Clostridioides difficile Infection in Hospitalized Pediatric Patients: Comparisons of Epidemiology, Testing, and Treatment from 2013–2019

Price T. Edwards, MD[a], **Cary W. Thurm, PhD**[b], **Matthew Hall, PhD**[b], **Jordan D. Busing, MD**[c], **Stacy A. Kahn, MD**[d], **Richard Kellermayer, MD, PhD**[a], **Larry K. Kociolek, MD, MSCI**[e], **Maria M. Oliva-Hemker, MD**[f], **Julia S. Sammons, MD, MSCE**[g], **Madison Weatherly**[d], **Kathryn M. Edwards, MD**[h], **Maribeth R. Nicholson, MD MPH**[h]

[a]Section of Gastroenterology, Hepatology, & Nutrition, Department of Pediatrics, Baylor College of Medicine and Texas Children's Hospital, Houston, Texas

[b]Children's Hospital Association, Lenexa, KS

[c]D. Brent Polk Division of Gastroenterology, Hepatology, and Nutrition, Vanderbilt University Medical Center, Nashville, TN.

[d]Division of Gastroenterology and Nutrition, Inflammatory Bowel Disease Center, Boston Children's Hospital, Harvard Medical School, Boston, MA.

[e]Ann and Robert H. Lurie Children's Hospital of Chicago, Northwestern University Feinberg School of Medicine, Chicago, IL

[f]Division of Pediatric Gastroenterology, Hepatology and Nutrition, Johns Hopkins University School of Medicine, Baltimore, Maryland.

[g]Division of Infectious Diseases, Department of Pediatrics, Perelman School of Medicine at the University of Pennsylvania, Philadelphia, PA

[h]Division of Infectious Diseases, Department of Pediatrics, Vanderbilt University Medical School, Nashville, TN

Abstract

Objectives: To compare the incidence, epidemiology, testing patterns, treatment and outcomes of *Clostridioides difficile* infection (CDI) among hospitalized pediatric patients from 2013–2019.

Study Design: The Pediatric Health Information System® (PHIS) database was queried for patient admissions (age 0–17 years) with International Classification of Disease (ICD) 9 and 10 codes for diagnoses of CDI with a billing code for a CDI-related antibiotic treatment.

Address correspondence to: Dr Maribeth Nicholson, Division of Pediatric Gastroenterology, Hepatology, and Nutrition, Monroe Carell Jr. Children's Hospital at Vanderbilt, 2200 Children's Way, Nashville, TN 37232, USA Tel.: +1 615 322 7449 Fax: +1 615 936 8128 maribeth.r.nicholson@vumc.org.

Results: 17,142 pediatric patients were identified, representing 23,052 admissions with CDI. Adjusted annual CDI incidence decreased over the study period from 7.09 cases per 10,000 patient days (95% CI: 6.15 – 8.18) in 2013 to 4.89 cases per 10,000 patient days (95% CI: 4.03 – 5.93) in 2019 (p<0.001). *C. difficile* specific testing also decreased during the study period (p<0.001). Chronic gastrointestinal conditions (36%) and malignancy (32%) were the most common comorbidities in CDI encounters. Oral metronidazole use decreased during the study period (p<0.01) and oral vancomycin use increased (p<0.001).

Conclusions: Our study demonstrates a decrease in CDI incidence in hospitalized pediatric patients, a notable change from prior studies, although this may have been influenced by altered testing patterns. We found a high incidence of CDI in patients with cancer and gastrointestinal conditions: groups that warrant targeted evaluation of CDI prevention and treatment.

Introduction

In the last two decades, *C. difficile* infection (CDI) has emerged as a significant public health threat, and an increase in the incidence of CDI was reported across nearly all geographic regions in both adults and children.[1–3] From 2001 to 2006, the rates of CDI nearly doubled in pediatric inpatients[4] and a population-based study demonstrated a 12.5-fold increase in CDI in children from 1991 through 2009.[5]

The last decade has also brought significant changes in the diagnosis and treatment of CDI. Testing algorithms have moved from toxin-based assays, to PCR-based testing, and finally, to multi-step algorithms; all with the goal of improving sensitivity of CDI detection while decreasing detection of *C. difficile* colonization.[3] Treatment recommendations in adults have shifted from metronidazole to vancomycin[3,6] with emerging evidence supportive of a similar approach in children.[7] To better understand the current incidence, diagnostic testing, comorbidity profiles, and treatment of pediatric CDI, in line with recent changes in guidance, we queried a large pediatric admissions database of hospital encounters from 2013 to 2019.

Methods

The Pediatric Health Information System® (PHIS) is an administrative database that contains inpatient data from 49 pediatric tertiary care centers in the United States. The PHIS database contains demographic information and diagnoses and compiles billing codes for procedures, medications, and laboratory tests performed during hospital admissions. Quality controls ensure accurate data collection across participating hospitals. Given the use of deidentified data, this study was determined to be non-human subjects research by the institutional review board.

For this study, a CDI encounter required an *International Classification of Disease (ICD) version 9 or 10* diagnosis code for CDI and a billing code for a CDI-specific antibiotic

therapy. Through a prior study involving a small cohort of hospitals from the PHIS databse, use of ICD 9 codes has been independently validated to have high specificity (99.89%) and sensitivity (80.73%) for CDI case identification.[8] To further improve case specificity in our study using a larger population of PHIS hospitals, a billing code for a CDI-specific antibiotic therapy was required. Use of ICD-9 with treatment charge has not been independently validated, but Shaklee et al found that including ICD-9 code with billing code for testing and treatment did result in a slight decrease in sensitivity to 76% but improvement in positive predictive value from 74% to 83%.[8] CDI-specific antibiotics included metronidazole (oral or intravenous), rifaximin, fidaxomicin, and vancomycin (oral). A diagnostic test was not required to be billed during the encounter and, due to PHIS database limitations, results of diagnostic testing were not available. In addition, testing for CDI prior to hospital admission could not be obtained through the PHIS database, as only inpatient records are available.

The PHIS database was queried for pediatric patient admissions (age <17 years) with a CDI encounter from 2013–2019. Data post-2019 was not collected as the goal of study was to evaluate CDI trends independent of the COVID-19 pandemic. Seven hospitals that did not report over the entire study period were excluded, leaving 42 hospitals with complete data for this retrospective study. Patient demographics, diagnosis codes, and encounter information were compiled for each hospital admission with CDI.

Comorbid conditions were identified by ICD 9 and ICD 10 diagnosis codes using the pediatric complex chronic conditions (CCC) classification system.[9] CCCs are defined as medical conditions expected to last at least 12 months, involve several organ systems or one organ system severely enough to require specialty pediatric care, and have a high probability of hospitalization.[10] This previously described and validated method for characterizing ICD-9/10–based pediatric complex chronic conditions is represented by 9 categories: neurologic and neuromuscular, cardiovascular, respiratory, renal and urologic, gastrointestinal, hematology and immunodeficiency, metabolic, malignancy, and neonatal. Complications were assessed at the patient-level vs. the encounter-level, and procedural codes (ie. colectomy) were billed during the same encounter as the CDI episode. Related to reliance on billing codes, timing of complications in relation to CDI could not be reliably determined.

Continuous variables were summarized with medians and interquartile ranges (IQR). Categorical variables were expressed as proportions. For regression analysis, incidence rates (cases /10,000 patient-days) were calculated overall and within each age group (<2, 2–5, and 6–17 years) for each year, and correlation was assessed using Spearman rank-order statistics. Adjusted rates were calculated using Poisson generalized linear models, controlling for hospital clustering and allowing for the presence of correlated data within hospitals, nonconstant variability between hospitals, and responses that are not normally distributed. Independent encounter-level variables included sex, race, ethnicity (Hispanic or non-Hispanic), and intensive care unit (ICU) admission.

To categorize testing trends during the study period, testing for CDI across all PHIS hospital encounters (not just those with a CDI encounter) was determined using billing data which included both single target approaches for *C. difficile* and multipathogen panels

(ie. gastrointestinal pathogen panels) and calculated per 10,000 patient days. Each encounter was characterized as having or not having a billing charge for a *C. difficile* specific test or a multipathogen panel. The inclusion of *C. difficile* as a target on multipathogen panels could not be determined through the PHIS database. Statistical significance was set at p<0.05. All statistical analyses were performed with SAS version 9.4 (SAS Institute, Cary, North Carolina).

Results

There were 26,592 encounters with an ICD-9 or 10 diagnosis of CDI which were further limited to those that included a billing code for CDI-specific antibiotic treatment (N=23,052). The 23,052 encounters represented 17,142 individual patients admitted to 42 children's hospitals from 2013–2019. CDI cases had a median age of 7 years (IQR 2–13), and 10,623 (46.1%) patients were female (Table I). Adjusted annual CDI incidence decreased over the study period from 7.09 cases per 10,000 patient days (95% CI: 6.15 – 8.18) in 2013 to 4.89 cases per 10,000 patient days (95% CI: 4.03 – 5.93) in 2019 (p<0.001). Excluding children 0–1 years old, the adjusted annual CDI incidence decreased over the study period from 20.87 cases per 10,000 patient days (95% CI: 18.13 – 24.02) in 2013 to 15.93 cases per 10,000 patient days (95% CI: 13.16 – 19.27) in 2019 (p<0.001). When evaluated by age, adjusted CDI incidence declined in all groupings, including children 0–1 year, 2–5 years, and 6–17 years (all p<0.001) during the study period (Figure 1a).

Among the 23,052 encounters with CDI, 17,247 (74.8%) had *C.difficile*-specific testing performed during their hospital admission and 3,636 (15.8%) had gastrointestinal panels performed. The most common type of *C. difficile* specific testing during the study period was nucleic acid amplification (e.g., polymerase chain reaction) testing (NAAT), which occurred in 14,673 encounters (63.7%). In those patients with an NAAT, there were 2,223 (15.2%) that had an additional *C. difficile*-specific test ordered during the encounter.

Due to the influence of testing rates on CDI incidence, testing per 10,000 patient days was evaluated throughout the study period in all PHIS encounters. The annual overall *C. difficile*-specific testing per 10,000 patient days decreased during the study period from 52.67 tests (95% CI: 44.67 – 62.11) in 2013 to 33.7 tests (95% CI: 29.48 – 38.52) in 2019 (p<0.001). When evaluated by age, the hospital-based rates of *C. difficile* specific testing decreased in children ages 0–1 year, 2–5 years, and 6–17 years (all p<0.001) (Figure 1b). When comparing changes in rates between *C. difficile* specific testing and CDI incidence using Spearmans Correlation, rates were highly correlated in those 0–1 year old (Corr=0.99, p<0.001), and not correlated in those 2–5 years old (corr=0.75, p=0.052) or 6–17 years old (Corr=0.68 (p=0.094). However, panel-based testing (which may or may not include *C. difficile*) increased during the study period (Figure 2; available at www.jpeds.com).

Based on CCC classifications, 19,355 (84%) of encounters were in children with a chronic condition. Chronic gastrointestinal conditions (9,332, 41%), malignancy (8,202, 36%), and immunodeficiency (5,520, 24%) were the conditions most frequently associated with CDI encounters (Table II). Nearly a quarter of patients with CDI patient encounters (5,629, 24%) had a gastrointestinal feeding device.

Oral metronidazole was used most frequently (mean annual use: 68.5%) throughout the study period. A decrease in oral metronidazole use was noted in 2018 and 2019 (trend: p<0.010), coincident with an increase in the use of oral vancomycin (trend: p<0.001) (Figure 3), which was used on average in 36.1% of encounters in 2019. Fidaxomicin use was low (mean annual use: 0.5%) during the study period.

The median length of stay for patients with CDI was 7 days (IQR 3–18). Severe outcomes, such as colectomy (74 patients, 0.3%), toxic megacolon (29 patients, 0.1%), and gastrointestinal perforation (91 patients, 0.4%), were uncommon; 55 (74%) of patients who underwent a colectomy also had a diagnosis of inflammatory bowel disease (IBD). There were 429 (1.9%) patients who died of any cause during their hospitalization in the study period but CDI-related causality could not be determined.

Discussion

In 2019, the Centers for Disease Control and Prevention included CDI as one of only five infections in the United States deemed an urgent threat, the highest level of concern to human health.[11] Concurrently, recent years have brought enhancements in antibiotic stewardship programs, infection control measures, CDI testing algorithms, and treatment approaches, all directly impacting the incidence and care of children with CDI. These factors illustrate the need for a contemporary assessment of pediatric CDI.

Despite previous studies demonstrating a significant increase in CDI incidence rates prior to 2013, there are limited recent data on CDI incidence, testing and treatment in hospitalized pediatric patients. Our very large cohort including 23,052 pediatric encounters with CDI from 42 tertiary care children's hospitals across the United States identified a decrease in the adjusted rates of CDI in hospitalized children from 7.09 cases per 10,000 patient days (95% CI: 6.15 – 8.18) in 2013 to 4.89 cases per 10,000 patient days (95% CI: 4.03 – 5.93) in 2019 (p<0.001). Several different initiatives may have contributed to this declining trend in incidence including increased utilization of Antibiotic Stewardship Programs (ASPs), better targeted cleaning protocols, and additional hospital contact precaution policies and procedures. Recent pediatric studies have shown decreases in antibiotic prescribing in both inpatient and outpatient settings,[12–14] an important factor when considering CDI risk and incidence in children.

Current data suggest that decreases in CDI incidence are most pronounced in those with healthcare-associated disease, defined as positive *C. difficile* testing collected > 3 days after admission to the facility.[3] Guh et al demonstrated that a national decline in the burden of CDI in the United States from 2011 to 2017 was primarily related to a decline in healthcare-associated CDI with no significant change in community-associated CDI.[15] Notably, although once considered primarily a hospital-acquired infection, community-associated (CA)-CDI has been demonstrated to represent 32–75% of CDI cases in population-based cohort studies.[16–18] A recent pediatric case-control study of CA-CDI demonstrated a substantial increase from 9.6 per 100,000 children in 2012 to a peak of 16.9 per 100,000 children in 2015.[19] As the PHIS database collects inpatient data only, we are unable to evaluate larger trends in CDI incidence in non-hospitalized children, a

cohort that requires additional attention and may not be reflected in the trends reported through our study. It is possible that ASPs, which historically have been primarily hospital-based, may have contributed to the differences in CDI incidence in the hospital versus community settings,[20,21] although many centers are now focusing on the outpatient antibiotic stewardship with increasing success.[22]

Of note, changes in incidence in our study may also be related to alterations in testing. *C. difficile*-specific testing decreased during the study period in all PHIS encounters but panel-based testing, interrogating for multiple enteric pathogens, increased during the study. The presence of *C. difficile* as a target on panel-based testing cannot be reliably determined through the PHIS database, nor can the precise results of laboratory testing, which are limitations of this study. Those use of alternative pediatric databases with laboratory results would be better suited to evaluate the type and frequency of *C. difficile* testing and its influence on current incidence rates, particularly considering changes in diagnostic algorithms in the last 10 years with movement from toxin-based testing, to nucleic-acid amplification-based testing (NAAT), and finally, to the use of multi-step algorithms.[3,6] However, a recent study mostly in adults but including some children demonstrated that, even when adjusting for the increased sensitivity of NAAT-based testing, the overall incidence of CDI decreased by 24% (95% CI, 6 to 36) from 2011 to 2017.[15]

Notably, the incidence of CDI in our study area is also likely influenced by issues of *C. difficile* colonization, loosely defined as the presence of *C. difficile* in the intestinal microbiota without accompanied clinical symptoms. Colonization with *C. difficile* occurs more frequently in children <2 years of age and in children with recent hospitalizations or additional comorbidities.[23] To date, current testing algorithms have demonstrated difficulty in the differentiation of *C. difficile* colonization versus infection[24] and a careful analysis of clinical symptoms and pre-test probability is warranted for best CDI diagnostics. Clinical symptoms could not be identified through the PHIS database and some children were likely diagnosed and treated for CDI outside of the established CDI clinical definitions.[3] It is also possible that the decreased incidence of CDI during the study period was influenced by increased recognition of *C. difficile* colonization, particularly in those under one year old, and more judicious testing and treatment. Our study identified a significant association of *C. difficile* specific testing rates and incidence in children 0–1 years old through the study period (Corr=0.99, p<0.001) which likely indicates the high rates of colonization, and therefore inter-connection of testing and incidence, in young children and infants.

Our study identified overall low rates of complications, similar to previous studies of CDI in children.[4,25] Complications occurred during the admission with CDI, but timing of the complication in relation to CDI or CDI-related causality could not be fully evaluated using the PHIS database. Colectomy was documented in only 0.3% of the patients in our cohort, which is consistent with previous pediatric data ranging from 0.1% to 1.2% and adult data reporting 0.3% to 1.9%.[2,4,26–28] However, most pediatric patients who had a colectomy in our cohort also had a diagnosis of, a known independent risk factor for colectomy.[29] It remains unclear if CDI causes worsening of IBD or if patients with severe IBD are at increased risk of acquiring CDI, an area that requires additional study. The 382 (1.8%) inpatient deaths noted during the study period is consistent with prior reported rates of

all-cause mortality in pediatric patients with CDI of 2–4%,[1,4,30] which remains significantly lower than all-cause mortality related to CDI in adults (13.7%).[25] Based on PHIS database limitations, we are unable to determine the cause of death in these patients or if CDI was a contributing factor; however, previous population-based pediatric studies have shown that CDI is an independent predictor of increased hospital stay and all-cause mortality, even when comorbidities are matched.[1] Rates of complications should be interpreted with caution, as using ICD codes to identify complications has not been independently validated.

Although data vary between studies, antibiotic exposure, proton pump inhibitor use, healthcare exposure, and the presence of underlying comorbidities have all been associated with increased risk of CDI.[3,31] Patients with gastrointestinal conditions, feeding tubes, and immunosuppressed status were highly represented in our study, and although a retrospective study without a matched cohort of patients without CDI cannot assess causality, these findings have been supported by other studies.[32–35] The identification of these high risk pediatric populations is critically important, both as a reminder to minimize additional risk factors such as unnecessary antibiotics in these highly vulnerable children and for focus of microbiota-targeting prophylactic treatments. Conversely, 16% of encounters in our study were in children without a chronic condition. Therefore, CDI can and does occur in otherwise healthy children and an appropriate index of suspicious is warranted in any child with a fitting clinical history.

In the 2017 The Infectious Diseases Society of America and The Society for Healthcare Epidemiology of America Guidelines, recommendations were made for the use of oral vancomycin over metronidazole in adult patients for severe and non-severe episodes of CDI, although metronidazole use was still acceptable in the setting of non-severe pediatric CDI due to its high efficacy, especially in CA-CDI.[3,19,35] These recommendations may have influenced the increasing use of vancomycin noted in our study (Figure 3). Notably, since the release of these guidelines, additional pediatric data have demonstrated earlier symptom resolution associated with vancomycin use over metronidazole use in non-severe CDI,[7] although larger studies are needed to guide practice patterns. In one cohort, transition from metronidazole to vancomycin was associated with lower rates of colectomy in adults with IBD, which also may inform prescribing practices in that subset of patients[36]. Fidaxomicin was infrequently used during our study period, but we anticipate that use will likely increase with a multicenter randomized control trial demonstrating higher rates of global cure for fidaxomicin versus vancomycin in children with CDI and recent Food and Drug Administration approval for pediatric use in 2020.[37–39]

Our study represents a large pediatric cohort, but reliance on billing, procedure codes, and the retrospective design are notable limitations in a study of this design. *C. difficile* testing could not be fully evaluated due to the initiation of multi-pathogen panels during the study period and differentiating colonization from CDI cannot be performed through the PHIS database. Finally, identifying complications, comorbidities, and outcomes from a retrospective database relies on accurate documentation of diagnosis codes during the hospital encounter, and sensitivity and specificity for CDI-related complication codes have not been established.

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Although rare, severe CDI complications do occur in pediatric patients, and prospective studies will be important to risk-stratify underlying conditions and to test preventive measures for high-risk groups. Continued reduction in the incidence and improved outcomes associated with pediatric CDI will need collaborative efforts to reduce unnecessary antibiotic exposures, identify high-risk groups, tailor infection prevention strategies, evaluate testing practices, and improve prophylaxis and treatment.

Funding:

Data Sharing Statement:

Data are available upon request.

Appreviations and Acronyms:

|	
CDI	*C. difficile* infection
PCR	polymerase chain reaction
COVID-19	
PHIS	Pediatric Health Information System
ICU	intensive care unit
ICD	International Classification of Disease
CCC	complex chronic conditions
IQR	interquartile range
IBD	inflammatory bowel disease
ASPs	antibiotic stewardship programs
CA-CDI	community-associated CDI
NAAT	nucleic-acid amplification-based testing
HCST	hematopoietic stem cell transplantation

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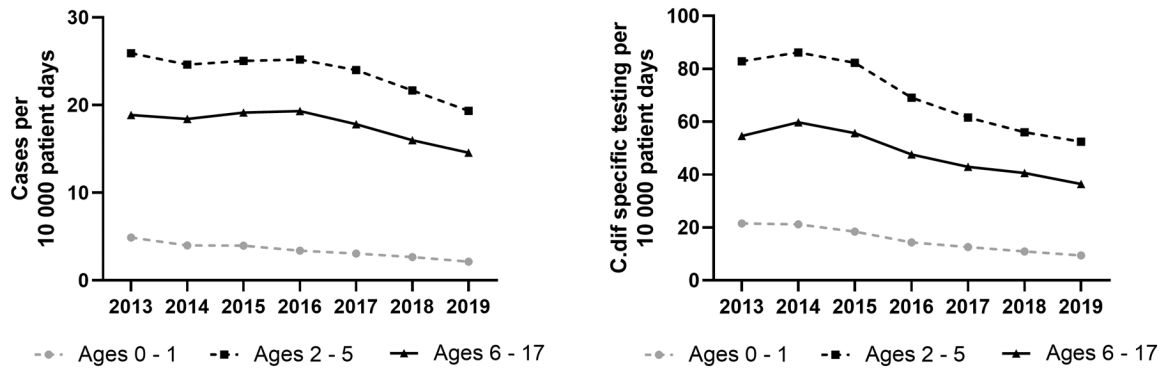
Figure 1).

A. The yearly incidence of hospital admissions with a diagnosis of CDI from 2013–2019 in 42 pediatric hospitals (per 10,000 patient-days) were calculated using Poisson generalized linear models, adjusted for patient characteristics and co-morbid conditions. B. Frequency of *C. difficile*-specific testing per 10,000 patient days.
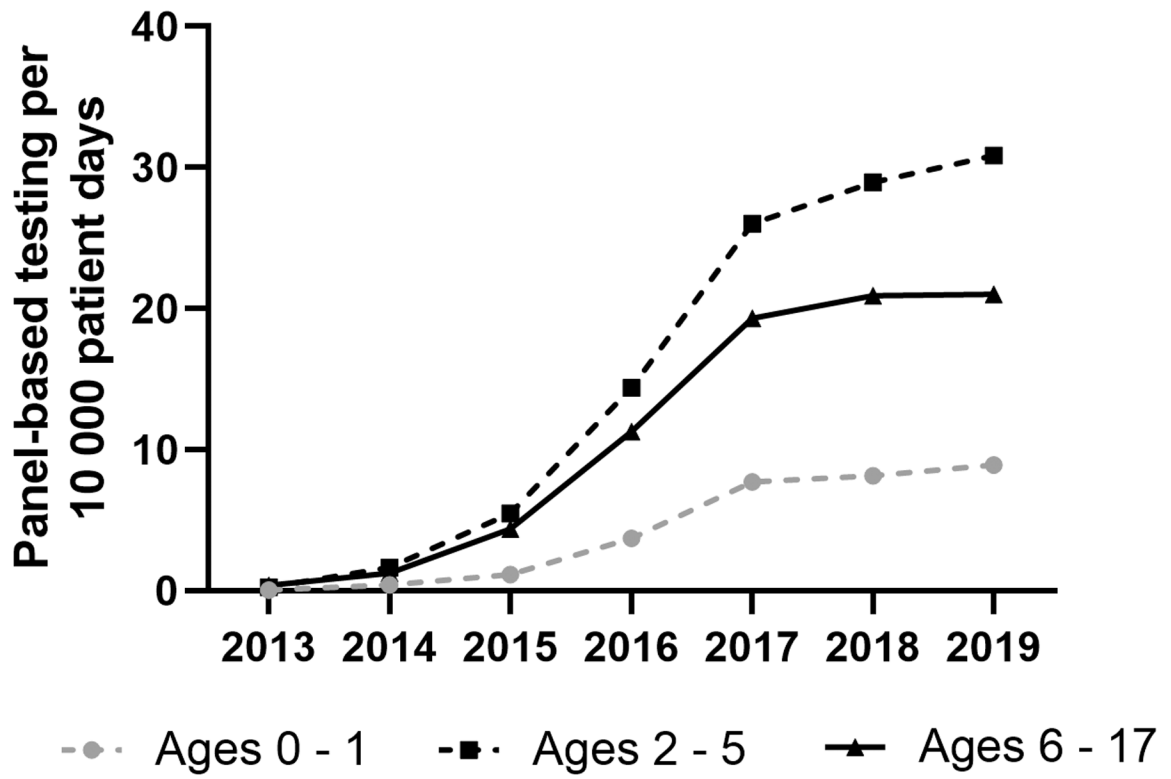
Figure 2).
Panel based testing rates per 10,000 patient days in hospitalized children.
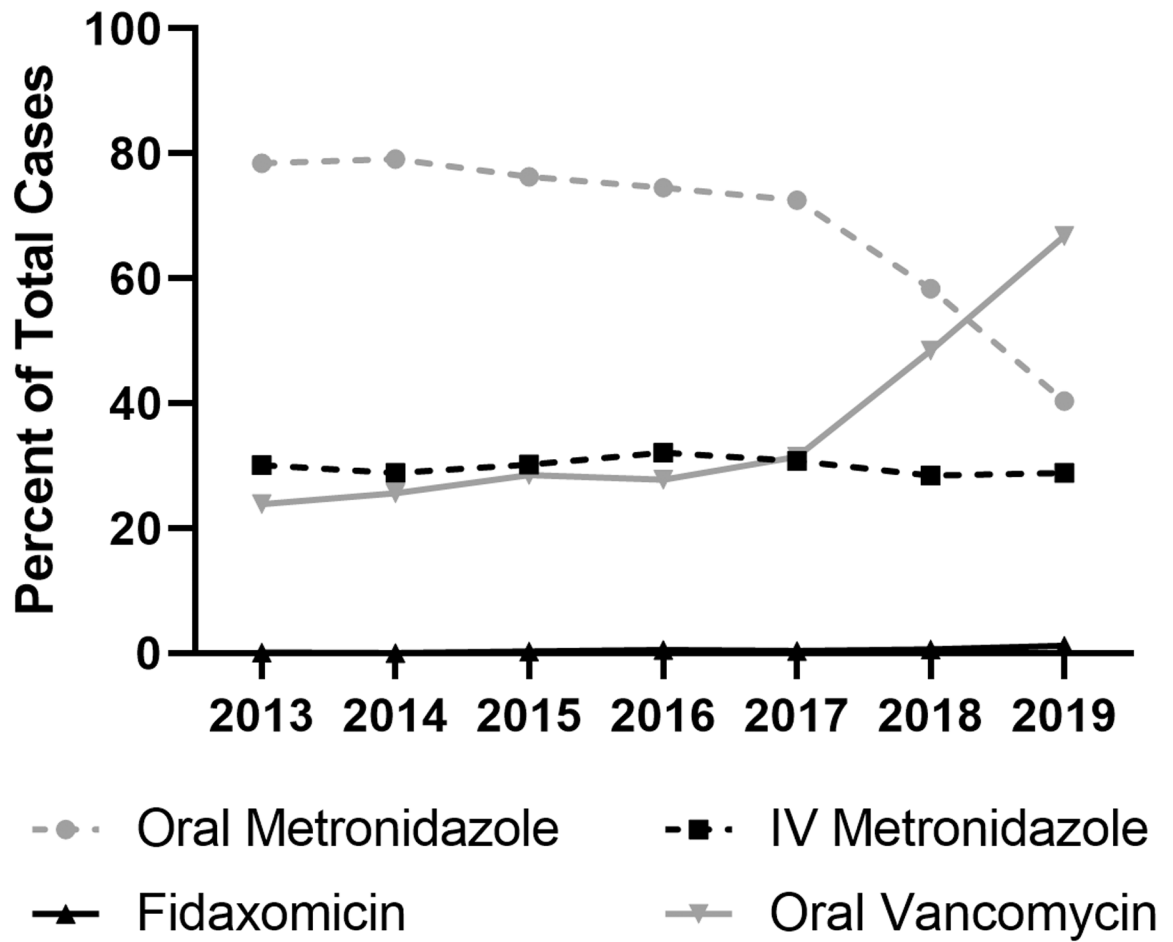
Figure 3).
Antibiotic use for the treatment of *C. difficile* infection in hospitalized children from 2013 to 2019.

Table 1.

Demographic summary of inpatient pediatric CDI encounters from 2013–2019 at 42 children's hospitals in the United States.

Age	
Median (IQR)	7 (2–13)
Ages 0 – 1	3,948 (17.1%)
Ages 2 – 5	6,438 (27.9%)
Ages 6 – 17	12,666 (55%)
Gender	
Female	10,623 (46.1%)
Male	12,429 (53.9%)
Race	
African American	2,650 (11.5%)
American Indian and Alaskan Native	137 (0.6%)
Asian and Pacific Islander	680 (2.9%)
Other	3,291 (14.3%)
Two or more races	1,393 (5.6%)
White	14,901 (64.6%)
Ethnicity	
Hispanic	5,155 (22.4%)
Median Days of Hospitalization Before Testing (IQR)	1 (0–6)
Median Length of Stay (IQR)	7 (3–18)
All-cause Mortality	429 (1.9%)
Gastrointestinal perforation	91 (0.4%)
Colectomy	74 (0.3%)
Colectomy in patients with IBD (percentage of total colectomies)	55 (74.3%)
Toxic Megacolon	29 (0.1%)

Table 2:

International Classification of Disease 9 and 10 codes of patients with CDI encounter grouped using Feudtner's Complex Chronic Conditions.

	Patient encounters with Condition within Organ System (percentage of total admissions)
Any Chronic Condition	19,355 (84%)
Cardiovascular	3,349 (14.5%)
Neurologic and Neuromuscular	3,955 (17.2%)
Respiratory	2,248 (9.8%)
Renal and Urologic	2,914 (12.6%)
Gastrointestinal	9,332 (40.5%)
Inflammatory Bowel Disease	1,749 (8%)
Gastrointestinal Devices (feeding tube or ostomy)	5,629 (24%)
Transplantation (Liver, Small Intestine, or Pancreas)	572 (2%)
Hematologic and/or Immunodeficiency	5,520 (23.9%)
Metabolic	4,514 (19.6%)
Malignancy	8,202 (35.6%)
Neoplasms	7,045 (31%)
Stem Cell Transplantation	883 (5%)
Neonatal (arising in perinatal period)	473 (2.1%)