH COVID-19 Facility Dataset • GDPH COVID-19 Testing Dataset • COVID-19 Reported Patient Impact and Hospital Capacity by State Timeseries dataset • U.S. Census Bureau data

Abbreviations: GDPH, Georgia Department of Public Health

CHAPTER 4: AIM 1 – NOROVIRUS CONTROL MEASURES IN HEALTHCARE SETTINGS

[Manuscript 1. This is an Accepted Manuscript of an article published by Taylor & Francis in *Expert Review of Anti-infective Therapy* on July 6, 2021, available online: https://www.tandfonline.com/doi/full/10.1080/14787210.2021.1949985.]

Associations of infection control measures and norovirus outbreak outcomes in healthcare settings: a systematic review and meta-analysis

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4.1 Abstract

Background: Although most norovirus outbreaks in high-income countries occur in healthcare facilities, information on associations between control measures and outbreak outcomes in these settings are lacking.

Methods: We conducted a systematic review/meta-analysis to assess associations between norovirus outbreak control measures and outcomes in hospitals and long-term care facilities (LTCFs), globally. Using regression analyses stratified by setting (hospital/LTCF), we compared durations, attack rates, and case counts for outbreaks in which control measures were report to be implemented to those in which they were not.

Results: We identified 102 papers describing 162 norovirus outbreaks. Control measures were reported to be implemented in 118 (73%) outbreaks and were associated with 0.6 (95% CI: 0.3-1.1) times smaller patient case counts and 0.7 (95% CI: 0.4, 1.0) times shorter

durations in hospitals but 1.5 (95% CI: 1.1-2.2), 1.5 (95% CI: 1.0-2.1) and 1.6 (95% CI: 1.0-2.6) times larger overall, resident, and staff case counts, respectively, and 1.4 (95% CI: 1.0-2.0) times longer durations in LTCFs.

Conclusions: Reported implementation of control measures was associated with smaller/shorter outbreaks in hospitals but larger/longer outbreaks in LTCFs. Control measures were likely implemented in response to larger/longer outbreaks in LTCFs, rather than causing them. Prospective observational or intervention studies are needed to determine effectiveness.

4.2 Background

Norovirus is the leading cause of outbreaks of acute gastroenteritis in the United States and other high-income countries, with more than 1,000 outbreaks and 40,000 associated illnesses reported each year in the U.S. alone.[94] The majority of outbreaks in high-income countries occur in healthcare facilities, including long-term care facilities (LTCFs) (52% of U.S. outbreaks) and hospitals (3% of U.S. outbreaks).[95,96] Transmission in these settings is facilitated by high levels of contact, communal living, and immunocompromised populations. Patients in hospitals and residents in LTCFs are also at greater risk of more severe and fatal illness due to underlying medical conditions and/or older age [26]. Ideally, introduction of norovirus into healthcare facilities could be prevented, but the virus is common in communities, with an estimated 19–21 million norovirus illnesses occurring in the U.S. each year,[97] and can easily be introduced into healthcare facilities through infected patients/residents, visitors, and staff.[31,94] Therefore, effective infection control measures are needed to mitigate transmission in LTCFs and hospitals.

There is currently no licensed vaccine or specific antiviral therapy available to prevent or treat norovirus infection, so infection control measures are the mainstay for curtailing transmission.[98] In the U.S., guidelines on how to prevent and control norovirus outbreaks in healthcare settings are largely based on a 2011 literature review by the Centers of Disease Control and Prevention (CDC), as advised by the Healthcare Infection Control Practices Advisory Committee (HICPAC), in which authors examined the evidence for norovirus control measure effectiveness in healthcare settings.[34] Guidelines on how to control norovirus outbreaks include, but are not limited to, the following measures: 1) enhanced hand hygiene (e.g., actively promoting adherence to hand hygiene, beyond routine practice), 2) enhanced environmental cleaning (e.g., increasing the frequency of cleaning and disinfection), 3) movement restrictions (e.g., patient cohorting, staff cohorting, limiting patient transfers, and ward closures), and 4) exclusion of ill staff from work until a minimum of 48 hours after resolution of symptoms (i.e., staff exclusions).[33] However, published evidence for the effectiveness of these control measures in mitigating norovirus transmission is lacking. While handwashing is well known to reduce the risk of diarrheal illness among individuals,[99-104] and environmental cleaning has been shown to reduce the risk of norovirus transmission,[103] the effectiveness of enhanced hand hygiene and environmental cleaning measures in controlling norovirus outbreaks in healthcare facilities has not been established.[34] Other recommended measures, such as movement restrictions and staff exclusions, have intuitive appeal, but have also not been proven effective in controlling norovirus outbreaks in healthcare facilities.[34] Moreover, in a systematic review by Harris et al. (2009), authors found no evidence that implementing any infection control measures decreased norovirus outbreak duration or attack rates in enclosed and semi-enclosed settings.[30] They concluded that the body of published literature at that time did not provide an evidence-base for the value of norovirus outbreak control measures.

Because the CDC/HICPAC prevention and control guidelines are updated as new information becomes available,[34,105] investigation into the associations between norovirus outbreak control measures and outbreak outcomes is warranted. To this end, we performed a systematic review of published healthcare facility norovirus outbreaks globally and a meta-analysis to assess the associations between the implementation of any control measures and specific control measures and the following outbreak outcomes: duration, attack rate, and size.

4.3 Methods

4.3.1 Systematic Review

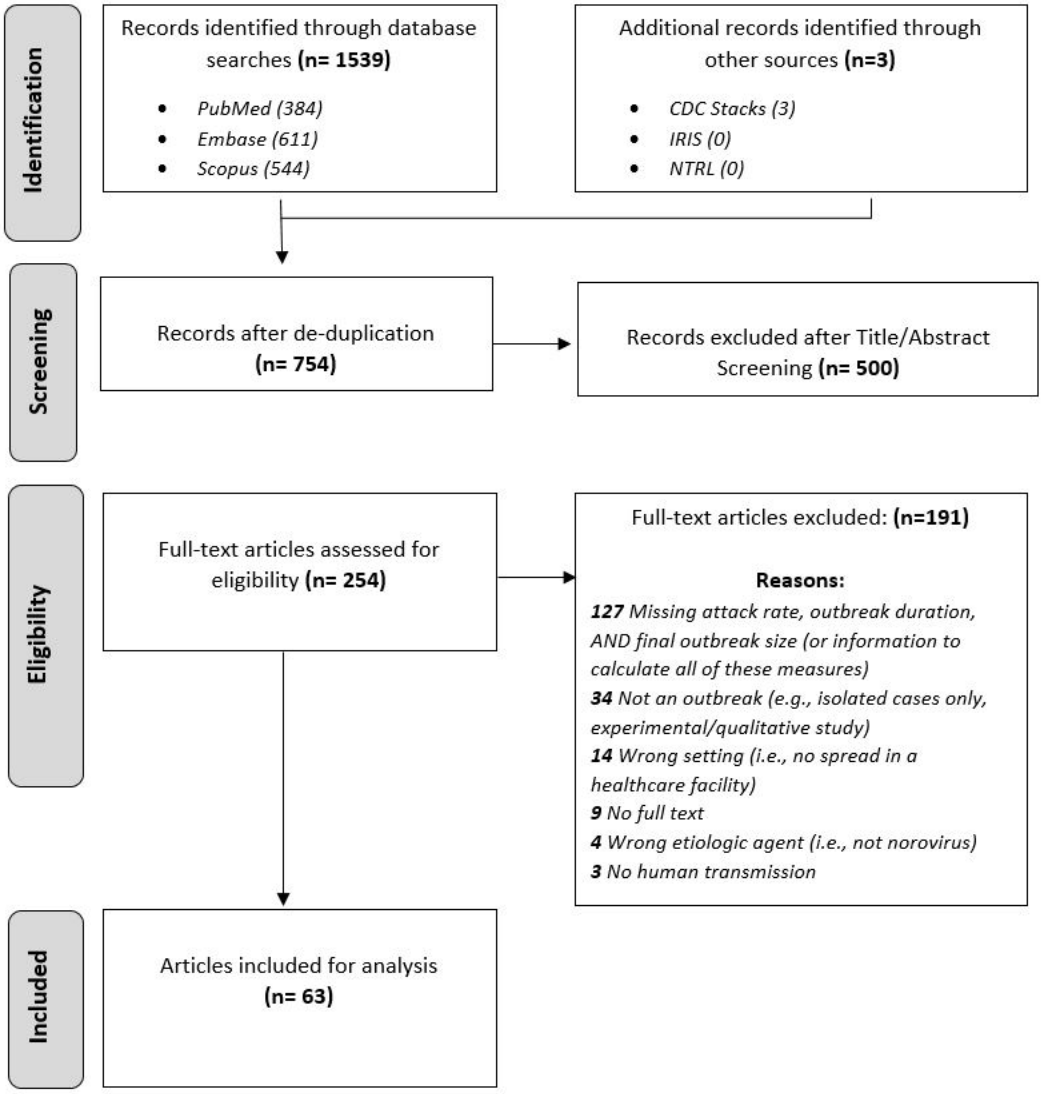
The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement was used as the guideline for conducting this review.[106] Literature search strategies were developed using medical subject headings (MeSH) and text words related to norovirus outbreaks in healthcare settings. *PubMed/MEDLINE*, *Embase (Elsevier)*, and *Scopus (Elsevier)* were searched for papers describing healthcare-associated norovirus outbreaks globally that were published from August 1, 2008 (the day after the last date included in the systematic review by Harris et al.[30] to July 31, 2019. Results were limited to those written in the English language. For the purposes of this review, we defined healthcare facilities as hospitals and LTCFs (nursing homes, skilled nursing facilities, and assisted living facilities).[3,107] Norovirus outbreaks were defined as two or more cases within a facility either suspected or laboratory-confirmed to be caused by norovirus infection.[108] To reduce reporting bias, the following gray literature sources (i.e., information published outside of traditional commercial publishers) were also searched (on September 13, 2019) for unpublished outbreak reports: the CDC Stacks, the World Health Organization (WHO)

Institutional Repository for Information Sharing (IRIS), and the National Technical Reports Library (NTRL). The search result records were imported into EndNote X9 for data management and deduplication. Seven hundred fifty-four (754) records were imported into the web-based application Covidence for screening (search details are available in Supplementary Table 4-1).

Papers were eligible for inclusion if they contained any of the following information on one or more norovirus outbreaks occurring in a hospital or LTCF: attack rates (or information on numbers at-risk and affected so that attack rates could be calculated), duration (or start and end dates so that duration could be calculated), and/or final sizes (i.e., the number of cases in an outbreak). Because outbreak attack rates and final case counts were often reported separately for staff and patients/residents, and/or as an overall measure (i.e., for both patients/residents and staff combined), papers were eligible for inclusion if they contained information on any of these measures. Outbreaks in which the mode of transmission was reported as foodborne or waterborne in origin were included only if there was also secondary spread.

All identified studies underwent a title and abstract screen by two independent reviewers based on the inclusion criteria described above. During full-text review, the reason for excluding papers was recorded and any discrepancies that arose were resolved by a third reviewer. Sixty-three (63) papers were identified for data extraction. The number of articles screened during this process can be found in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart (Figure 4-1).

Figure 4-1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart of review process



The following data were extracted by one reviewer from all included studies: outbreak duration; attack rates for patients/residents, staff, and overall (and the number of cases and individuals at-risk from which attack rates could be calculated); case counts for patients/residents, staff, and overall; whether or not any infection control measures were implemented, per reporting in the paper; information on specific control measures implemented, per reporting in the paper; country where the outbreak took place; and outbreak setting (i.e., hospital or LTCF). Lastly, the dataset from our current review was combined with that from the previous review by Harris et al. (2009).[30] Therefore, papers published on or prior to July 31, 2019 were also included in this review and meta-analysis. Because the previous review included information on norovirus outbreaks from all enclosed and semi-enclosed settings, previous review data were restricted to healthcare facility outbreaks and combined with the current review data. Any questions we had about the previous review data were clarified through direct communication with the first author.

4.3.2 Meta-analysis

To examine the associations between infection control measures and norovirus outbreak outcomes, we compared outbreak duration, attack rates, and case counts for outbreaks in the combined dataset in which infection control measures were implemented to outbreaks in which they were not implemented, per reporting in the paper. The main exposure of interest was implementation of any control measures and this dichotomous predictor variable was defined as follows: if papers reported that control measures were implemented at any point during the outbreak, outbreaks were classified as having had control measures implemented; otherwise outbreaks were classified as having not had control measures implemented. Because information on timing of control measure implementation was

missing for the majority (72%) of outbreaks in which control measures were reportedly implemented, it was not included in the analyses.

For this meta-analysis, there were seven outcomes of interest: outbreak duration, outbreak attack rates among patients/residents, staff, and overall, and case counts among patients/residents, staff, and overall (Table 4-1). Outbreak outcomes were calculated from the raw data whenever possible. When calculating attack rates, all patients/residents and staff in the entire facility (i.e., not only those in affected wings/units/floors) were considered at-risk. If calculated outcomes differed from those reported in the paper, we used calculated, rather than reported, outcome values for our analyses.

Table 4-1. Outbreak outcomes and their definitions

Outbreak outcome	**Definition**
Duration	Difference in days between first and last illness onset dates for a given outbreak, including the first illness onset date (considered outbreak day 1)
Attack rates[a,b]	Number of symptomatic cases divided by total number of individuals at-risk
Overall	*Patients/residents and staff; does not include facility visitors*
Patients/residents	*Hospital patients or LTCF residents only*
Staff	*Hospital or LTCF staff only*
Case counts[a,b]	Total number of symptomatic cases reported for a given outbreak
Overall	*Patients/residents and staff; does not include facility visitors*
Patients/residents	*Hospital patients or LTCF residents only*
Staff	*Hospital or LTCF staff only*

[a] Excludes individuals who tested positive for norovirus but did not exhibit symptoms.

[b] If reported for patients/residents only (and not staff), or staff only (and not patients/residents), unreported outcomes were coded as missing (and not 0).

In meta-analyses, statistical heterogeneity is assessed to determine whether individual study results are consistent and can be combined into one summary measure.[109] To visually assess statistical heterogeneity in outcomes, we constructed forest plots, in which individual outbreak outcomes, stratified by the reported implementation of control measures (i.e., the exposure), were shown. Variances and confidence intervals were calculated by assuming attack rates for each outbreak followed binomial distributions and case counts and outbreak durations for each outbreak followed Poisson distributions. We were unable to calculate variances and confidence intervals for outbreak attack rates if the number of cases or individuals at-risk were not reported in the paper. Furthermore, we calculated Cochran's Q-statistic, a weighted sum of squares,[110] to quantitatively assess the heterogeneity of each outcome within an exposure category. Because some outbreaks had 0 reported cases among staff, the variance for staff attack rate and case count were also equal to 0 for these outbreaks. We added 0.01 to the variance of these variables for Q-statistic calculations. Additionally, to assess the quality of evidence, we characterized outbreak reports based on the following measures of quality: 1) a case definition was provided, 2) an outbreak definition was provided, and 3) the day on which control measures were implemented was reported.

Meta-regression mixed effects models were used to assess associations between the implementation of any and specific control measures, per reporting in the paper, and all outcome variables (duration, attack rates, and case counts). We used the following regression models: 1) log-linear model of outbreak duration (the natural log of duration was taken so that it met assumptions of normality), 2) linear model of attack rates, and 3) negative binomial generalized linear model of reported case counts, to account for over-dispersion. When presenting results, we exponentiated regression coefficients from the log-

linear and negative binomial models so that results could be interpreted on the multiplicative scale. Using a directed acyclic graph (DAG) to inform the modeling approach, outbreak setting and country were determined *a priori* to be potentially confounding variables for all associations (Supplementary Figure 4-1). Setting was controlled for through stratification and a random intercept for country was included in all models to account for within- and across- country variability. Because we intended to make inferences beyond the specific countries included in this review, we chose a random, rather than fixed effect for country. However, in a separate analysis, we included country in the model as a fixed effect and assessed the interaction between country and control measures and found no evidence of an interaction, which may be due to insufficient power. When examining associations between control measures and outbreak outcomes, we weighted all outbreaks equally. We categorized specific control measures into four categories, which were determined *a priori*: 1) enhanced hand hygiene, 2) enhanced environmental cleaning, 3) movement restrictions, and 4) staff exclusions. We assumed the residual heterogeneity, e_{ij}, and random slopes, α_{0i}, b_{0i}, and ε_{0i}, were independent and identically distributed (iid) with mean zero and their respective variances. The models used for these regression analyses are below:

$$\ln\left(Duration_{ij}\right) = (A_0 + \alpha_{0i}) + A_1 ControlMeasure_{ij} + e_{ij}$$

$$AttackRate_{ij} = (\beta_0 + b_{0i}) + \beta_1 ControlMeasure_{ij} + e_{ij}$$

$$\ln\left(CaseCounts_{ij}\right) = (E_0 + \varepsilon_{0i}) + E_1 ControlMeasure_{ij} + e_{ij}$$

$$j = individual\ outbreak$$

$$i = country\ of\ outbreak$$

$$AttackRate\ and\ CaseCounts = overall,\ patients/residents\ only,\ or\ staff\ only$$

ControlMeasures = any, enhanced hand hygiene, enhanced environmental cleaning, movement restrictions, or staff exclusions

We assessed the sensitivity of results using the following restricted datasets: 1) outbreaks with 10 or more cases, 2) outbreaks from the current review only (i.e., excluding outbreaks from the previous review),[30] and 3) full paper outbreak reports (from the current review only). The first sensitivity analysis was used to address the issue of reverse causation. Reverse causation occurs when the exposure-outcome process is reversed, and associations are seen because the outcome causes the exposure, rather than the exposure causing the outcome.[111] In this analysis, reverse causation would mean that control measures were implemented in response to larger and longer outbreaks, rather than control measures affecting outbreak outcomes. The second sensitivity analysis was used to address discrepancies in the previous and current review data that may have arisen from the systematic reviews and data extractions being performed by different research groups at different times. The third sensitivity analysis was used to address bias from exposure misclassification, in which outbreaks with control measures implemented were potentially misclassified as not having had control measures implemented because control measures were not reported in the paper. Full papers (i.e., excluding abstracts), and particularly full paper outbreak reports, defined here as any paper in which the primary purpose was to describe one or more outbreaks (i.e., excluding research papers and surveillance reports), are probably more likely to include full outbreak information, and therefore less subject to information bias. To examine this further, we compared the percent of outbreaks with reported control measures and outbreak outcome information for outbreaks described in full paper outbreak reports to those not described in full paper outbreak reports. Information on

whether papers were full paper outbreak reports was only available in the current review data.

4.4 Results

4.4.1 Systematic Review

Sixty-three (63) papers from the current review were combined with 39 papers from the previous review, for a total of 102 papers included in the analyses (Figure 4-1). Twenty-two (22) of these papers included information on two or more outbreaks, resulting in a total of 162 outbreaks: 107 (66%) from the current review and 55 (34%) from the previous review. There were approximately equal numbers of hospital outbreaks (78, 48%) and LTCF outbreaks (80, 49%) in the dataset. Four (4) outbreaks (3%) took place in a combined hospital and LTCF setting and were included in the restricted datasets for both hospital and LTCF outbreaks. Of the 84 outbreaks that took place in a LTCF or LTCF and hospital, 70 (83%) included information on the type of LTCF, the majority of which were nursing homes (56, 80%). Other LTCFs included adult group care (5, 7%), psychiatric care (5, 7%), assisted living (3, 4%), and a rehabilitation center (1, 1%). Lastly, the majority (88%) of outbreaks occurred in high-income countries, with the rest occurring in upper middle-income countries (Table 4-2).

Table 4-2. Outbreaks reported by country and setting

	Outbreak Setting				
Country	**Hospital (n (%))**	**LTCF (n (%))**	**Hospital & LTCF (n (%))**	**Total (n = 162) (n (%))**	**Reference(s)**
Australia	1 (11)	8 (89)	0 (0)	9 (6)	112-116
Austria	4 (67)	1 (17)	1 (17)	6 (4)	117-120
Belgium	2 (100)	0 (0)	0 (0)	2 (1)	121,122
Brazil	1 (50)	1 (50)	0 (0)	2 (1)	123,124
Canada	3 (60)	2 (40)	0 (0)	5 (3)	125-128
China	16 (94)	1 (6)	0 (0)	17 (11)	129-133
Finland	1 (100)	0 (0)	0 (0)	1 (1)	134
France	0 (0)	8 (100)	0 (0)	8 (5)	135-137
Germany	1 (100)	0 (0)	0 (0)	1 (1)	138
Greece	3 (100)	0 (0)	0 (0)	3 (2)	139-141
Israel	0 (0)	6 (100)	0 (0)	6 (4)	142
Italy	1 (50)	1 (50)	0 (0)	2 (1)	143,144
Japan	0 (0)	6 (75)	2 (25)	8 (5)	145-148

Malta	0 (0)	1 (100)	0 (0)	1 (1)	[149]
Netherlands	4 (27)	11 (73)	0 (0)	15 (9)	[150-154]
New Zealand	2 (100)	0 (0)	0 (0)	2 (1)	[155]
Portugal	0 (0)	1 (100)	0 (0)	1 (1)	[156]
Spain	1 (33)	2 (67)	0 (0)	3 (2)	[157-159]
Switzerland	4 (100)	0 (0)	0 (0)	4 (3)	[160-163]
Taiwan	0 (0)	7 (100)	0 (0)	7 (4)	[164-167]
United Kingdom	14 (100)	0 (0)	0 (0)	14 (9)	[168-180]
United States	20 (44)	24 (53)	1 (2)	45 (28)	[181-213]

Of the 162 reported outbreaks, at least one control measure was implemented in 118 (73%), per reporting in the paper. The implementation of any control measures, per reporting in the paper, was more common in hospital outbreaks (82%) than LTCF outbreaks (65%). Furthermore, the most common control measure implemented in all settings was enhanced hand hygiene (67%), followed by movement restrictions (63%), enhanced environmental cleaning (59%), and staff exclusions (43%) (Table 4-3). The day on which control measures were implemented was only reported for 28% of outbreaks in which control measures were reported to have been implemented, and therefore was not included in regression analyses. For those that did include information on the day control measures were first implemented, the median day of implementation was day 5 (IQR: 3-10 days) of the outbreak. Lastly, full paper outbreak reports were more likely to include information on any control measures and all specific control measures, with the exception of staff exclusions, compared to non-full paper outbreak reports (Supplementary Table 4-2).

Table 4-3. Control measures reported to be implemented by setting

	No. outbreaks (%) with reported control measure per setting		
Control measure	Hospital (n = 78)	LTCF (n = 80)	All settings[a] (n = 162)
Any control measures	64 (82)	52 (65)	118 (73)
Enhanced hand hygiene	56 (72)	50 (63)	108 (67)
Enhanced environmental cleaning	53 (68)	41 (51)	96 (59)
Movement restrictions	53 (68)	47 (59)	102 (63)
Staff exclusions	31 (40)	36 (45)	69 (43)

[a] Four outbreaks occurred in both hospital and LTCF settings and were included only under “All settings”.

4.4.2 Meta-analysis

We examined associations between reported control measures and each outbreak outcome separately. Of the 162 outbreaks in the dataset, the majority (64%) were missing at least one of the seven outcome variables: duration, attack rates (overall, among patients/residents, and among staff), and case counts (overall, among patients/residents, and among staff). As expected, outcome variables were highly correlated. Attack rates and case counts were positively correlated (R^2 = 0.4, 0.2, and 0.3 for overall, patient/resident, and staff, respectively). Outbreak duration was positively correlated with case counts (R^2 = 0.4, 0.3, and 0.3 for overall, patient/resident, and staff case counts, respectively), but not attack rates, with the exception of staff attack rates (R^2 = 0.3). Lastly, patient attack rate was positively correlated with staff attack rate, as was patient case count with staff case count (R^2 = 0.6 each).

Using forest plots and Cochran's Q-statistic, we did not find evidence that outbreak duration and overall and patient/resident case counts were heterogeneous within exposure categories, but we did find evidence for heterogeneity among attack rates (overall, patients, and staff) and staff case counts (Supplementary Figure 4-2). We therefore stratified the dataset by outbreak setting (hospitals and LTCFs) for all regression analyses. While some outcomes were still heterogeneous even in the stratified datasets, the heterogeneity was reduced.

In our quality of evidence assessment, we found that only 33 (28%) outbreaks in which control measures were reported to have been implemented had information on when control measures were implemented. The majority (113, 70%) of outbreaks included a case definition, however outbreaks in which control measures were reported to have been implemented were more likely to include a case definition compared to those in which they

were not (76% vs. 55% of outbreaks, respectively). Finally, few outbreaks (44, 27%) included an outbreak definition, and this information was again more likely to be reported for outbreaks in which control measures were reported to have been implemented compared to those in which they were not (31% vs. 18% of outbreaks, respectively).

Among hospital outbreaks, we found that patient case counts were 0.6 (95% CI: 0.3, 1.1) times smaller for outbreaks in which control measures were implemented compared to those in which they were not, per reporting in the paper (Table 4-4). Conversely, among LTCF outbreaks, we found that overall, resident, and staff case counts were 1.5 (95% CI: 1.1, 2.2), 1.5 (95% CI: 1.0, 2.1), and 1.6 (95% CI: 1.0, 2.6) times larger, respectively, for outbreaks in which control measures were implemented compared to those in which they were not, per reporting in the paper. Lastly, among hospital outbreaks, we found that outbreaks in which control measures were reported to be implemented were 0.7 (95% CI: 0.4, 1.0) times shorter than those in which they were not reported to be implemented. Conversely, among LTCF outbreaks, we found that outbreaks in which control measures were reported to be implemented were 1.4 (95% CI: 1.0, 2.0) times longer than those in which they were not reported to be implemented. While results also suggest that control measures may be associated with smaller staff attack rates in hospital outbreaks, confidence intervals for associations between control measures and all attack rates were wide and therefore associations could not be determined.

Table 4-4. Comparison of outbreaks by reported implementation of any infection control measures

Outcome/ Setting[a]	No. outbreaks (%) reporting any control measures	Median (IQR) Any control measures reported: Yes	Median (IQR) Any control measures reported: No	Association[b] (95% CI) with reported implementation of any control measures
Hospitals				
Duration (days)	58 (84)	15 (12, 21.3)	26 (23, 54)	0.7 (0.4, 1.0)[c]
Attack Rates (%)				
Overall	25 (83)	21.5 (11.5, 29.0)	22.5 (21.1, 44.3)	-7.4 (-23.9, 9.8)[d]
Patient	51 (88)	25.8 (15, 41.7)	22.5 (15.4, 30.8)	3.8 (-13.1, 21.1)[d]
Staff	31 (82)	16.9 (3.3, 30)	31 (24.7, 50)	-14.8 (-27.8, -1.8)[d]
Case Counts				
Overall	53 (85)	28 (11, 60)	38 (20, 122)	0.8 (0.4, 1.6)[c]
Patient	61 (85)	14 (9, 32)	44 (7.5, 81)	0.6 (0.3, 1.1)[c]
Staff	55 (86)	16 (3, 32)	28 (15, 60)	0.8 (0.3, 2.0)[c]
LTCFs				
Duration (days)	42 (64)	22 (11.3, 29.8)	14.5 (9, 24.5)	1.4 (1.0, 2.0)[c]
Attack Rates (%)				

Overall	20 (49)	42.7 (19.2, 48.5)	30.1 (19.3, 45.7)	6.4 (-3.9, 17.0)[d]
Resident	45 (67)	41.3 (22, 54.3)	34.0 (21.4, 50.3)	4.5 (-5.9, 14.5)[d]
Staff	26 (54)	23.7 (11.6, 38.3)	23.2 (10.8, 43.0)	-2.7 (-11.8, 6.8)[d]
Case Counts				
Overall	36 (55)	68.5 (31, 107.3)	53 (27.3, 76.3)	1.5 (1.1, 2.2)[c]
Resident	45 (62)	41 (21, 74)	30 (16, 52.3)	1.5 (1.0, 2.1)[c]
Staff	39 (58)	25 (7.5, 50)	16 (10.5, 28.3)	1.6 (1.0, 2.6)[c]

[a] Four outbreaks took place in both a hospital and LTCF and were included in both hospital and LTCF settings.

[b] Log-normal linear mixed regression was used for duration, linear mixed regression for attack rates, and mixed negative binomial regression for case counts. All regression models included any control measures and a random intercept for country of outbreak as independent variables.

[c] On the multiplicative scale; exponentiated regression coefficients are shown.

[d] On the additive scale.

When examining specific control measures in hospital outbreaks, we found that enhanced hand hygiene measures and enhanced environmental cleaning were associated with 0.6 (95% CI: 0.4, 0.8) and 0.7 (95% CI: 0.5, 1.0) times shorter outbreak durations, respectively (Table 4-5). Furthermore, we found the following associations between specific control measures and final case counts: 1) enhanced hand hygiene measures were associated with 0.5 (95% CI: 0.3, 0.9) times smaller patient case counts, 2) movement restrictions were associated with 1.7 (95% CI: 0.9, 3.0) and 1.7 (95% CI: 0.9, 3.5) times larger overall and staff case counts, respectively, and 3) staff exclusions were associated with 1.4 (95% CI: 0.8, 2.3) and 1.5 (95% CI: 0.8, 2.9) times larger overall and staff case counts, respectively. Lastly, while results suggest that enhanced hand hygiene measures, enhanced environmental cleaning, and movement restrictions may also be associated with smaller staff attack rates, results were too imprecise to make conclusions about associations between any specific control measures and attack rates.

Table 4-5. Associations between implementation of specific infection control measures and outcome variables by setting

	Association[b] (95% CI) with reported implementation of specific control measure			
Outcome/ Setting[a]	**Enhanced hand hygiene**	**Enhanced environmental cleaning**	**Movement restrictions**	**Staff exclusions**
Hospitals				
Duration (days)	0.6 (0.4, 0.8)	0.7 (0.5, 1.0)	1.0 (0.7, 1.4)	0.9 (0.6, 1.2)[c]
Attack Rates (%)				
Overall	-0.2 (-16.7, 15.8)	-0.2 (-16.7, 15.8)	-10.0 (-26.4, 7.6)	-9.2 (-22.1, 4.8)[d]
Patient	-6.2 (-19.6, 6.8)	-1.9 (-15.1, 10.9)	6.0 (-7.4, 18.3)	9.1 (-1.3, 19.3)[d]
Staff	-16.7 (-28.9, -4.7)	-13.8 (-24.9, -2.9)	-19.0 (-32.4, -5.4)	-8.7 (-19.2, 2.1)[d]
Case Counts				
Overall	0.7 (0.4, 1.3)	0.8 (0.5, 1.5)	1.7 (0.9, 3.0)	1.4 (0.8, 2.3)[c]
Patient	0.5 (0.3, 0.9)	0.9 (0.5, 1.5)	0.9 (0.5, 1.6)	1.0 (0.6, 1.7)[c]
Staff	0.7 (0.3, 1.5)	0.7 (0.3, 1.4)	1.7 (0.9, 3.5)	1.5 (0.8, 2.9)[c]
LTCFs				
Duration (days)	1.4 (1.0, 2.0)	1.2 (0.8, 1.7)	1.6 (1.1, 2.2)	2.1 (1.5, 2.8)[c]
Attack Rates (%)				

Overall	7.7 (-2.4, 18.3)	-2.8 (-17.0, 10.8)	1.6 (-10.2, 12.9)	1.5 (-10.5, 12.3)[d]
Resident	4.9 (-5.4, 14.6)	-8.6 (-18.4, 1.2)	-1.6 (-11.1, 7.8)	-3.4 (-12.7, 6.0)[d]
Staff	-0.9 (-10.1, 8.4)	-10.2 (-19.4, -0.7)	-3.5 (-12.4, 6.2)	-0.4 (-9.8, 9.3)[d]
Case Counts				
Overall	1.5 (1.1, 2.2)	1.2 (0.8, 1.8)	1.6 (1.1, 2.3)	1.7 (1.2, 2.4)[c]
Resident	1.5 (1.0, 2.1)	1.2 (0.8, 1.7)	1.5 (1.1, 2.2)	1.4 (1.0, 2.0)[c]
Staff	1.7 (1.1, 2.7)	1.5 (1.0, 2.5)	1.6 (1.0, 2.5)	1.9 (1.2, 3.0)[c]

[a] Four outbreaks took place in both a hospital and LTCF and were included in both hospital and LTCF settings.

[b] Log-normal linear mixed regression was used for duration, linear mixed regression for attack rates, and mixed negative binomial regression for case counts. All regression models included the specific control measure and a random intercept for country of outbreak as independent variables.

[c] On the multiplicative scale; exponentiated regression coefficients are shown.

[d] On the additive scale.

When examining specific control measures in LTCF outbreaks, we similarly found that results suggest enhanced environmental cleaning may be associated with smaller staff attack rates, but that results were too imprecise to make conclusions about the associations between specific control measures and attack rates (Table 4-5). However, we did find the following associations between specific control measures and outbreak duration and case counts: 1) enhanced hand hygiene measures were associated with 1.4 (95% CI: 1.0, 2.0) times longer durations and 1.5 (95% CI: 1.1, 2.2), 1.5 (95% CI: 1.0, 2.1), and 1.7 (95% CI: 1.1, 2.7) times larger overall, resident, and staff case counts, respectively, 2) enhanced environmental cleaning was associated with 1.5 (95% CI: 1.0, 2.5) times larger staff case counts, 3) movement restrictions were associated with 1.6 (95% CI: 1.1, 2.2) times longer durations and 1.6 (95% CI: 1.1, 2.3), 1.5 (95% CI: 1.1, 2.2), and 1.6 (95% CI: 1.0, 2.5) times larger overall, resident, and staff case counts, respectively, and 4) staff exclusions were associated with 2.1 (95% CI: 1.5, 2.8) times longer durations and 1.7 (95% CI: 1.2, 2.4), 1.4 (95% CI: 1.0, 2.0), and 1.9 (95% CI: 1.2, 3.0) times larger overall, resident, and staff case counts, respectively.

In sensitivity analyses, results for the associations between outbreak outcomes and the reported implementation of any control measures were robust, with one exception when the data were restricted to full paper outbreak reports. In this sensitivity analysis for hospital outbreaks, the association between any control measures and duration disappeared and the association between any control measures and smaller patient case counts persisted but the confidence intervals became too wide to make conclusions. In sensitivity analyses examining associations between outbreak outcomes and the reported implementation of specific control measures, results were generally robust, with a few exceptions for hospital outbreaks. First, when data were restricted to full paper outbreak reports, the associations

between enhanced hand hygiene measures and duration and patient case counts became inconclusive due to large confidence intervals. Second, the association between enhanced environmental cleaning and duration disappeared when data were restricted to new data only, and reversed when data were restricted to full paper outbreak reports. Lastly, the association between movement restrictions and overall and staff case counts largely disappeared when data were restricted to outbreaks with 10 or more cases and to full paper outbreak reports (Supplementary Figures 4-4 – 4-8).

4.5 Discussion

Our aim was to search the scientific literature to identify norovirus outbreaks in healthcare facilities globally and examine associations between control measures and outbreak duration, attack rate, and size. From these reports, in hospital outbreaks, we found that patient case counts were smaller and durations were shorter when control measures were implemented compared to when they were not, per reporting in the paper. Conversely, in LTCF outbreaks, case counts (overall, residents, and staff) were larger and durations were longer when control measures were implemented compared to when they were not, per reporting in the paper. Both findings were robust in sensitivity analyses.

The direction of the association between control measures and outbreak outcomes was as expected in hospitals, but was opposite of expected in LTCFs. We hypothesize that outbreak control measures in LTCFs are more likely to be implemented for larger and longer outbreaks than smaller and shorter outbreaks. While this may also be true in hospitals, we believe it is to a lesser extent, as control measures were not associated with larger or longer outbreaks in this setting. It may be that LTCFs have more limited resources

and personnel compared to hospitals, and therefore control measures may only be implemented once LTCF outbreaks reach a certain size or duration (i.e., a threshold of outbreak severity). In other words, control measures may be implemented later in LTCF outbreaks compared to hospital outbreaks. However, while there is evidence that LTCFs in the U.S. and other high-income countries are underfunded and understaffed,[214-218] studies comparing funding and staffing levels in LTCFs to those in hospitals are lacking, as are studies comparing the implementation of norovirus outbreak control measures in these two settings, so we can only speculate. In addition, there are several other important differences between hospitals and LTCFs. First, hospitals typically provide acute care to patients requiring immediate yet brief medical treatment, whereas LTCFs typically provide long-term care, including both medical and personal, to people who are unable to live independently. Therefore, the average length of stay for hospital patients is much shorter than that for LTCF residents (4.6 vs. 485 days, respectively).[14,219] Second, LTCFs and hospitals have different physical designs, with LTCFs often emulating a residential, non-institutional environment that includes common areas where residents can socialize.[220] Lastly, hospitals are typically larger than LTCFs, with an average of 160 beds per hospital compared to 110 beds per nursing home in the U.S.[14,221] While these are all important differences, we do not believe they explain the opposite association between control measures and outbreak outcomes in LTCFs. We accounted for setting (hospital vs. LTCF) through stratification, so while these are not confounding factors, they, in part, may underlie different patterns observed. However, without more detailed outbreak data, including case counts by day (i.e., outbreak curves) and timing of control measure implementation, we were unable to examine reasons for the opposite association in LTCFs further.

In general, we also found that specific control measures were associated with smaller outbreak size and shorter duration in hospitals but larger outbreak size and longer duration in LTCFs. Among hospital outbreaks, enhanced hand hygiene measures were associated with smaller outbreak size and shorter durations, findings that were generally robust in sensitivity analyses. Among LTCF outbreaks, enhanced hand hygiene measures, enhanced environmental cleaning, movement restrictions and staff exclusions were associated with larger outbreak size and longer durations, findings that were also robust in sensitivity analyses. A notable exception, however, was the association between movement restrictions and larger outbreak size and/or longer duration in both hospitals and LTCFs. We hypothesize that hospitals are more likely than LTCFs to implement any control measures in response to smaller outbreaks, but that movement restrictions, such as closure of affected clinical areas (i.e., ward closures), which are generally more extreme and costlier to implement,[222] may only be implemented for larger outbreaks. While studies examining the threshold (e.g., certain outbreak size) at which ward closures are typically implemented are lacking, the current CDC/HICPAC prevention and control guidelines mentions that the threshold for ward closure should vary and depend on facility risk assessments.[34] Thresholds for implementing any other control measures are not mentioned, suggesting that ward closures, unlike other control measures, may typically be implemented only once outbreaks reach a certain threshold. In sensitivity analyses, the association between movement restrictions and larger outbreak size in hospitals largely disappeared, supporting this hypothesis. However, as noted above, without more detailed outbreak data, we were unable to examine this further.

We note a number of limitations in our study. First, in our quality of evidence assessment, we found that a substantial number of outbreaks had missing information for variables we

examined as indicators of quality, and that outbreaks in which control measures were not reported to be implemented were more likely to be missing this information. Similarly, some outbreaks were likely misclassified as not having had control measures implemented. However, expected bias from this misclassification would be toward the null, and control measures were found to be associated with smaller outbreak size in hospitals despite this potential bias. Second, analyses were subject to bias from reverse causation. In sensitivity analyses, we found associations between control measures and larger and longer outbreaks in LTCFs persisted, leading us to believe that we were unsuccessful in completely removing this bias. Third, there was insufficient information on timing of control measure implementation, so we could not examine this further. Control measures implemented earlier in an outbreak, before transmission is well established, are likely more effective in mitigating transmission compared to control measures implemented later. Similarly, we only had information on whether control measures were reportedly implemented, and not on the quality of or adherence to control measures, and were therefore unable to include this information in our analyses. Fourth, healthcare facilities, and LTCFs in particular, can be highly heterogeneous, both within and between countries. However, due to insufficient sample size, we were unable to examine control measure effectiveness in more specific settings (e.g., nursing homes, assisted living facilities, etc.). Fifth, attack rate calculations can vary substantially depending on the definition used for individuals at-risk (e.g., the entire facility, affected wards/units only, etc.). While we calculated attack rates whenever possible (using a consistent definition of individuals at-risk), some attack rates could not be calculated due to insufficient information, and the definition used for individuals at-risk was not always available. Lastly, while we searched *PubMed/MEDLINE*, *Embase (Elsevier)*, *Scopus (Elsevier)* and the gray literature, some

data may be missing from this review if eligible papers were published exclusively on other databases.

Owing to the limitations described above, we were unable to examine the causal effect of control measure implementation on norovirus outbreak outcomes in healthcare settings. Instead, our study provides a summary of these associations. More research is needed to determine the effectiveness, as well as cost-effectiveness, of outbreak control measures in these settings. For example, interventions such as closure of affected wards/units are very costly, so their effectiveness should be considered in light of impacts on the provisions of health services. While randomized control trials, in which healthcare facilities are randomized to implement specific control measures upon detection of norovirus cases, could lead to unbiased estimates of control measure effectiveness, these trials are not ethical nor feasible. However, hundreds of norovirus outbreaks are reported annually in the U.S. alone. If a focused effort was made to record the timing and characteristics of control measures implemented during these outbreaks, more could be learned about control measure effectiveness. Future studies should focus on prospectively collecting detailed information on outbreak control measures (e.g., specific control measures implemented, when they were implemented, and adherence to control measure protocols) from a representative sample of healthcare facility norovirus outbreaks and examining differences in outbreak outcomes. In particular, timing of control measure implementation is likely an important predictor of outbreak outcomes and should be considered in future studies.

4.6 Conclusions

By reviewing the relevant literature, we found that hospital outbreaks in which control measures were implemented were smaller in size and shorter in duration compared to hospital outbreaks in which control measures were not implemented, per reporting. Conversely, we found that LTCF outbreaks in which control measures were implemented were larger in size and longer in duration compared to LTCF outbreaks in which control measures were not implemented, per reporting. Control measures in LTCFs may be more likely to be implemented in response to larger and longer outbreaks, therefore explaining the reversed association. Longitudinal observational or intervention studies are needed to determine any causal associations and the effectiveness of norovirus outbreak control measures in healthcare settings.

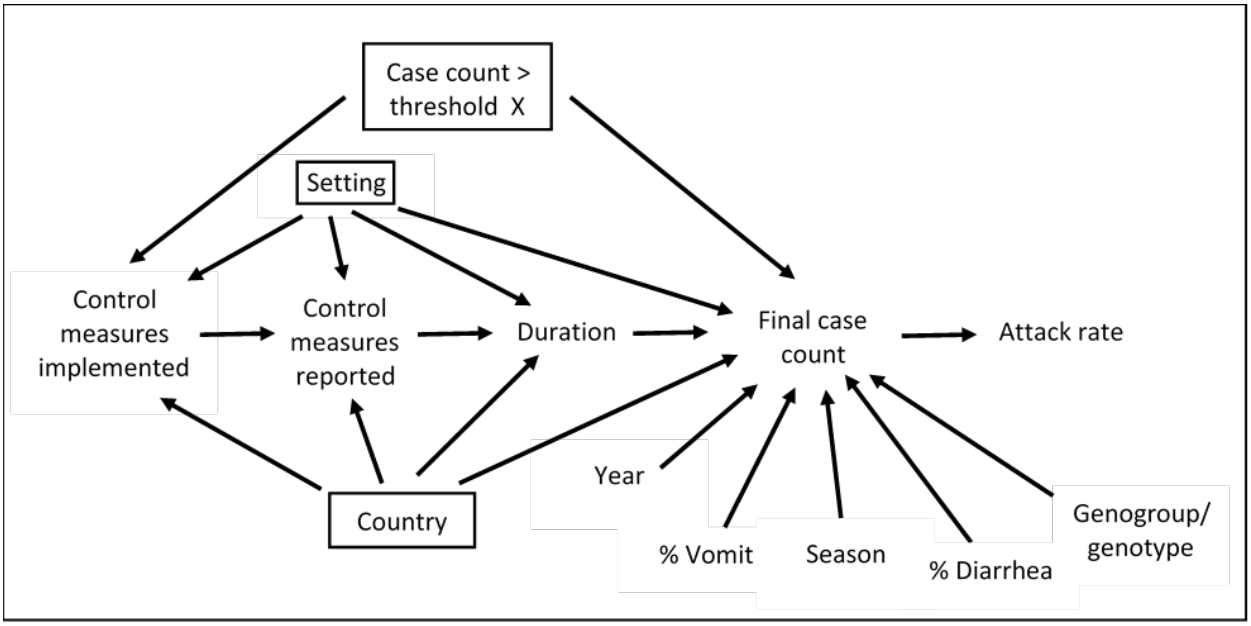
4.7 Supplementary File

Results from the current review data only (i.e., excluding data from the previous review by Harris et al.)

We examined several variables that were only available in the current review data, including case definition details, outbreak report date, genetic information, other pathogens detected, detailed control measure information, and symptom information. Of the 107 outbreaks from the current review data, 16 (15%) included the day on which the outbreak was reported to the health department, with a median report day of 5.5 (IQR: 3, 10.8). Similar to the total dataset, the majority of outbreaks from the current review data included a case definition (76, 66%). However, the details of these case definitions varied. Of the 76 outbreaks with case definitions, 27 (36%) included a definition for diarrhea (e.g., three or more loose stools within a 24-hour period), 20 (26%) required cases to have a positive norovirus test, 19 (25%) specified a timeframe within which cases had to develop symptoms, 15 (20%) excluded cases with other known causes, and 8 (11%) included separate definitions for confirmed and probable cases. We also examined genetic information and whether other pathogens were detected. Sixty-four (60%) outbreaks included genetic information, the majority of which detected norovirus genogroup GII (60, 94%), while only 3 (5%) detected norovirus genogroup GI. One outbreak detected both genogroups GI and GII. Genotype information was available for 56 (52%) outbreaks, the majority of which detected norovirus GII.4 (39, 70%). Of these GII.4 outbreaks, 21 (54%) included information on species. New Orleans and Sydney were the most commonly reported GII.4 norovirus species, detected in 6 (29%) outbreaks each, followed by Den Haag (5, 24%), and Apeldoorn, Hunter, Minerva, and Yerseke, detected in one outbreak each. In addition, 11 (10%) outbreaks reported

detection of other pathogens as well, the most common of which was C. difficile, which was detected in 7 (64%) outbreaks.

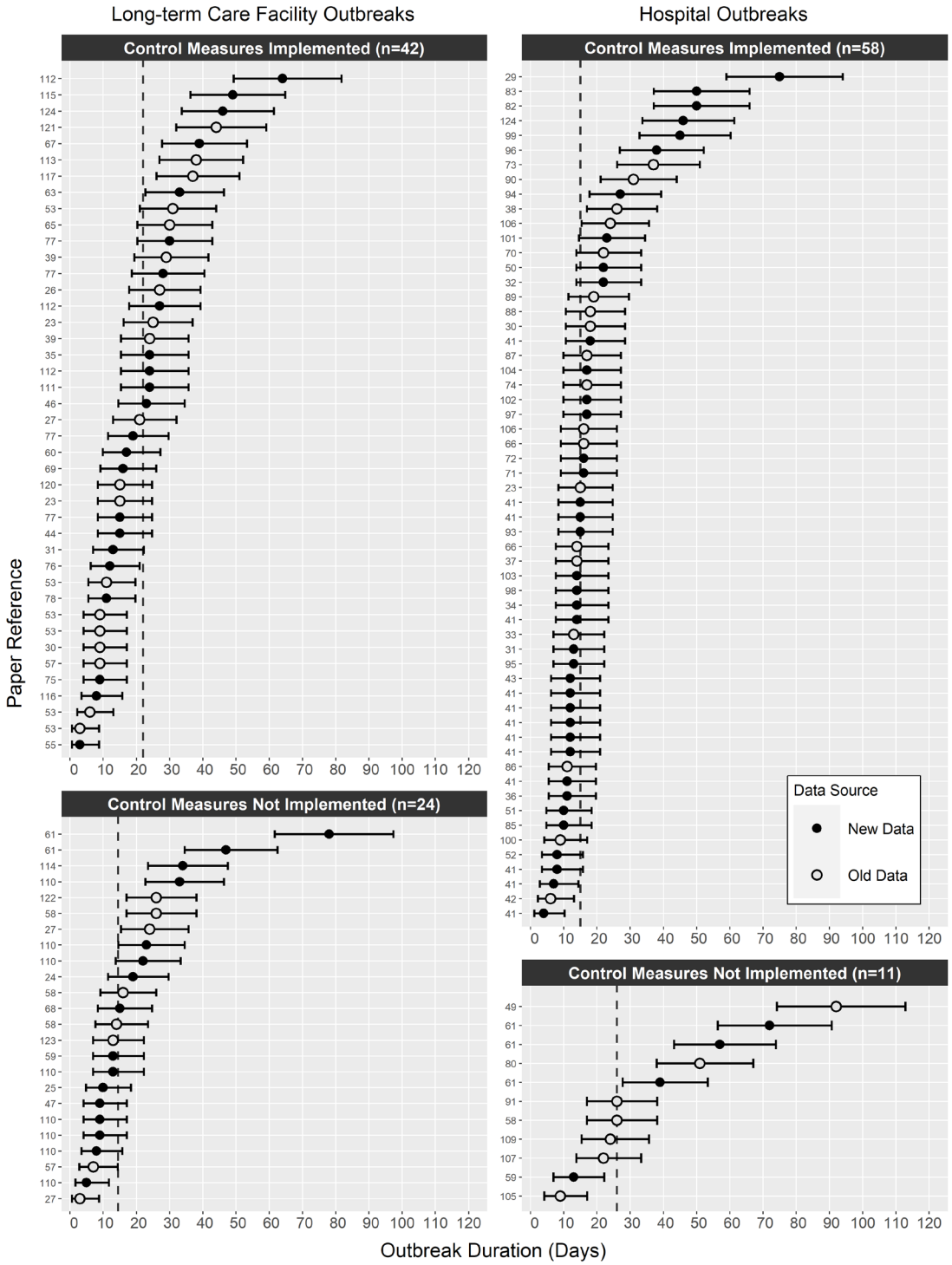
Supplementary Figure 4-1. Directed acyclic graph (DAG) for informing the modeling approach *a priori*



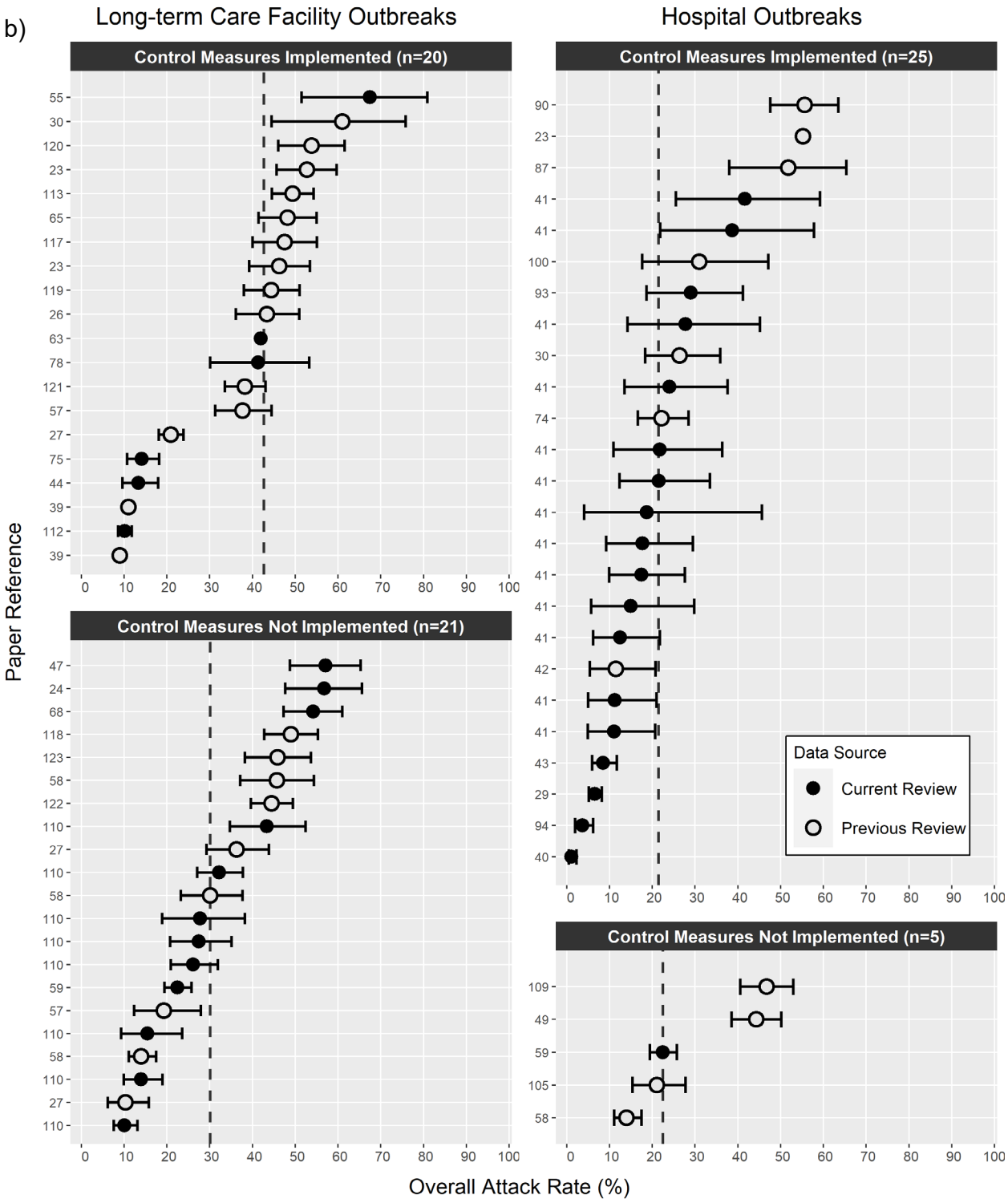
* Variables in black boxes were found *a priori* to be potential confounders and were controlled for in the analyses

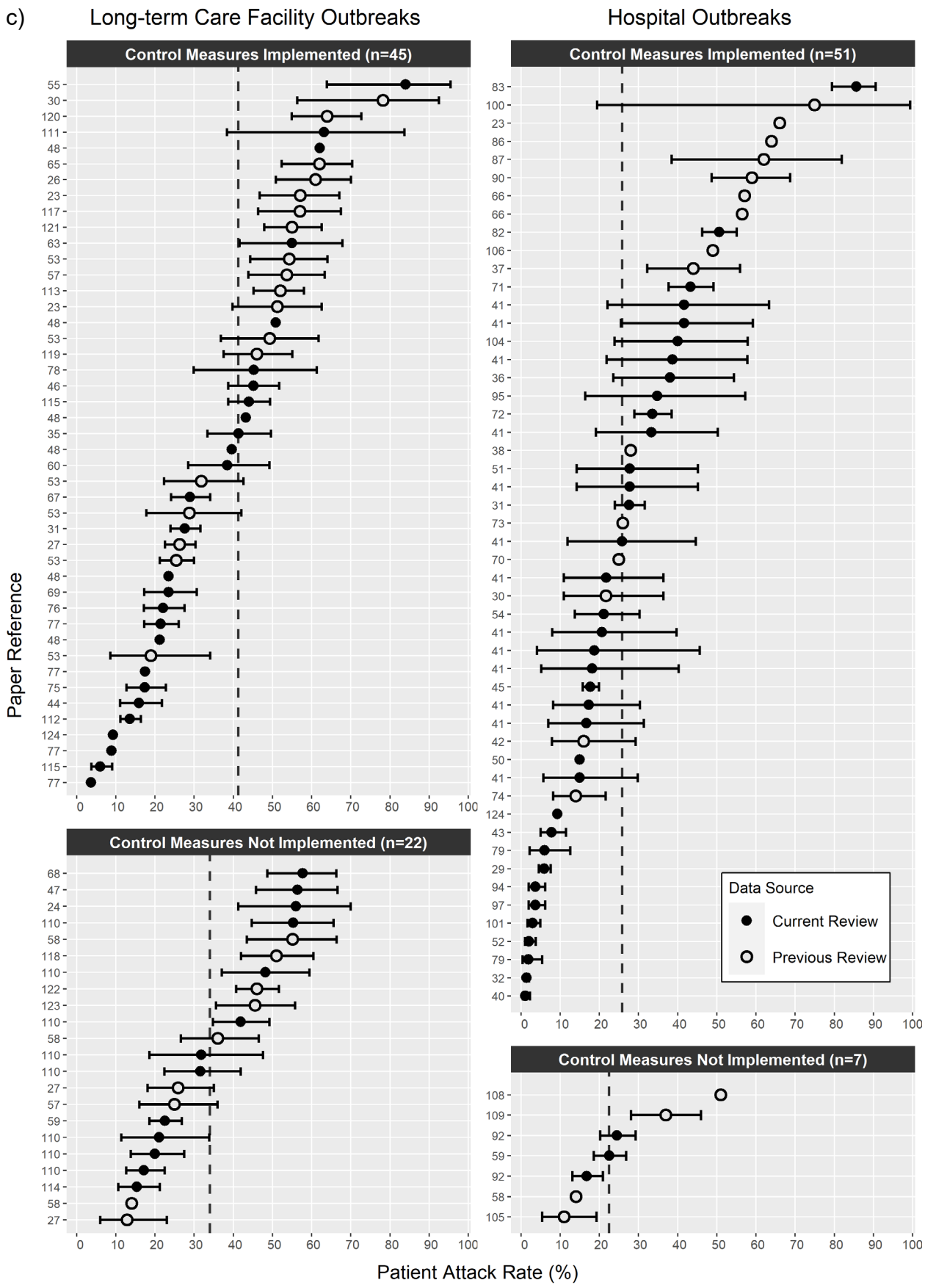
Supplementary Figure 4-2. Forest plots displaying heterogeneity by setting, control measure implementation, and data source for the following outcomes: a) outbreak duration, b) overall attack rates, c) patient attack rates, d) staff attack rates, e) overall case counts, f) patient case counts, and g) staff case counts, with median values shown by dashed vertical lines.

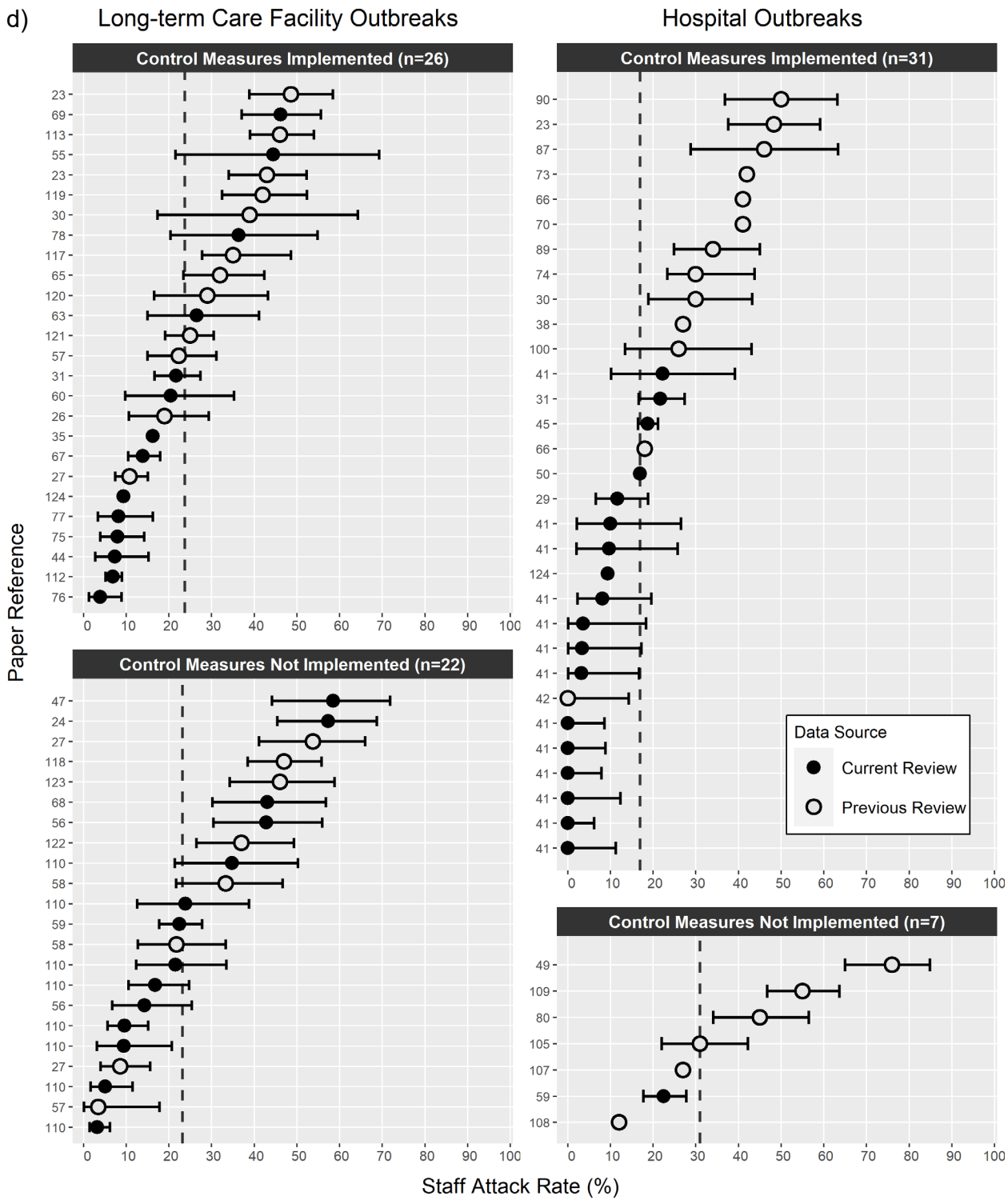
a)

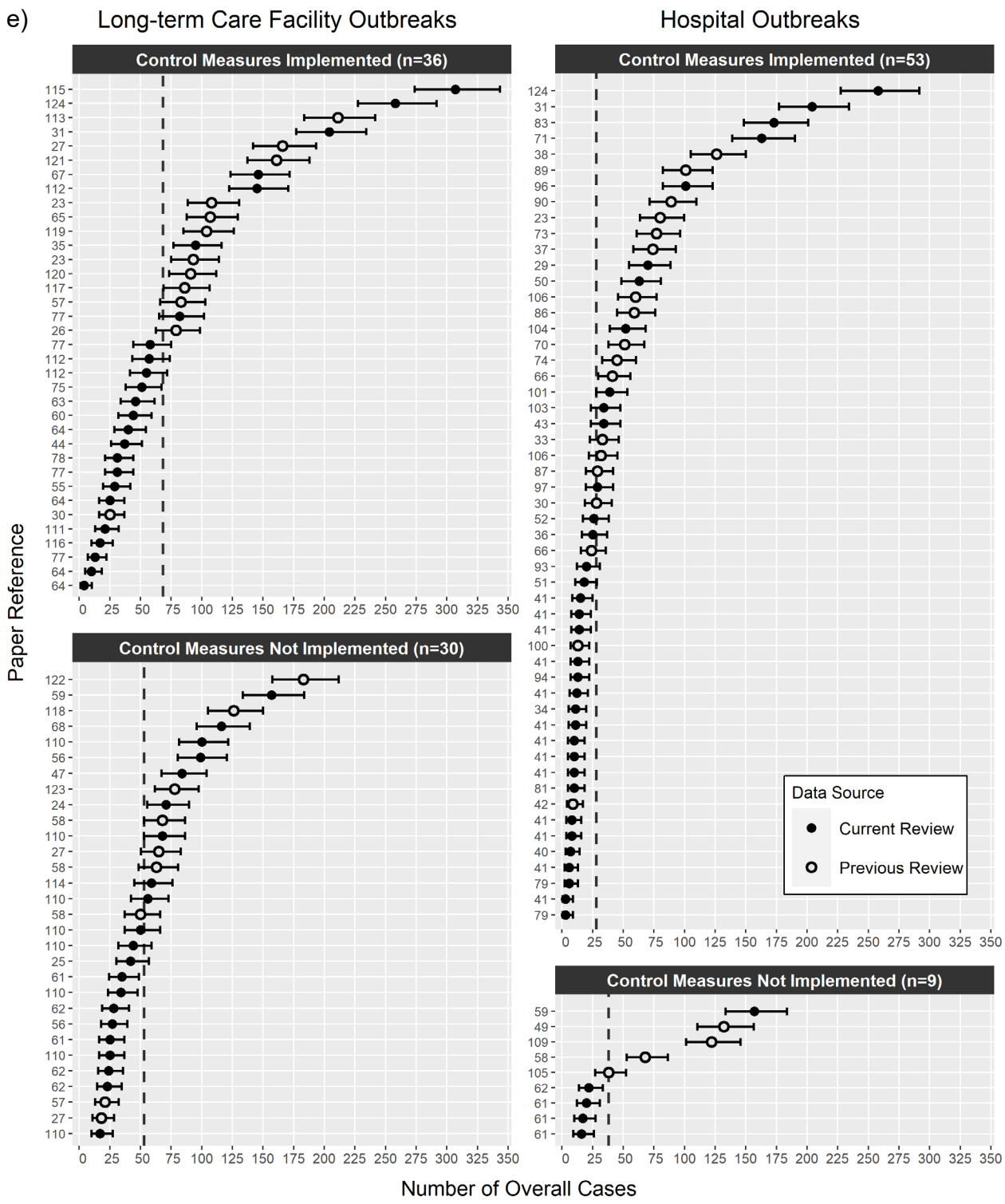


b)

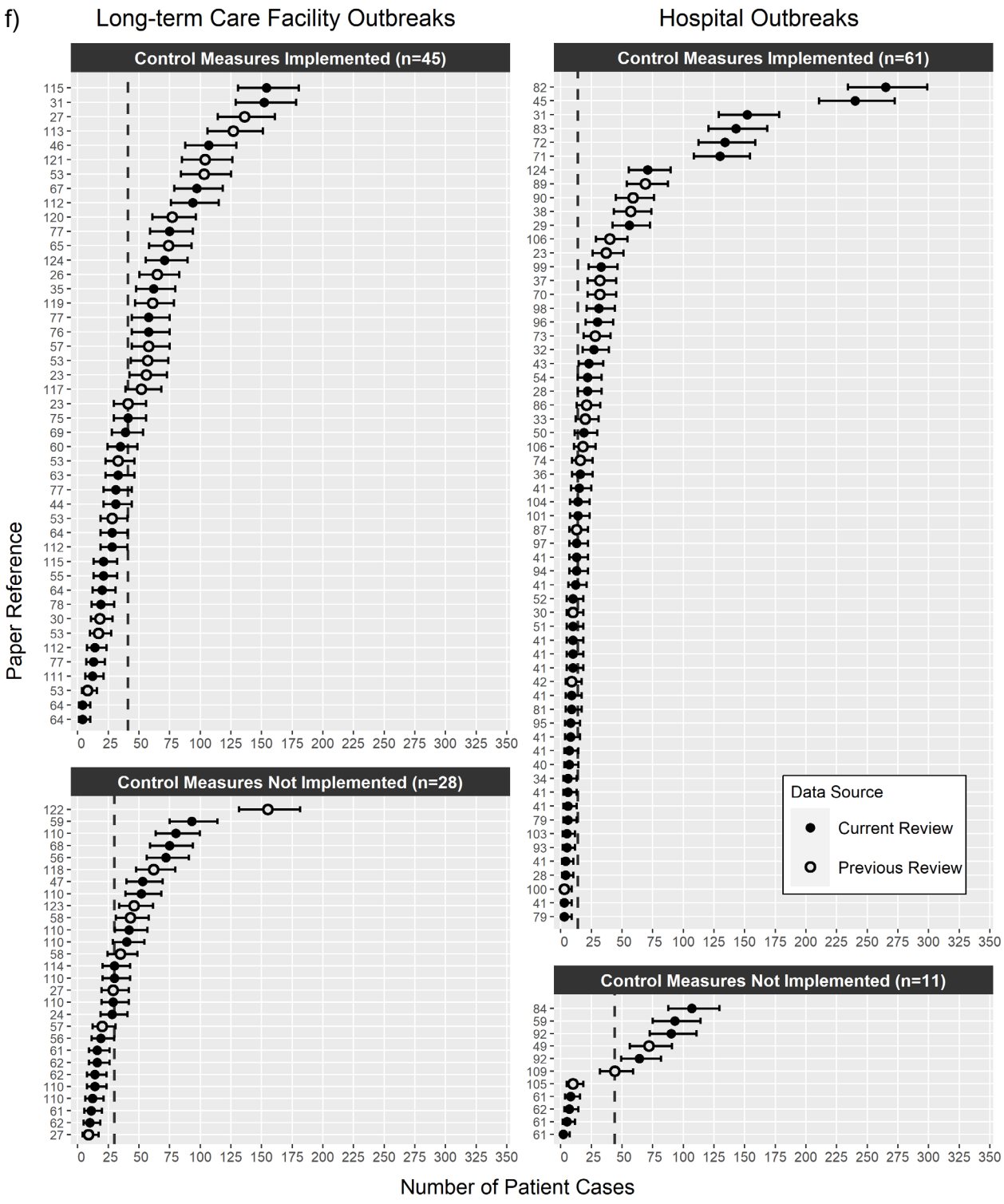

Long-term Care Facility Outbreaks
Hospital Outbreaks
Control Measures Implemented (n=20)
Control Measures Not Implemented (n=21)
Control Measures Implemented (n=25)
Control Measures Not Implemented (n=5)
Paper Reference
Overall Attack Rate (%)
Data Source
Current Review
Previous Review

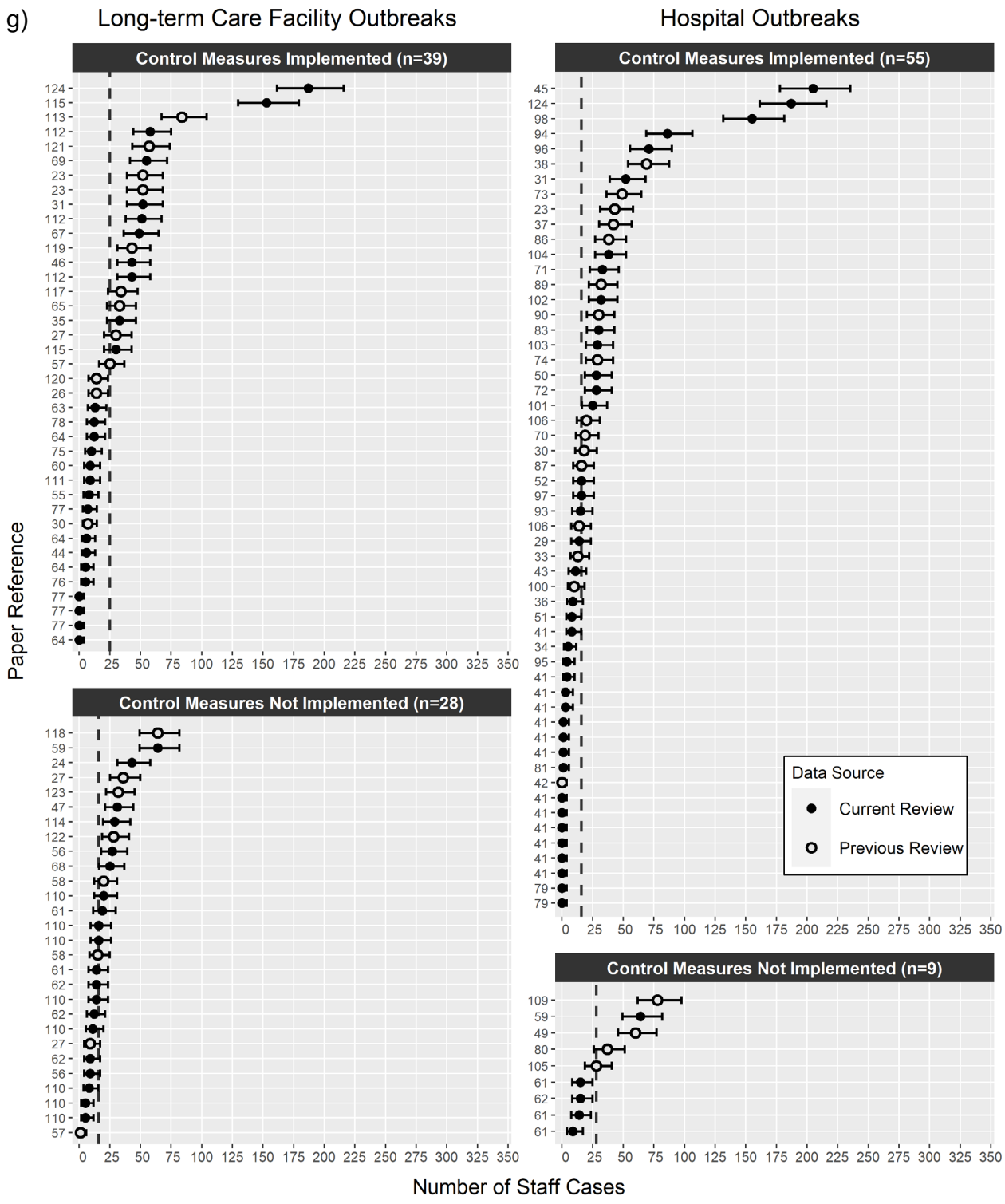

c)
Long-term Care Facility Outbreaks
Hospital Outbreaks
Control Measures Implemented (n=45)
Control Measures Implemented (n=51)
Control Measures Not Implemented (n=22)
Control Measures Not Implemented (n=7)
Paper Reference
Patient Attack Rate (%)
Data Source
Current Review
Previous Review


d)
Long-term Care Facility Outbreaks
Hospital Outbreaks
Control Measures Implemented (n=26)
Control Measures Not Implemented (n=22)
Control Measures Implemented (n=31)
Control Measures Not Implemented (n=7)
Paper Reference
Staff Attack Rate (%)
Data Source
Current Review
Previous Review

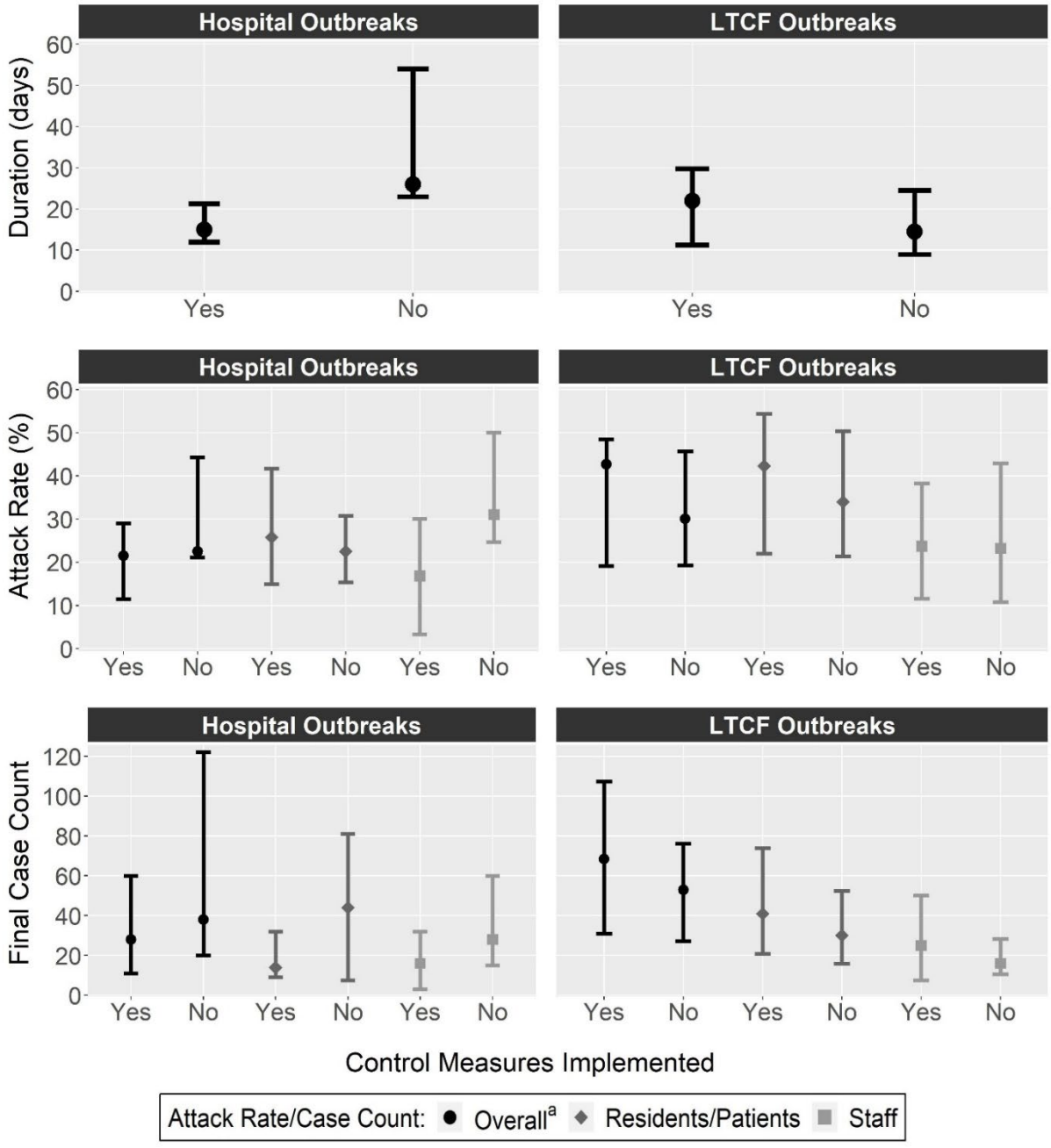

e)
Long-term Care Facility Outbreaks
Hospital Outbreaks
Control Measures Implemented (n=36)
Control Measures Not Implemented (n=30)
Control Measures Implemented (n=53)
Control Measures Not Implemented (n=9)
Paper Reference
Number of Overall Cases
Data Source
Current Review
Previous Review

f)


Long-term Care Facility Outbreaks
Hospital Outbreaks
Control Measures Implemented (n=45)
Control Measures Implemented (n=61)
Control Measures Not Implemented (n=28)
Control Measures Not Implemented (n=11)
Paper Reference
Number of Patient Cases
Data Source
Current Review
Previous Review


g)
Long-term Care Facility Outbreaks
Hospital Outbreaks
Control Measures Implemented (n=39)
Control Measures Not Implemented (n=28)
Control Measures Implemented (n=55)
Control Measures Not Implemented (n=9)
Paper Reference
Number of Staff Cases
Data Source
Current Review
Previous Review

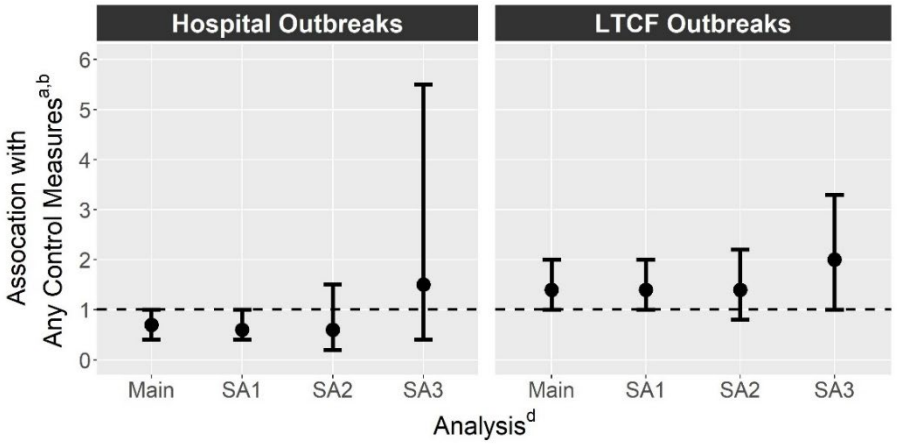
Supplementary Figure 4-3. Median measures of outbreak severity (duration, attack rates, and case counts) and corresponding inter-quartile ranges (IQRs) by setting and control measure implementation.



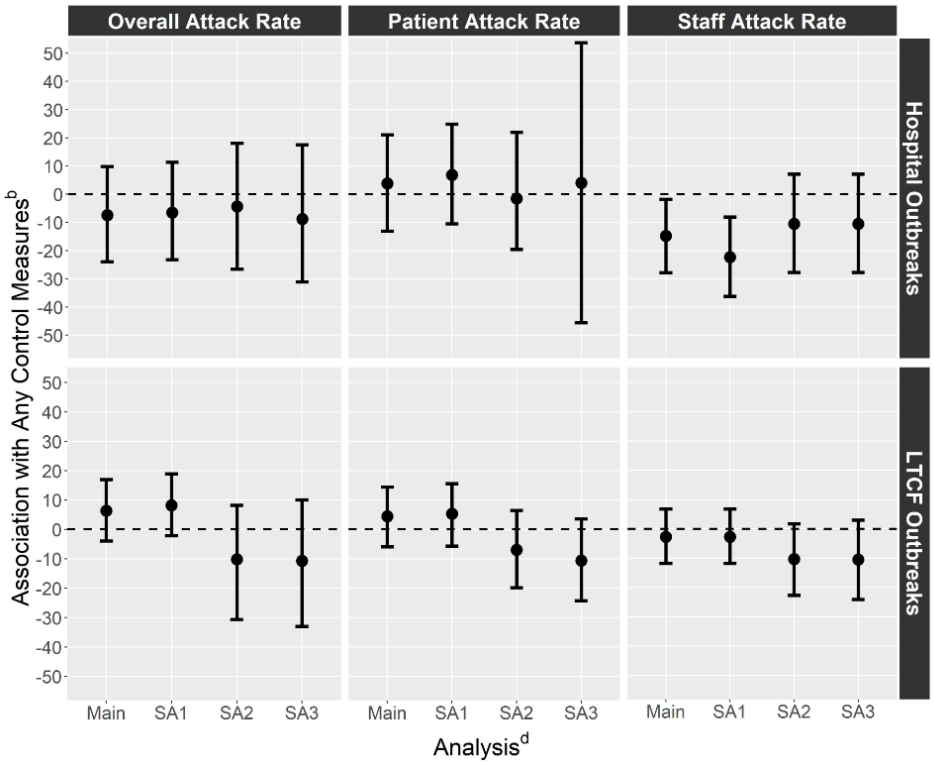
[a] Overall attack rates and case counts include both residents/patients and staff.

Supplementary Figure 4-4. Associations between implementation of any infection control measures and the following measures of outbreak severity: a) outbreak duration, b) attack rates, and c) final case counts, by regression analysis.

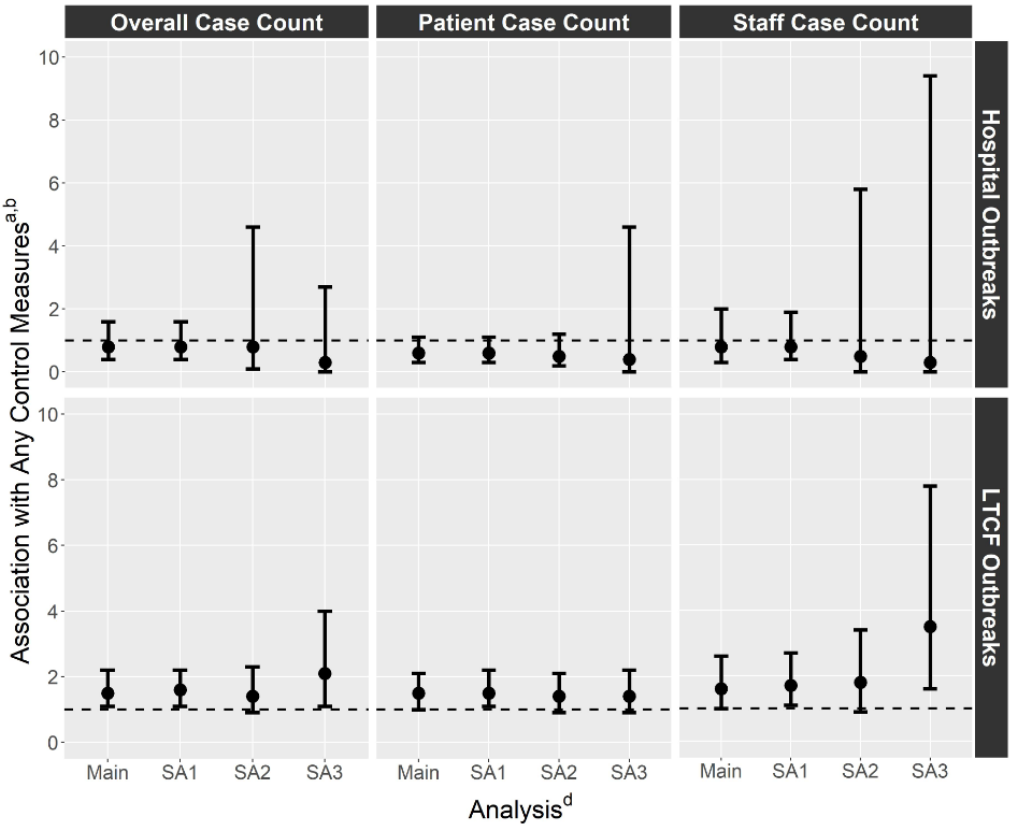
a) Linear associations between implementation of any infection control measures and outbreak duration.



b) Linear associations between implementation of any infection control measures and attack rates.



c) Negative binomial associations between implementation of any infection control measures and final case counts.



[a] All regression models included any control measure and a random intercept for country of outbreak as independent variables. Estimates for Duration and Case Counts were exponentiated.

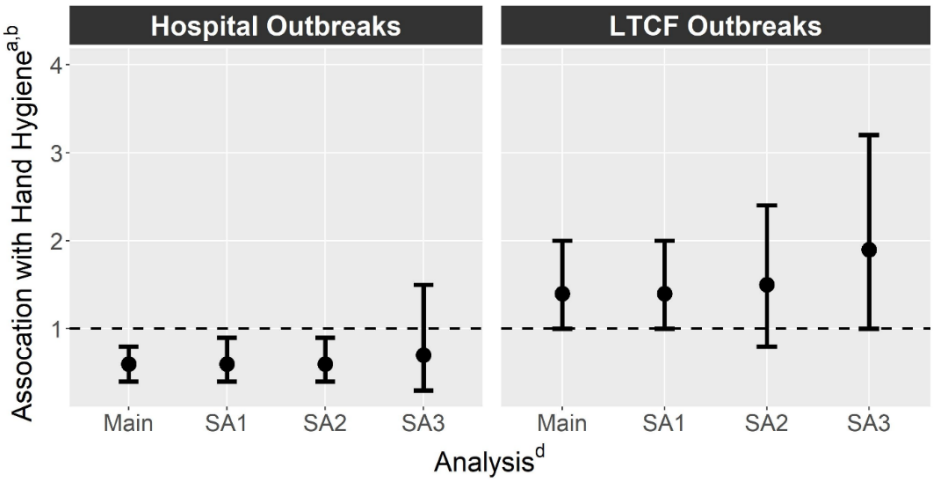
[b] Point estimates and 95% confidence intervals are shown. Horizontal dashed lines represent null values for associations.

[c] Overall attack rates and case counts include residents/patients and staff.

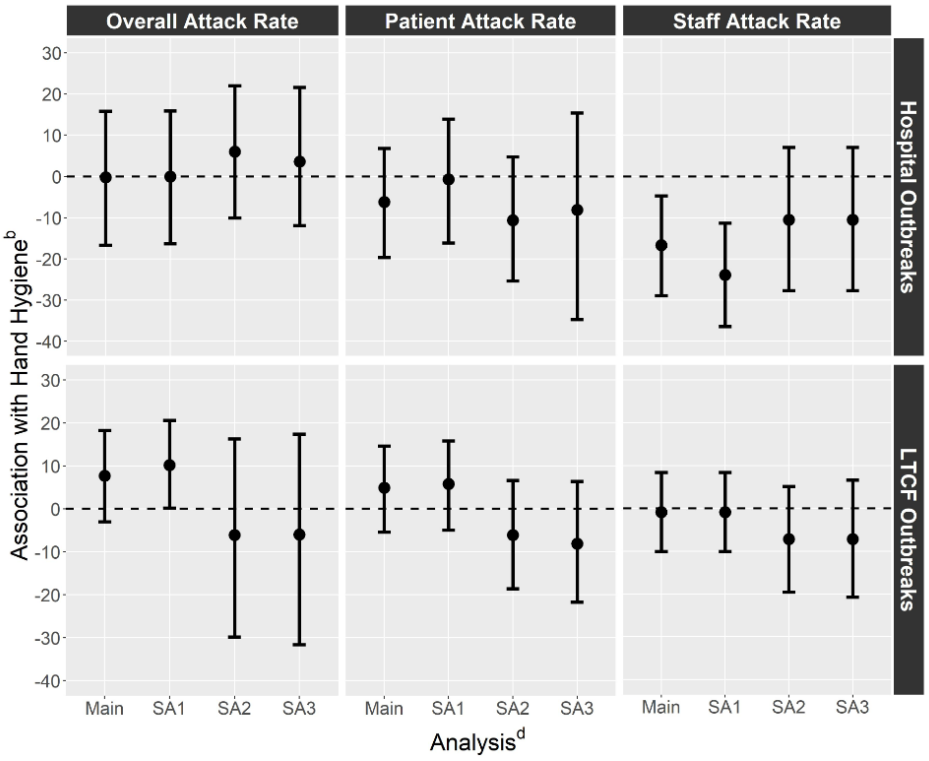
[d] Analyses include the main analysis with the full dataset, and sensitivity analyses restricting the data to the following datasets: SA1) outbreaks that reported 10 or more cases, SA2) outbreaks from the current review (i.e., excluding outbreaks from the previous review), and SA3) outbreaks from the current review from full papers in which the main purpose of the paper was to report the outbreak.

Supplementary Figure 4-5. Associations between implementation of enhanced hand hygiene measures and the following measures of outbreak severity: a) outbreak duration, b) attack rates, and c) final case counts, by regression analysis.

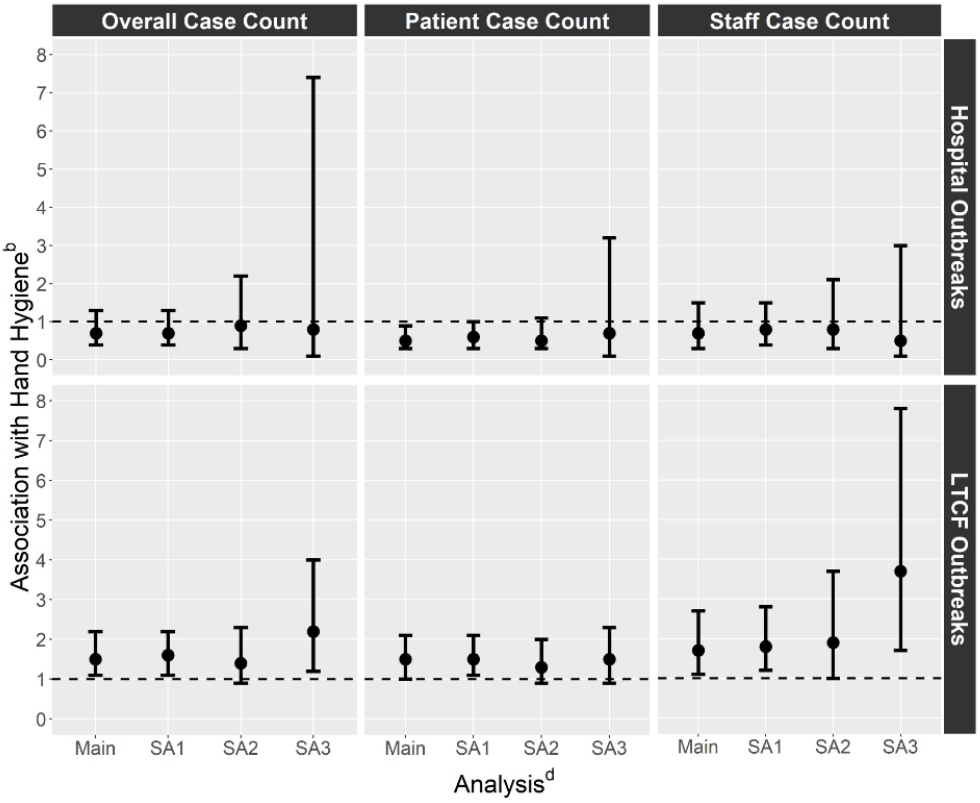
a) Linear associations between implementation of enhanced hand hygiene measures and outbreak duration.



b) Linear associations between implementation of enhanced hand hygiene measures and attack rates.



c) Negative binomial associations between implementation of enhanced hand hygiene measures and final case counts.



[a] All regression models included enhanced hand hygiene and a random intercept for country of outbreak as independent variables. Estimates for Duration and Case Counts were exponentiated.

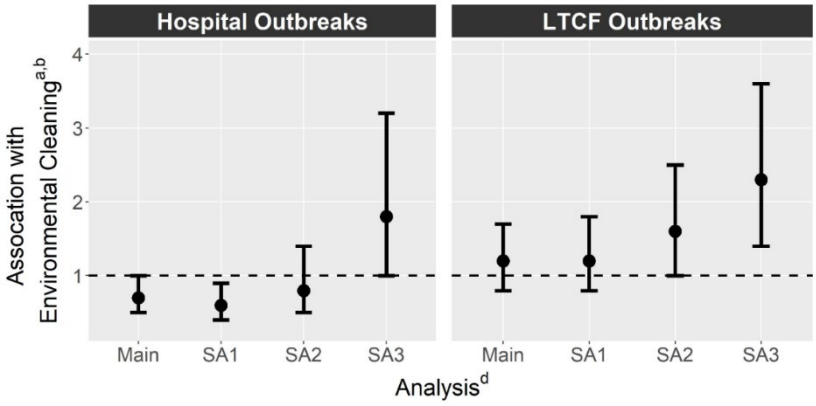
[b] Point estimates and 95% confidence intervals are shown. Horizontal dashed lines represent null values for associations.

[c] Overall attack rates and case counts include residents/patients and staff.

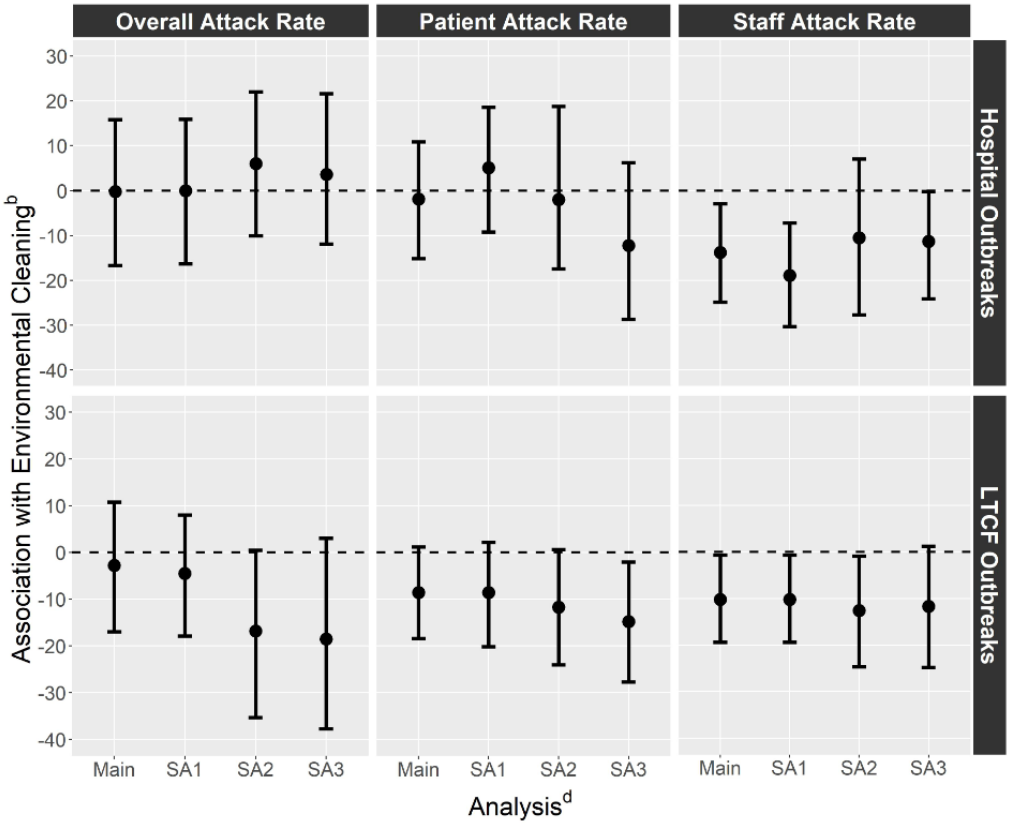
[d] Analyses include the main analysis with the full dataset, and sensitivity analyses restricting the data to the following datasets: SA1) outbreaks that reported 10 or more cases, SA2) outbreaks from the current review (i.e., excluding outbreaks from the previous review), and SA3) outbreaks from the current review from full papers in which the main purpose of the paper was to report the outbreak.

Supplementary Figure 4-6. Associations between implementation of enhanced environmental cleaning and the following measures of outbreak severity: A) outbreak duration, B) attack rates, and C) final case counts, by regression analysis.

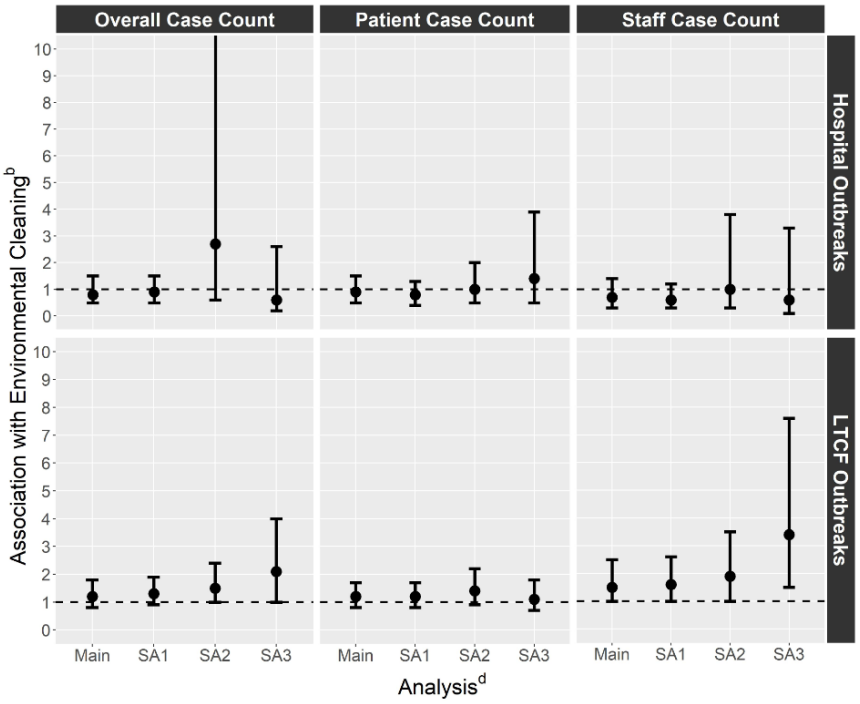
a) Linear associations between implementation of enhanced environmental cleaning and outbreak duration.



b) Linear associations between implementation of enhanced environmental cleaning and attack rates.



c) Linear associations between implementation of enhanced environmental cleaning and final case counts[e].



[a] All regression models included enhanced environmental cleaning and a random intercept for country of outbreak as independent variables. Estimates for Duration and Case Counts were exponentiated.

[b] Point estimates and 95% confidence intervals are shown. Horizontal dashed lines represent null values for associations.

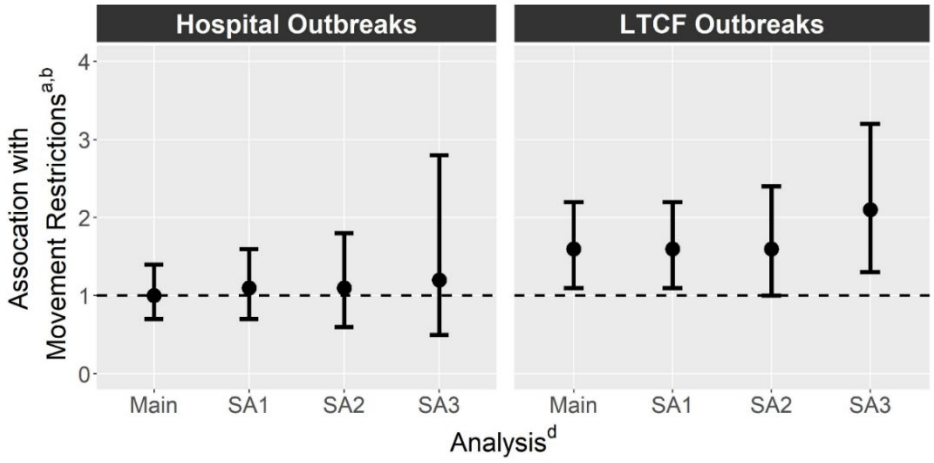
[c] Overall attack rates and case counts include residents/patients and staff.

[d] Analyses include the main analysis with the full dataset, and sensitivity analyses restricting the data to the following datasets: SA1) outbreaks that reported 10 or more cases, SA2) outbreaks from the current review (i.e., excluding outbreaks from the previous review), and SA3) outbreaks from the current review from full papers in which the main purpose of the paper was to report the outbreak.

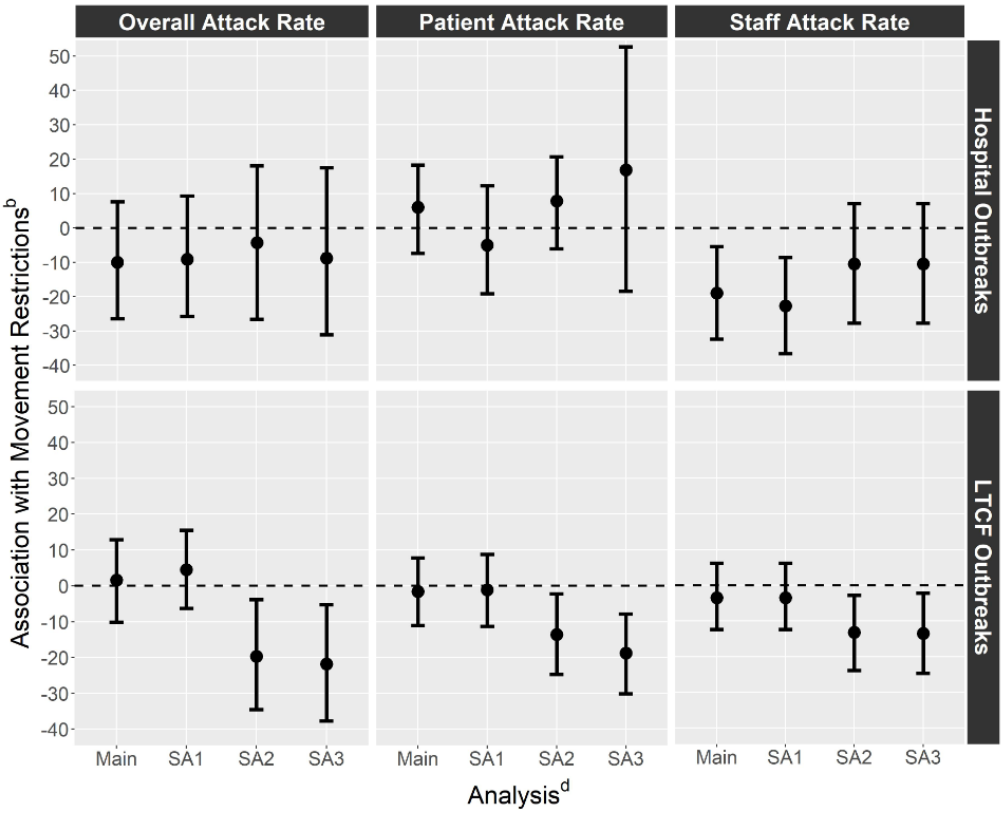
[e] Note that some upper confidence intervals are not shown in the figure so that trends in point estimates can be seen.

Supplementary Figure 4-7. Associations between implementation of staff and/or patient/resident movement restrictions and the following measures of outbreak severity: a) outbreak duration, b) attack rates, and c) final case counts, by regression analysis.

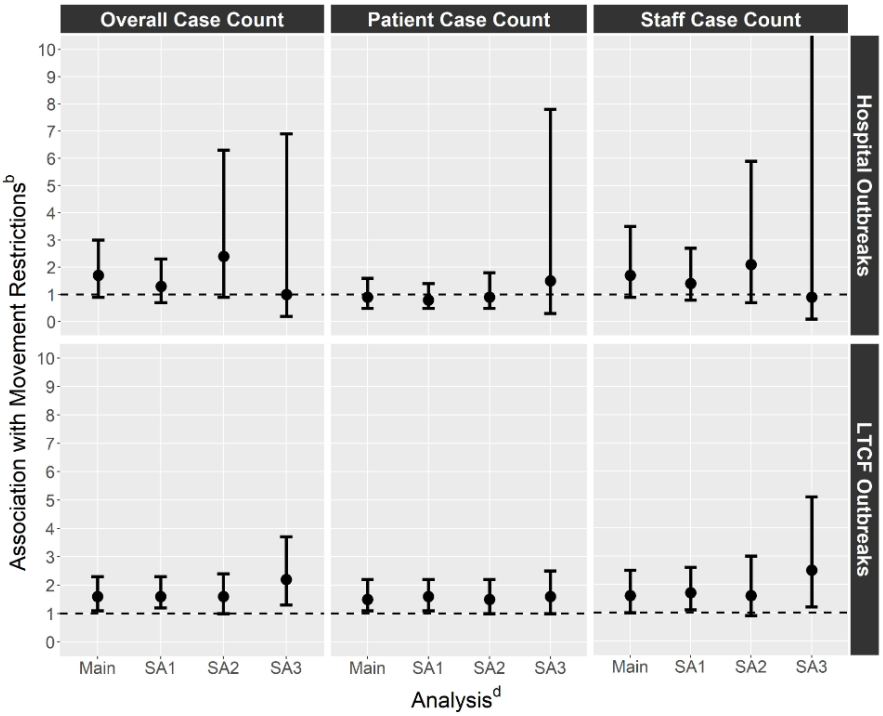
a) Linear associations between implementation of movement restrictions and outbreak duration.



b) Linear associations between implementation of movement restrictions and attack rates.



c) Negative binomial associations between implementation of movement restrictions and final case counts[e].



[a] All regression models included movement restrictions and a random intercept for country of outbreak as independent variables. Estimates for Duration and Case Counts were exponentiated.

[b] Point estimates and 95% confidence intervals are shown. Horizontal dashed lines represent null values for associations.

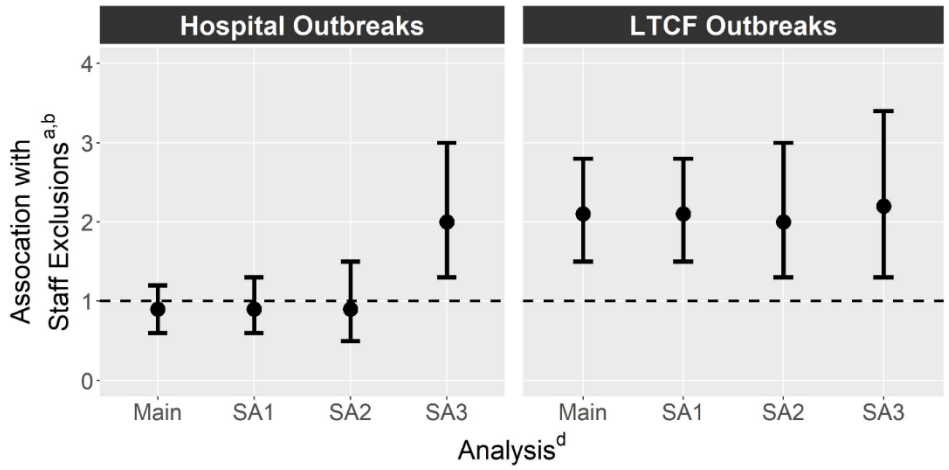
[c] Overall attack rates and case counts include residents/patients and staff.

[d] Analyses include the main analysis with the full dataset, and sensitivity analyses restricting the data to the following datasets: SA1) outbreaks that reported 10 or more cases, SA2) outbreaks from the current review (i.e., excluding outbreaks from the previous review), and SA3) outbreaks from the current review from full papers in which the main purpose of the paper was to report the outbreak.

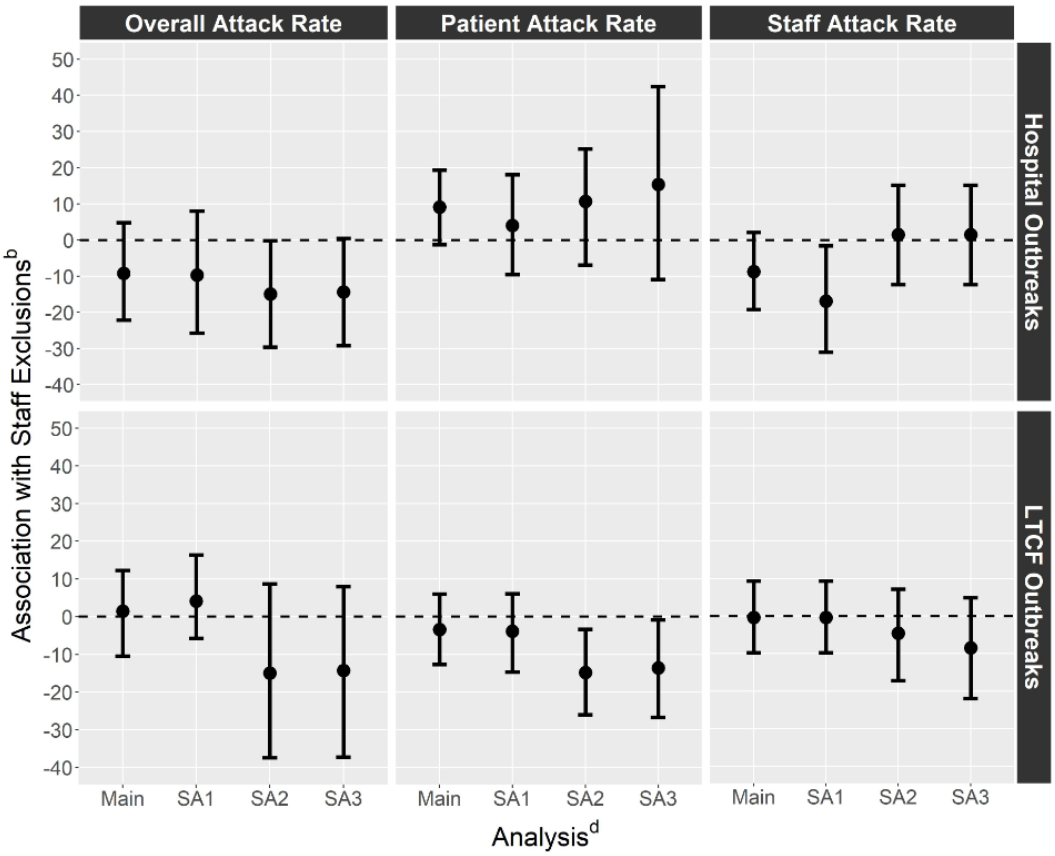
[e] Note that some upper confidence intervals are not shown in the figure so that trends in point estimates can be seen.

Supplementary Figure 4-8. Associations between implementation of ill staff exclusions and the following measures of outbreak severity: a) outbreak duration, b) attack rates, and c) final case counts, by regression analysis.

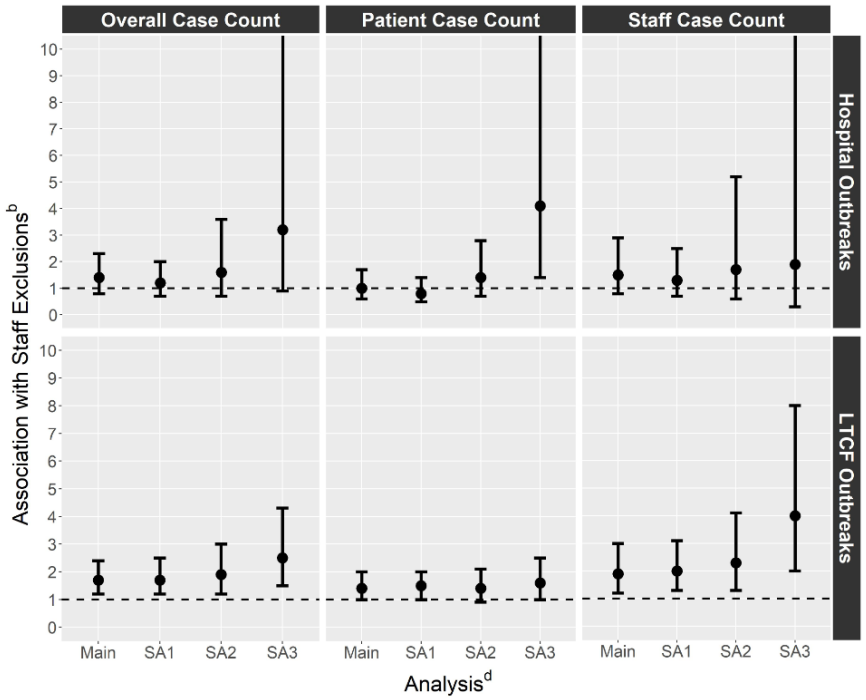
a) Linear associations between implementation of staff exclusions and outbreak duration.



b) Linear associations between implementation of staff exclusions and attack rates.



c) Negative binomial associations between implementation of staff exclusions and final case counts[e].



[a] All regression models included staff exclusions and a random intercept for country of outbreak as independent variables. Estimates for Duration and Case Counts were exponentiated.

[b] Point estimates and 95% confidence intervals are shown. Horizontal dashed lines represent null values for associations.

[c] Overall attack rates and case counts include residents/patients and staff.

[d] Analyses include the main analysis with the full dataset, and sensitivity analyses restricting the data to the following datasets: SA1) outbreaks that reported 10 or more cases, SA2) outbreaks from the current review (i.e., excluding outbreaks from the previous review), and SA3) outbreaks from the current review from full papers in which the main purpose of the paper was to report the outbreak.

[e] Note that some upper confidence intervals are not shown in the figure so that trends in point estimates can be seen.

Supplementary Table 4-1. PubMed search strategy for publication

#1	Norovirus*[tw] OR norwalk[tw]
#2	Hospital*[tw] OR Nursing home*[tw] OR Residential[tw] OR “Long term care” OR “assisted living” OR "Hospitals"[Mesh] OR "Residential Facilities"[Mesh] OR "Long-Term Care"[Mesh]
#3	Outbreak*[tw] OR Transmi*[tw] OR Epidemic*[tw]
#4	(#1 AND #2 AND #3)
#5	#4 AND English[lang)]
#6	#5 AND ("2008/08/01"[PDAT] : "2019/07/31"[PDAT])

Supplementary Table 4-2. Control measures reported to be implemented by report type

	No. outbreaks (%) with reported control measure		
Control measure	**Full paper outbreak reports (n = 64)**	**Non-full paper outbreak reports (n = 98)**	**All outbreaks (n = 162)**
Any control measures	52 (81)	66 (67)	118 (73)
Hand hygiene	49 (77)	59 (60)	108 (67)
Environmental cleaning	45 (70)	51 (52)	97 (60)
Movement restrictions	46 (72)	56 (57)	102 (63)
Staff exclusions	27 (42)	42 (43)	69 (43)

Supplementary Table 4-3. Outbreak outcome missingness by report type

	No. outbreaks (%) missing information		
Outbreak outcome	**Full paper outbreak reports (n = 64)**	**Non-full paper outbreak reports (n = 98)**	**Difference in percent missing (%)**
Duration	6 (9)	25 (26)	93
Overall attack rate	31 (48)	62 (63)	27
Patient/resident attack rate	6 (9)	35 (36)	117
Staff attack rate	25 (39)	54 (55)	34
Overall case count	11 (17)	27 (28)	46
Patient/resident case count	1 (2)	19 (19)	170
Staff case count	7 (11)	27 (28)	86

Supplementary Table 4-4. Percentages of cases with symptom by population

Symptom	Population	No. of Outbreaks with Information	Median % of cases with symptom (IQR)
Diarrhea	Patients/residents only	11	80 (75, 100)
	Staff only	6	76 (71, 88)
	Patients/residents & staff	17	78 (67, 86)
Vomiting	Patients/residents only	12	40 (32, 58)
	Staff only	5	57 (46, 68)
	Patients/residents & staff	14	54 (42, 66)

CHAPTER 5: AIM 2 – SARS-COV-2 TRANSMISSION IN LONG-TERM CARE FACILITIES

[Manuscript 2]

The role of staff in transmission of SARS-CoV-2 in long-term care facilities: analysis of COVID-19 cases and outbreaks in Fulton County, Georgia, March 2020 to September 2021

Carly Adams, Allison Chamberlain, Yuke Wang, Mallory Hazell, Sarita Shah, David P. Holland, Fazle Khan, Neel Gandhi, Scott Fridkin, Jon Zelner, Benjamin A. Lopman

5.1 Abstract

Background: U.S. long-term care facilities (LTCFs) have experienced a disproportionate burden of COVID-19 morbidity and mortality.

Methods: We examined SARS-CoV-2 transmission in 60 LTCFs in Fulton County, Georgia, from March 2020 to September 2021. Using the Wallinga-Teunis method to estimate the time-varying reproduction number, R(t), and linear mixed regression models, we examined associations between case characteristics and R(t).

Findings: Case counts, outbreak size/duration, and R(t) declined rapidly and remained low after vaccines were first distributed to LTCFs in December 2020, despite increases in community incidence in summer 2021. Staff cases were more infectious than resident cases (average individual reproduction number, R_i = 0.6 [95% CI: 0.4-0.7] and 0.1 [95% CI: 0.1-0.2], respectively). Unvaccinated resident cases were slightly more infectious than

vaccinated resident cases (R_i = 0.5 [95% CI: 0.4-0.6] and 0.1 [95% CI: 0.0-0.7], respectively), but estimates were imprecise.

Interpretation: COVID-19 vaccines slowed transmission and contributed to reduced caseload in LTCFs. However, due to data limitations, we were unable to determine whether breakthrough vaccinated cases were less infectious than unvaccinated cases. Staff cases were six times more infectious than resident cases, suggesting that staff were the primary drivers of SARS-CoV-2 transmission in LTCFs.

5.2 Background

Nursing homes and other long-term care facilities (LTCFs) in the U.S. have been disproportionately affected by COVID-19. Due to the congregate nature of LTCFs, close and frequent contact between residents and staff, and the vulnerable population served (generally older adults with underlying medical conditions), SARS-CoV-2, the virus that causes COVID-19, can spread rapidly in LTCFs, resulting in high morbidity and mortality.[63,223] In response to the pandemic threat, the Centers for Medicare and Medicaid Services (CMS) required nursing homes to restrict visitation and resident movements starting in March 2020.[58] Still, nursing home staff still had to enter and leave and new residents were being admitted, remaining potential sources of SARS-CoV-2 introduction. As the pandemic progressed, additional infection prevention and control (IPC) measures were introduced into LTCFs, including routine testing of staff in August 2020,[224] and COVID-19 vaccines in December 2020.[65] As of September 2021, COVID-19 outbreaks had been reported in nearly all 15,600 nursing homes in the U.S., resulting in more than 1.3 million confirmed cases and nearly 140,000 confirmed deaths among residents and staff.[52,53] By

March 2021, it was estimated that nearly 1 in 12 U.S. LTCF residents had died from COVID-19.[56]

Reflecting these national trends, LTCF residents in Fulton County, Georgia, the most populous county in the state which contains Atlanta and the surrounding metro area, were disproportionately affected by COVID-19, especially early in the pandemic. Despite accounting for <1% of the population, nearly 20% of cases and >50% of COVID-19 deaths in Fulton County occurred among LTCF residents between March and June 2020.[225]

Interventions in LTCFs (e.g., masking and case isolation) aim to interrupt virus transmission. However, transmission is rarely observed directly and the transmission process of SARS-CoV-2 remains incompletely understood, especially in these LTCF settings. Therefore, a better quantitative understanding of transmission is critical. The reproduction number (R) and how it varies over time (R(t)) quantifies transmission and can be inferred from case counts and knowledge of a pathogen's natural history.[70] In this study, we used data on the timing and magnitude of COVID-19 outbreaks in Fulton County LTCFs to examine temporal trends in SARS-CoV-2 transmissibility. Then, we aimed to identify characteristics of cases (resident or staff, vaccination status, and disease severity) associated with greater infectiousness.

5.3 Methods

5.3.1 Data

With the goal of inferring transmission patterns over time, we used surveillance data on cases of COVID-19 curated by the state and county health departments. First, we used this dataset to infer how transmission varied over time, quantified as the time-varying

reproduction number, R(t). Then, we linked these data with case characteristics, including vaccination status, to examine whether certain groups played a larger role in transmission. In collaboration with Fulton County Board of Health (FCBOH) epidemiology staff, we developed an analysis plan for a dataset derived from the Georgia Department of Public Health's (GDPH) statewide COVID-19 data from the State Electronic Notifiable Disease Surveillance System (SendSS) (i.e., the surveillance dataset). Deidentified, individual-level data were downloaded on September 12, 2021 and restricted to confirmed and probable cases reported from March 2, 2020 to September 12, 2021 (Supplementary Figure 5-1). Cases with positive results from reverse-transcription polymerase chain reaction (RT-PCR) tests were classified as confirmed and cases lacking RT-PCR results but meeting other testing, clinical, epidemiologic, and/or vital records criteria (e.g., a positive antigen test with clinical/epidemiologic evidence) were classified as probable.[226] Because cases outside of Fulton County could not be consistently linked to individual LTCFs, we focused our analysis on Fulton County. Data were restricted to cases associated with Fulton County LTCFs, including skilled nursing (also known as nursing homes) and assisted living facilities, using unique facility identifiers provided by the Fulton County Board of Health (FCBOH). To determine COVID-19 vaccination status of cases, we used data from the GDPH COVID-19 Vaccine Breakthrough Dashboard Dataset (i.e., the vaccine dataset), which were provided by the FCBOH.

Cases hospitalized at any time during their illness were categorized as hospitalized. COVID-19 deaths were defined as confirmed cases that were reported as deceased, had COVID-19 indicated as the cause of death on death certificates, or had evidence that COVID-19 contributed to death.[226] If cases were missing information on COVID-19 death, we assumed they did not die from COVID-19 (Supplementary Table 5-1). When examining

COVID-19 hospitalizations and deaths, data were restricted to cases with symptom onset dates prior to August 1, 2021 to account for lags in hospitalization and death.

Missing symptom onset dates were imputed based on first positive specimen collection date, when available, or case report date (Supplementary Figure 5-4).[227] The number of days between symptom onset and first positive specimen collection or case report date were modeled using negative binomial regression with the first positive specimen collection or case report date as the predictor (Supplementary Figures 5-5 – 5-6). For asymptomatic cases (n=677), imputed symptom onset dates, which were needed to calculate R(t), can be interpreted as the time that they developed weak/negligible symptoms.

5.3.2 Cases and outbreak characteristics

The following variables were considered in our study: LTCF role (resident or staff), vaccination status, hospitalization, and COVID-19 death. LTCF role was determined using a number of variables, including whether “Staff” was entered into free-text fields and age of cases (Supplementary Figure 5-2). We also conducted a sensitivity analysis in which we assumed all cases missing “Staff” in free text fields were residents, as FCBOH members were instructed to enter “Staff” for all staff cases, and to leave these fields blank for resident cases.

Using the surveillance and vaccine datasets, we categorized cases as vaccinated if they had received at least one vaccine dose ≥14 days prior to their first positive specimen collection date (Supplementary Figure 5-3). Information on full or partial vaccination, vaccine manufacturer, and date of most recent dose was available for cases in the vaccine dataset. For fully vaccinated cases, we inferred the date of their first dose based on recommended vaccine dosing intervals.[228] If cases were not in the vaccine dataset, but

were listed as vaccinated in the surveillance dataset (n=33, 83%), we categorized them as vaccinated. For these cases, we could not determine the number of doses received. Therefore, for all analyses, we classified both partially and fully vaccinated cases as 'vaccinated', and could not examine partial and full vaccination status separately.

For the purposes of this analysis, COVID-19 outbreaks were defined as ≥2 reported case(s) of COVID-19 among residents and/or staff in a LTCF. If no new cases were reported for >14 days, the outbreak was considered to have ended and subsequent cases were considered part of a new outbreak. Singleton cases were defined as those with dates of onset 14 days before or after other cases in a facility. To fully investigate transmission, it is critical to include singleton and other non-transmitting cases, so these are included in all such analyses. Singleton cases and outbreaks are referred to collectively as "events". The terms "cases" (singleton or outbreak-associated) and "outbreaks" have precise meanings and are used accordingly throughout the paper.

5.3.3 Time periods examined

To examine trends in cases, outbreaks, and transmissibility, we divided the data into three periods corresponding to different waves of COVID-19: March 11 - September 26, 2020 (wave 1), September 27, 2020 - March 21, 2021 (wave 2), and March 22 - September 12, 2021 (wave 3). Waves were determined by visually examining Fulton County LTCF case counts by report date. We also considered the following dates: May 31, 2020 (shortly after states began lifting community pandemic restrictions and CMS released reopening guidelines for U.S. nursing homes),[59,229] August 31, 2020 (shortly after CMS began requiring routine COVID-19 testing of nursing home staff),[224] and December 31, 2020 (shortly after the first COVID-19 vaccines were distributed to U.S. nursing homes).[65]

5.3.4 SARS-CoV-2 transmissibility

We quantified SARS-CoV-2 transmissibility by the time-varying reproduction number, R(t), which is the expected number of cases directly caused by a single infectious individual with symptom onset at time *t*. We estimated R(t) using the Wallinga-Teunis method,[70] which has also been used to examine SARS-CoV-2 transmissibility in the Georgia community.[227] The Wallinga-Teunis method estimates probabilities of transmission between any pair of cases in an outbreak using symptom onset dates and the distribution of the serial interval, defined as the time interval between symptom onset in a primary (infector) and secondary case (infectee). These probabilities are used to construct epidemic trees, from which R(t) can be estimated. We simulated 1,000 epidemic trees for each outbreak, creating a total of 1,000 datasets. Each dataset contained R(t) estimates for all outbreaks from a single simulation. Outbreaks were defined based on symptom onset dates and were considered over if no new cases developed symptoms within 14 days of the last symptom onset date. Outbreaks were assumed to be independent and completely enumerated, such that cases from different outbreaks could not infect one another and all individuals involved in transmission were captured. Singleton cases were automatically assigned a R(t) of 0. All cases in our dataset had symptom onset >14 days prior to data download, so right censoring could be ignored.[230]

A key input for the Wallinga-Teunis method is the serial interval. The serial interval is the time between equivalent stages in the infection process (e.g., symptom onset) in successive pairs of cases, so is required to infer the likelihood that one person acquired infection from another. To estimate the serial interval, we examined known transmission pairs, identified by case interviews and contact tracing, of LTCF resident and staff cases in Georgia (Supplementary Figure 5-7). These transmission pairs were used for serial interval

calculations only. Transmission pairs with serial intervals <1 or >50 days were excluded. We identified a total of 184 known transmission pairs, from which the serial interval was estimated to follow a Gamma(1.4, 5.9) distribution using a maximum likelihood method.[227] We also examined whether the serial interval distribution changed over time, and found no meaningful differences between time periods (Supplementary Table 5-2, Supplementary Figure 5-8).

To examine temporal trends in R(t) among Fulton County LTCF cases, we plotted daily R(t) estimates with a locally estimated scatterplot smoothing (LOESS) trendline. Because R(t) naturally declines as outbreaks progress and individuals acquire immunity, only R(t) estimates for the first 5 outbreak days (defined as symptom onset days for an individual outbreak excluding days with no cases) were examined.

Next, to identify if there are characteristics associated with heightened infectiousness, we modeled the relationship between R(t), as determined from the above approach, and various case variables. To examine associations between characteristics and R(t), we used linear mixed regression models. Model covariates were determined a priori using a directional acyclic graph (Supplementary Figure 5-9). The unit of analysis for regression models was symptom onset day, rather than individuals. To incorporate the uncertainty of R(t) estimates into regression results, we used R(t) estimates from all 1,000 simulations and combined regression results using Rubin's Rules.[231,232] We fitted four separate models based on the following form:

$$R(t,j) = \left(\beta_1 + b_{1j}\right)(y_t - n_t) + \left(\beta_2 + b_{2j}\right)n_t$$

where *R(t,j)* is the time-varying reproduction number for cases with symptom onset on day *t* in the j^{th} facility, y_t is the number of cases with symptom onset on day *t*, n_t is the number of

cases with symptom onset on day *t* who were residents, and $y_t - n_t$ is the number of cases with symptom onset on day *t* who were staff. In the subsequent three models, n_t represents vaccinated, not hospitalized, and survived from COVID-19. The intercept was constrained to equal zero so that R(t) equaled zero for days with no cases. Random slopes were included to account for correlation in R(t) within facilities and to allow associations between R(t) and case characteristics to vary by facility. For LTCF role, the model can be interpreted as follows: the expected value of R(t) increased by β_1 for every staff case and by β_2 for every resident case. Because the intercept was constrained to equal zero, we can interpret β_1 and β_2 as the average individual reproduction number, R_i, (i.e., the number of secondary cases, irrespective of case characteristics, infected by a single case) for staff and resident cases, respectively.

We determined a priori that vaccination status may confound the association between LTCF role and R(t). Because the unit of analysis for regression models was symptom onset day, and multiple cases in an outbreak could have the same symptom onset day, we could not directly adjust for individual vaccination status. Therefore, we considered only unvaccinated cases by restricting the data in the model to symptom onset dates prior to vaccine administration. Similarly, when examining the association between vaccination status and R(t), we considered only resident cases by restricting the data to days on which only residents (and not staff) had symptom onset. Lastly, when examining associations between measures of disease severity (hospitalization and death) and R(t), we considered only resident cases, unvaccinated cases, and changes in time by restricting the data to days prior to vaccine administration and days on which only residents had symptom onset (overall, prior to vaccine administration, and during the first and second pandemic waves).

All statistical analyses were performed using *R* v.4.1.1. R(t) was calculated using the *EpiEstim* package v.2.2-4. This activity was determined by the Georgia Department of Public Health Institutional Review Board to be non-research and consistent with public health surveillance as per title 45 code of Federal Regulations 46.102(l)(2).

5.4 Results

5.4.1 Case and outbreak characteristics

A total of 2,849 LTCF cases were included in the analysis, of which 2,093 (73%) were residents and 756 (27%) were staff (Table 5-1). Compared to staff cases, resident cases were older and more likely to have been hospitalized or died from COVID-19, and a lower proportion were Black or female. Of the 299 cases with symptom onset after December 31, 2020, 13 (4%) were vaccinated, of which 9 were residents (5% of resident cases) and 4 were staff (4% of staff cases).

Table 5-1. Characteristics of Fulton County, Georgia long-term care facility COVID-19 cases[a] reported March 11, 2020 to September 12, 2021 by LTCF role (resident or staff)

Characteristic	Resident cases (n = 2,093)	Staff cases (n = 756)	All cases (n = 2,849)
Age; years (median (IQR))	77 (67, 86)	47 (36, 56)	70 (55, 83)
Race/ethnicity (N (%))[b,c]			
Black	1,187 (59)	579 (80)	1,766 (65)
White	737 (37)	91 (13)	828 (30)
Other	79 (4)	50 (7)	129 (5)
Female (N (%))[b]	1,228 (59)	648 (86)	1,876 (66)
Hospitalized (N (%))[b]	623 (40)	39 (6)	662 (30)
COVID-19 death (N (%))[b]	489 (24)	5 (1)	494 (18)

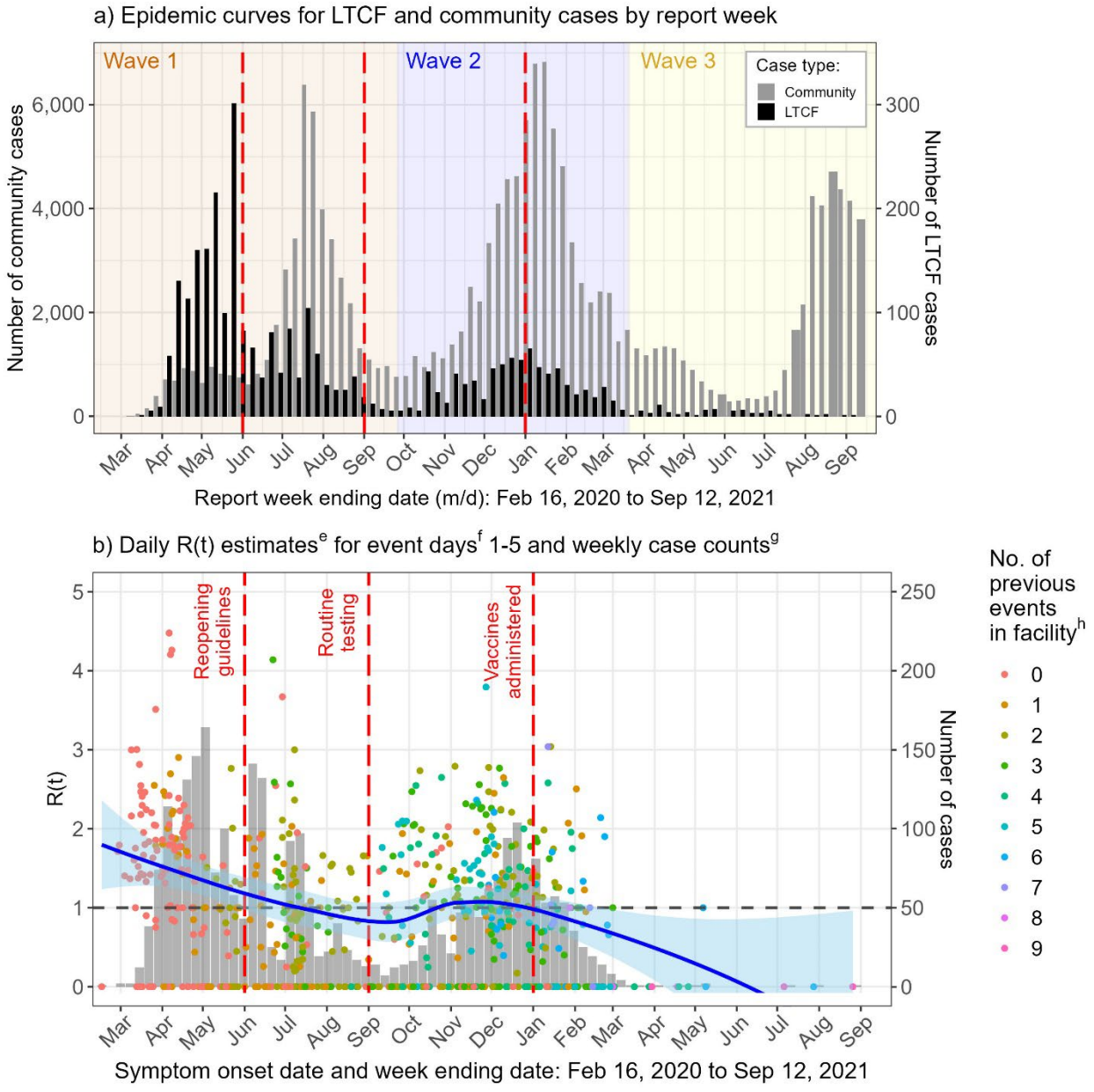
[a] Confirmed and probable cases were included in the analysis.

[b] Percentages were calculated by excluding cases with missing information.

[c] Race/ethnicity was categorized as non-Hispanic Black, non-Hispanic White, or Other; Other race/ethnicity included Hispanic (any race), Asian, and individuals who reported their race as “other”.

The first LTCF pandemic wave was the largest with 2,010 cases, followed by the second wave with 763 cases and the third wave with 76 cases (Figure 5-1a, Table 5-2). Despite increases in community cases in the third wave (as a result of the Delta variant),[48] LTCF incidence declined rapidly and remained low after December 2020, with averages of 8.4 cases reported/day in 2020 and 1.5 cases reported/day in 2021. Over the study period, the percentage of cases, hospitalizations, and deaths in Fulton County that occurred in LTCFs declined (Supplementary Figure 5-10). Overall, 1.7% of cases (n=2,849), 7.2% of hospitalizations (n=661), and 19.3% of deaths (n=492) in Fulton County occurred in LTCFs.

Figure 5-1. Epidemic curves for Fulton County, Georgia community[a] and long-term care facility (LTCF) COVID-19 cases[b] with pandemic waves[c] shown by shaded regions (a) and trends in the COVID-19 time-varying reproduction number, R(t), in Fulton County, Georgia LTCFs (b) with dates examined[d] shown by dashed vertical lines



[a] Cases that were not residents or staff in LTCFs were considered community cases.

[b] Confirmed and probable cases were included in the analysis.

[c] Waves were determined by weekly Fulton County LTCF case counts based on report dates. The first wave includes cases reported prior to September 27, 2020, the second wave includes cases reported September 27, 2020 to March 21, 2021, and the third wave includes cases reported March 22, 2021 to September 12, 2021. Note that symptom onset dates occurred earlier than report dates.

[d] Dates examined include: May 31, 2020 (shortly after states began lifting pandemic restrictions in the community and the Centers for Medicare and Medicaid [CMS] released reopening guidelines for U.S. nursing homes), August 31, 2020 (shortly after CMS began requiring routine COVID-19 testing of nursing home staff), and December 31, 2020 (shortly after the first COVID-19 vaccines were administered to LTCF residents and staff).

[e] R(t) for symptom onset days (rather than individuals) are shown. A dashed horizontal line at R(t) = 1 signifies the extinction threshold below which each case, on average, infects less than one other case. A locally estimated scatterplot smoothing (LOESS) trendline with 95% confidence intervals is shown in blue.

[f] Event day refers to the day of an individual event on which cases had symptom onset, excluding days on which no cases had symptom onset. For example, if an event consisted of cases with symptom onsets on May 1, May 5, and May 7, 2020, the corresponding event days would be 1, 2, and 3, respectively.

[g] Case counts (for all event days) by symptom onset week are shown by gray bars.

[h] Refers to the number of prior events in a facility. For example, a daily R(t) estimate shown in pink (for 0 previous events) is an R(t) estimate from the first event that occurred in a facility.

Table 5-2. Characteristics of Fulton County, Georgia long-term care facility COVID-19 cases and outbreaks[a] reported March 11, 2020 to September 12, 2021 by pandemic wave[b,c]

Measure		Wave 1	Wave 2	Wave 3	Total study period
Facilities reporting cases (N)		56	49	20	60
Total cases (N)		2,010	763	76	2,849
Singleton cases (N)		54	49	28	131
Total outbreaks (N)		74	61	13	148
Events[d] per facility	(med [IQR])	2 (1, 3)	2 (1, 3)	2 (1, 3)	4.5 (3, 6.3)
	(mean [min, max])	2.3 (1, 5)	2.2 (1, 6)	2 (1, 5)	4.7 (1, 11)
Event[d] size[e]	(med [IQR])	2.5 (1, 15)	2 (1, 5)	1 (1, 2)	2 (1, 7)
	(mean [min, max])	15.7 (1, 190)	7 (1, 76)	1.8 (1, 9)	10.2 (1, 190)
Event[d] length[f]	(med [IQR])	65 (34, 75)	36 (19, 49)	1 (1, 12)	51 (23, 75)
	(mean [min, max])	56.9 (1, 122)	38 (1, 93)	9.6 (1, 42)	50.6 (1, 122)

Abbreviations: med, median; IQR, interquartile range; min, minimum; max, maximum

[a] COVID-19 outbreaks were defined as 2 or more cases reported in the same facility. If no new cases were reported in more than 14 days, the outbreak was considered over and any cases reported after 14 days were considered part of a separate outbreak.

[b] Wave 1 included cases reported prior to September 27, 2020; wave 2 included cases reported September 27, 2020 to March 21, 2021; wave 3 included cases reported March 22, 2021 to September 12, 2021.

[c] Two outbreaks involved cases with report dates in both waves 2 and 3. These outbreaks were categorized into waves based on the first outbreak report date.

[d] Events include both singleton cases and outbreaks with two or more cases.

[e] Event size is the number of cases in an event.

[f] Event length is the time, in days, between the first and last case report date for an event.

A total of 279 COVID-19 events (including singleton cases and outbreaks) from 60 LTCFs were reported over the study period (Table 5-2). While the average number of events reported per facility remained about the same, the average event size decreased from 15.7 cases in the first wave to 7.0 and 1.8 cases in the second and third waves, respectively. The average event length decreased from 56.9 days in the first wave to 38.0 and 9.6 days in the second and third waves, respectively. Furthermore, the proportion of singleton cases increased from 42% in the first wave to 45% and 68% in the second and third waves, respectively. After December 2020, ≥50% of events consisted of singleton cases (Supplementary Figure 5-11).

5.4.2 Time-varying reproduction number and R(t)

In order to examine transmission patterns unaffected by depletion of susceptibles from the current event, we estimated R(t) in the initial days of each. R(t) estimates for event days 1-5 declined from March to September 2020, increased slightly from the end of September to the end of November 2020, and then declined from December 2020 to September 2021 (Figure 5-1b). After January 2021, R(t) remained below 1, eventually declining to 0 by June 2021.

5.4.3 Associations between case characteristics and R(t)

Next, using regression models, we examined heterogeneity in infectiousness as a function of case characteristics. Staff cases were estimated to be more infectious than resident cases (average R_i = 0.6 [95% CI: 0.4, 0.7] and 0.1 [95% CI: 0.1, 0.2], respectively); these associations were unchanged after accounting for vaccination (Table 5-3). Results were similar in a sensitivity analysis in which we assumed all cases missing “Staff” from free text fields were residents (Supplementary Table 5-3). Among residents in the first pandemic

wave, hospitalized cases were estimated to be more infectious than non-hospitalized cases (average R_i = 0.6 [95% CI: 0.4, 0.9] and 0.1 [95% CI: 0.0, 0.3], respectively) and cases who died from COVID-19 were estimated to be more infectious than case who survived (average R_i = 0.8 [95% CI: 0.5, 1.2] and 0.2 [95% CI: 0.0, 0.4], respectively). However, during the second pandemic wave, hospitalized and non-hospitalized resident cases were equally infectious, as were resident cases who died and survived from COVID-19. Vaccinated resident cases were less infectious than unvaccinated resident cases (average R_i = 0.1 [95% CI: 0.0, 0.7] and 0.5 [95% CI: 0.4, 0.6], respectively), however confidence intervals largely overlapped.

Table 5-3. Associations[a] between the COVID-19 time-varying reproduction number, R(t), and case characteristics in Fulton County, Georgia long-term care facilities for cases reported March 11, 2020 to September 12, 2021[b]

		Days included[c]					
Characteristic		**All** R_i **(95% CI)**	**Residents only** R_i **(95% CI)**	**Pre-vaccination** R_i **(95% CI)**	**Pre-vaccination, Residents only** R_i **(95% CI)**	**Wave 1, Residents only** R_i **(95% CI)**	**Wave 2, Residents only** R_i **(95% CI)**
Vaccinated	Yes	0.2 (0.0, 0.8)	0.1 (0.0, 0.7)	–	–	–	–
	No	0.4 (0.3, 0.5)	0.5 (0.4, 0.6)	–	–	–	–
LTCF role	Staff	0.6 (0.4, 0.7)	–	0.6 (0.5, 0.7)	–	–	–
	Resident	0.1 (0.1, 0.2)	–	0.1 (0.0, 0.1)	–	–	–
Hospitalized	Yes	0.4 (0.2, 0.5)	0.6 (0.4, 0.8)	0.4 (0.2, 0.5)	0.6 (0.4, 0.8)	0.6 (0.4, 0.9)	0.6 (0.4, 0.8)
	No	0.4 (0.3, 0.5)	0.4 (0.3, 0.6)	0.4 (0.3, 0.5)	0.4 (0.3, 0.5)	0.1 (0.0, 0.3)	0.6 (0.4, 0.8)
COVID-19 death	Yes	0.3 (0.2, 0.5)	0.8 (0.6, 1.1)	0.4 (0.2, 0.6)	1.0 (0.7, 1.2)	0.8 (0.5, 1.2)	0.6 (0.4, 0.9)
	No	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	0.4 (0.3, 0.5)	0.2 (0.0, 0.4)	0.6 (0.4, 0.7)

Abbreviations: R_i, individual reproduction number; CI, confidence interval; LTCF, long-term care facility

[a] Associations between case characteristics and R(t) were examined using linear mixed regression models. Regression coefficients can be interpreted as the average individual reproduction number, R_i, (i.e., the number of secondary cases infected by a single case) for cases with different characteristics.

[b] Associations between hospitalizations and deaths and R(t) were restricted to symptom onset dates prior to August 1, 2021 (6 weeks prior to data download) to account for lags in hospitalization and death. Associations between vaccination and R(t) were restricted to symptom onset dates after December 31, 2020, the approximate date when COVID-19 vaccines were first distributed to U.S. nursing homes.

[c] The analysis was stratified by the following symptom onset days: 1) all days during the study period, 2) days on which only resident cases had symptom onset, 3) days prior to vaccine distribution (January 1, 2021), 4) days prior to vaccine distribution on which only resident cases had symptom onset, 5) days in the first pandemic wave (prior to September 27, 2020) on which only resident cases had symptom onset, and 6) days in the second pandemic wave (September 27, 2020 to March 21, 2021) on which only resident cases had symptom onset.

5.5 Discussion

We examined SARS-CoV-2 transmission dynamics in Fulton County LTCFs, leading to several important findings. First, case counts, event (singleton cases and outbreaks) size and duration, and SARS-CoV-2 transmissibility rapidly declined and remained low after December 2020, when COVID-19 vaccines were first distributed to U.S. LTCF residents and staff, despite increases in community incidence in summer 2021. Second, within LTCFs, staff cases were about six times more infectious than resident cases. Third, resident cases with severe outcomes, including hospitalization and COVID-19 death, were more infectious than resident cases without severe outcomes, but only during the first pandemic wave (prior to October 2020). Finally, breakthrough vaccinated resident cases appeared to be slightly less infectious than unvaccinated resident cases, however results were inconclusive due to small sample sizes. While results regarding the relative infectiousness of vaccinated cases were inconclusive, as, fortunately, there were very few breakthrough vaccinated cases, the declines in case counts, event size/duration, and SARS-CoV-2 transmissibility after vaccines were introduced suggests that vaccines were effective in reducing transmission in LTCFs.

Other studies have similarly found that the burden of COVID-19 in U.S. LTCFs declined over time,[233] and that vaccines accelerated declines.[234] Decreases in SARS-CoV-2 transmission in Fulton County LTCFs can likely be attributed to improved IPC measures, such as improved access to personal protective equipment (PPE), increased testing, and COVID-19 vaccines. Indeed, while there were extreme shortages of PPE in LTCFs as late as August 2020,[235] these shortages improved after summer 2020.[236] Testing capacity in LTCFs also improved,[236] and a previous study found that routine testing of asymptomatic staff in Fulton County LTCFs led to reduced SARS-CoV-2 transmission.[64] Lastly, nearly

80% of U.S. nursing home residents were vaccinated by February 2021,[236] which likely contributed to the rapid declines in SARS-CoV-2 transmission after December 2020.

While LTCF transmission trends may also be explained by trends in community transmission, case counts in LTCFs remained low after December 2020, despite the surge in community cases in summer 2021. Therefore, factors other than community transmission likely contributed to declines in LTCF transmission. Moreover, while event size and duration decreased over time, the number of events reported per facility remained the same and the proportion of events consisting of singleton cases increased. This suggests that the number of introductions from the community remained about the same, and that declines in transmission were likely due to improved IPC measures, including resident vaccination. Finally, LTCF transmission trends may also be attributed to decreases in population susceptibility from prior infection. However, staff turnover rates in nursing homes are high, with an average annual turnover rate of 128%,[237] and while staff could also have acquired immunity from community infections, infection rates in the community were much lower than those in LTCFs.[238] Furthermore, new LTCF residents were still being admitted even early in the pandemic,[239] so it is unlikely that a decrease in susceptibility from prior infection alone explains trends in transmission.

Our study is the first, to our knowledge, to quantify the difference in infectiousness between LTCF residents and staff. We found that staff were substantially more infectious than residents, which is likely because staff typically care for multiple residents and also interact with other staff, whereas residents were largely confined to their rooms.[58] This has important implications for IPC practices in LTCFs, as it provides evidence that staff are the primary drivers of SARS-CoV-2 transmission in this setting. Therefore, interventions targeted at LTCF staff, such as ensuring staff have access to PPE and PPE training, routine

testing of unvaccinated, asymptomatic staff,[240] and vaccination campaigns targeted at staff, could greatly reduce transmission in LTCFs. Because vaccination acceptance among LTCF staff remains low, with more than a quarter of U.S. nursing home staff still not fully vaccinated as of October 31, 2021,[241] improving vaccination rates among staff should remain a top priority.

Our finding that resident cases with more severe disease were more infectious than those with less severe disease may be explained by higher viral loads and/or more prolonged and intensive care requirements (prior to hospitalization or death) for more severe cases.[242] While these cases may also have been more easily identified and placed on transmission-based precautions (TBP), PPE shortages early in the pandemic,[235] along with overwhelming numbers of COVID-19 cases, may have made TBP difficult to follow, so these cases remained more infectious. During the second pandemic wave, resident cases with more severe disease were as infectious as those with less severe disease, suggesting that IPC practices may have improved.

We note a number of limitations in our study. First, LTCF role had to be inferred based on age and other variables, potentially resulting in misclassification. However, results were similar in a sensitivity analysis in which we assumed all cases missing “Staff” in free text fields were residents. Second, due to insufficient data, we were unable to examine the relative infectiousness of staff with different job roles (e.g., patient-care staff compared to administrative staff). Third, we could not examine exact dates for policy changes in individual facilities, as these dates were facility-specific. Fourth, we assumed that all cases involved in outbreaks were captured, but some cases, especially asymptomatic infections, were likely unreported. However, routine testing of staff most likely led to increased detection of asymptomatic infections. Fifth, missing vaccination dates may have resulted in

the misclassification of vaccination status. This, combined with small case counts, led to inconclusive results for vaccination status. Moreover, we were unable to examine the relative infectiousness of fully vaccinated (vs. partially/not vaccinated) cases. Sixth, serial interval calculations excluded serial intervals <1 day, which may have resulted in an overestimate of the serial interval. Lastly, this study focused on LTCFs in Fulton County, Georgia, and therefore findings may not be generalizable to all U.S. LTCFs.

5.6 Conclusions

Improved IPC measures, and COVID-19 vaccines in particular, contributed to declines in COVID-19 case counts, event size and duration, and SARS-CoV-2 transmissibility in Fulton County, Georgia LTCFs. While we were unable to determine the relative infectiousness of vaccinated vs. unvaccinated cases, the rapid declines in transmission after vaccines were introduced suggests that vaccines were effective in reducing SARS-CoV-2 transmission. Staff were estimated to be about six times more infectious than residents, suggesting that staff are the main drivers of SARS-CoV-2 transmission in LTCFs. Findings lend support for additional IPC policies that target LTCF staff.

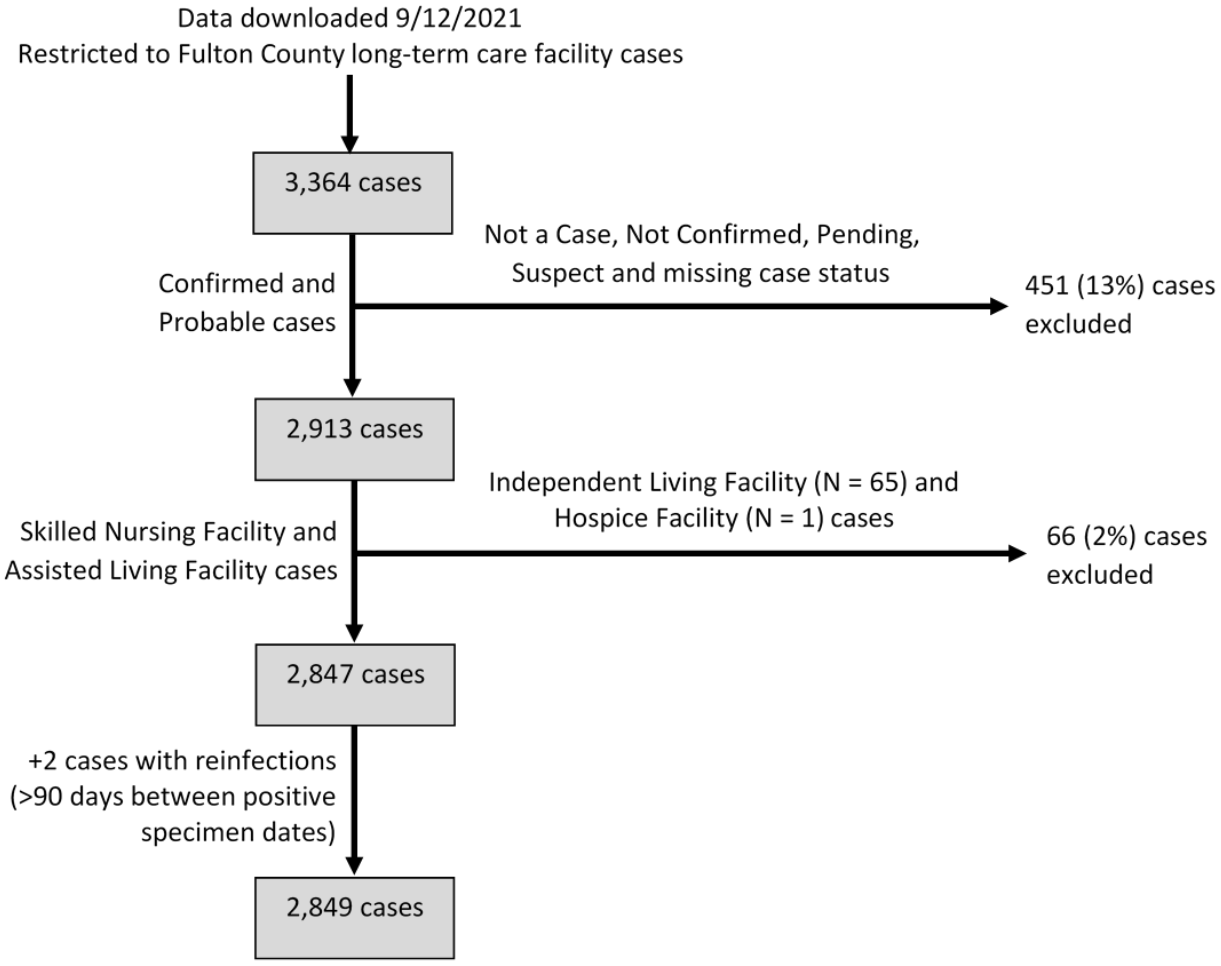
5.7 Acknowledgements

This work was supported by the Agency for Healthcare Research and Quality (R01 HS025987), the National Science Foundation (2032084), and the Emory Covid-19 Response Collaborative, which is funded by a grant from the Robert W. Woodruff Foundation. JZ was supported by award 1 U01 IP001138-01 from the Centers for Disease Control and Prevention. We thank the Georgia Department of Public Health and the Fulton

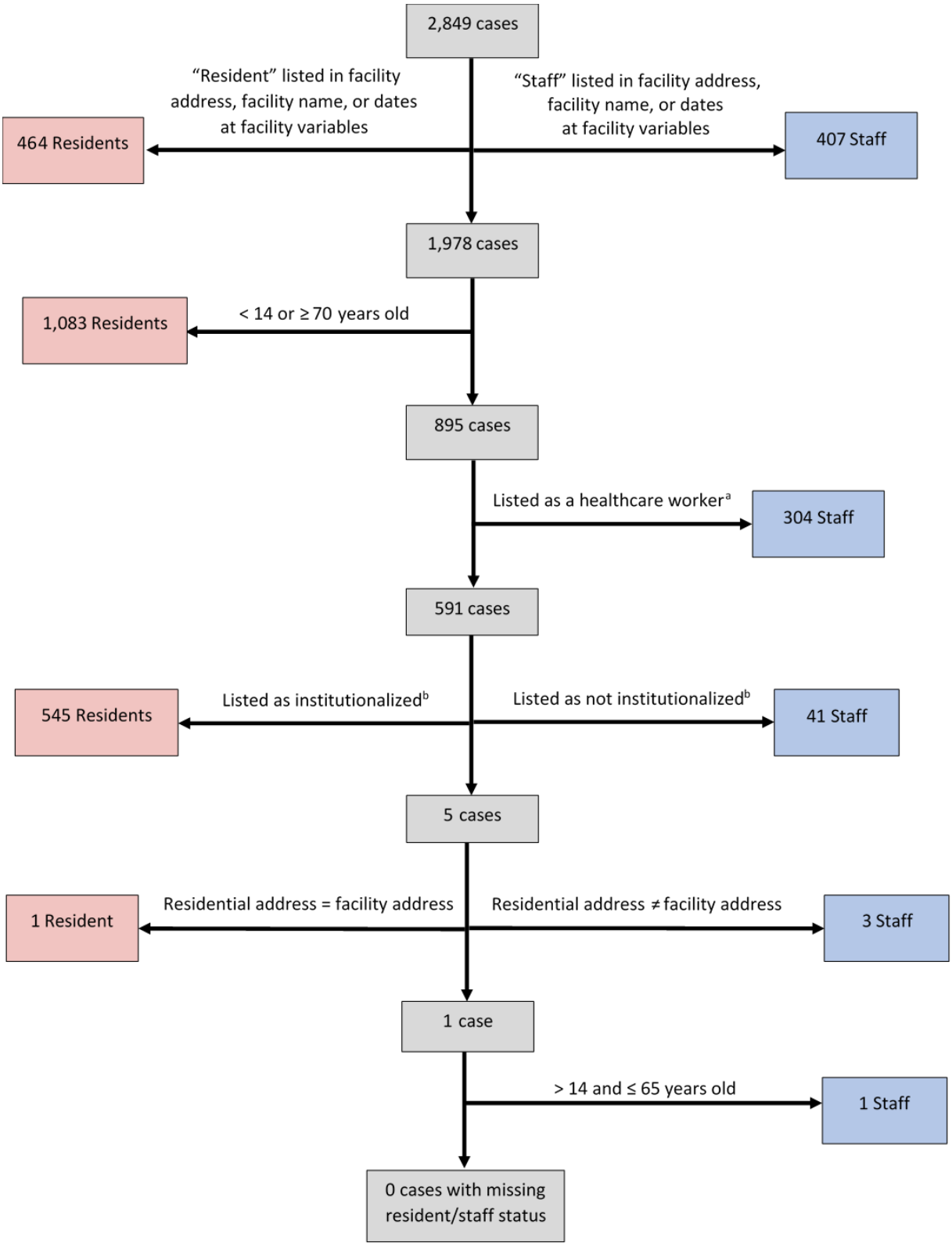
County Board of Health for supplying data for this project. The contents herein are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the Georgia Department of Public Health or the Fulton County Board of Health.

5.8 Supplementary File

Supplementary Figure 5-1. Decision tree for case inclusion and exclusion in the data analysis



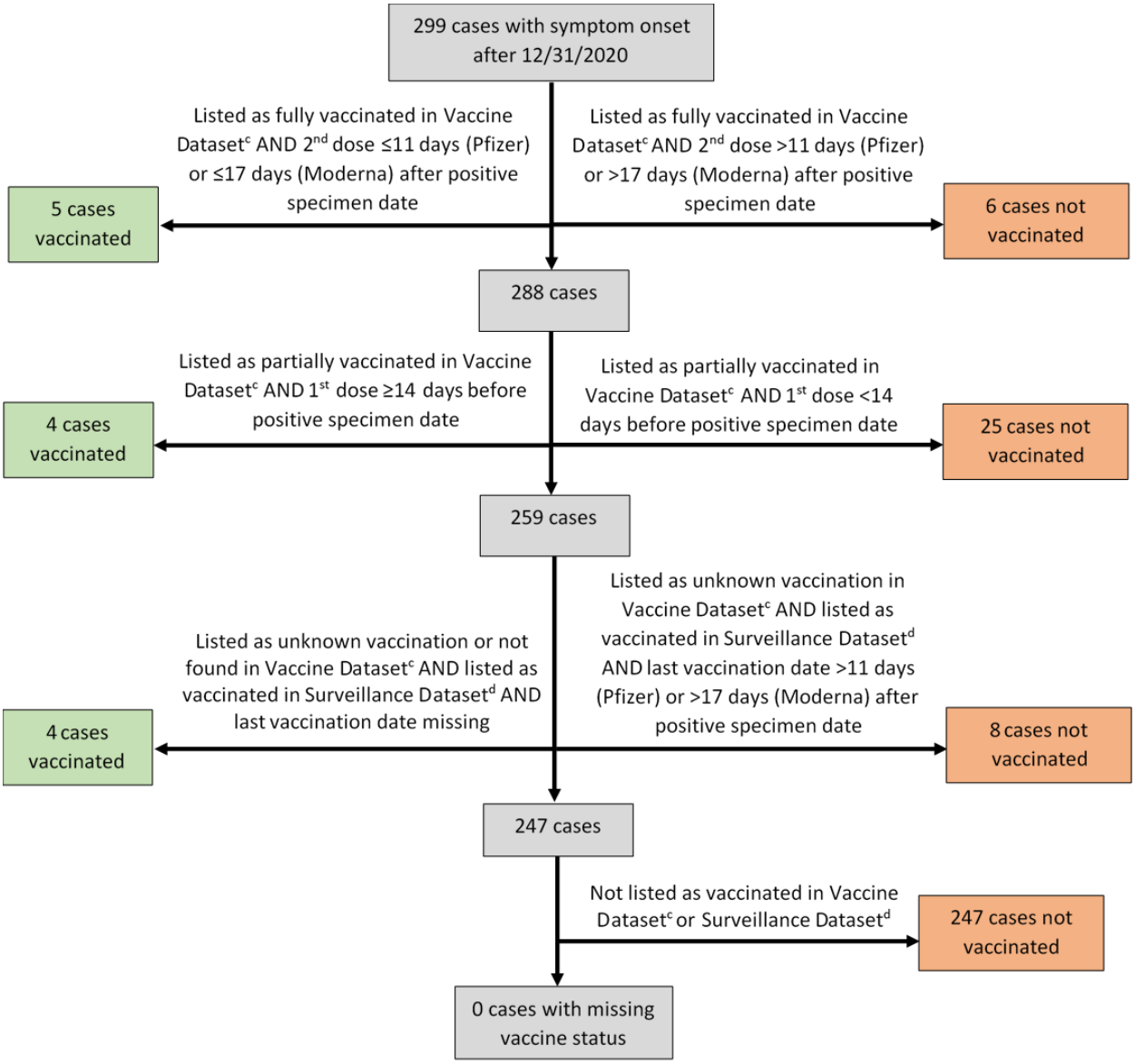
Supplementary Figure 5-2. Decision tree for categorizing cases as long-term care facility residents or staff



[a] Cases were listed as healthcare workers (yes or no) if they worked in a healthcare setting (with or without direct patient contact).

[b] Cases were listed as institutionalized (yes or no) on the case report form if they had been institutionalized (long-term care facility, skilled nursing facility, etc.) at any time during the 30 days prior to the specimen collection date.

Supplementary Figure 5-3. Decision tree for categorizing cases with symptom onset (imputed or empirical) after December 31, 2020[a] as vaccinated[b] or unvaccinated against SARS-CoV-2



[a] Shortly after vaccines were first administered to U.S. long-term care facility residents and staff.

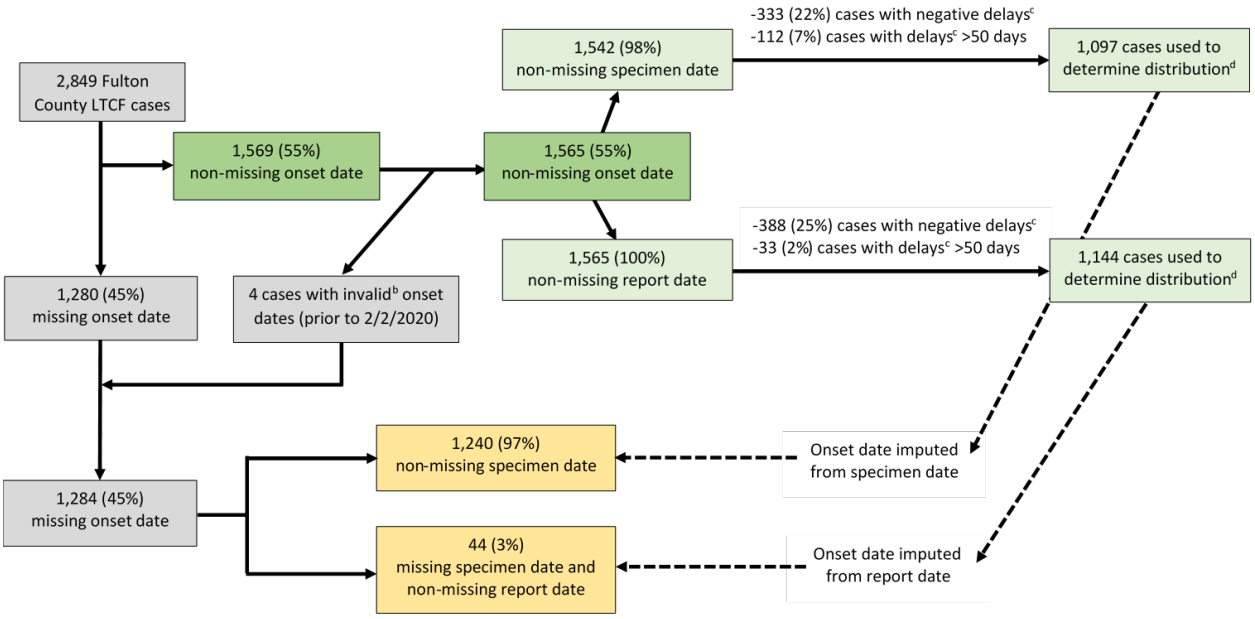
[b] Cases were considered vaccinated if they received at least one vaccine dose prior to their first positive specimen collection date. All vaccinated cases with available vaccine

manufacturer information received a Pfizer-BioNTech or Moderna vaccine, both of which require two shots. Recommended dosing intervals are 17–25 days and 24–32 days for Pfizer-BioNTech and Moderna, respectively.

[c] The Vaccine Dataset refers to the COVID-19 Vaccine Breakthrough Dashboard Dataset, which contains vaccination records for persons in Georgia.

[d] The Surveillance Dataset refers to the Georgia COVID-19 surveillance Dataset. In this dataset, cases were classified as vaccinated (yes/no).

Supplementary Figure 5-4. Decision tree for case inclusion and exclusion in symptom onset date imputations[a]



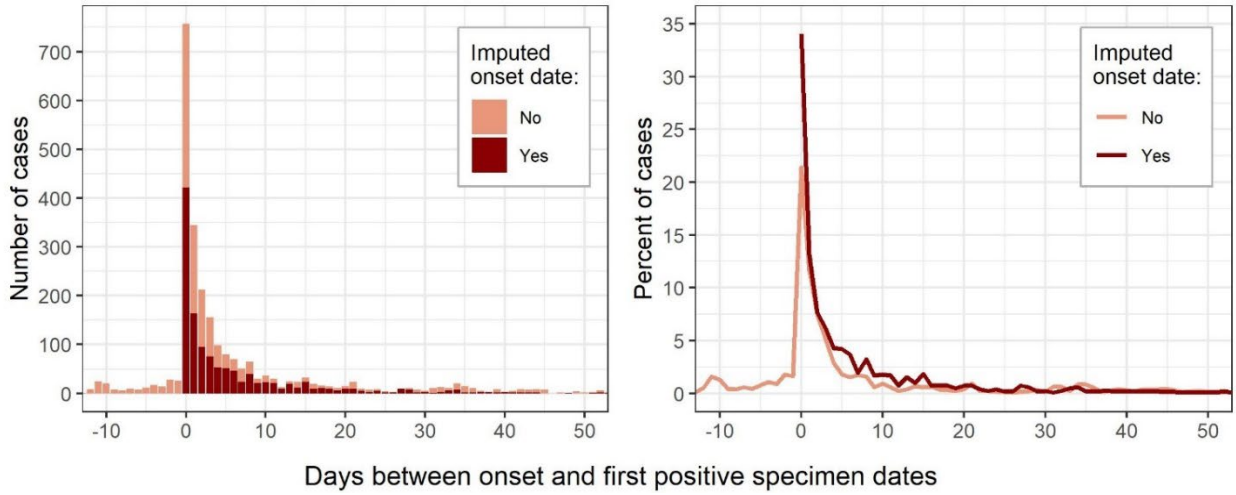
[a] Symptom onset dates were imputed for cases with missing or invalid symptom onset dates using the first positive specimen collection date when available, or case report date, otherwise.

[b] Invalid symptom onset dates were those >1 month prior to the first case report date in Georgia.

[c] Delays are the time in days between symptom onset and first positive specimen collection date or case report date.

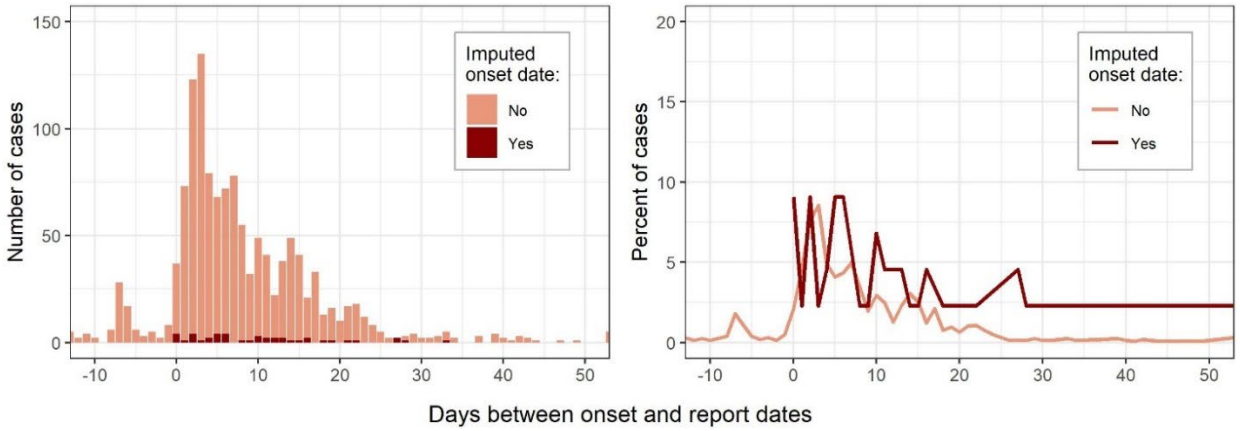
[d] Negative binomial distributions were used. The number of days between symptom onset date and first positive specimen collection date or report date was modeled using negative binomial regression with the first positive specimen collection date or report date as the predictor.

Supplementary Figure 5-5. Comparison of days between symptom onset and first positive specimen collection dates for cases with imputed[a] and non-imputed symptom onset dates



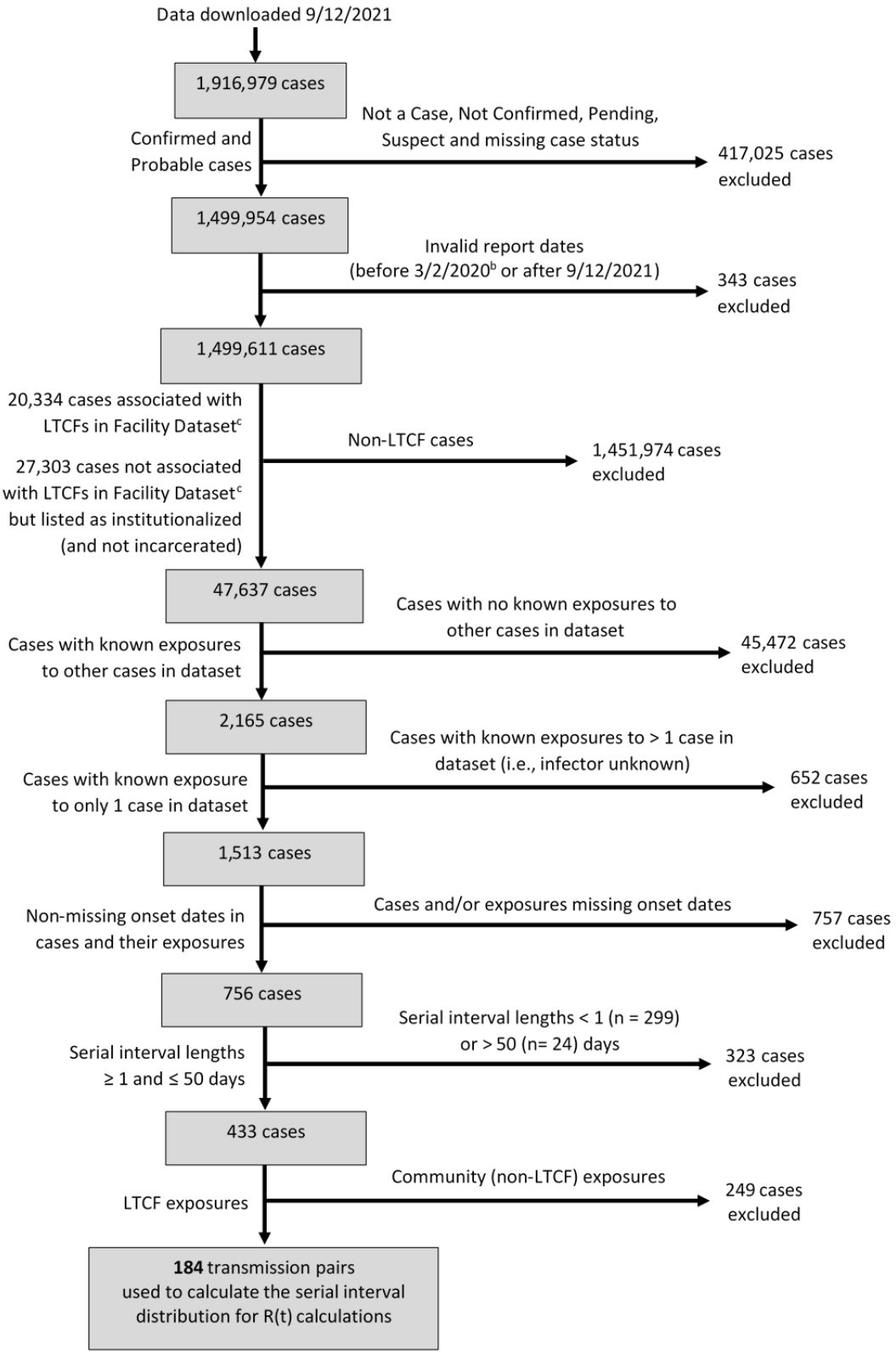
[a] Only cases with imputed symptom onset dates based on first positive specimen collection dates (and not report dates) are shown.

Supplementary Figure 5-6. Comparison of days between symptom onset and case report dates for cases with imputed[a] and non-imputed symptom onset dates



[a] Only cases with imputed symptom onset dates based on report dates (and not first positive specimen collection dates) are shown.

Supplementary Figure 5-7. Decision tree for case inclusion and exclusion in COVID-19 serial interval[a] calculations for Georgia long-term care facilities



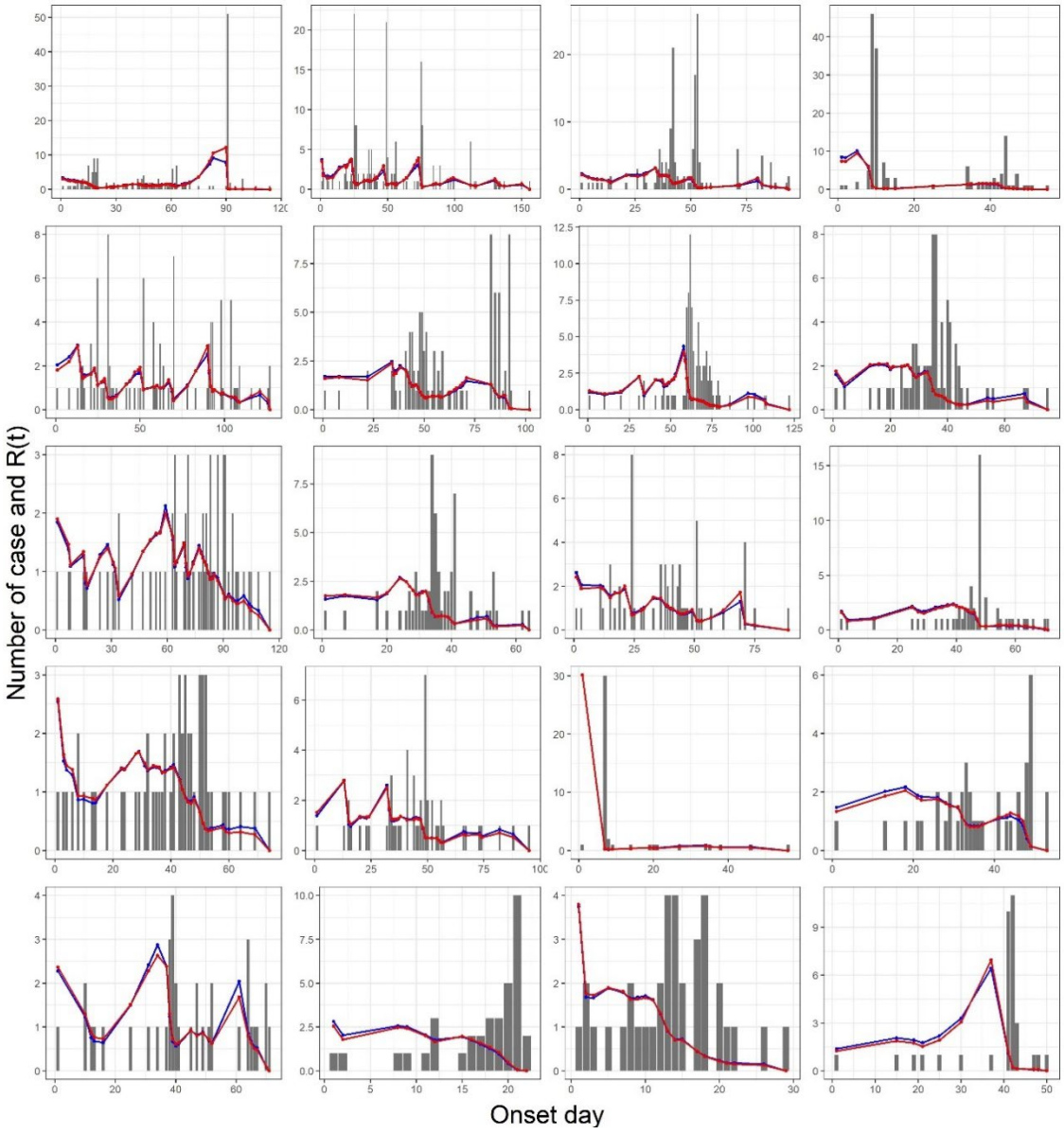
Abbreviations: LTCF, long-term care facility; R(t), time-varying reproduction number; n, number

[a] The serial interval is defined as the time, in days, between symptom onset in a primary case (infector) and a secondary cases (infectee).

[b] The first COVID-19 case in Georgia was reported 3/2/2020.

[c] The Facility Dataset is a separate surveillance dataset that includes cases associated with facilities, including LTCFs, and the type and name of facilities with which they are associated.

Supplementary Figure 5-8. Comparison[a] of time-varying reproduction numbers, R(t), calculated using one serial interval distribution[b] for the entire study period (in red) and three separate serial interval distributions for different time periods[c] (in blue) with case counts by symptom onset day[d] shown by gray bars



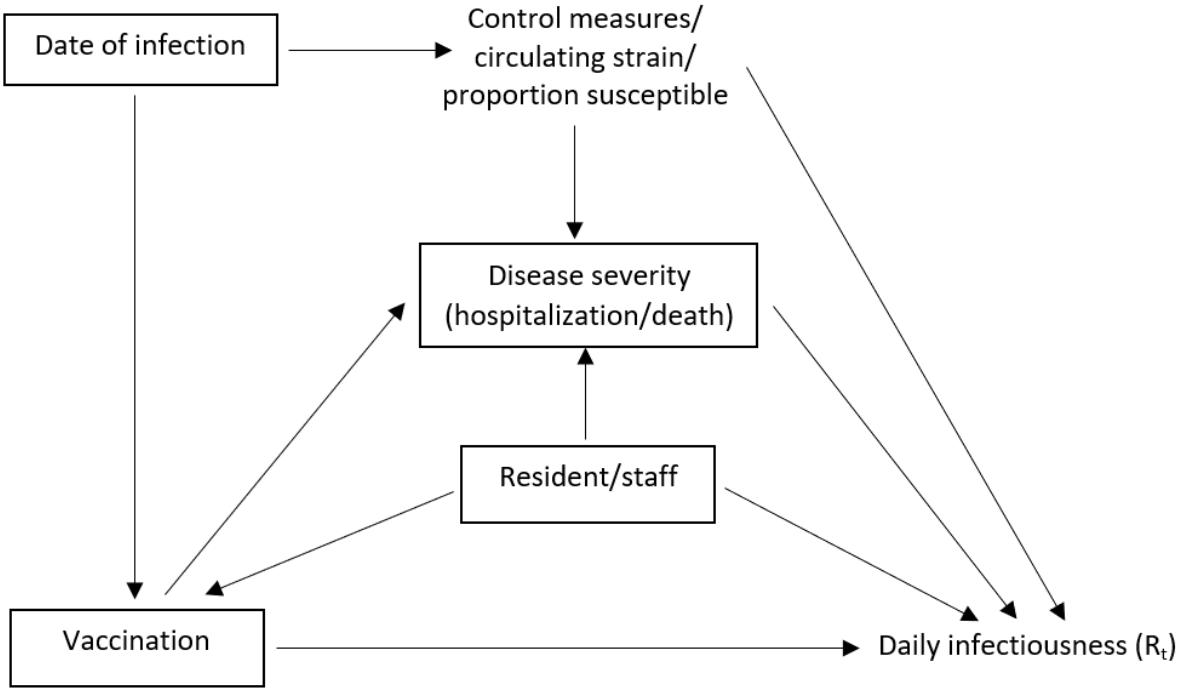
[a] Plots for 20 skilled nursing facility outbreaks lasting 15 days or longer are shown. Plots for other skilled nursing facility outbreaks and assisted living facility outbreaks showed similar R(t) estimates for the different serial interval distributions.

[b] The serial interval is defined as the time, in days, between symptom onset in primary cases and the secondary cases they infect.

[c] Serial interval distributions were calculated for the following time periods: February to May, 2020, June to December, 2020, and January to August, 2021 (there were no symptom onset dates after August 2021). Time periods were selected based on the numbers of available cases from which to calculate distributions and important long-term care facility pandemic response changes.

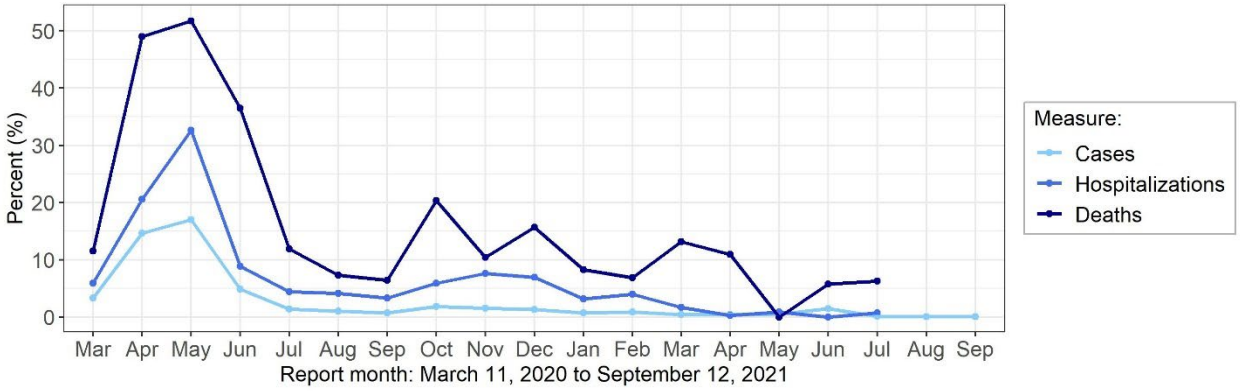
[d] Symptom onset day is the day of the outbreak, with outbreaks beginning on the first day a case(s) had symptom onset.

Supplementary Figure 5-9. Directional Acyclic Graph (DAG) for associations between daily infectiousness, quantified by the time-varying reproduction number (R(t)), and case characteristics[a]



[a] Variables surrounded by black boxes indicate variables included in regression models.

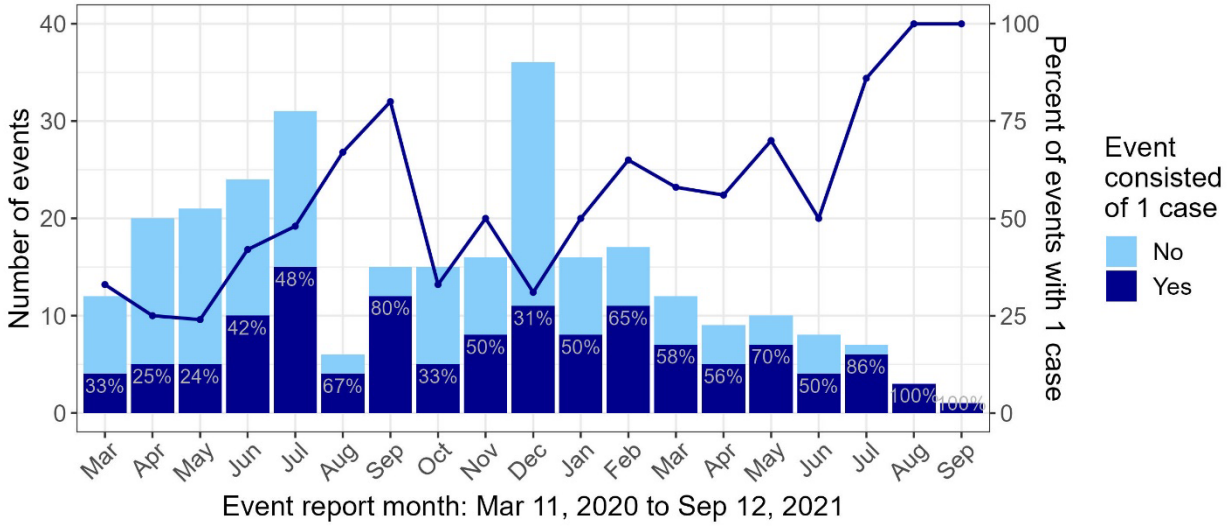
Supplementary Figure 5-10. Percentages of COVID-19 cases, hospitalizations and deaths in Fulton County that occurred among LTCF residents and staff by report month: March 11, 2020 to September 12, 2021[a]



Abbreviations: LTCF, long-term care facility

[a] Data for hospitalizations and deaths were restricted to cases reported prior to August 1, 2021 (6 weeks prior to data download) to account for lags in hospitalization and death.

Supplementary Figure 5-11. Number and percent[a] of COVID-19 events[b], as defined by report date, consisting of a singleton case by outbreak report month[c]



[a] Numbers of events are shown by bars and percentages of events consisting of 1 case are shown by the line and text in bars

[b] COVID-19 events were defined as 1 or more cases reported in the same facility. If no new cases were reported in more than 14 days, the event was considered over and any cases reported after 14 days were considered part of a separate event.

[c] Event report month was determined by the first case report date for each event.

Supplementary Table 5-1. Number and percent of cases with missing information by variable

Variable	Missingness [N (%)] (n = 2,849)
Report date	0 (0)
Gender	2 (0)
Age	12 (0)
First positive specimen collection date	67 (2)
Race/ethnicity	126 (4)
Hospitalized[a]	611 (21)
Asymptomatic[a]	1,086 (38)
Symptom onset date[b]	1,284 (45)
COVID-19 death[a,c]	1,371 (48)
Underlying condition(s)[a]	2,106 (74)
Vaccinated[a,d]	241 (81)

[a] These are dichotomous (Yes/No) variables.

[b] Missing symptom onset dates were imputed, after which no cases were missing symptom onset dates.

[c] Cases missing COVID-19 death information were assumed to not have died from COVID-19. After making this assumption, 70 (2%) cases with COVID-19 death “Under Review” were still categorized as missing.

[d] Missingness for vaccination status was only examined for cases with symptom onset after December 31, 2020 (n=299). Cases were categorized as vaccinated or unvaccinated using information from the COVID-19 Surveillance Dataset, the COVID-19 Vaccine Breakthrough

Dashboard Dataset, and a decision tree, after which no cases were missing vaccination status.

Supplementary Table 5-2. Comparison of gamma serial interval distributions[a] for the entire study period and three different time periods[b]

Time period[b]	Number of cases[c]	Shape parameter	Scale parameter	Mean (in days)	Standard deviation
Total	184	1.4	5.9	8.0	6.9
Feb-May 2020	89	1.4	6.9	9.4	8.0
Jun-Dec 2020	59	1.6	4.4	7.0	5.5
Jan-Aug 2021	36	1.2	5.3	6.4	5.9

[a] The serial interval is defined as the time, in days, between symptom onset in primary cases and the secondary cases they infect. Serial interval distributions were used to calculate time-varying reproduction numbers, R(t).

[b] Time periods were selected based on the numbers of available cases from which to calculate distributions and important long-term care facility pandemic response changes.

[c] Serial interval distributions were calculated from long-term care facility (LTCF) cases in Georgia exposed to one known LTCF case with non-missing symptom onset dates.

Supplementary Table 5-3. Sensitivity analysis for associations[a] between the COVID-19 time-varying reproduction number, R(t), and long-term care facility (LTCF) role (resident or staff) in Fulton County, Georgia LTCFs for cases reported March 11, 2020 to September 12, 2021

		Main analysis[c]	**Sensitivity analysis[d]**
Days included[b]	**LTCF role**	**R_i (95% CI)**	**R_i (95% CI)**
All	Staff	0.6 (0.4, 0.7)	0.6 (0.2, 1.0)
	Resident	0.1 (0.1, 0.2)	0.2 (0.0, 0.5)
Pre-vaccination	Staff	0.6 (0.5, 0.7)	0.7 (0.2, 1.1)
	Resident	0.1 (0.0, 0.1)	0.2 (0.0, 0.5)

Abbreviations: R_i, individual reproduction number; CI, confidence interval; LTCF, long-term care facility

[a] Associations between case characteristics and R(t) were examined using linear mixed regression models. Regression coefficients can be interpreted as the average individual reproduction number, R_i, (i.e., the number of secondary cases infected by a single case) for cases with different characteristics.

[b] The analysis was stratified by the following symptom onset days: 1) all days during the study period, and 2) days prior to vaccine distribution (January 1, 2021).

[c] LTCF role for the main analysis was determined using a decision tree that incorporated a number of variables in the dataset, including whether “Resident” or “Staff” was entered into free-text fields and age of cases

[d] LTCF role for the sensitivity analysis was determined based on whether “Resident” or “Staff” was entered into free-text fields. If “Staff” was not entered into free text fields, cases were assumed to be residents.

CHAPTER 6: AIM 3 – TRENDS IN COVID-19 CASE-FATALITY IN GEORGIA, USA

[Manuscript 3]

Declining COVID-19 case-fatality in Georgia, USA, March 2020 to March 2021: a sign of real improvement or a broadening epidemic?

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6.1 Abstract

Background: The crude COVID-19 case fatality ratio (CFR) in the U.S. has declined. This may be due to improved clinical care and/or other factors.

Methods: We used multivariable logistic regression, adjusted for age and other individual-level characteristics, to examine associations between report month and mortality among confirmed and probable COVID-19 cases and hospitalized cases in Georgia reported March 2, 2020 to March 31, 2021.

Results: Compared to August 2020, mortality risk among cases was lowest in November 2020 (OR = 0.84; 95% CI: 0.78-0.91) and remained lower until March 2021 (OR = 0.86; 95% CI: 0.77-0.95). Among hospitalized cases, mortality risk increased in December 2020 (OR = 1.16, 95% CI: 1.07-1.27) and January 2021 (OR = 1.25; 95% CI: 1.14-1.36), before declining until March 2021 (OR = 0.90, 95% CI: 0.78-1.04).

Conclusions: After adjusting for other factors, including the shift to a younger age distribution of cases, we observed lower mortality risk from November 2020 to March 2021 compared to August 2020 among cases. This suggests that improved clinical management may have contributed to lower mortality risk. Among hospitalized cases, mortality risk increased again in December 2020 and January 2021, but then decreased to a risk similar to that among all cases by March 2021.

6.2 Background

Despite stay-at-home orders and other extraordinary public health efforts, COVID-19 was the third leading cause of death in the United States in 2020.[243] While U.S. case counts have followed complex patterns, the crude case fatality ratio (CFR), or the proportion of identified cases who died, declined between May 2020 and January 2021.[74] One possible explanation for this decline is that improved clinical management led to increased survival among cases. However, because the crude CFR is not adjusted for other variables, additional factors must be considered before concluding that declines are a result of improved clinical care. First, the COVID-19 case distribution in the U.S. shifted to a younger demographic,[80] and younger individuals are less susceptible to severe disease. Second, the number of cases among long-term care facility (LTCF) residents, who have an increased risk of severe illness,[65] declined over time. Lastly, testing among the general population increased as the pandemic progressed, leading to an increased detection of less severe cases.[87]

In this analysis, we examined the risk of COVID-19 death among reported cases in the state of Georgia. The first case of COVID-19 was reported in Georgia on March 2, 2020.[244] As of

June 1, 2021, there have been nearly 900,000 confirmed cases of COVID-19 and 18,000 deaths reported in the state.[226] The primary aim of this study was to examine temporal changes in the risk of COVID-19 mortality among cases in Georgia, and to determine the extent to which trends could be explained by shifts in case demographics and setting as opposed to improved survival. A second aim of this study was to examine individual-level risk factors for COVID-19 mortality. Lastly, because mortality trends among hospitalized cases, compared to all cases, are less affected by changes in testing and reporting, as only more severe cases are hospitalized, we also examined temporal changes in risk and individual-level risk factors for COVID-19 mortality among hospitalized cases in Georgia.

6.3 Methods

6.3.1 Data description

We used individual-level COVID-19 surveillance data collected by the Georgia Department of Public Health (GDPH). Data were downloaded on June 13, 2021 and restricted to confirmed and probable cases reported March 2, 2020 to March 31, 2021, approximately 2.5 months prior to data download to account for lags in reporting and death. Cases with positive results from reverse-transcription polymerase chain reaction (RT-PCR) tests were classified as confirmed, and cases lacking RT-PCR results but meeting other testing, clinical, epidemiologic, and/or vital records criteria were classified as probable.[226] Confirmed cases that were reported as deceased, had COVID-19 indicated as the cause of death on death certificates, or had evidence that COVID-19 contributed to death were classified as COVID-19 deaths.[226] We also used information from the following datasets: 1) GDPH RT-PCR testing data, 2) 2010 census data from the U.S. Census Bureau[92] and rural-urban

continuum codes from the U.S. Department of Agriculture,[93] and 3) COVID-19 Reported Patient Impact and Hospital Capacity by State Timeseries data.[91]

The following individual-level variables were included in our study: COVID-19 death, case report month, race/ethnicity, age, gender, LTCF role (LTCF resident or non-LTCF resident) and metro-urban status (metro-urban, nonmetro-urban, or nonmetro-rural). If cases were missing information on COVID-19 death, we assumed they did not die from COVID-19. Cases with COVID-19 death listed as “Under Review” were excluded from all analyses. We categorized reported race/ethnicity as Hispanic/Latino (any race), and non-Hispanic/Latino Black, Asian, White, or Other. The Other race/ethnicity category included American Indian/Alaska Native (1.6%), Native Hawaiian/Pacific Islander (2.4%), and “other” (96.0%). To determine LTCF role, cases were first categorized as LTCF-associated and then as residents or staff based on a decision tree (Supplementary Figure 6-1). Lastly, metro-urban status was determined using cases’ county of residence (county where case usually resided at the time of exposure/infection, 98.9%), when available, and current county (county where case was at the time of initial report, 1.1%) otherwise.

6.3.2 Risk factors for COVID-19 death: all cases

To identify temporal and demographic factors associated with COVID-19 death among cases in Georgia, we used univariable and multivariable logistic regression. The following independent variables were included in the multivariable analysis: report month, race/ethnicity, age, gender, LTCF role, and metro-urban status. Due to uncertainty in testing and reporting early in the pandemic, the month of August 2020, a mid-point in the study period, was used as the reference category for report month.

Cases missing report month and/or LTCF role were excluded from analyses, as these variables were rarely missing (<0.05%). Missing race/ethnicity, age, gender, and metro-urban status were imputed using multivariate imputation by chained equations (MICE).[245] All variables included in the multivariable analysis, and also hospitalization, were included in imputation models. Variables for interactions between report month and age and race and age were included in imputation models using a transform–impute–transform approach.[246] These interaction terms were identified prior to imputations by performing interaction assessments of all pairs of independent variables for cases and hospitalized cases with complete information. Using the 'mice' package in R,[247] we created 15 imputed datasets with 20 iterations each. Imputation models were checked by comparing distributions of imputed variables and regression coefficients for individual datasets. Lastly, because multiple imputation can produce invalid results,[248] we also performed a sensitivity analysis in which we excluded cases missing any information from the model (i.e., complete case analysis).

6.3.3 Risk factors for COVID-19 death: hospitalized cases

To identify temporal and demographic factors associated with COVID-19 death among hospitalized cases, we again used univariable and multivariable logistic regression models. We used the same 15 imputed datasets from the analysis of all cases, but restricted the data to cases that were reported as hospitalized in the original, non-imputed dataset. The same variables included in the multivariable regression analysis for all cases were included in the analysis for hospitalized cases.

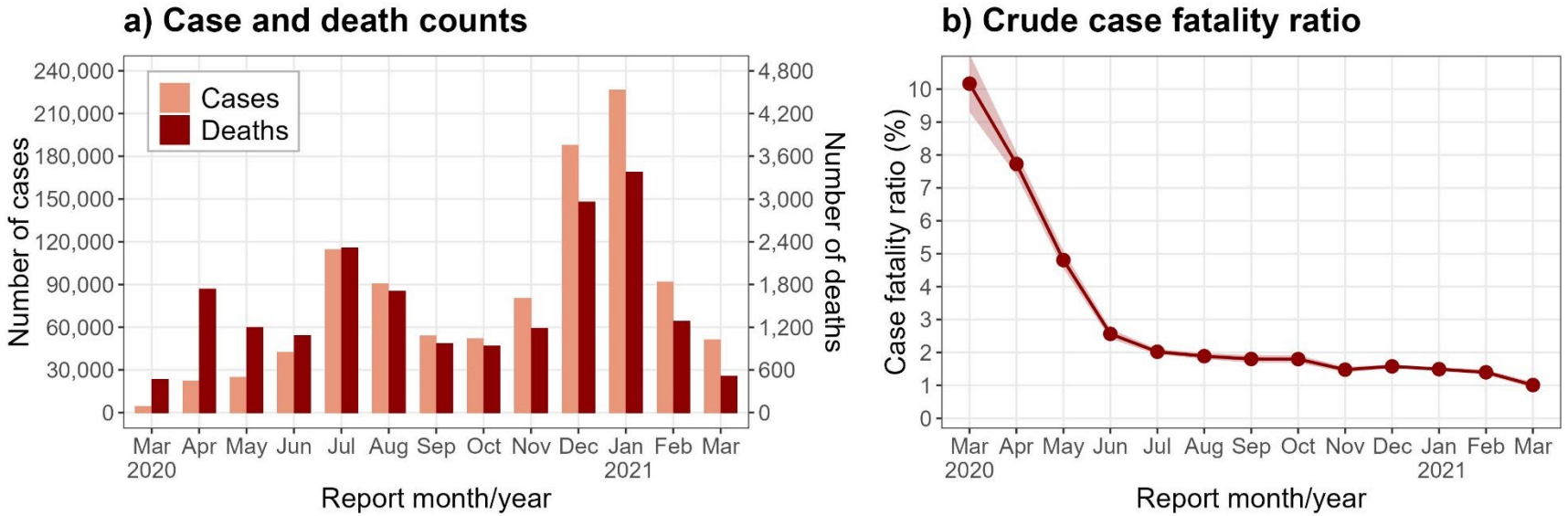
All statistical analyses were performed using *R* v.4.0.5. This activity was determined by the Georgia Department of Public Health Institutional Review Board to be non-research and

consistent with public health surveillance as per title 45 code of Federal Regulations 46.102(l)(2).

6.4 Results

After excluding cases with COVID-19 mortality listed as “Under Review” (n = 1,801; 8.4% of confirmed or possible COVID-19 deaths) and cases missing report month (n = 326; 0.03% of cases) and/or LTCF role (n = 21; 0.002% of cases), a total of 1,043,407 confirmed and probable COVID-19 cases, 65,870 hospitalizations (6.3% of cases) and 19,754 deaths (1.9% of cases) were included in the analyses. Cases with COVID-19 mortality listed as “Under Review” were slightly less likely to be Black or Hispanic/Latino and more likely to be female or LTCF residents compared to confirmed deaths (Supplementary Table 6-1). The crude CFR, or the number of COVID-19 deaths divided by the number of cases reported in a given month, was 1.9%. COVID-19 case counts peaked in July 2020 and January 2021, and then decreased sharply from January to March 2021 (Figure 6-1). Death counts followed a similar pattern, but with an additional peak in April 2020. The crude CFR declined sharply from 10.2% in March 2020 to 2.0% in July 2020, then decreased gradually to a minimum of 1.1% in March 2021 (Figure 6-1). The number of reported RT-PCR tests was greatest in July/August 2020 and December 2020/January 2021 (Figure 6-2). Finally, monthly percent positivity peaked in March 2020 (31.5%), June 2020 (17.2%), and January 2021 (16.3%) (Figure 6-2).

Figure 6-1. Confirmed and probable COVID-19 case[a] and death[b] counts and crude case fatality ratio[c] by report month in Georgia, USA: March 2, 2020 – March 31, 2021

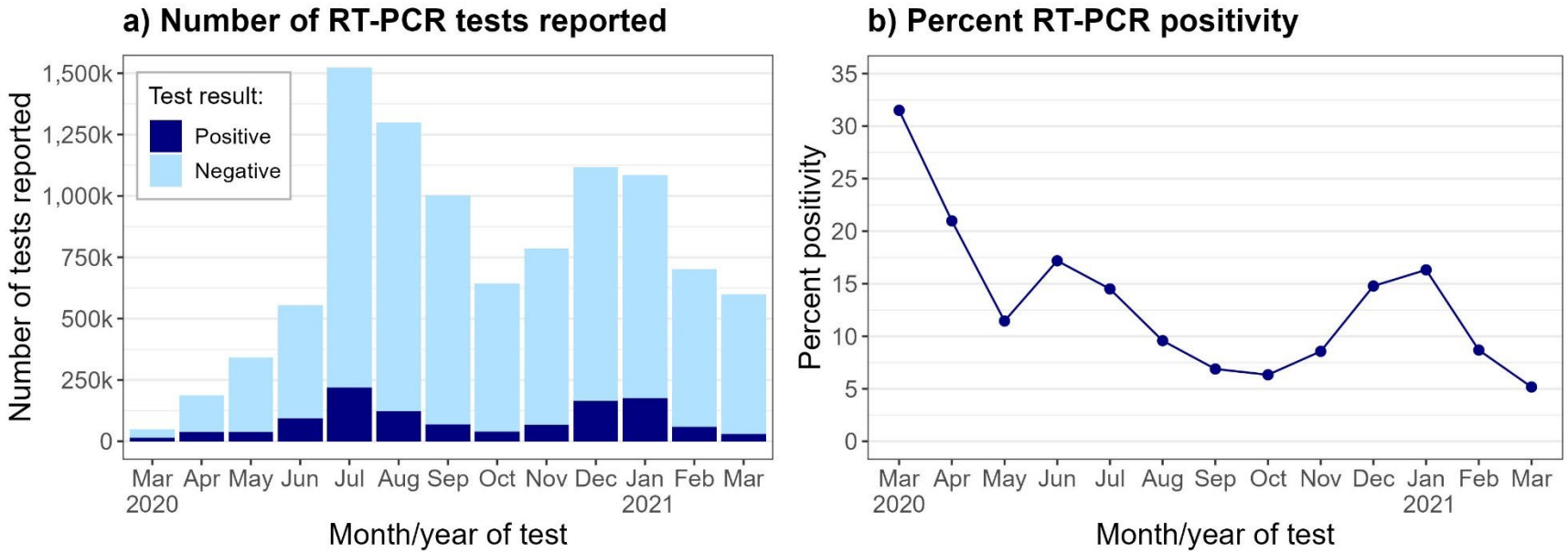


[a] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic, and/or vital records criteria.

[b] COVID-19 deaths were confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death.

[c] The crude case fatality ratio was calculated by dividing the number of COVID-19 deaths reported in a given month by the number of confirmed and probable cases reported that month.

Figure 6-2. Number of COVID-19 RT-PCR tests by test result reported to the State of Georgia and COVID-19 percent positivity[a] by month: March 2, 2020 – March 31, 2021



Abbreviations: RT-PCR, reverse-transcription polymerase chain reaction; k, thousand

[a] Percent positivity was calculated by dividing the number of positive RT-PCR tests by the number of total RT-PCR tests reported to the State of Georgia by month, multiplied by 100.

In a crude analysis comparing COVID-19 deaths to all cases and hospitalized cases, COVID-19 deaths were older, less likely to be Hispanic/Latino or female, and more likely to be LTCF residents (Table 6-1). They were also more likely than all cases but about as likely as hospitalized cases to be in nonmetro-rural counties, and more likely than all cases but less likely than hospitalized cases to be Black.

Table 6-1. Characteristics of confirmed and probable COVID-19 cases[a,b], hospitalizations, and deaths[c] in Georgia, USA: March 2, 2020 – March 31, 2020

Characteristic	All cases (n = 1,043,407)	Hospitalized cases (n = 65,870)	Deaths (n = 19,754)
Race/ethnicity (N (%))[d,e]			
White	456,995 (51.2)	29,535 (46.0)	11,493 (58.3)
Asian	22,927 (2.6)	1,202 (1.9)	371 (1.9)
Black	268,631 (30.1)	25,428 (39.6)	6,732 (34.2)
Hispanic/Latino	105,084 (11.8)	6,768 (10.5)	1,028 (5.2)
Other	38,839 (4.4)	1,245 (1.9)	87 (0.4)
Age; years (median (IQR))	39 (24, 55)	62 (48, 74)	75 (65, 84)
Female (N (%))[d]	560,107 (54.2)	33,611 (51.1)	9,314 (47.2)
LTCF resident (N (%))	31,956 (3.1)	6,941 (10.5)	6,097 (30.9)
Metro-urban status (N (%))[d,f]			
Metro-urban	852,000 (81.8)	50,267 (76.3)	14,321 (72.5)
Nonmetro-urban	169,527 (16.3)	13,654 (20.7)	4,846 (24.5)
Nonmetro-rural	19,623 (1.9)	1,929 (2.9)	580 (2.9)

Abbreviations: N, number; IQR, interquartile range; LTCF, long-term care facility

[a] Cases with missing information were not included in the table (i.e., imputed values were excluded).

[b] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic, and/or vital records criteria.

[c] COVID-19 deaths were confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death.

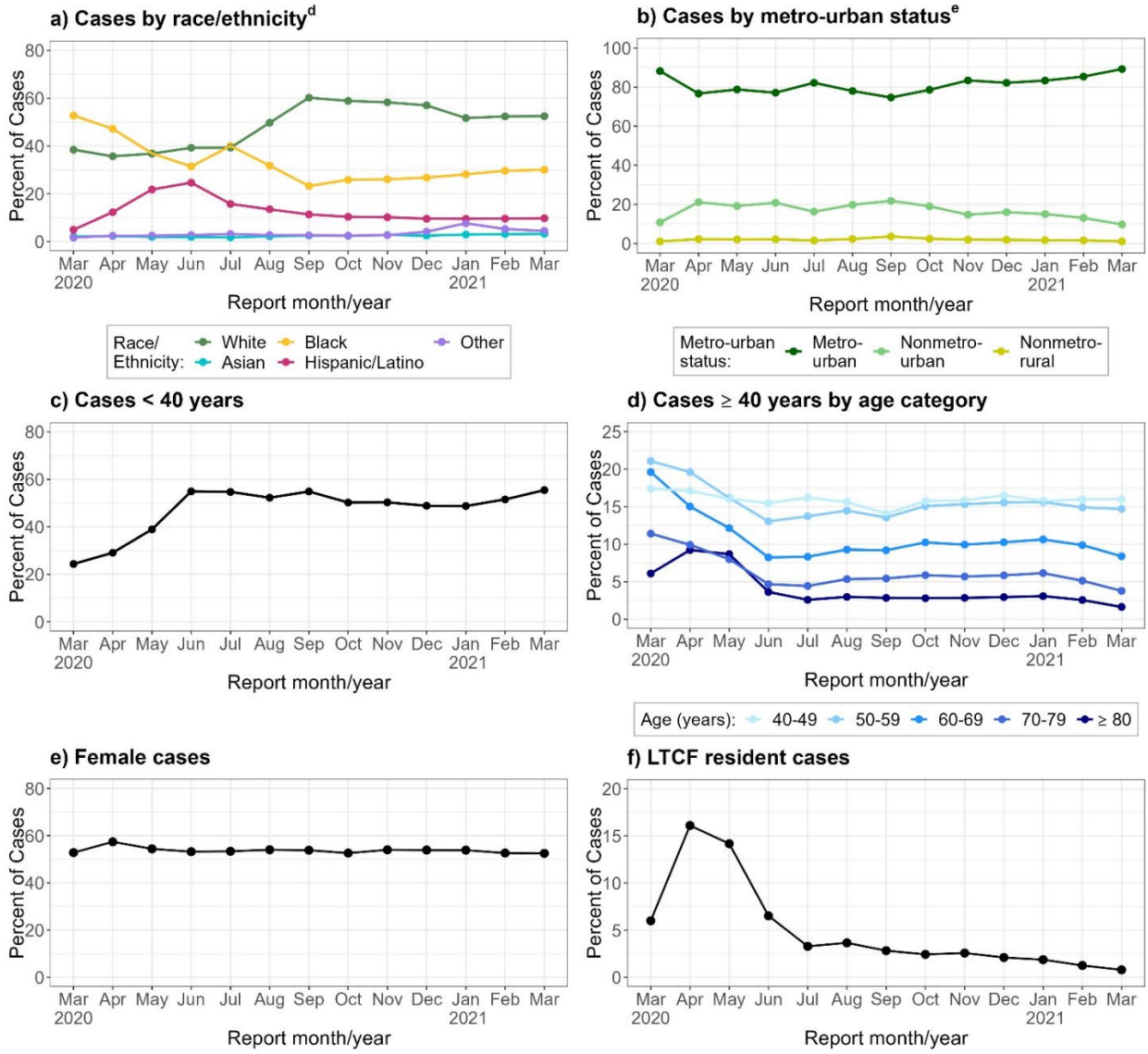
[d] Percentages were calculated by excluding cases with missing information (there was no missingness for LTCF role).

[e] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White, or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and those who reported their race as “other”.

[f] Metro-urban status is the classification of a case’s county of residence (i.e., usual residence at time of exposure/infection), when available, and current county (i.e., location at time of initial report) otherwise.

The distributions of race/ethnicity, age, and LTCF role changed over the study period (Figure 6-3). The proportion of cases that were Black was highest in March 2020 (52.7%) and then generally decreasing until September 2020, and the proportion of cases that were Hispanic/Latino increased substantially from 5.0% in March 2020 to 24.7% in June 2020 before declining. The proportion of cases that were <40 years of age increased each month until June 2020 and then plateaued. Lastly, the proportion of cases that were LTCF residents peaked early at 16.1% in April 2020 before declining. Similar trends were seen among COVID-19 deaths, however there was no obvious trend in the age distribution, with the majority of deaths being ≥70 years throughout the study period (Supplementary Figure 6-2).

Figure 6-3. Characteristics[a] of confirmed and probable COVID-19 cases[b,c] by report month in Georgia, USA: March 2, 2020 – March 31, 2020



Abbreviations: LTCF, long-term care facility

[a] Note the change in scale between plots.

[b] Cases with missing information were not included in plots (i.e., imputed values were excluded).

[c] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic, and/or vital records criteria.

[d] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White, or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and those who reported their race as “other”; cases with non-missing race information but missing ethnicity information were assumed to be non-Hispanic/Latino.

[e] Metro-urban status is the classification of a case’s county of residence (i.e., usual residence at time of exposure/infection), when available, and current county (i.e., location at time of initial report) otherwise.

Finally, we examined trends in hospital capacity by plotting the percentages of hospital inpatient beds and adult intensive care unit (ICU) beds that were occupied by COVID-19 patients by month in Georgia. The percent of COVID-19-occupied inpatient beds peaked three distinct times in April 2020 (14.2%), July 2020 (18.7%), and January 2021 (25.7%) (Supplementary Figure 6-3). The percent of COVID-19-occupied ICU beds was highest in August 2020 (40.2%), when the data first became available, and January 2021 (46.5%).

6.4.1 Risk factors for COVID-19 death: all cases

To examine associations between COVID-19 mortality and report month among cases, we imputed missing values for race/ethnicity (14.5%), gender (1.0%), age (0.4%), and metro-urban status (0.2%). We found that the distributions of imputed variables and regression results were consistent across the 15 imputed datasets (Supplementary Figures 6-4 – 6-6). After accounting for case demographics/location, we found that the odds of death, compared to the August 2020 reference, was highest in March 2020 (OR = 3.58; 95% CI: 3.17-4.04) and lowest in November 2020 (OR = 0.84; 95% CI: 0.78-0.91), but did not decrease monotonically during this time (Table 6-2, Supplementary Figure 6-7). Instead, the odds of death increased in June 2020 (OR = 1.21; 95% CI: 1.11-1.32) and July 2020 (OR = 1.27; 95% CI: 1.18-1.36). After November 2020, the odds of death remained consistently low until the end of the study period.

Table 6-2. Logistic regression results for associations between report month and case characteristics and COVID-19 death[a] among confirmed and probable COVID-19 cases[b] and hospitalized cases in GA, USA: March 2, 2020 – March 31, 2021

	All cases		Hospitalized cases	
	Univariable	**Multivariable[c]**	**Univariable**	**Multivariable[c]**
Variable	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Report month/year				
March 2020	5.88 (5.29, 6.55)	3.58 (3.17, 4.04)	1.35 (1.19, 1.54)	1.44 (1.26, 1.66)
April 2020	4.35 (4.07, 4.66)	1.74 (1.61, 1.88)	1.62 (1.48, 1.77)	1.27 (1.15, 1.40)
May 2020	2.63 (2.44, 2.83)	1.11 (1.02, 1.21)	1.65 (1.48, 1.83)	1.27 (1.12, 1.43)
June 2020	1.37 (1.27, 1.48)	1.21 (1.11, 1.32)	0.95 (0.85, 1.06)	1.03 (0.92, 1.16)
July 2020	1.07 (1.01, 1.14)	1.27 (1.18, 1.36)	0.97 (0.89, 1.06)	1.10 (1.00, 1.20)
August 2020	Ref	Ref	Ref	Ref
September 2020	0.95 (0.88, 1.03)	1.05 (0.97, 1.15)	0.97 (0.87, 1.08)	0.95 (0.85, 1.07)
October 2020	0.95 (0.88, 1.03)	1.03 (0.95, 1.12)	0.96 (0.86, 1.07)	0.95 (0.85, 1.07)
November 2020	0.78 (0.72, 0.84)	0.84 (0.78, 0.91)	0.97 (0.88, 1.08)	0.91 (0.82, 1.02)
December 2020	0.83 (0.78, 0.88)	0.91 (0.86, 0.98)	1.25 (1.16, 1.36)	1.16 (1.07, 1.27)
January 2021	0.79 (0.74, 0.84)	0.84 (0.79, 0.90)	1.36 (1.25, 1.47)	1.25 (1.14, 1.36)

February 2021	0.74 (0.68, 0.79)	0.91 (0.84, 0.98)	1.15 (1.04, 1.27)	1.11 (1.00, 1.24)
March 2021	0.53 (0.48, 0.59)	0.86 (0.77, 0.95)	0.76 (0.66, 0.86)	0.90 (0.78, 1.04)
Race/ethnicity[d,e]				
White	Ref	Ref	Ref	Ref
Asian	0.63 (0.57, 0.70)	1.39 (1.24, 1.55)	0.97 (0.85, 1.11)	1.47 (1.27, 1.70)
Black	1.00 (0.97, 1.03)	1.54 (1.49, 1.59)	0.67 (0.64, 0.70)	1.03 (0.99, 1.08)
Hispanic/Latino	0.38 (0.36, 0.41)	1.40 (1.31, 1.51)	0.40 (0.37, 0.44)	1.11 (1.02, 1.22)
Other	0.09 (0.07, 0.11)	0.16 (0.13, 0.20)	0.14 (0.11, 0.18)	0.20 (0.15, 0.27)
Age (years)[d]				
< 40	Ref	Ref	Ref	Ref
40-49	4.92 (4.36, 5.55)	4.82 (4.27, 5.44)	2.56 (2.19, 2.98)	2.40 (2.05, 2.80)
50-59	13.81 (12.43, 15.34)	13.37 (12.03, 14.86)	4.92 (4.29, 5.63)	4.50 (3.93, 5.16)
60-69	46.07 (41.70, 50.90)	42.32 (38.28, 46.78)	9.79 (8.60, 11.14)	8.58 (7.53, 9.79)
70-79	125.55 (113.80, 138.52)	109.21 (98.87, 120.62)	16.55 (14.56, 18.81)	13.96 (12.25, 15.91)
≥ 80	352.26 (319.45, 388.43)	255.64 (231.19, 282.66)	30.96 (27.22, 35.21)	23.60 (20.67, 26.94)
Gender[d]				
Male	Ref	Ref	Ref	Ref

Female	0.75 (0.73, 0.77)	0.58 (0.56, 0.60)	0.72 (0.69, 0.75)	0.68 (0.65, 0.70)
LTCF role				
Non-resident	Ref	Ref	Ref	Ref
Resident	17.23 (16.67, 17.80)	2.81 (2.70, 2.92)	4.40 (4.18, 4.64)	2.33 (2.20, 2.47)
Metro-urban status[d,f]				
Metro-urban	Ref	Ref	Ref	Ref
Nonmetro-urban	1.72 (1.67, 1.78)	1.30 (1.26, 1.35)	1.28 (1.22, 1.34)	1.18 (1.12, 1.24)
Nonmetro-rural	1.78 (1.64, 1.94)	1.14 (1.04, 1.25)	1.08 (0.97, 1.21)	0.95 (0.84, 1.07)

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference; LTCF, long-term care facility

[a] COVID-19 deaths were confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death.

[b] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic, and/or vital records criteria

[c] Multivariable models included the following independent variables: report month, race/ethnicity, age, gender, LTCF role, and metro-urban status.

[d] Missing values for race/ethnicity, age, gender, and metro-urban status were imputed using multivariate imputation by chained equations (MICE).

[e] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White, or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander, and those who reported their race as "other".

[f] Metro-urban status is the classification of a case's county of residence (i.e., usual residence at time of exposure/infection), when available, and current county (i.e., location at time of initial report) otherwise.

Furthermore, in the multivariable analysis, we found that Asian, Black, and Hispanic/Latino cases had higher odds of death compared to White cases (ORs = 1.39 [95% CI: 1.24-1.55], 1.54 [95% CI: 1.49-1.59], and 1.40 [95% CI: 1.31-1.51], respectively), and cases with other race had lower odds of death (OR = 0.16; 95% CI: 0.13-0.20) (Table 6-2). Compared to cases <40 years, the odds of death increased monotonically with age from an OR of 4.82 (95% CI: 4.27-5.44) for cases 40-49 years to an OR of 255.64 (95% CI: 231.19-282.66) for cases ≥80 years. We also found that females had a lower odds of death compared to males (OR = 0.58; 95% CI: 0.56-0.60) and LTCF residents had a higher odds of death compared to non-LTCF residents (OR = 2.81; 95% CI: 2.70-2.92). Finally, the odds of death for cases in nonmetro-urban and nonmetro-rural counties were greater than that for cases in metro-urban counties (ORs = 1.30 [95% CI: 1.26-1.35] and 1.14 [95% CI: 1.04-1.25], respectively). Of note, age is a likely confounder of the associations between report month, race/ethnicity, and LTCF role and COVID-19 death, as ORs for these variables changed meaningfully after age was added to the model (Supplementary Figure 6-8). Lastly, in a sensitivity analysis excluding cases with missing data, we found that results were comparable to those from our main analysis (Supplementary Table 6-2).

6.4.2 Risk factors for COVID-19 death: hospitalized cases

To examine associations between COVID-19 mortality and report month among hospitalized cases, we excluded cases that were not hospitalized (n = 548,453; 52.6%) or had missing hospitalization information (n = 429,084; 41.1%) from the analysis. After accounting for case demographics/location, we found slightly different trends in the risk of COVID-19 death compared to all cases. Most notably, compared to August 2020, the odds of death among hospitalized cases were higher in December 2020, January 2021, and February 2021 (ORs = 1.16 [95% CI: 1.07-1.27], 1.25 [95% CI: 1.14-1.36] and 1.11 [95%

CI: 1.00-1.24, respectively), whereas the odds of death among all cases were lower during these months. However, the odds of death among hospitalized cases declined from January to March 2021, and the odds of death in March 2021, compared to August 2020, was again lower (OR = 0.90; 95% CI: 0.78-1.04) (Table 6-2, Supplementary Figure 6-7). Associations between COVID-19 mortality and case characteristics were similar for all cases and hospitalized cases, with the exceptions of race/ethnicity and metro-urban status. Unlike among all cases, Black and White hospitalized cases had about an equal odds of dying, as did hospitalized cases in nonmetro-rural and metro-urban counties (Table 6-2).

6.4.3 Evidence for interactions: all cases and hospitalized cases

Among all cases and hospitalized cases, we found evidence for interactions between report month and age and race and age. Of note, Black race/ethnicity appeared to be a greater risk factor for COVID-19 mortality among younger cases and, to a lesser extent, younger hospitalized cases, with the odds of death among all Black cases decreasing monotonically with age from an OR of 2.84 (95% CI: 2.25-3.59) for cases <40 to an OR of 1.29 (95% CI: 1.20-1.37) for cases ≥80 years (Supplementary Figures 6-9 – 6-10).

6.5 Discussion

Similar to national trends, the COVID-19 CFR declined in Georgia between March 2020 and March 2021. We investigated the extent to which this decline could be the result of shifting case characteristics. Indeed, we found that Asian, Black, and Hispanic/Latino race/ethnicity, male gender, being a LTCF resident, being in a nonmetro-urban or nonmetro-rural county and, especially, older age were associated with higher mortality among COVID-19 cases. Nevertheless, after adjusting for all these factors, we still observed lower mortality risk from

November 2020 to March 2021, compared to August 2020, among cases. Because COVID-19 testing became more widely available in Georgia prior to August 2020, it is unlikely that these trends can be completely explained by changes in testing. This suggests that improvements in clinical care, such as the use of remdesivir,[75] dexamethasone,[76,77] and monoclonal antibody treatment,[78,79] may have contributed to lower mortality risk. It is also possible that early COVID-19 vaccinations, which are more effective against severe disease and death than asymptomatic infection or mild disease,[86] contributed to lower mortality risk in January, February, and March, 2021.

We also found that trends in mortality risk among hospitalized cases differed from that among all cases. Most notably, mortality risk among hospitalized cases increased again in December 2020 and January 2021. We hypothesize that this increase in risk was primarily due to increases in COVID-19 hospital occupancy rates, which may have led to increased mortality due to an overwhelmed healthcare system,[249,250] and/or to sicker patients being admitted given limited capacity, thus inflating mortality risk. In fact, we found that months in which COVID-19 occupancy rates were greatest corresponded to months in which the risk of death was greatest among hospitalized cases. Once COVID-19 occupancy rates decreased in February and March 2021, the risk of death among hospitalized cases decreased as well. This finding has important public health implications, as it suggests that surveillance of hospital occupancy rates could be used to predict and prepare for increases in deaths. To determine the utility of hospital occupancy surveillance, future studies should use a more granular time scale (e.g., days or weeks) to determine if, and to what extent, there is a lag in deaths following increases in hospital occupancy rates.

Similar trends in adjusted mortality risk among hospitalized COVID-19 cases were found in national studies of acute care hospitals[251,252] and the Department of Veterans Affairs

healthcare system,[253] however these studies did not examine trends after November 2020. Other studies have similarly found that older age,[81-83] male sex,[81-83,251,252,254] and Asian race/ethnicity[255-257] are associated with increased COVID-19 mortality risk among cases. Our finding that cases in nonmetro-rural counties, compared to cases in metro-urban counties, had a greater risk of COVID-19 death is consistent with evidence that individuals in rural U.S. counties face disparities in access to healthcare.[258,259] However, among hospitalized cases, we found no association between nonmetro-rural county and COVID-19 death, possibly because cases in nonmetro-rural counties were less likely to be tested for COVID-19, therefore inflating mortality risk among all cases, or because cases in nonmetro-rural counties were being transferred to larger, urban hospitals where COVID-19 occupancy rates may have been lower, resulting in improved survival. Without more detailed data on hospitalizations, we were unable to examine this further. Lastly, there is currently mixed evidence for associations between Hispanic/Latino and Black race/ethnicity and increased mortality risk among cases. While some studies have found that Hispanic/Latino and Black cases have an increased mortality risk,[256,257] other studies have found no evidence of an increased risk.[255,260,261] Furthermore, among hospitalized cases, we found no association between Black race/ethnicity and COVID-19 death, possibly because Black individuals were less likely to be tested, therefore inflating the mortality risk among all Black cases,[256,261] or because Black individuals, who are less likely than White individuals to have health insurance in Georgia,[262] had less access to or were less likely to seek non-hospital care.[263] While less access to hospital care could also explain this finding, we found that Black and White cases who died were about equally likely to have been hospitalized or to have missing hospitalization information.

We note a number of limitations with this analysis. First, limited testing early in the pandemic inflated the risk of COVID-19 mortality among reported cases. To address this, we compared the risk of death for each month to that of August 2020, a month in which testing was more widely available in Georgia. Furthermore, we examined trends among hospitalized cases, which are less subject to bias from changes in testing. Second, universal testing of patients on hospital admission, which was widely implemented once diagnostics tests became widely available in spring/summer 2020 (A. Hall, personal communication, February 22, 2022), may have decreased the mortality risk. However, we observed an increased mortality risk among hospitalized cases in December 2020 and January 2021, which cannot be explained by universal testing. Third, increases in partial immunity from prior infection as the pandemic progressed, which could not be accounted for in this analysis, may also have contributed to declines in mortality risk. However, SARS-CoV-2 reinfections during the time period of this study were uncommon,[264] so it is unlikely that partial immunity among re-infected individuals contributed meaningfully to the decreased CFR. Fourth, information on hospitalization was missing for almost half of cases, so some cases missing hospitalization information were likely misclassified as having not been hospitalized. For this reason, our main analysis examined COVID-19 mortality among all case, rather than hospitalized cases. Fifth, race/ethnicity was frequently missing. To address this, we used MICE to impute missing information. Sixth, due to missingness, we were unable to include vaccination status in our analyses. Future studies should examine associations between COVID-19 vaccination and mortality risk in Georgia.

6.6 Conclusions

After adjusting for individual-level characteristics, the risk of COVID-19 mortality among cases was lower from November 2020 to March 2021 compared to August 2020, suggesting that improved clinical management may have contributed to lower mortality risk. Among hospitalized cases, mortality risk increased again in December 2020 and January 2021, but then decreased to a risk similar to that among all cases by March 2021.

6.7 Declarations

Funding

This work was supported by the Agency for Healthcare Research and Quality [grant number R01 HS025987] and the National Science Foundation [grant number 2032084]. This work was also supported by the Emory Covid-19 Response Collaborative, which is funded by a grant from the Robert W. Woodruff Foundation.

Acknowledgements

We thank the Georgia Department of Public Health for supplying data for this project. The contents herein are those of the authors and do not necessarily represent the official views of, nor an endorsement by, the Georgia Department of Public Health.

Conflicts of interest

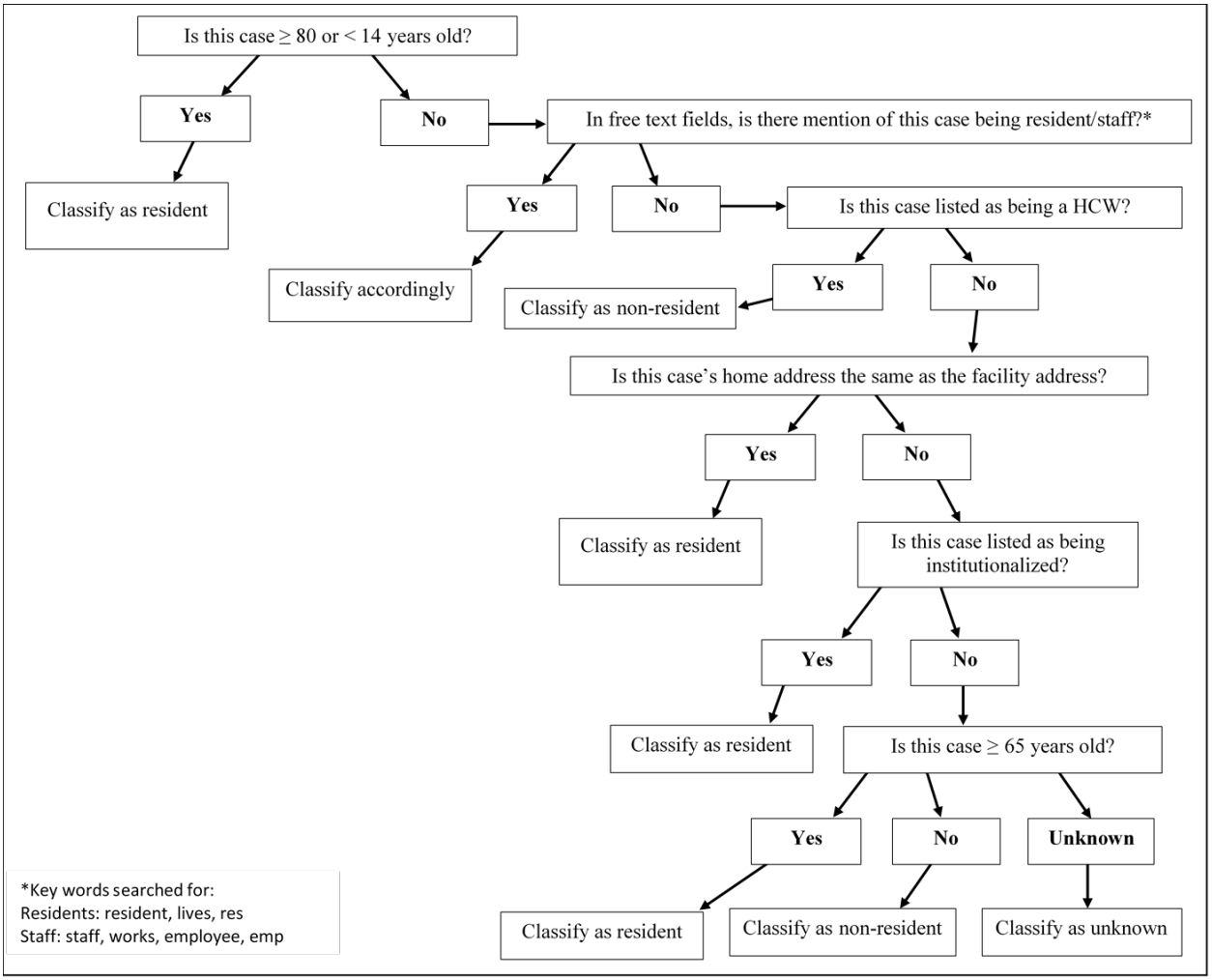
Benjamin A. Lopman reports grants and personal fees from Takeda Pharmaceuticals and personal fees from the World Health Organization, outside the submitted work. Allison Chamberlain is a consultant with the Fulton County Board of Health.

Authors' Contributions

Benjamin A. Lopman: Conceptualized, Supervision, Writing- Reviewing and Editing. Carly Adams: Data analysis, Writing- Original draft preparation. Pascale Wortley: Subject matter expertise, Writing- Reviewing and Editing. Allison Chamberlain: Subject matter expertise, Writing- Reviewing and Editing.

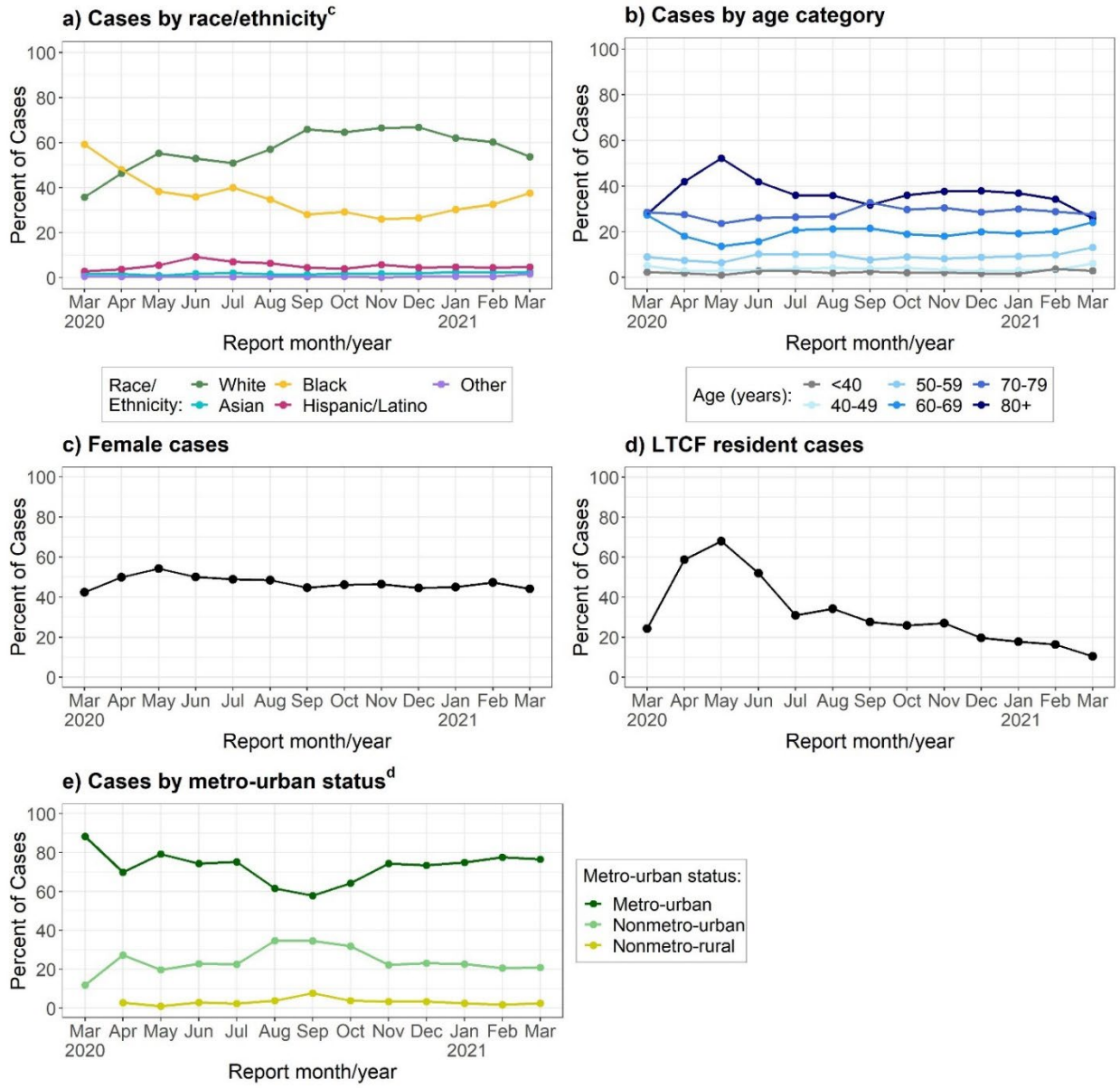
6.8 Supplementary File

Supplementary Figure 6-1. Decision tree for classifying LTCF-associated cases as residents or non-residents



Abbreviations: LTCF, long-term care facility; HCW, healthcare worker

Supplementary Figure 6-2. Characteristics of COVID-19 deaths[a,b] by report month in Georgia, USA: March 2, 2020 – March 31, 2020



Abbreviations: LTCF, long-term care facility

[a] Cases with missing information were not included in plots (i.e., imputed values were excluded)

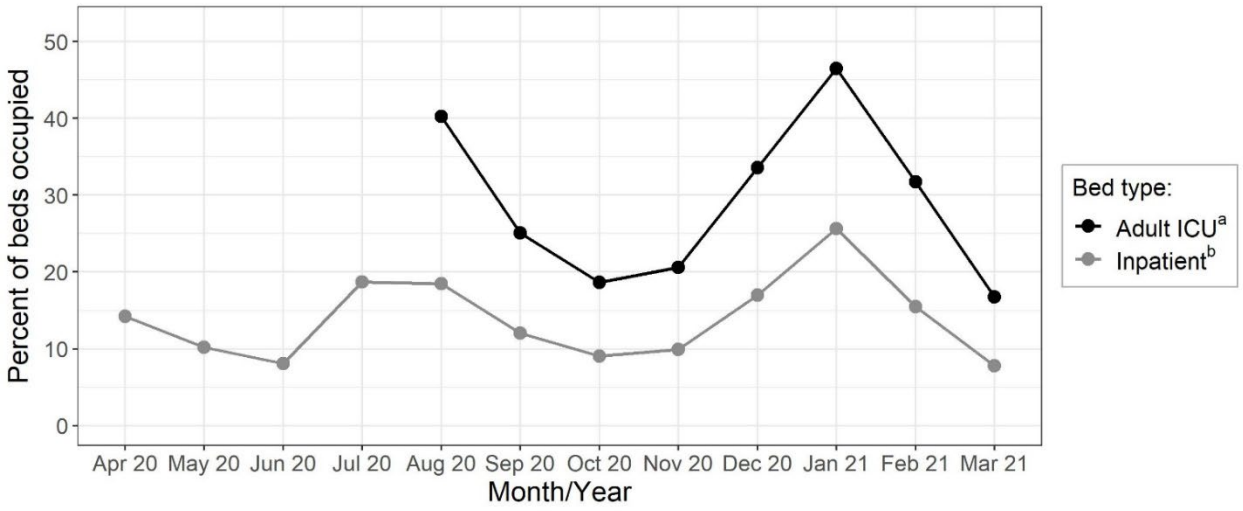
[b] COVID-19 deaths were defined as confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with

COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

[c] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

[d] Metro-urban status is the classification of a case’s county of residence, when available, and current county otherwise

Supplementary Figure 6-3. Percent of hospital beds occupied by COVID-19 patients in Georgia by month: April 1, 2020 – March 31, 2021



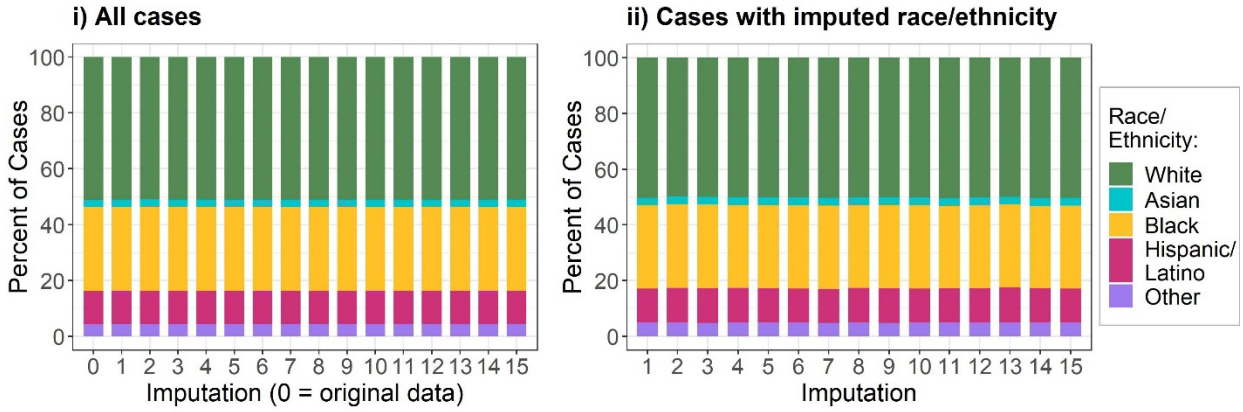
Abbreviations: ICU, intensive care unit

[a] Adult ICU bed occupancy was calculated by dividing the total number of staffed adult ICU beds occupied by COVID-19 patients by the total number of staffed adult ICU beds for a given month; data prior to August 2020 are not shown due to limited reporting by hospitals

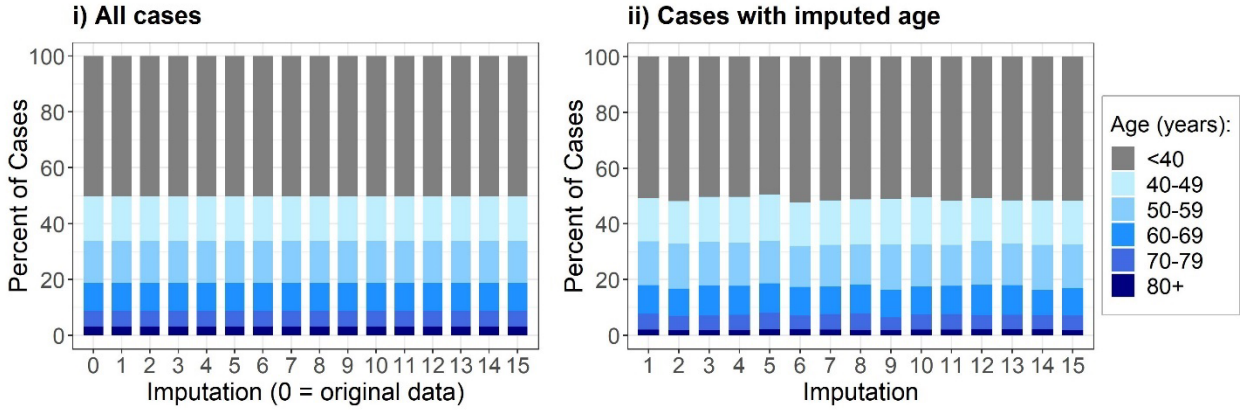
[b] Inpatient bed occupancy was calculated by dividing the total number of staffed inpatient beds, including all overflow, observation, and active surge/expansion beds used for inpatients and all ICU beds, occupied by COVID-19 patients by the total number of all staffed inpatient beds reported by Georgia hospitals for a given month

Supplementary Figure 6-4. Distributions of imputed variables across datasets[a] among all cases (i) and cases with imputed data only (ii).

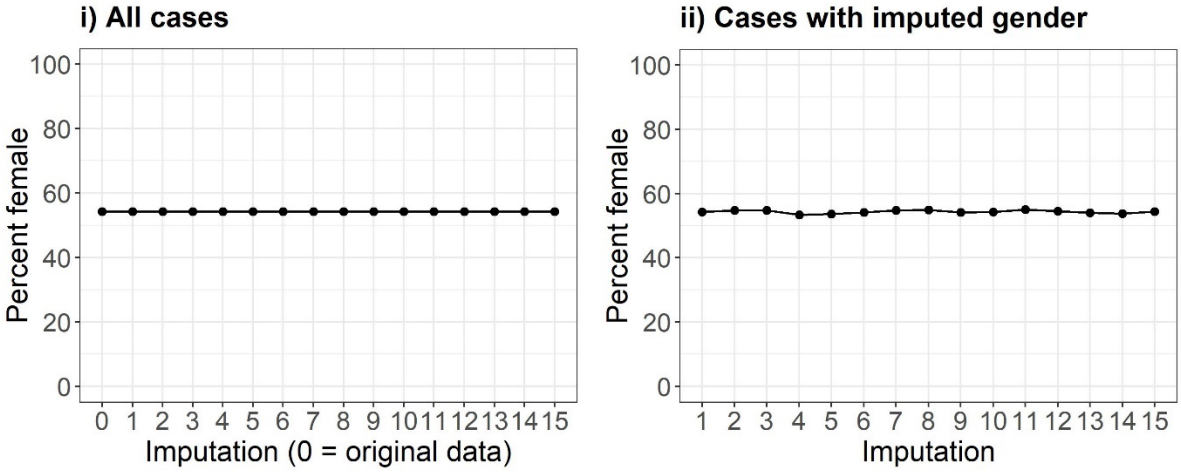
a) Race/ethnicity[b]



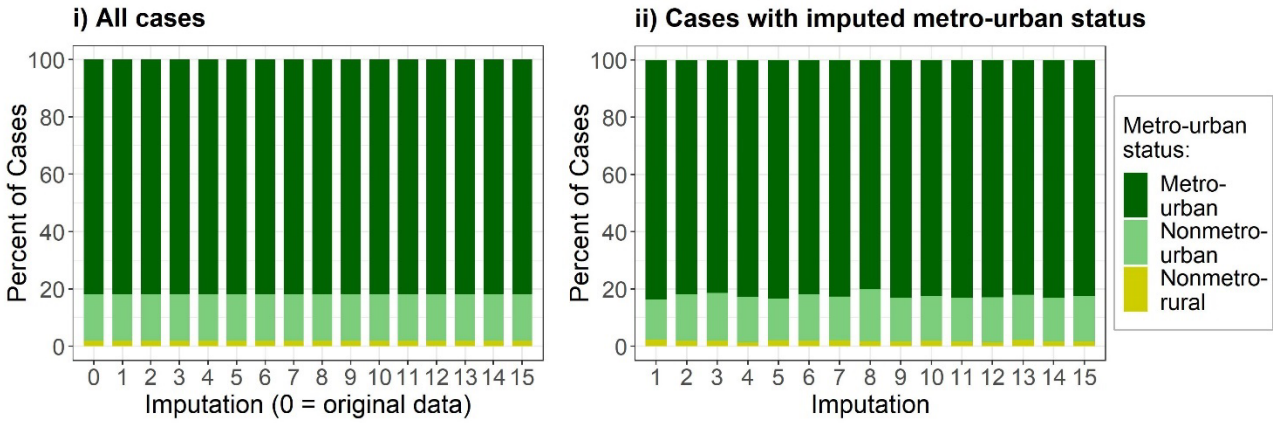
b) Age



c) Gender



d) Metro-urban status[c]



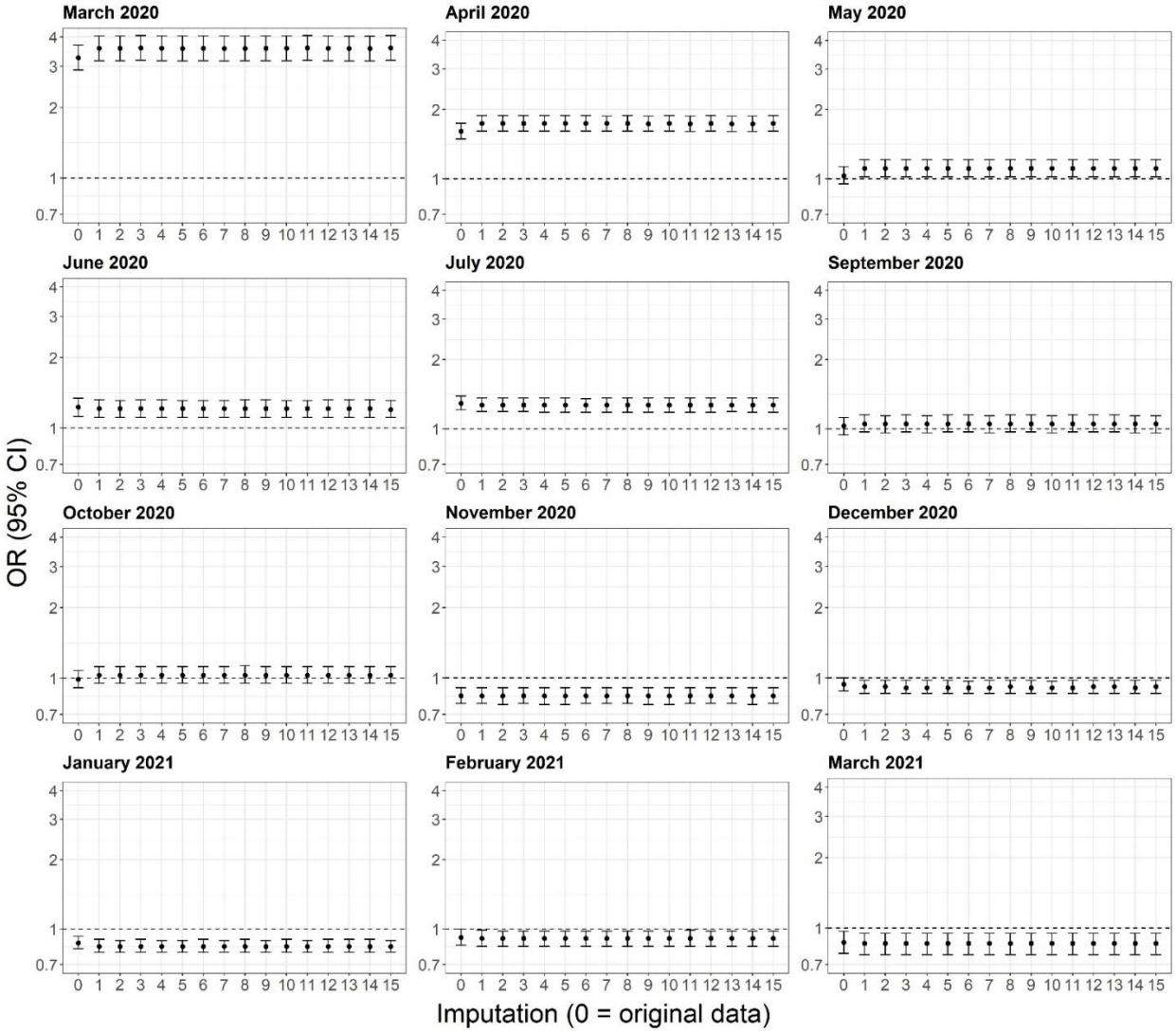
[a] Dataset "0" is the original dataset with non-imputed values; percentages for the original dataset were calculating by excluding cases with missing information

[b] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as "other"

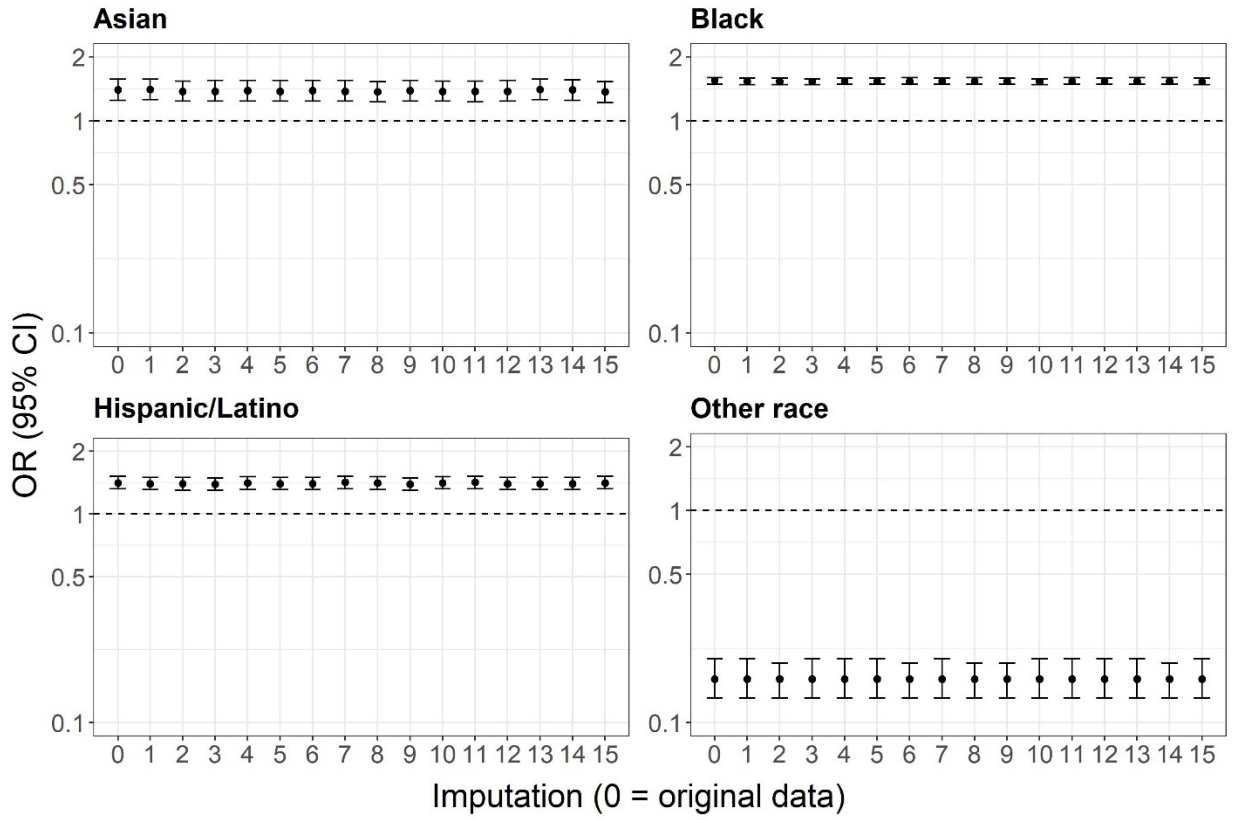
[c] Metro-urban status is the classification of a case's county of residence, when available, and current county otherwise

Supplementary Figure 6-5. Multivariable[a] logistic regression results from individual datasets[b] for associations between report month and case characteristics and COVID-19 death[c] among confirmed and probable COVID-19 cases[d] in GA, USA: March 2, 2020 – March 31, 2020

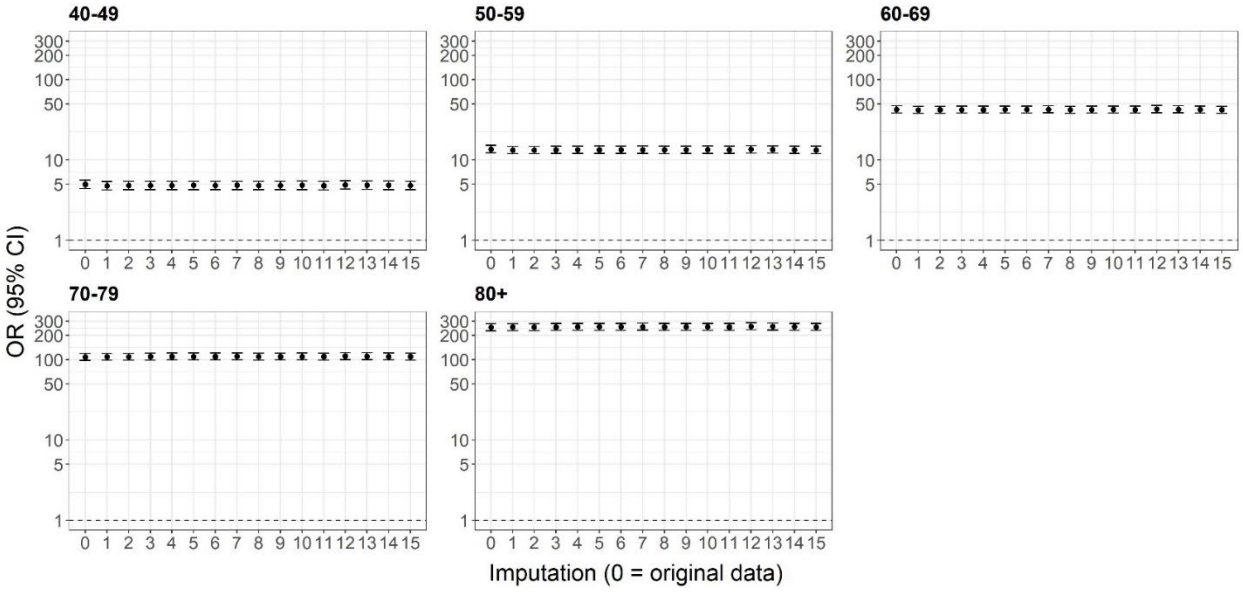
a) Report month (reference = August 2020)



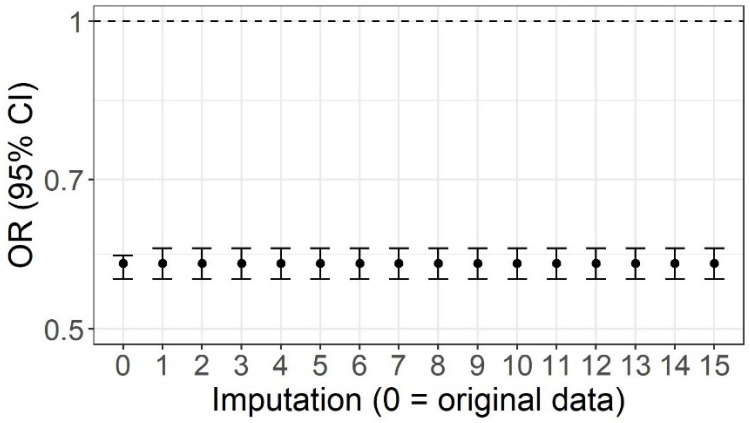
b) Race/ethnicity[e] (reference = White)



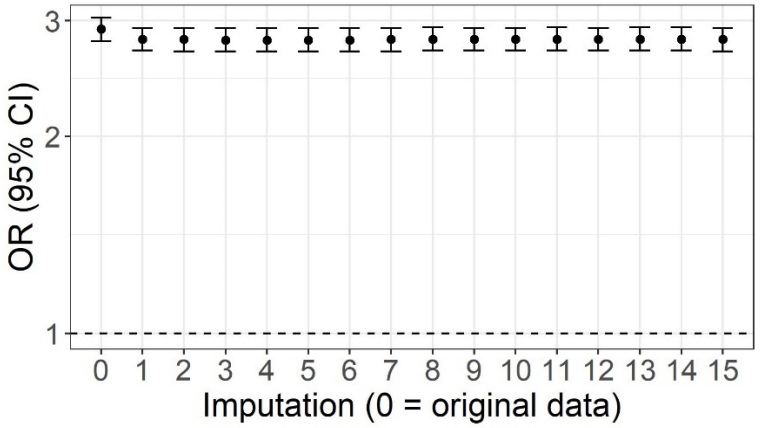
c) Age (reference = <40 years)



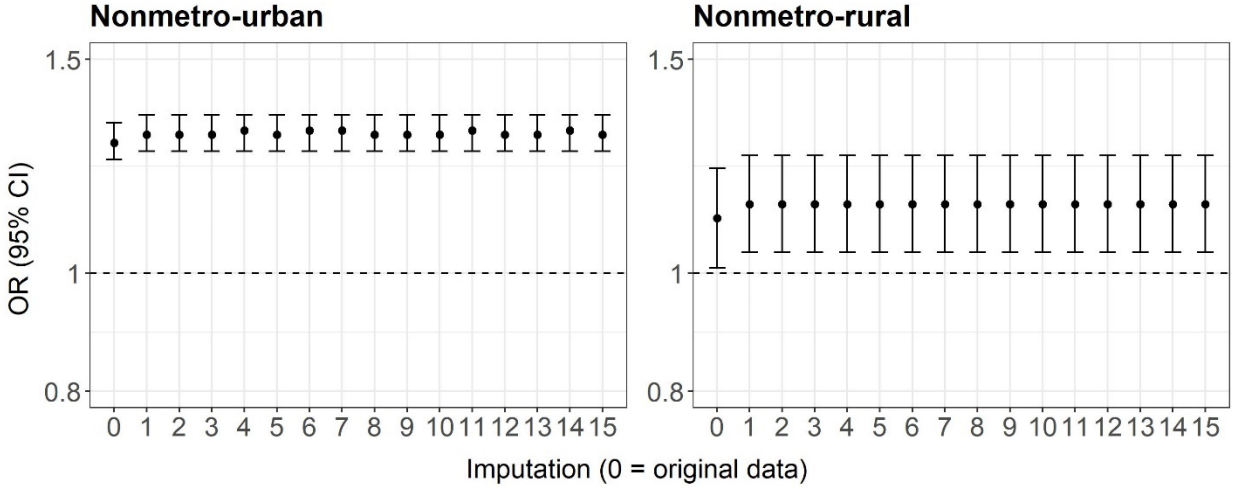
d) Female gender (reference = male)



e) LTCF resident (reference = non-LTCF resident)



f) Metro-urban status[f] (reference = non-metro urban)



Abbreviations: OR, odds ratio; CI, confidence interval; LTCF, long-term care facility

[a] All models included the following independent variables: report month, race/ethnicity, age, gender, LTCF role, and metro-urban status

b Dataset “0” is the original dataset with non-imputed values; regression models for the original dataset excluded cases with missing information (i.e., complete case analyses)

[c] COVID-19 deaths were defined as confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

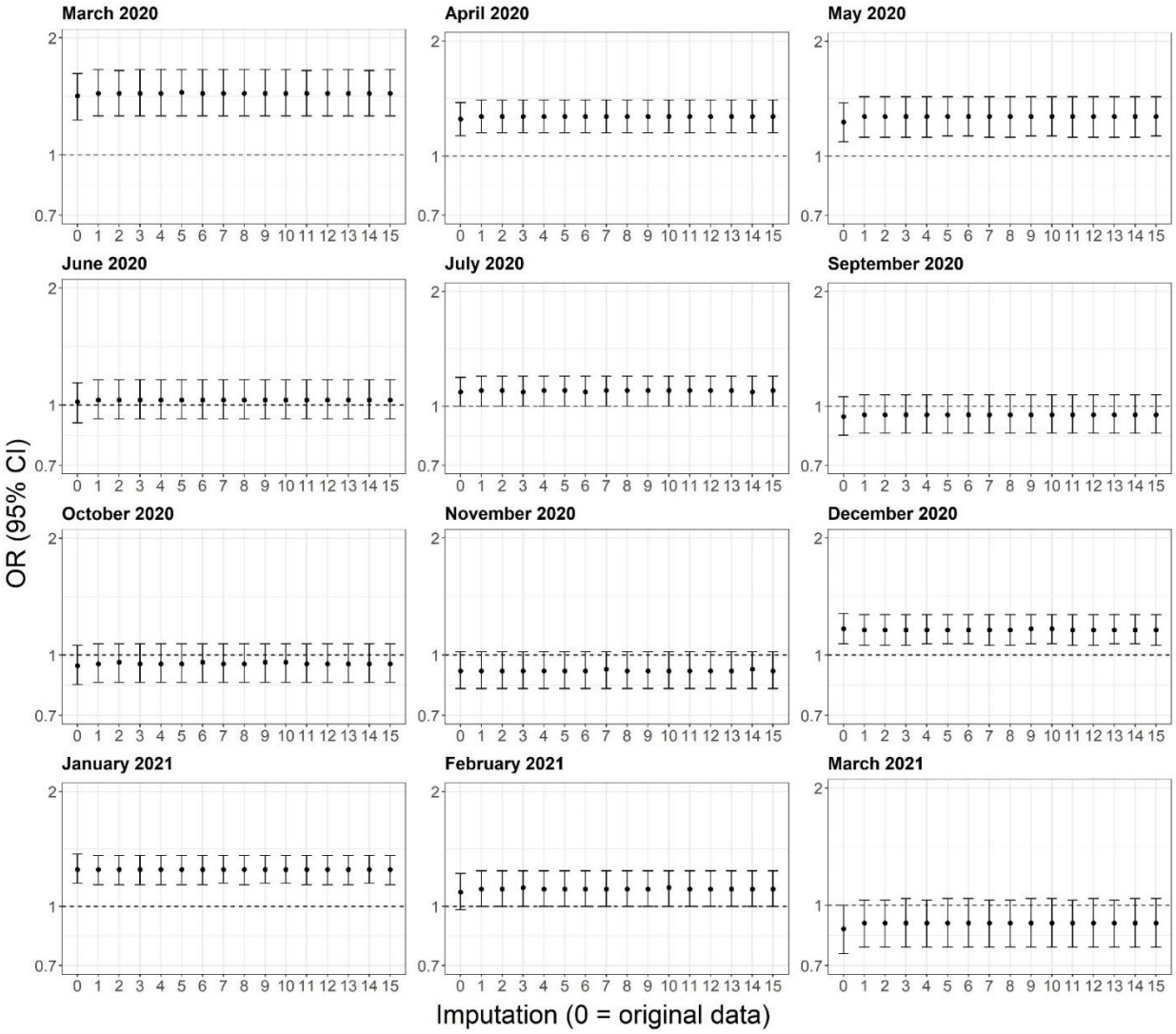
[d] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

[e] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

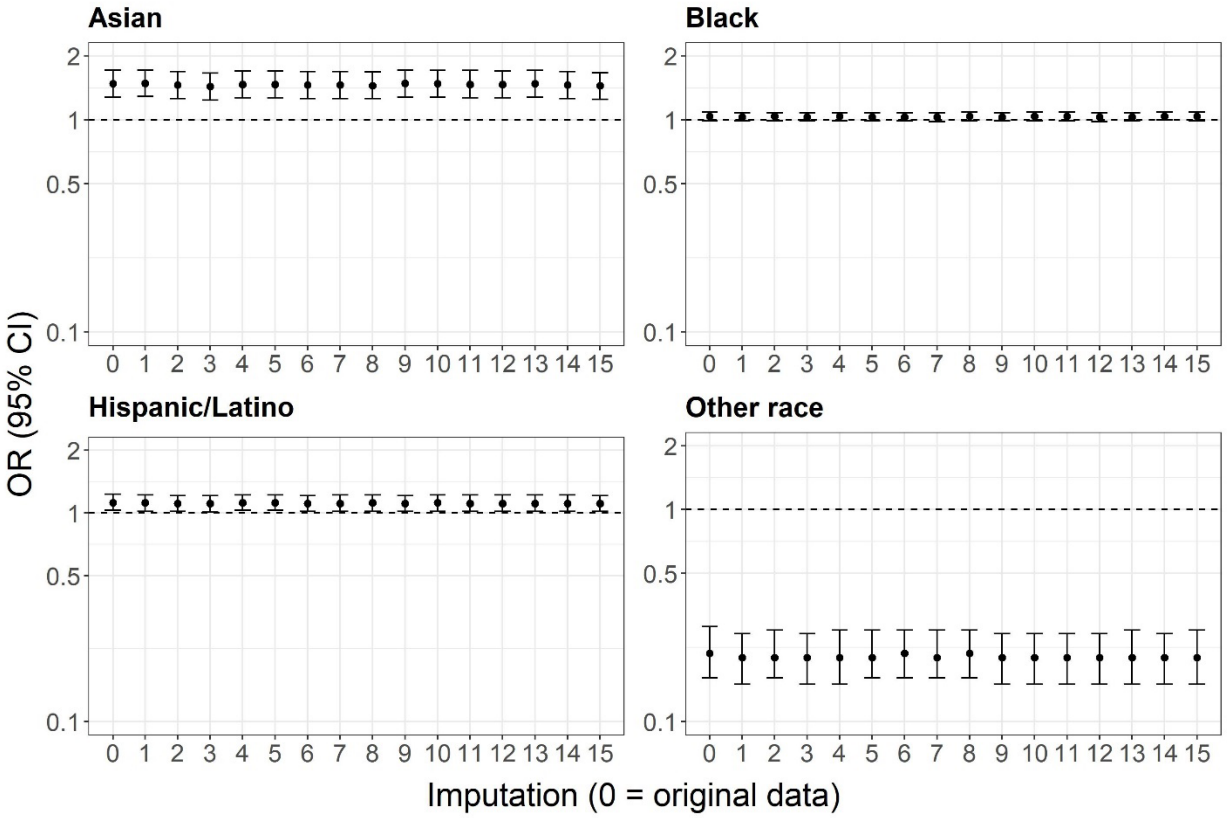
[f] Metro-urban status is the classification of a case’s county of residence, when available, and current county otherwise

Supplementary Figure 6-6. Multivariable[a] logistic regression results from individual datasets[b] for associations between report month and case characteristics and COVID-19 death[c] among confirmed and probable COVID-19 cases[d] that were hospitalized in GA, USA: March 2, 2020 – March 31, 2020

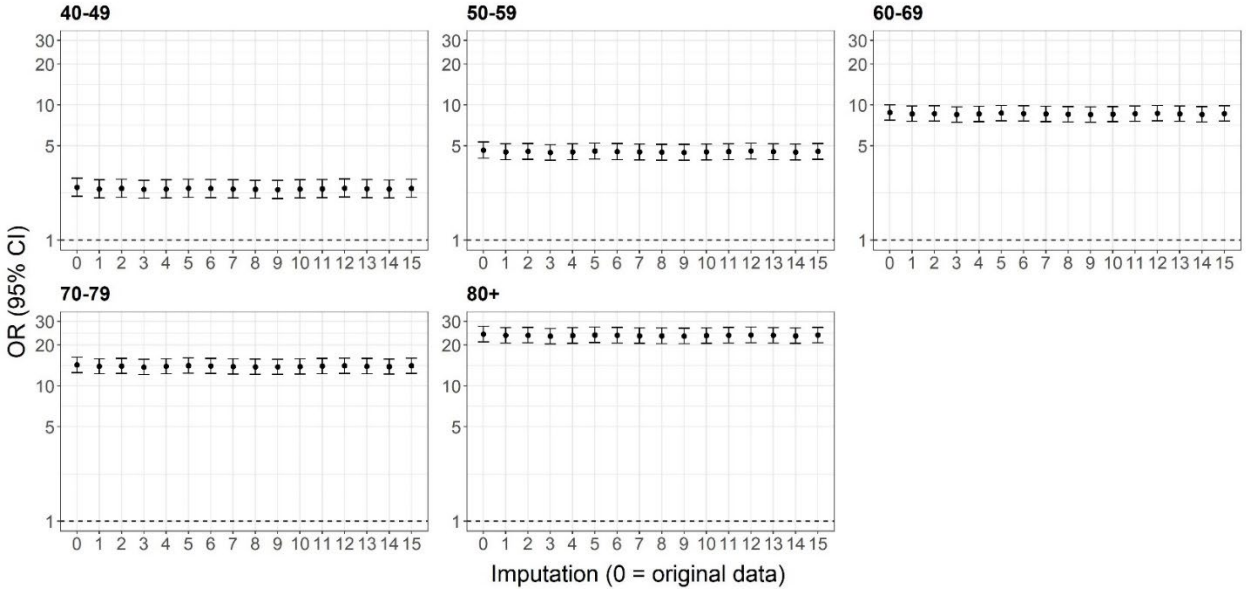
a) Report month (reference = August 2020)



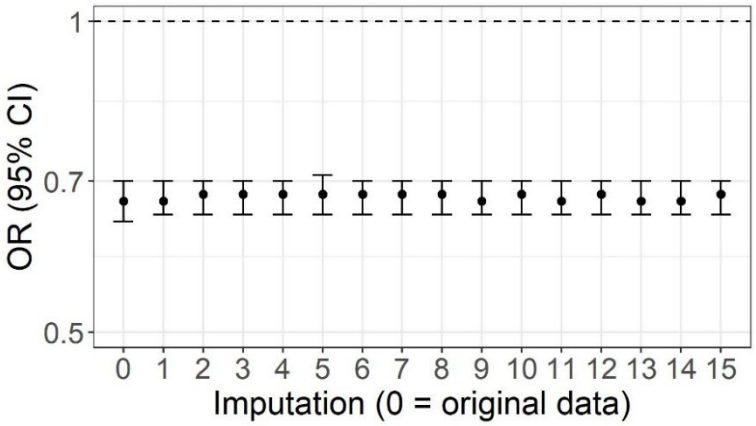
b) Race/ethnicity[e] (reference = White)



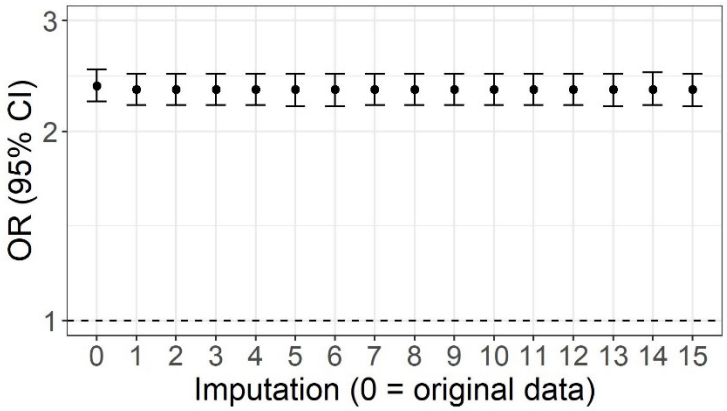
c) Age (reference = <40 years)



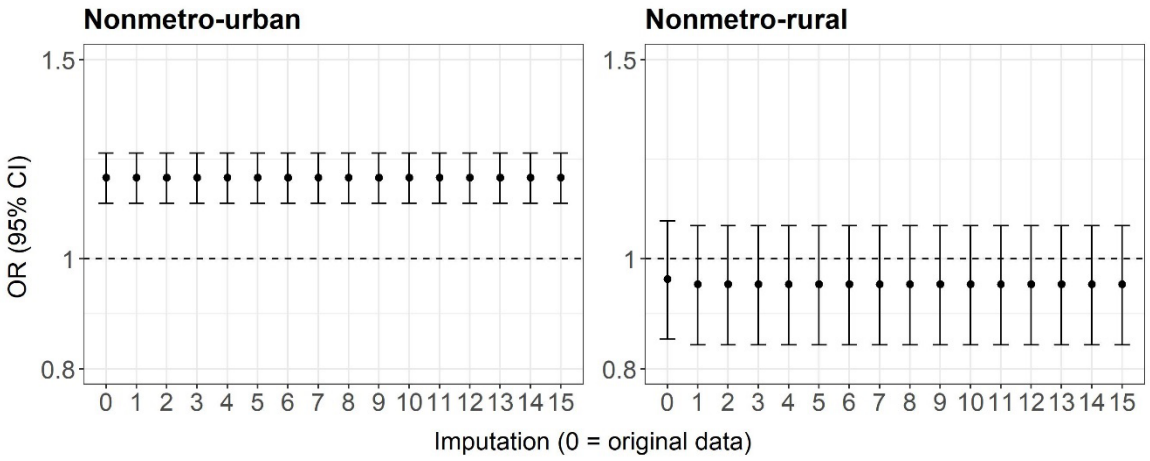
d) Female gender (reference = male)



e) LTCF resident (reference = non-LTCF resident)



f) Metro-urban status[f] (reference = non-metro urban)



Abbreviations: OR, odds ratio; CI, confidence interval; LTCF, long-term care facility

[a] All models included the following independent variables: report month, race/ethnicity, age, gender, LTCF role, and metro-urban status

[b] Dataset “0” is the original dataset with non-imputed values; regression models for the original dataset excluded cases with missing information (i.e., complete case analyses)

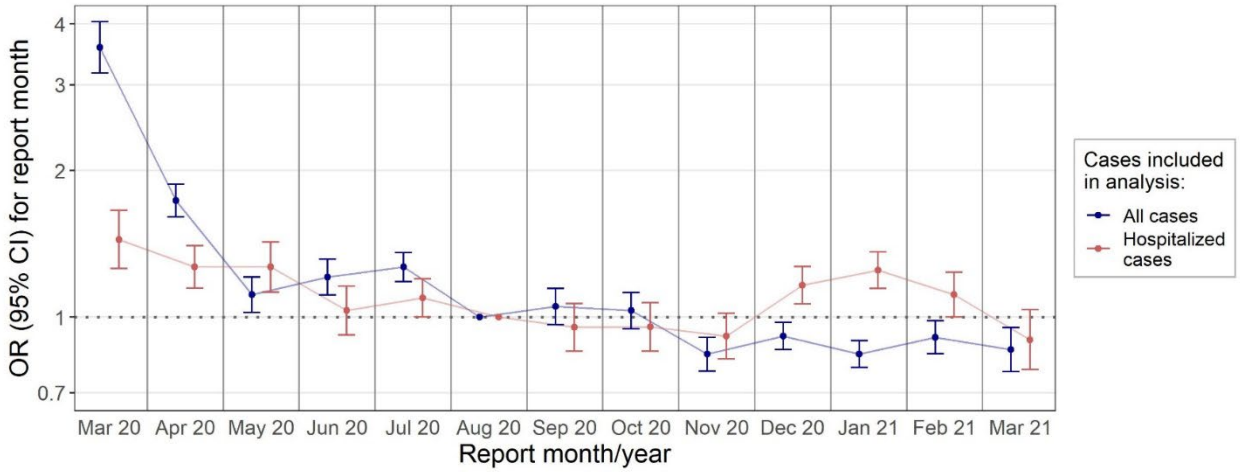
[c] COVID-19 deaths were defined as confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

[d] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

[e] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

[f] Metro-urban status is the classification of a case’s county of residence, when available, and current county otherwise

Supplementary Figure 6-7. Multivariable logistic regression[a] odds ratios for associations between report month and COVID-19 death[b] among all cases (confirmed and probable)[c] and hospitalized cases of COVID-19 in GA, USA: March 2, 2020 – March 31, 2020



Abbreviations: OR, odds ratio; CI, confidence interval

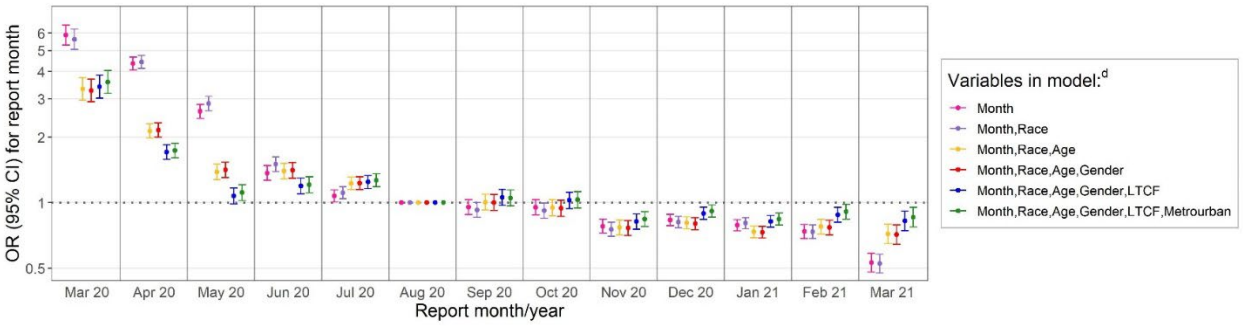
[a] Logistic regression models included the following independent variables: report month, race/ethnicity, age, gender, LTCF role, and metro-urban status; metro-urban status is the classification of a case's county of residence, when available, and current county otherwise

[b] COVID-19 deaths were confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

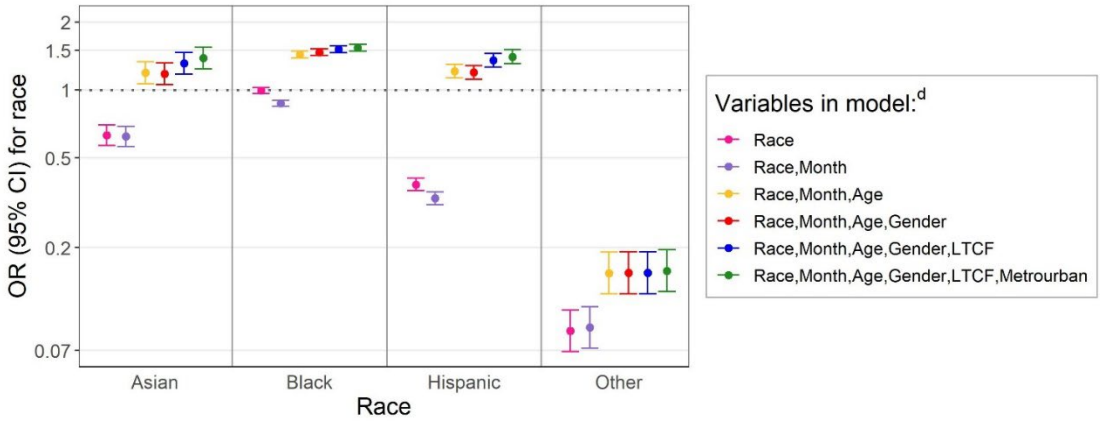
[c] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

Supplementary Figure 6-8. Examining confounding[a] for associations between report month and case characteristics and COVID-19 death[b] among confirmed and probable COVID-19 cases[c] in GA, USA: March 2, 2020 – March 31, 2020

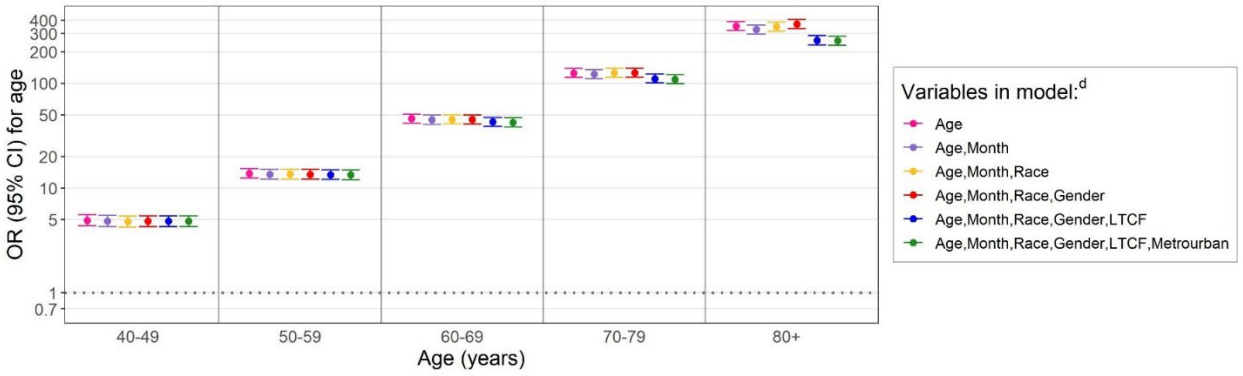
a) Report month (reference = August)



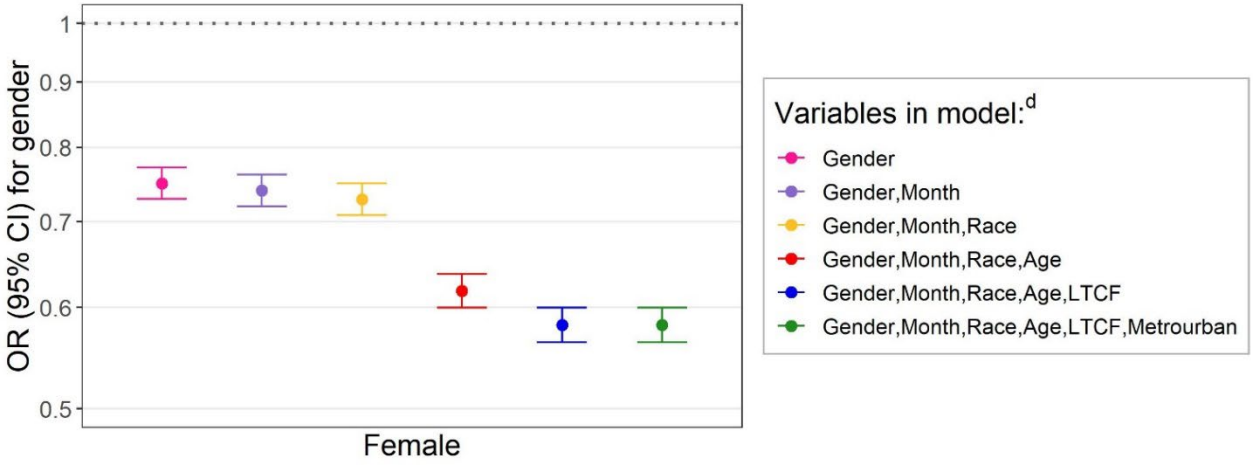
b) Race/ethnicity[e] (reference = White)



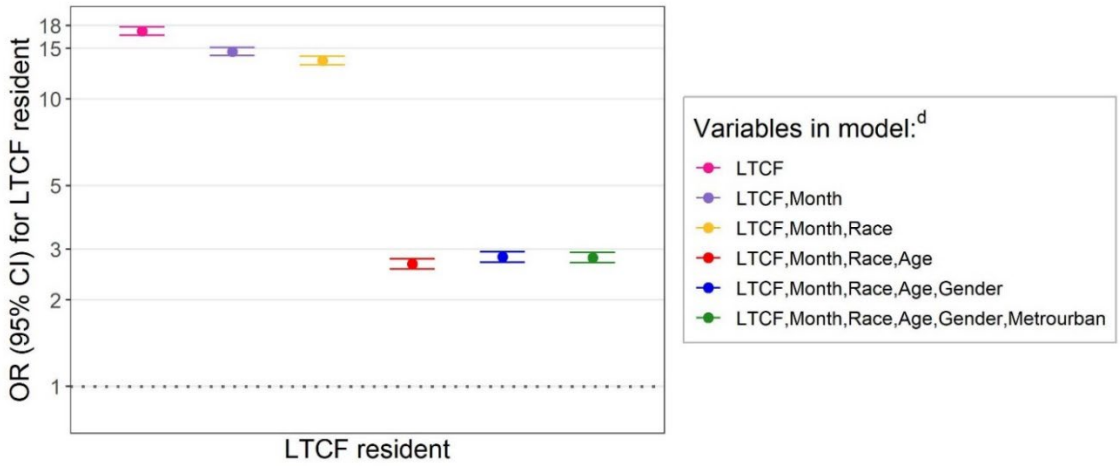
d) Age (reference = < 40 years)



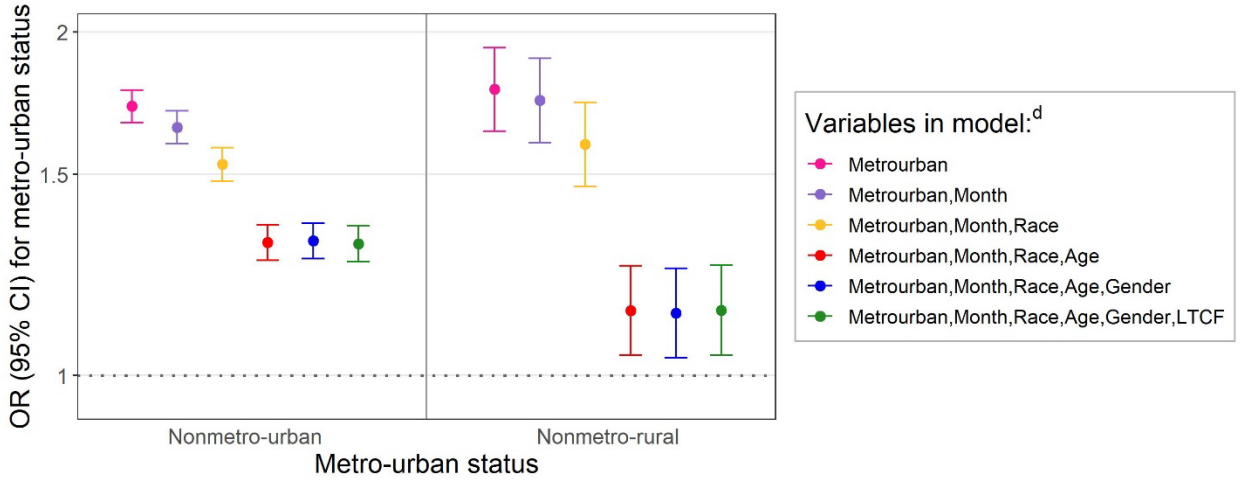
e) Gender (reference = male)



f) LTCF role (reference = non-LTCF resident)



g) Metro-urban status[f] (reference = metro-urban)



Abbreviations: OR, odds ratio; CI, confidence interval; LTCF, long-term care facility

[a] Confounding by a variable is indicated if results change meaningfully when the variable is added to the model

[b] COVID-19 deaths were confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

[c] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

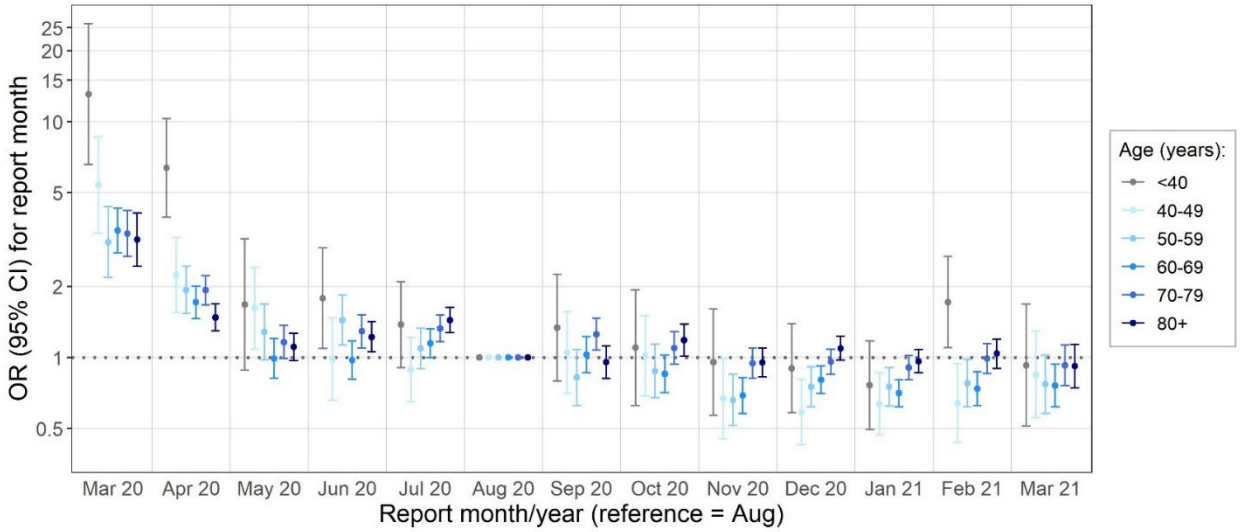
[d] Variables included in the models: report month (month), race/ethnicity (race), age, gender, LTCF role (LTCF), and metro-urban status (metrourban)

[e] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

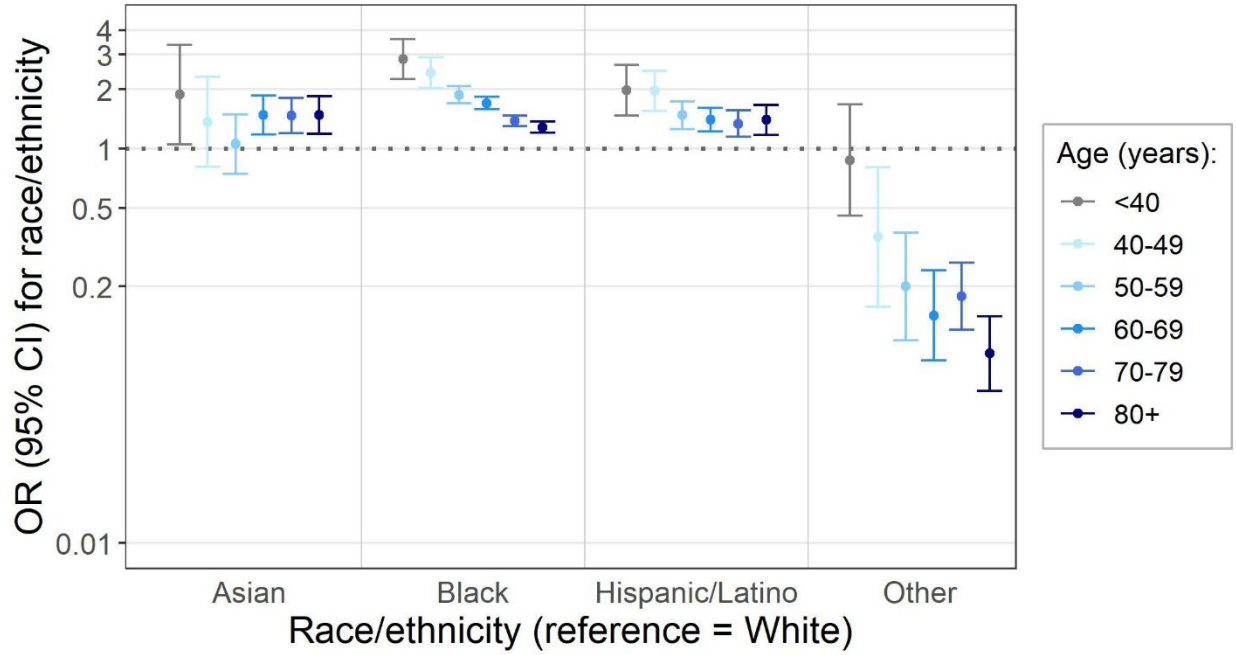
[f] Metro-urban status is the classification of a case’s county of residence, when available, and current county otherwise

Supplementary Figure 6-9. Contrast statements for interactions in logistic regression analysis[a] for confirmed and probable COVID-19 cases[b] in GA, USA: March 2, 2020 – March 31, 2020

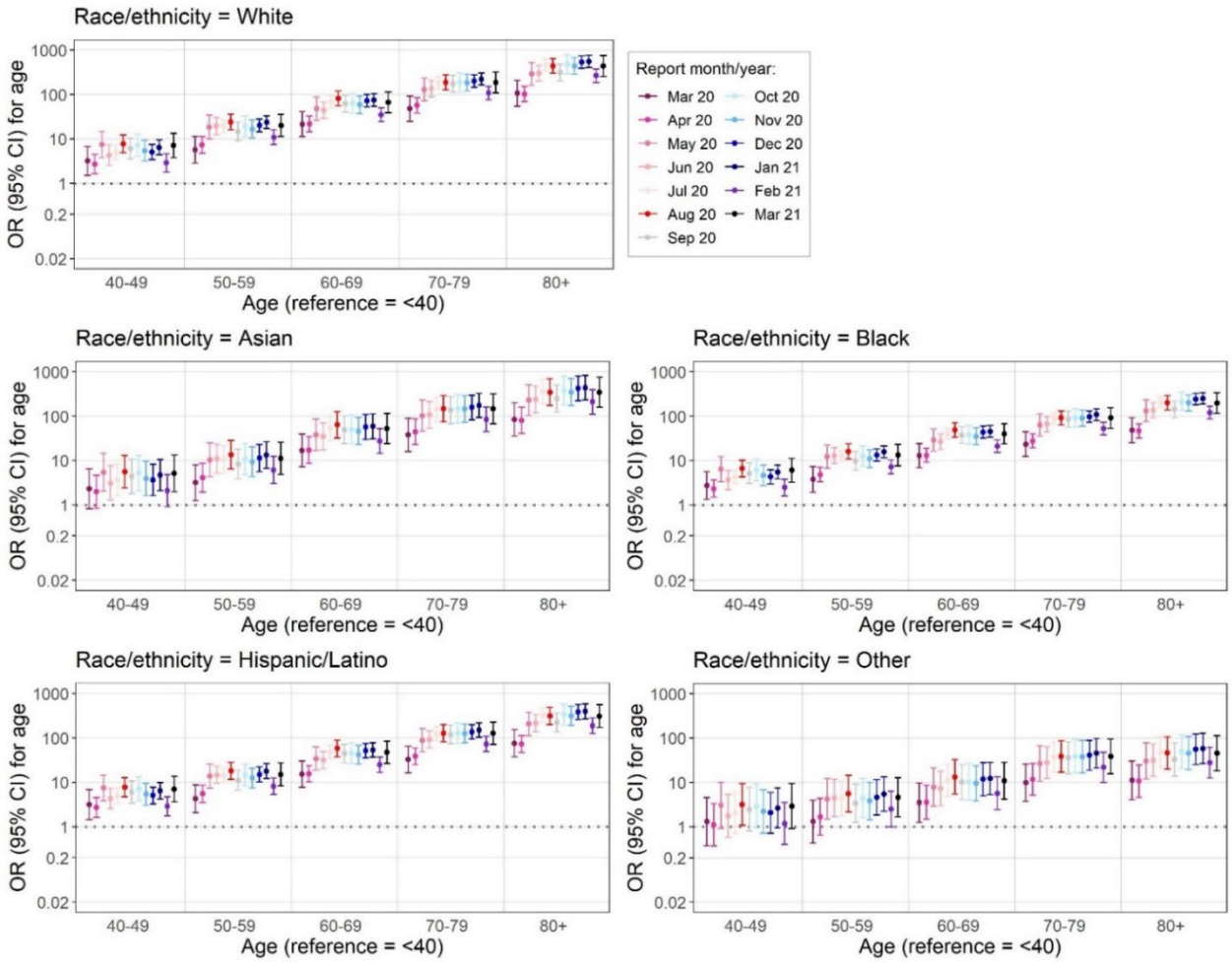
a) Interaction between report month and age; ORs for report month are shown



b) Interaction between race/ethnicity[c] and age; ORs for race/ethnicity are shown



c) Interactions between age and report month and race/ethnicity[c]; ORs for age are shown



Abbreviations: ORs, odds ratios; CI, confidence interval

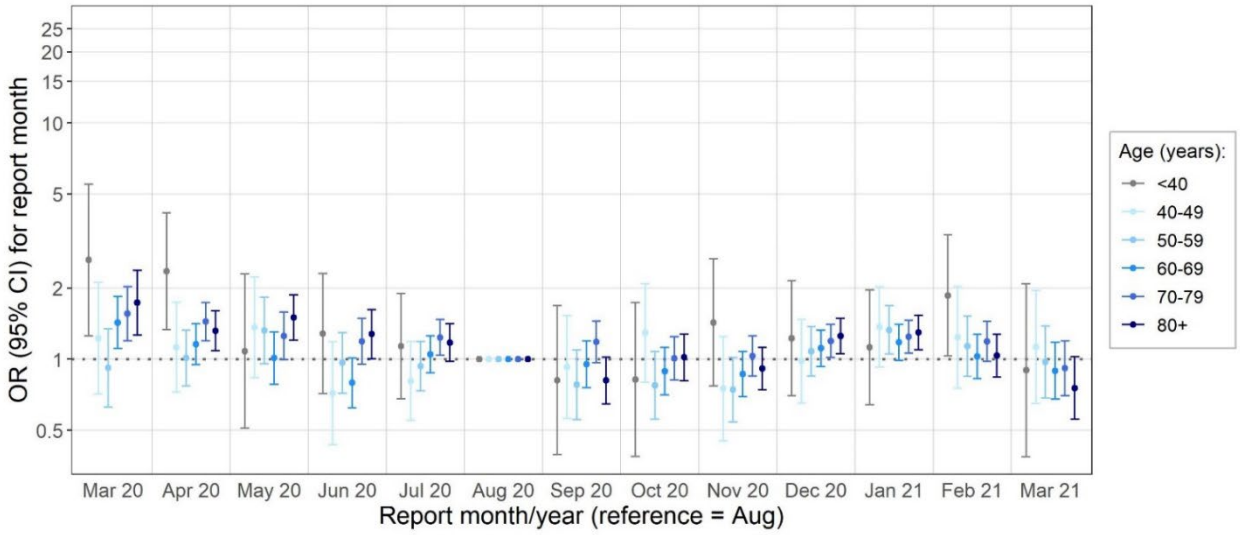
[a] Evidence for interaction was assessed using imputed data; in addition to interaction terms, the model included the following independent variables: report month, race/ethnicity, age, gender, long-term care facility (LTCF) role, and metro-urban status

[b] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

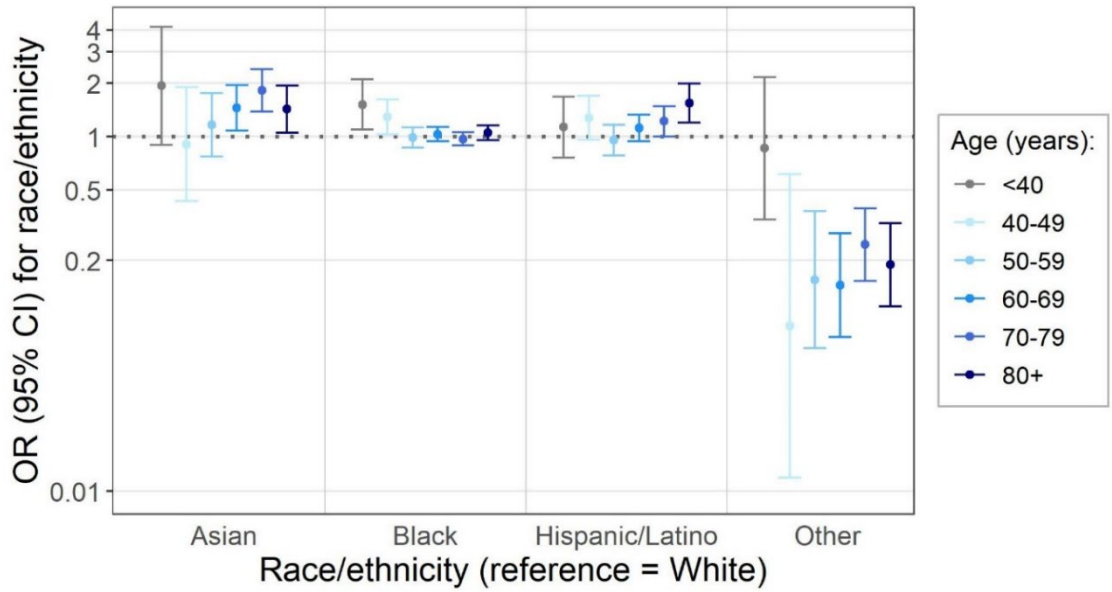
[c] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

Supplementary Figure 6-10. Contrast statements for interactions in logistic regression analysis[a] for confirmed and probable hospitalized COVID-19 cases[b] in GA, USA: March 2, 2020 – March 31, 2020

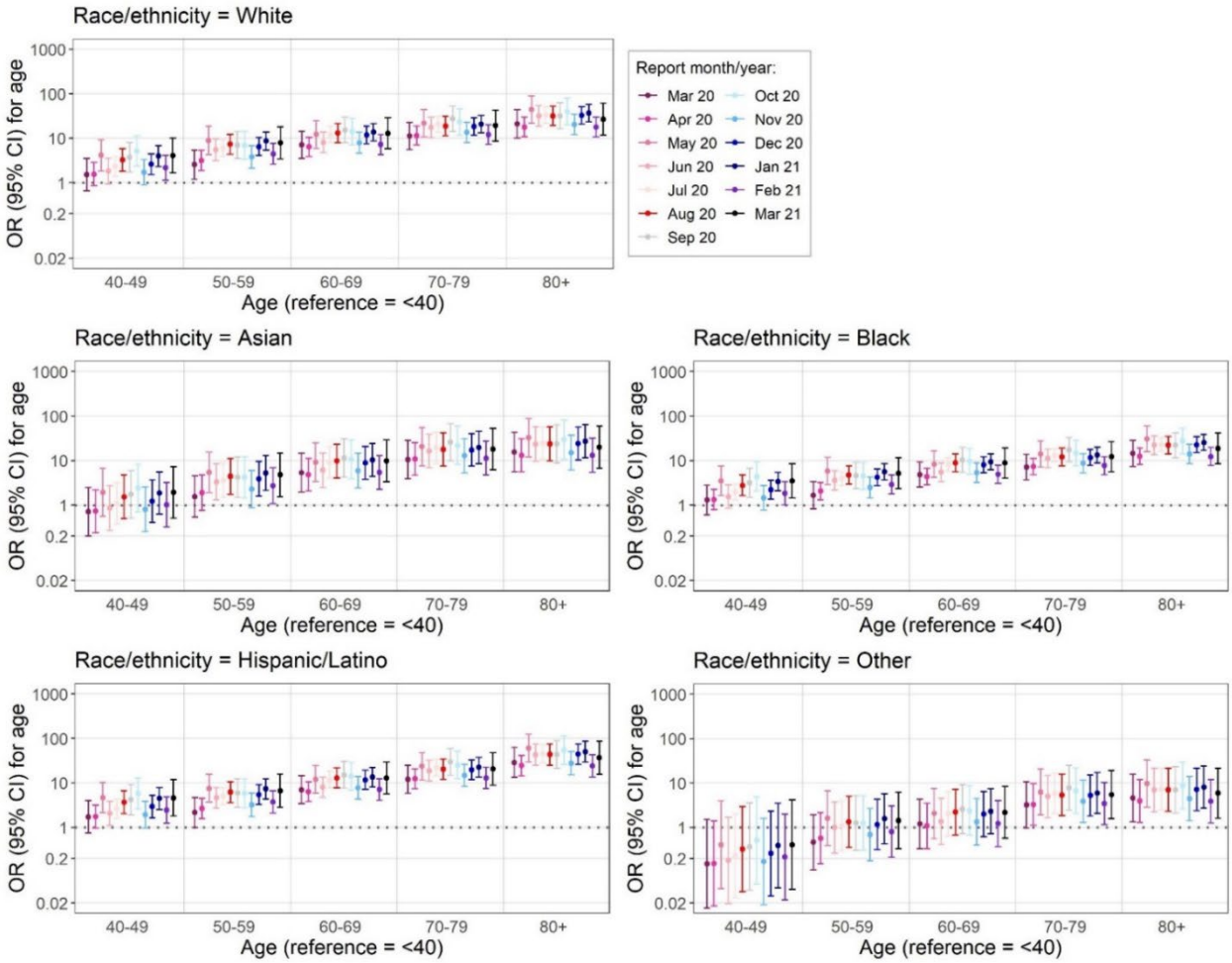
a) Interaction between report month and age; ORs for report month are shown



b) Interaction between race/ethnicity[c] and age; ORs for race/ethnicity are shown



c) Interactions between age and report month and race/ethnicity[c]; ORs for age are shown



Abbreviations: odds ratios, ORs; confidence interval, CI

[a] Evidence for interaction was assessed using imputed data; in addition to interaction terms, the model included the following independent variables: report month, race/ethnicity, age, gender, long-term care facility (LTCF) role, and metro-urban status

[b] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

[c] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

Supplementary Table 6-1. Characteristics of confirmed COVID-19 deaths[a,b] and COVID-19 deaths under review[c] in Georgia, USA: March 2, 2020 – March 31, 2020

Characteristic	**Confirmed deaths** (n = 19,754)	**Deaths under review** (n =1,801)
Report month/year (N (%))		
March 2020	469 (2.4)	7 (0.4)
April 2020	1,740 (8.8)	206 (11.4)
May 2020	1,198 (6.1)	181 (10.0)
June 2020	1,086 (5.5)	117 (6.5)
July 2020	2,315 (11.7)	171 (9.5)
August 2020	1,709 (8.7)	120 (6.7)
September 2020	972 (4.9)	68 (3.8)
October 2020	937 (4.7)	46 (2.6)
November 2020	1,185 (6.0)	131 (7.3)
December 2020	2,960 (15.0)	271 (15.0)
January 2021	3,381 (17.1)	279 (15.5)
February 2021	1,285 (6.5)	132 (7.3)
March 2021	517 (2.6)	72 (4.0)
Race/ethnicity (N (%))[d,e]		
White	11,493 (58.3)	1,172 (67.3)
Asian	371 (1.9)	22 (1.3)
Black	6,732 (34.2)	479 (27.5)
Hispanic/Latino	1,028 (5.2)	58 (3.3)
Other	87 (0.4)	11 (0.6)

Age; years (median (IQR))	75 (65, 84)	73 (57, 84)
Female (N (%))[e]	9,314 (47.2)	1,012 (56.3)
LTCF resident (N (%))	6,097 (30.9)	725 (40.3)
Metro-urban status (N (%))[e,f]		
Metro-urban	14,321 (72.5)	1,326 (73.7)
Nonmetro-urban	4,846 (24.5)	429 (23.8)
Nonmetro-rural	580 (2.9)	45 (2.5)

Abbreviations: N, number; IQR, interquartile range; LTCF, long-term care facility

[a] Cases with missing information were not included in the table (i.e., imputed values were excluded)

[b] Confirmed COVID-19 deaths were defined as confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

[c] COVID-19 deaths under review were deaths that could not be classified as confirmed COVID-19 deaths but may still be classified as such, pending additional information

[d] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as “other”

[e] Percentages were calculated by excluding cases with missing information (there was no missingness for report month or LTCF role)

[f] Metro-urban status is the classification of a case’s county of residence, when available, and current county otherwise

Supplementary Table 6-2. Multivariable[a] logistic regression results for associations between report month and case characteristics and COVID-19 death[b] among confirmed and probable COVID-19 cases[c] in GA, USA: March 2, 2020 – March 31, 2020

	All cases		Hospitalized cases	
	Main analysis[d]	**Sensitivity analysis[e]**	**Main analysis[d]**	**Sensitivity analysis[e]**
Variable	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**	**OR (95% CI)**
Report month/year				
March 2020	3.58 (3.17, 4.04)	3.26 (2.89, 3.69)	1.44 (1.26, 1.66)	1.42 (1.23, 1.62)
April 2020	1.74 (1.61, 1.88)	1.61 (1.49, 1.74)	1.27 (1.15, 1.40)	1.25 (1.13, 1.38)
May 2020	1.11 (1.02, 1.21)	1.03 (0.95, 1.13)	1.27 (1.12, 1.43)	1.23 (1.09, 1.38)
June 2020	1.21 (1.11, 1.32)	1.23 (1.12, 1.34)	1.03 (0.92, 1.16)	1.02 (0.90, 1.14)
July 2020	1.27 (1.18, 1.36)	1.29 (1.21, 1.39)	1.10 (1.00, 1.20)	1.09 (1.00, 1.19)
August 2020	Ref	Ref	Ref	Ref
September 2020	1.05 (0.97, 1.15)	1.03 (0.94, 1.12)	0.95 (0.85, 1.07)	0.94 (0.84, 1.06)
October 2020	1.03 (0.95, 1.12)	0.99 (0.91, 1.08)	0.95 (0.85, 1.07)	0.94 (0.84, 1.06)
November 2020	0.84 (0.78, 0.91)	0.84 (0.78, 0.91)	0.91 (0.82, 1.02)	0.91 (0.82, 1.02)
December 2020	0.91 (0.86, 0.98)	0.94 (0.88, 1.00)	1.16 (1.07, 1.27)	1.17 (1.07, 1.28)

January 2021	0.84 (0.79, 0.90)	0.87 (0.82, 0.93)	1.25 (1.14, 1.36)	1.25 (1.15, 1.37)
February 2021	0.91 (0.84, 0.98)	0.92 (0.85, 1.00)	1.11 (1.00, 1.24)	1.09 (0.98, 1.22)
March 2021	0.86 (0.77, 0.95)	0.87 (0.78, 0.97)	0.90 (0.78, 1.04)	0.87 (0.75, 1.00)
Race/ethnicity[f]				
White	Ref	Ref	Ref	Ref
Asian	1.39 (1.24, 1.55)	1.40 (1.25, 1.57)	1.47 (1.27, 1.70)	1.48 (1.28, 1.72)
Black	1.54 (1.49, 1.59)	1.55 (1.49, 1.60)	1.03 (0.99, 1.08)	1.04 (0.99, 1.09)
Hispanic/Latino	1.40 (1.31, 1.51)	1.41 (1.32, 1.52)	1.11 (1.02, 1.22)	1.12 (1.03, 1.23)
Other	0.16 (0.13, 0.20)	0.16 (0.13, 0.20)	0.20 (0.15, 0.27)	0.21 (0.16, 0.28)
Age (years)				
< 40	Ref	Ref	Ref	Ref
40-49	4.82 (4.27, 5.44)	4.96 (4.39, 5.61)	2.40 (2.05, 2.80)	2.46 (2.11, 2.88)
50-59	13.37 (12.03, 14.86)	13.59 (12.21, 15.12)	4.50 (3.93, 5.16)	4.62 (4.02, 5.30)
60-69	42.32 (38.28, 46.78)	42.46 (38.35, 47.02)	8.58 (7.53, 9.79)	8.78 (7.69, 10.02)
70-79	109.21 (98.87, 120.62)	107.60 (97.26, 119.04)	13.96 (12.25, 15.91)	14.28 (12.51, 16.29)
≥ 80	255.64 (231.19, 282.66)	252.09 (227.60, 279.22)	23.60 (20.67, 26.94)	24.16 (21.13, 27.62)
Gender				

Male	Ref	Ref	Ref	Ref
Female	0.58 (0.56, 0.60)	0.58 (0.56, 0.59)	0.68 (0.65, 0.70)	0.67 (0.64, 0.70)
LTCF role				
Non-resident	Ref	Ref	Ref	Ref
Resident	2.81 (2.70, 2.92)	2.91 (2.79, 3.03)	2.33 (2.20, 2.47)	2.36 (2.23, 2.51)
Metro-urban status[g]				
Metro-urban	Ref	Ref	Ref	Ref
Nonmetro-urban	1.30 (1.26, 1.35)	1.28 (1.24, 1.33)	1.18 (1.12, 1.24)	1.18 (1.12, 1.24)
Nonmetro-rural	1.14 (1.04, 1.25)	1.11 (1.01, 1.22)	0.95 (0.84, 1.07)	0.96 (0.85, 1.08)

Abbreviations: OR, odds ratio; CI, confidence interval; Ref, reference; LTCF, long-term care facility

[a] All models included the following independent variables: report month, race/ethnicity, age, gender, LTCF role, and metro-urban status

[b] COVID-19 deaths were defined as confirmed cases that were reported as deceased by healthcare providers or medical examiners/coroners, identified by death certificates with COVID-19 indicated as the cause of death, or had evidence that COVID-19 contributed to death

[c] Confirmed cases were lab-confirmed by reverse-transcription polymerase chain reaction (RT-PCR); probable cases lacked RT-PCR results but met other testing, clinical, epidemiologic and/or vital records criteria

[d] Missing values for race/ethnicity, age, gender and/or metro-urban status were imputed using multivariate imputation by chained equations (MICE)

[e] Cases with missing values for any variables in the model were excluded (i.e., complete case analysis)

[f] Race/ethnicity was categorized as Hispanic/Latino (any race) and non-Hispanic/Latino Black, Asian, White or Other; Other race/ethnicity included American Indian/Alaska Native, Native Hawaiian/Pacific Islander and those who reported their race as "other"

[g] Metro-urban status is the classification of a case's county of residence, when available, and current county otherwise

CHAPTER 7: CONCLUSIONS AND PUBLIC HEALTH IMPLICATIONS

7.1 Overview

A high burden of morbidity and mortality in U.S. LTCFs can be attributed to norovirus outbreaks[20] and, more recently, COVID-19 outbreaks.[52,53] Effective norovirus and COVID-19 outbreak prevention and control measures are needed to reduce the burden of disease in this setting. Moreover, the general U.S. population has also experienced substantial morbidity and mortality from the COVID-19 pandemic,[72] and examining trends in case fatality could lead to a better understanding of the changing relative burden of COVID-19 in LTCFs and whether case management in the general population has improved. The primary goals of this research were to inform data-driven guidelines for the prevention and control of norovirus and COVID-19 outbreaks in LTCFs and to examine possible explanations for trends in COVID-19 case fatality in the general population.

7.2 Contributions of each specific aim

7.2.1 Aim 1 – Norovirus control measures in healthcare settings

In Aim 1, we searched the scientific literature to identify norovirus outbreaks in healthcare facilities (hospitals and LTCFs) globally and found that hospital outbreaks in which control measures were reported to be implemented were smaller in size and shorter in duration compared to hospital outbreaks in which control measures were not reported to be implemented. Conversely, LTCF outbreaks in which control measures were reported to be implemented were larger in size and longer in duration compared to LTCF outbreaks in

which control measures were not reported to be implemented. We believe that control measures in LTCFs were more likely to be implemented in response to larger and longer outbreaks, rather than being the cause of them. While this may also have been true in hospitals, it was likely to a lesser extent. These findings suggest that LTCFs may have insufficient resources to respond to norovirus outbreaks, and therefore may only implement control measures once outbreaks reach a certain size or duration. Therefore, addressing issues of resource shortages in LTCFs, such as staffing and PPE shortages, could lead to more rapid outbreak response and a lower burden of norovirus gastroenteritis in this setting. Furthermore, we found that enhanced hand hygiene measures, in particular, were associated with smaller and shorter outbreaks in hospitals, lending support for the use of enhanced hand hygiene measures to control norovirus outbreaks in hospitals.

Findings from this aim highlight two important areas for future research. First, future studies should examine differences in norovirus outbreak responses between hospitals and LTCFs, including the timing of control measure implementation in each setting, and potential reasons for differences in outbreak response. While there is evidence that LTCFs have frequent staffing shortages,[214-218] which could contribute to delays in control measure implementation, there has been no formal comparison, to our knowledge, of staffing and other resource shortages between hospitals and LTCFs. Examining differences in outbreak response between hospitals and LTCFs could help determine why control measures are associated with smaller and shorter outbreaks in hospitals but not LTCFs, and provide evidence that increasing staffing levels and allocating additional resources to LTCFs could reduce the burden of norovirus outbreaks in this setting.

Second, and most importantly, our study was unable to examine the causal effect of control measures on norovirus outbreak outcomes in healthcare settings. Because randomized

control trials are neither feasible nor ethical, future studies should prospectively collect detailed information on outbreak control measures (e.g., specific control measures implemented, when they were implemented, and adherence to control measure protocols) from a representative sample of healthcare facility norovirus outbreaks and examine the effects of control measures on outbreak outcomes. With prospectively collected data, temporality (i.e., knowledge that the cause preceded the effect) could be established and causal associations between control measures and outbreak outcomes could be examined. Furthermore, detailed data on LTCF norovirus outbreaks could be used to inform mechanistic models (e.g., compartmental models), which could also be used to examine control measure effectiveness in LTCFs. Due to differences between hospitals and LTCFs, analyses examining norovirus outbreak control measure effectiveness in healthcare facilities should be stratified by or restricted to specific healthcare settings. Through these analyses, we could identify which specific control measures are most effective at minimizing norovirus transmission and should be prioritized, and which control measures are ineffective and potentially costly and/or disruptive and should be avoided. Ultimately, these studies could lead to more data-driven norovirus outbreak control measures and a lower burden of norovirus gastroenteritis in healthcare facilities.

Lessons learned from examining norovirus outbreak control measures in LTCFs are also applicable to the current COVID-19 pandemic. Detailed, facility-level data on COVID-19 outbreak control measures, including which control measures were implemented and when, are lacking. A concerted effort should be made to collect these data so that the effectiveness of COVID-19 control measures in LTCFs can be examined. This way, the most effective control measures can be identified and prioritized during future pandemic waves and future pandemics.

7.2.2 Aim 2 – SARS-CoV-2 transmission in long-term care facilities

In Aim 2, we characterized COVID-19 cases and outbreaks and examined SARS-CoV-2 transmission dynamics in Fulton County, Georgia LTCFs from March 2020 to September 2021. We quantified transmission by the time-varying reproduction number, R(t), and examined associations between case characteristics, including LTCF role (resident or staff), vaccination status, and disease severity, and R(t). We found that case counts, outbreak size and duration, and R(t) decreased as the pandemic progressed, with the greatest declines after December 2020, when COVID-19 vaccines were first distributed to U.S. LTCFs, despite increases in community incidence in summer 2021. Furthermore, we found that staff cases were substantially more infectious than resident cases and that resident cases with more severe outcomes, including hospitalization and, especially, COVID-19 death, were more infectious than resident cases with less severe outcomes, but only in the first pandemic wave (prior to October 2020).

These findings have several important public health implications. First, they suggest that COVID-19 infection prevention and control measures in LTCFs improved over time, and that vaccines were effective in accelerating declines in case counts and R(t), likely by reducing susceptibility to disease. Similarly, findings suggest that infection prevention and control measures in the beginning of the pandemic (e.g., universal masking and resident cohorting) were likely inadequate in preventing transmission from severely ill residents to staff and other residents, but that these infection prevention and control measures improved in the second pandemic wave. Second, these findings suggest that LTCF staff are driving SARS-CoV-2 transmission in LTCFs, and that IPC measures that target LTCF staff could greatly reduce the burden of COVID-19 in this setting. This could include ensuring that staff have access to adequate PPE and training in its use and vaccination campaigns that target

LTCF staff. The latter is particularly important, as vaccination acceptance among LTCF staff remains low,[66] and improving vaccination rates among staff could further reduce susceptibility in the LTCF population, leading to further declines in transmission.

Due to limitations in the data, we were unable to make conclusions about the relative infectiousness of vaccinated cases compared to unvaccinated cases. While COVID-19 vaccines are effective against SARS-CoV-2 infection and, especially, severe disease,[47] future studies should examine vaccine effectiveness against SARS-CoV-2 infectiousness, particularly in LTCFs. Additionally, we were unable to examine the relative infectiousness of staff with different job roles. It is possible that staff with specific job roles (e.g., certified nursing assistants) are more infectious than other staff, such that targeting these staff for interventions could greatly reduce transmission. Lastly, future studies should examine the effects of specific COVID-19 intervention measures on case counts, outbreak sizes and durations, and R(t) in LTCFs. While we were able to approximate the dates on which LTCFs implemented different intervention measures (e.g., visitor restrictions), we were unable to examine exact dates that interventions were implemented or lifted, as these dates were facility-specific. A detailed analysis of the effectiveness of different intervention measures on reducing SARS-CoV-2 transmission in LTCFs could lead to more effective prevention and control measures in the future.

7.2.3 Aim 3 – Trends in COVID-19 case-fatality in the general population

In Aim 3, we examined trends in the COVID-19 case fatality ratio (CFR) in the state of Georgia for cases reported between March 2020 and March 2021 and found that declines in the CFR could not be completely explained by a changing case mix (e.g., cases becoming younger or less likely to be LTCF residents). Furthermore, we found that trends among hospitalized cases differed from that among all cases. Most notably, while the risk of

mortality, adjusted for age and other individual-level characteristics, among all cases remained low in winter 2020/2021, the risk of mortality among hospitalized cases increased again during this time before declining again by March 2021. Lastly, we found that Asian, Black, and Hispanic/Latino race/ethnicity, male gender, being a LTCF resident, being in a nonmetro-urban or nonmetro-rural county and, especially, older age were associated with higher mortality among COVID-19 cases.

These findings have several important public health implications. First, they suggest that improved clinical management may have contributed to lower mortality risk later in the pandemic. While other studies have found that COVID-19 treatments, such as remdesivir,[75] dexamethasone,[76,77] and monoclonal antibody treatment,[78,79] have led to lower case fatality among individuals, our study supports that improved case management may have contributed to lower case fatality among the population. Second, findings suggest that trends in case fatality among hospitalized cases may be subject to selection bias, and that severity of disease among patients being admitted to hospitals should be considered when examining these trends. During surges in COVID-19 caseload, sicker patients may be more likely to be admitted due to limited capacity, resulting in inflated mortality risk. While increased mortality risk may also be attributable to hospital strain,[249,250] it is unlikely that hospital strain alone can explain the increases in mortality risk among hospitalized cases in winter 2020/2021, as we would also expect to see increased mortality risk among all cases during this time. While it is also possible that changes in testing contributed to a lower mortality risk among all cases in winter 2020/2021, as mortality trends among all cases, compared to hospitalized cases, are more affected by changes in testing and reporting, testing was widely available by winter 2020/2021, so it is unlikely that changes in testing alone explain these trends.

Several important questions were raised by this analysis that should be addressed in future studies. First, future research should consider individual-level COVID-19 treatment information when examining trends in COVID-19 case fatality. This could help answer whether improvements in COVID-19 treatments contributed to declines in the CFR. Furthermore, as new treatments become available, including remdesivir (the first treatment to be approved by the U.S. Food and Drug Administration),[265] monoclonal antibodies, dexamethasone, and molnupiravir,[266] future studies should examine the effects of these new treatments on the CFR. Second, future studies should examine trends in COVID-19 severity among hospitalized cases upon admission to determine whether increased mortality during COVID-19 surges is the artefact of a sicker patient population. Third, underlying reasons for the increased mortality risk among Asian, Black, and Hispanic/Latino cases compared to White cases should be examined. For instance, is increased case fatality due to differences in care-seeking behaviors (e.g., seeking care less often and/or delaying seeking care), differential case management (e.g., receiving different treatments than White cases), and/or differences in underlying health conditions? Determining the underlying reasons for these differences could lead to more targeted interventions that aim to improve COVID-19 outcomes among minority groups. Lastly, future studies should examine the effects of COVID-19 vaccines on the CFR. While declines in the CFR from January to March 2021 may be partially attributable to COVID-19 vaccines, we were unable to examine this further due to limited individual-level information on vaccine status. Moreover, because the majority of adults in the U.S. did not become eligible for COVID-19 vaccination until March or April 2021,[267] declines in the CFR would likely not be fully observed until several months after our study period. However, because vaccines have been shown to be effective not only against infection and mild disease, but also, and especially, against severe disease and death (even with emergence of the new Delta and

Omicron variants),[86,268,269] we hypothesize that the CFR has further declined due to vaccines.

7.3 Reflections

Working on this dissertation research during the COVID-19 pandemic was both challenging and rewarding. Shortly after my original dissertation aims were approved by the PhD committee in Fall 2019, the COVID-19 pandemic turned the world upside down. As an individual, I am fortunate that the pandemic has had relatively minimal effect on my life, compared to others who have lost their childcare, jobs, loved ones, and even their lives to COVID-19. As an infectious disease epidemiologist, it has been both exciting to have the opportunity to respond to a pandemic of this magnitude (hopefully a once-in-a-lifetime pandemic), and challenging to work in an environment where the situation is constantly evolving. I have found that being flexible is critical, and that while projects may not work out as expected, they still lead to new and exciting learning opportunities.

Prior to defending my dissertation proposal, I had the unique opportunity to modify two of my aims to focus on COVID-19, rather than norovirus, to address the urgent need for answers regarding COVID-19. However, after defending my proposal, it was necessary for me to modify these two aims again in Spring 2021. For my second dissertation aim, I originally intended to examine COVID-19 control measure effectiveness in Georgia LTCFs using a compartmental model and a counterfactual framework. However, because I was unable to link LTCF-associated cases in Georgia to individual facilities, and because information on staffing numbers and contact patterns among residents and staff in LTCFs were lacking, I had insufficient data to parameterize my model. Therefore, I decided to

modify this aim to instead focus on SARS-CoV-2 transmission patterns in Fulton County LTCFs using the time-varying reproduction number, R(t), and regression models, rather than a compartmental model. While the methods used in this aim changed substantially, I was still able to examine transmission patterns in LTCFs and to contribute to the growing body of literature on COVID-19 prevention and control in this setting. Moreover, this gave me the opportunity to collaborate with the Fulton County Board of Health on their COVID-19 response and to participate in their data discussions.

For my third dissertation aim, I originally intended to use data from the ongoing study "Comprehensively Profiling Social Mixing Patterns in Nursing Homes to Model COVID-19 Transmission (Nursing Home Mix)" to characterize social contact patterns among nursing home residents and staff in Georgia. Because I had been involved in the grant writing, IRB approval, and participant recruitment for this study, I was very familiar with the project. However, due to the substantial burden that COVID-19 placed on nursing home staff in Fall 2020, it was extremely difficult to recruit participants (nursing home staff) for this study. After making several changes to the study protocol, so that all recruitment and study activities could be completed entirely online, we were able to recruit >300 participants by June 2021. While I am still involved in the Nursing Home Mix project, for which the data analysis, which is being led by a colleague, is ongoing, I was unable to use these data for my dissertation. However, during winter 2020/2021, while we were working on participant recruitment and data collection for Nursing Home Mix, reports of the declining COVID-19 CFR in the U.S. were gaining attention from the media, as was speculation about potential reasons for the decline. This led my advisor to suggest that I examine the CFR in Georgia to determine to what extent trends could be explained by improved case management as opposed to shifts in case demographics. While this analysis began as a brief report, it soon evolved into a

much larger and more rigorous study. In order to dedicate the time needed to complete this analysis, I decided to modify my dissertation aim 3 to focus on the declining COVID-19 CFR in Georgia, rather than social mixing patterns in LTCFs. In making this change, I hope that results from this aim can fill a critical knowledge gap regarding COVID-19 case fatality.

While these modifications to my dissertation, first to focus on COVID-19 and then again to focus on different COVID-19-related topics/methods due to data limitations, may have slightly delayed completion of my dissertation, I hope that in making these changes, this research can be more impactful. I'm grateful for the opportunities to collaborate with my committee members, the Georgia Department of Public Health, and the Fulton County Board of Health, and to contribute to the growing body of knowledge on COVID-19.

7.4 Summary

The burden of norovirus and COVID-19 in long-term care facilities is substantial, and the COVID-19 pandemic is an urgent threat to public health in both long-term care facilities and the general population. Quantifying associations between control measures and norovirus outbreak outcomes and identifying risk factors for SARS-CoV-2 transmission in long-term care facilities brings us closer to establishing effective outbreak control measures that can be used to minimize norovirus and SARS-CoV-2 transmission in this setting. Moreover, examining trends in the COVID-19 case fatality ratio in the general population leads to a better understanding of mortality risk among cases and how this risk can be minimized. Collectively, the results of this dissertation research contribute to the body of literature on norovirus control measures and SARS-CoV-2 transmission dynamics in long-term care facilities and COVID-19 case fatality in the general population.

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CHAPTER 10. APPENDIX

10.1 Abbreviations

ALF	Assisted living facility
CDC	Center for Disease Control and Prevention
CFR	Case fatality ratio
CI	Confidence interval
CMS	Centers for Medicare and Medicaid Services
CNA	Certified Nursing Assistant
COVID-19	Coronavirus Disease 2019
ECRC	Emory COVID-19 Response Collaborative
FCBOH	Fulton County Board of Health
GDPH	Georgia Department of Health and Human Services
HICPAC	Healthcare Infection Control Practices Advisory Committee
ICU	Intensive care unit
IPC	Infection prevention and control
IQR	Interquartile range
IRIS	Institutional Repository for Information Sharing
LTCF	Long-term care facility
MESH	Medical subject headings
MICE	Multivariate imputation by chained equations
NTRL	National Technical Reports Library
OR	Odds ratio
RT-PCR	Reverse-transcription polymerase chain reaction

PPE	Personal protective equipment
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PUI	Person(s) under investigation
R_0	Basic reproduction number
R_E	Effective reproduction number
R_i	Individual reproduction number
R(t)	Time-varying reproduction number
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SendSS	State Electronic Notifiable Disease Surveillance System
SNF	Skilled nursing facility
U.S.	United States
WHO	World Health Organization

10.2 Publications, presentations, and funding-related activities

In addition to my dissertation work, I have also had the opportunity to work on several other projects during my time as a PhD student at Emory. The publications, presentations, and grants that resulted from these projects, along with my dissertation research, are listed below.

10.2.1 Peer Reviewed Publications

1. Howard-Anderson J*, Adams C*, Dube WC, Smith TC, Sherman AC, Edupuganti N, Mendez M, Chea N, Magill SS, Espinoza DO, Zhu Y, Phadke VK, Edupuganti S, Steinberg JP, Lopman BA, Jacob JT, Fridkin SK, Collins MH (* indicates co-first authorship). Occupational Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel: A 6-month prospective analysis of the COVID-19 Prevention in Emory Healthcare Personnel (COPE) Study. *Infect Control Hosp Epidemiol*. Feb 14 2022:1-30. doi:10.1017/ice.2021.518
2. Amin A, Kellogg JT, Adams C, Dube WC, Collins MH, Lopman BA, Johnson TM, Weitz J, Fridkin SK. Risk factors for severe acute respiratory coronavirus 2 (SARS-CoV-2) seropositivity among nursing home staff. *Antimicrobial Stewardship & Healthcare Epidemiology*. Oct 28 2021;1(1):E35. doi:10.1017/ash.2021.193
3. Wang Y, Siesel C, Chen Y, Lopman BA, Edison L, Thomas M, Adams C, Lau M, Teunis P. Severe Acute Respiratory Syndrome Coronavirus 2 Transmission in Georgia, USA, February 1-July 13, 2020. *Emerg Infect Dis*. Aug 16 2021;27(10)doi:10.3201/eid2710.210061
4. Adams C, Peterson SR, Hall AJ, Parashar U, Lopman BA. Associations of infection control measures and norovirus outbreak outcomes in healthcare settings: a

systematic review and meta-analysis. *Expert Rev Anti Infect Ther*. Aug 4 2021:1-12. doi:10.1080/14787210.2021.1949985

5. Howard-Anderson J, Adams C, Sherman AC, Dube WC, Smith TC, Edupuganti N, Chea N, Magill SS, Espinoza DO, Zhu Y, Phadke VK, Edupuganti S, Steinberg JP, Lopman BA, Jacob JT, Collins MH, Fridkin SK. Occupational Risk Factors for SARS-CoV-2 Infection among Healthcare Personnel: A Cross-Sectional Analysis of Subjects Enrolled in the COPE Study. *Infect Control Hosp Epidemiol*. Feb 9 2021:1-20. doi:10.1017/ice.2021.54
6. Adams C, Young D, Gastanaduy PA, Paul P, Marsh Z, Hall AJ, Lopman B. Quantifying the roles of vomiting, diarrhea, and residents vs. staff in norovirus transmission in U.S. nursing home outbreaks. *PLoS Comput Biol*. Mar 27 2020;16(3):e1007271. doi:10.1371/journal.pcbi.1007271
7. Zelner J, Adams C, Havumaki J, Lopman B. Understanding the Importance of Contact Heterogeneity and Variable Infectiousness in the Dynamics of a Large Norovirus Outbreak. *Clin Infect Dis*. Jan 16 2020;70(3):493-500. doi:10.1093/cid/ciz220

10.2.3 Presentations

1. Adams C. Temporal changes in COVID-19 mortality in the state of Georgia. The Emory COVID-19 Response Collaborative (ECRC) Student Presentations, Virtual, April 2021. (contributed, oral)
2. Adams C. A Closer Look at the COVID-19 Case Fatality Rate in Georgia, USA. Emory University Research and Progress Day, Virtual, September 2020. (contributed, oral)

3. Adams C, Young D, Gastanaduy PA, Paul P, Marsh Z, Hall AJ, Lopman B. Quantifying the roles of vomiting, diarrhea, and residents vs. staff in norovirus transmission in U.S. nursing home outbreaks. 7th International Calicivirus Conference, Sydney, Australia, October 2019. (contributed, oral and poster)
4. Adams C, Young D, Gastanaduy PA, Paul P, Marsh Z, Hall AJ, Lopman B. Quantifying the roles of vomiting, diarrhea, and residents vs. staff in norovirus transmission in U.S. nursing home outbreaks. 7th International Conference on Infectious Disease Dynamics (Epidemics7), Charleston, NC, December 2019. (contributed, poster)
5. Adams C, Lopman B. Understanding Transmission of Norovirus in Long-term Care Facilities: a modeling study. NoroCORE Final Showcase Meeting, Atlanta, GA, March 2018. (contributed, poster)

10.2.4 Grants

1. Rollins School of Public Health (RSPH) – Rapid COVID-19 Pilot Grant. Comprehensively Profiling Social Mixing Patterns in Nursing Homes to Model COVID-19 Transmission (Nursing Home Mix). Role: grant writer and research assistant; Funded Amount: $50,000; Duration: 1 year; Start Date: 05/18/20