RESEARCH ARTICLE

Incidence of *Clostridioides difficile* Infections across Acute Care, Long-Term Acute Care, and Rehabilitation Facilities during the COVID-19 Pandemic in Los Angeles County, California

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ABSTRACT: During the first surge of the COVID-19 pandemic in 2020, hospitalized COVID-19 patients were frequently prescribed broad-spectrum antibiotics. Overuse of antibiotics can result in an imbalance of gut microbiota, which can cause antibiotic-associated diarrhea. Severe antibiotic-associated diarrhea is usually caused by a *Clostridioides difficile* infection (CDI). They can cause severe gastrointestinal disease and inflammation of the colon, which may lead to worse COVID-19 outcomes. Limited research has investigated the relationship between CDI and COVID-19 in a region with high population density. This study investigates the incidence of CDI across Acute Care, Long-Term Acute Care (LTAC), and Rehabilitation facilities in Los Angeles County, California, before and during the pandemic (January 2017-December 2022). This study used data from the 2017-2022 California Department of Public Health's (CDPH) CDI database. The findings indicated that CDI's overall Standard Infection Ratio (SIR) remained relatively stable during the pandemic, with a slight increase in the SIR of LTAC facilities during the latter half of the pandemic. In the future, it is important to investigate the SIR of CDI in a large sample of LTAC facilities during COVID-19 outbreaks further.

KEYWORDS: Translational medical sciences; Disease Detection and Diagnosis; COVID-19; Healthcare-Associated Infections; *Clostridioides difficile*.

Introduction

The COVID-19 pandemic can be attributed to the global transmission of the coronavirus, an infectious disease derived from the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) virus.[1] The transmission of COVID-19 primarily occurs through respiratory droplets, direct human-to-human contact, and contact with contaminated surfaces or fomites.[2] Common symptoms encompass fever or chills, cough, shortness of breath or breathing difficulties, fatigue, muscle or body aches, headaches, loss of taste or smell, sore throat, congestion or runny nose, nausea, and diarrhea.[3] However, relatively large populations of those with the virus remain asymptomatic.[4] While COVID-19 can cause severe illness, it is generally characterized by a case mortality rate of approximately 1.1% in the United States. Within the United States, a significant concentration of COVID-19 cases is observed in Los Angeles County, California, where there is a cumulative total of 3,811,975 COVID-19 cases and 36,836 associated fatalities.[5] The selection of Los Angeles County for this study is based on its status as the region with the most substantial COVID-19 impact in California.[6] Throughout the pandemic, Los Angeles County exhibited a high COVID-19 test positivity rate of 24.98%, in contrast to the statewide rate of 14% in California.[7,8]

The global healthcare landscape has faced unprecedented challenges due to the COVID-19 pandemic, resulting in various strains on healthcare systems. Notably, there has been an upsurge in healthcare-associated infections (HAIs) during the Covid-19 pandemic.[9] *Clostridioides difficile* infection (CDI) is one of the most frequently reported HAIs due to the frequent prescription of antibiotics and elevated risk of the spread of germs in the hospital environment.[10] *Clostridioides difficile* is a spore-forming bacterium with a presence in the gastrointestinal systems of both human and animal hosts. This pathogen is primarily transmitted through the fecal-oral route, with key risk factors including antibiotic therapy, advanced age (65+), and prolonged hospital or nursing home admissions contributing to infection. CDIs span a spectrum of gastrointestinal symptoms, ranging from mild to severe diarrhea, with the most severe form often developing into colitis.[11]

Since the onset of the COVID-19 pandemic, some studies have suggested that the incidence of CDI has increased. In contrast, others have suggested it has decreased, prompting inquiries into the potential mechanisms linking COVID-19 and CDI, which may encompass gut dysbiosis, non-compliance with hand hygiene protocols, and inadequate antibiotic stewardship.[12,14] The use of broad-spectrum antibiotics in treating bacterial co-infections increased to more than 72% during the pandemic, likely contributing to the heightened CDI incidence and the emergence of resilient *Clostridioides difficile* strains.[13] Overuse of antibiotics disrupts the normal gut flora, elevating the risk of CDI and fostering the proliferation of antibiotic-resistant strains.[14] Furthermore, COVID-19 infection can compromise the immune system and disrupt the gut microbi-

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ome, increasing an individual's vulnerability to CDI.[15,16] The immune response to the SARS-CoV-2 virus is similar to that of a CDI, such that inflammatory cytokines are upregulated, which can lead to the development of other intestinal diseases. In turn, the inflammatory response caused by CDI can further add to the systemic inflammation caused by COVID-19. This may worsen outcomes in COVID-19 patients, underscoring why CDI must be addressed.[16,17] National-level comparisons between the pre-COVID era and the COVID-19 pandemic have uncovered a general decrease in CDI incidence over the pandemic.[18] However, controversy arose when individual hospitals analyzed their CDI and COVID-19 trends. One single-center study noted the incidence of CDI remained stable despite decreased testing due to potential over-testing or inappropriate testing before the pandemic or more thoughtful testing during the first surge.[19] Another single-study noted an increase in CDI SIR over the pandemic.[20] Thus, it is important to continue gathering evidence to define this relationship better.

The primary objective of this study is to analyze the trends in CDIs in acute care, long-term acute care (LTAC), and rehabilitation facilities during the pandemic in Los Angeles County. CDI data was sourced from the 2017-2022 California Department of Public Health's Hospital (CDPH) CDI database. The selection of Los Angeles County as our study area stems from its status as the county with the most severe cumulative COVID-19 outcomes in California, highlighting the urgency of understanding the CDI-COVID-19 relationship in this specific region. This analysis can inform strategies for CDI mitigation in diverse geographic regions, ultimately leading to reduced healthcare expenditures and improved patient outcomes. To shine light on conflicting findings about CDI incidence during the pandemic, it is necessary to bridge the gap between single-center sites and national-level data and to understand the incidence of CDI at a county or state level. To our knowledge, our study is the first to compare CDI incidence across different facility types within a single county during the pandemic.

Methods

Study Design:

This incidence study utilized the CDPH CDI database. Specifically, this analysis used the 2017-2022 CDI datasets, which included hospitalization from 1 January 2017 to 31 December 2022, and was made available to the public.[21] The CDPH CDI database contains data regarding the county, facility type, patient stay length, and the Standardized Infection Ratio.[21]

The CDPH CDI database includes the number of CDI reported by each California hospital in the specified reporting year. Beginning in 2017 for each California hospital, the annual CDI dataset consists of the number of CDI predicted to occur in each hospital based on its specific facility-level characteristics. The observed (reported) number of CDI is then compared to the predicted number of CDI in a ratio called the Standardized Infection Ratio or SIR. The predicted number of CDI cases in this study was estimated based on the 2015 national baseline data, adjusting for significant risk factors outlined in the NHSN Guide to the SIR.[22] SIR is a standard metric used to measure change in HAIs. SIR values greater than 1 indicate that observed infections exceed the predicted number of infections, whereas SIR values less than 1 indicate the opposite.[22] The SIR is a metric that summarizes an individual hospital's HAI prevention progress compared with the national baseline and state-specific prevention goals.[22]

Our goal was to investigate and compare the different trends of CDI incidence in Acute Care, Long-Term Acute Care (LTAC), and Rehabilitation facilities. Acute Care facilities are a level of health care in which a patient is treated for a brief but severe episode of illness, for conditions resulting from disease or trauma, and during recovery from surgery. LTAC facilities are hospitals for patients with complex conditions requiring an average stay of 25 days or longer (Figure 1). LTAC conditions include Alzheimer's disease and other cognitive impairments, disabilities, and chronic conditions such as heart disease, diabetes, and arthritis.[23] A Rehabilitation facility is an acute care facility exclusively providing evaluation and restoration of function for patients who have lost function due to acute or chronic pain, musculoskeletal problems, stroke, or catastrophic events resulting in paralysis.

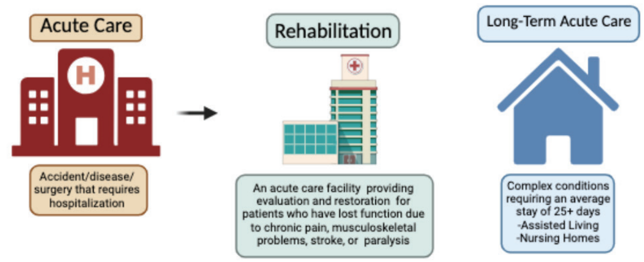

Figure 1: A comparison of Acute Care, Rehabilitation, and Long-term Acute Care facilities in Los Angeles County. The arrow denotes that patients in Acute Care facilities are transferred to Rehabilitation facilities if continued care is needed.

Statistical Methods:

All healthcare facilities in Los Angeles County were analyzed from the CDPH CDI database, which is freely accessible to the public. The facilities were grouped by their classification: Acute Care, LTAC, and Rehabilitation. Depending on the year, Los Angeles County contained 80-83 Acute Care Hospitals, 8-9 LTACs, and 25-28 Rehabilitation Hospitals/Units. All facilities had reported their individual SIR to the CDPH. The SIR for each facility type was calculated by dividing the sum of observed cases by the sum of predicted cases across all facilities of that type for each year between 2017-2022. The overall SIR was also calculated after aggregating all facility types for each year.

Result and Discussion

Baseline Characteristics:

A total of 6,449 people were hospitalized with CDI from 2017-2019 (pre-COVID-19) and 4,353 from 2020-2022 (during COVID-19) across 80-83 Acute Care Hospitals, 8-9 LTACs, and 25-28 Rehabilitation Hospitals/Units within Los Angeles County, California.

Standard Incidence Ratio (SIR):

The SIR for each facility type and overall SIR across facilities is displayed in Table 1. CDPH split their data from 2020 into two parts (Table 1): January-June 2020 is named 2020, and July-December 2020 is named 2020.5 for simplicity. Across all types of facilities, there was a decrease in CDI from 2017-2020. However, in the second half of 2020 (July-December), there was a modest 0.01 increase in the overall SIR compared to the first half of 2020 (January-June). Notably, LTAC facilities in Los Angeles County had the greatest SIR increase during the COVID-19 pandemic compared to Acute Care and Rehabilitation facilities (Figure 2). As previously mentioned, SIR decreased over time, except for the second half of 2020 (July-December). The following paragraphs will discuss these trends and contextualize the results in greater detail.

Table 1: *Clostridioides difficile* infection in Acute Care, Long-Term Acute Care (LTAC), and Rehabilitation facilities during the COVID-19 pandemic. The 95% Confidence Intervals (CI) are indicated within the parentheses. The year-to-year changes in the overall SIR indicate a general trend of decreasing CDI from 2017-2022.

CDI SIR Data				
Year	LTAC	Acute	Rehab	Overall SIR
2017	1.02 (0.90, 1.16)	0.90 (0.87, 0.94)	1.17 (0.94, 1.43)	0.92 (0.88, 0.95)
2018	0.93 (0.80, 1.06)	0.72 (0.69, 0.75)	0.59 (0.45, 0.75)	0.73 (0.70, 0.76)
2019	0.86 (0.73, 0.99)	0.64 (0.61, 0.67)	0.45 (0.33, 0.59)	0.65 (0.62, 0.68)
2020	0.45 (0.33, 0.58)	0.61 (0.56, 0.66)	0.59 (0.39, 0.84)	0.59 (0.54, 0.63)
2020.5	0.41 (0.31, 0.54)	0.62 (0.58, 0.67)	0.56 (0.36, 0.80)	0.60 (0.56, 0.64)
2021	0.60 (0.50, 0.71)	0.58 (0.55, 0.61)	0.53 (0.39, 0.70)	0.58 (0.55, 0.61)
2022	0.46 (0.37, 0.57)	0.59 (0.56, 0.62)	0.48 (0.35, 0.63)	0.57 (0.55, 0.60)

LTAC Facilities: CDI SIR Increase:

In Figure 2, the SIR of CDIs in LTAC hospitals was sharply increased compared to Acute Care and Rehabilitation facilities during the beginning of the COVID-19 pandemic (2020-2021).

Overall SIR Increase during 2020:

At the beginning of the pandemic in 2020, the overall SIR of CDI increased slightly by +0.01.

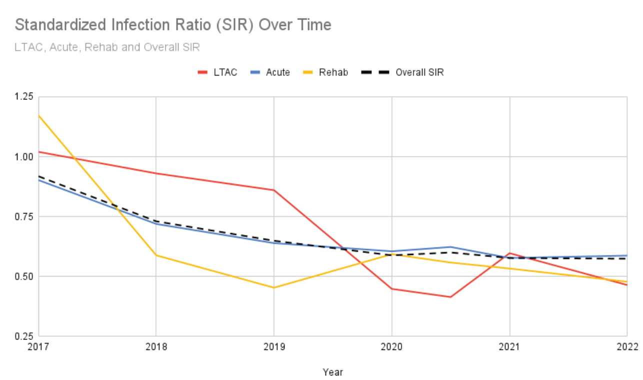

Figure 2: *Clostridioides difficile* infection Standard Infection Ratio (SIR) in Acute Care, Long-Term Acute Care (LTAC), and Rehabilitation facilities in Los Angeles County during the COVID-19 pandemic. LTAC facilities had the greatest increase in SIR from the second half of 2020 (July-December) to 2021 compared to Acute Care and Rehabilitation facilities.

Discussion:

Our study made the following key conclusions: (1) The overall SIR had a decreasing trend before the pandemic and remained relatively stable during the pandemic, with a slight increase from the first half of 2020 (January-June) to the second half of 2020 (July-December) and (2) LTAC was the only facility type that had a CDI SIR increase during the pandemic, from the second half of 2020 (July-December) to 2021.

The overall SIR decreased from 2017-2022, except for a +0.01 increase from the first half of 2020 (January-June) to the second half of 2020 (July-December). Antibiotics were prescribed for COVID-19 patients regardless of reported severity. The lack of treatment strategy led to the overuse of antibiotics, which may have contributed to the slight increase in CDI observed in 2020.[24] The estimate for the overall SIR for the first half of 2020 (January-June) was 0.59 (CI: 0.54, 0.63) which is very similar to the estimate of 0.60 (CI: 0.56, 0.64) for the second half of 2020 (July-December). It is unclear if the number of CDI infections and the +0.01 increase in SIR from the first half to the second half of 2020 would be drastic enough to warrant changing current CDI protocols or practices in clinical settings. Therefore, the +0.01 increase in SIR may be negligible, and further investigation is needed to determine its clinical significance. From 2020-2022, the CDI SIR generally remained relatively stable, with an overall change fluctuating ±0.01-0.02 year-to-year. These results may suggest a limited co-infection rate between COVID-19 and CDI.

In 2017, national standards and precautions for CDIs were established. The effects of these antimicrobial stewardship interventions may account for the steady decline in CDI SIR before 2020.[22] No additional CDI interventions were introduced during the pandemic in Los Angeles County. LTAC was the only facility type with a CDI SIR increase greater than +0.01 during the pandemic from the second half of 2020 (July-December) to 2021. LTAC facilities experienced the greatest increase in SIR, but acute care and rehabilitation centers' SIR remained relatively stable during the pandemic. LTACs are at the highest risk for CDI due to higher exposure to antibiotics, the advanced age of patients, multiple comorbid conditions, and communal living conditions.[25] Major long-term care subgroups are elderly disabled, nonelderly disabled (under age 65), developmentally disabled, and mentally ill, most of whom require assistance in eating, toileting, mobility, dressing, and bathing.[26] This may explain the increased CDI incidence in LTAC facilities throughout the first part of the pandemic. This drastic increase in CDI incidence in LTACs may also be due to the small sample size, with only 8 LTAC facilities reporting CDI data from 2017-2022, making the SIR for this facility type less precise. The less precise SIR for LTACs is confirmed by the large CIs seen with the LTAC SIRs.

In future research, it would be important to perform cost-benefit analyses to discern the efficacy of CDI interventions across different sex and age groups. Based on our study, we hypothesize that targeting older individuals in a large sample of LTAC facilities is advisable, given their heightened susceptibility to infection resulting from advanced age, comorbidities, and communal living arrangements.[25]

Limitations:

The relatively stable CDI incidence we observed during the COVID-19 pandemic in 2020-2022 could possibly be explained by the decrease in CDI testing during the pandemic.[19] Additionally, reporting requirements for HAIs were not consistently enforced during this period.[27] Moreover, hospi-

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tal occupancy rates experienced a substantial surge, at times exceeding 100% capacity.[28] With an increased hospital occupancy, HAI testing should correspondingly increase, yet they decreased. These interconnected factors underscore the complex challenges healthcare systems face during the pandemic, impacting both the diagnosis and reporting of CDIs. This may explain the lower-than-hypothesized SIR of CDIs later in the pandemic.

It is important to note that our findings primarily allow us to discern patterns and suggest a potential link between COVID-19 and an elevated incidence of CDI. Still, we cannot definitively establish a causal relationship. To ensure causation between COVID-19 infection and CDI, specific individuals with COVID-19 must be analyzed if they later acquired a CDI. This type of retrospective cohort study will further expand research relating to COVID-19 and CDI by providing and focusing on specific individualistic outcomes within a population and allowing for temporality to be confirmed. While our research provides valuable insights into the possible association between COVID-19 and CDI, it should be interpreted cautiously, considering the limitations stemming from the testing and reporting during this period.

Conclusion

CDI incidence remained relatively stable during the COVID-19 pandemic in hospitals in Los Angeles County, California. However, from the second half of 2020 (July-December) to 2021, patients in primarily LTAC facilities had an increase in CDIs. Many single-center studies have associated the increased CDI incidence with the COVID-19 pandemic. In contrast, national-level studies have suggested a decrease in or stable CDI incidence over the pandemic, which our study aligned with. Future research must further investigate the causality between COVID-19 and CDI incidence, or the lack thereof, and focus on sampling a variety of LTAC facilities during COVID-19 outbreaks, which may be at higher risk.

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