Infect Dis Ther (2022) 11:111–126
https://doi.org/10.1007/s40121-021-00480-0

ORIGINAL RESEARCH

Budget Impact Analysis of Fidaxomicin Versus Vancomycin for the Treatment of *Clostridioides difficile* Infection in the United States

Yiling Jiang · Eric M. Sarpong · Pamela Sears · Engels N. Obi

Received: October 1, 2020 / Accepted: June 10, 2021 / Published online: July 22, 2021

ABSTRACT

Introduction: Fidaxomicin is as effective as vancomycin in treating *Clostridioides difficile* infection (CDI) but more effective at preventing recurrence. However, because fidaxomicin is more costly than vancomycin, its overall value in managing CDI is not well understood. This study assessed the budget impact of introducing fidaxomicin versus vancomycin for the treatment of adults with CDI from a hospital perspective in the US.

Methods: A cohort-based decision analytic model was developed over a 1-year horizon. A hospital with 10,000 annual hospitalizations was simulated. The model considered two adult populations: patients with no prior CDI episode and patients with one prior CDI episode. Two scenarios were assessed per population: 15% fidaxomicin/85% vancomycin use and 100% vancomycin use. Model inputs were obtained from published sources and expert opinion. Model outcomes included cost, payment, and revenue at the hospital level, per treated CDI patient, and per admitted patient. Budget impact was calculated as the difference in revenue between scenarios. One-way sensitivity analyses tested the effects of varying model inputs on the budget impact.

Results: In patients with no prior CDI episode, treatment with fidaxomicin resulted in potential savings over 1 year of $1105 at the hospital level, $14 per treated CDI patient, and $0.11 per admitted patient. In patients with one prior CDI episode, fidaxomicin use was associated with potential savings over 1 year of $1150 at the hospital level, $74 per treated CDI patient, and $0.12 per admitted patient. Savings were driven by a reduced rate of CDI recurrence with fidaxomicin treatment and uptake of fidaxomicin. Sensitivity analyses indicated savings when inputs were varied in most scenarios.

Conclusion: Budgetary savings can be achieved with fidaxomicin due to reduced CDI recurrence as a result of a superior sustained clinical response. Our results support considering the broader benefits of fidaxomicin, beyond its cost, when making formulary inclusion decisions.

Y. Jiang (✉)
Merck Sharp & Dohme (UK) Ltd., 120 Moorgate, London EC2Y 9AL, UK
e-mail: yiling.jiang1@msd.com

E. M. Sarpong · P. Sears · E. N. Obi
Merck & Co., Inc., 200 Galloping Hill Road, Kenilworth, NJ 07033, USA

PLAIN LANGUAGE SUMMARY

Clostridioides difficile infection (CDI) is a common hospital-acquired infection that affects about half a million people in the US each year. In some patients who have already had CDI, it can recur. These recurrent infections can be difficult to treat, and they place a burden on the healthcare system. CDI is usually treated with the antibiotics fidaxomicin or vancomycin. Fidaxomicin is as effective as vancomycin for treating CDI but is even more effective than vancomycin at preventing CDI recurrence. However, fidaxomicin is more expensive. In this study, we estimated the impact of replacing vancomycin with fidaxomicin for treating CDI on the budget of a typical US hospital. We estimated that treating 15% of patients with CDI using fidaxomicin in place of vancomycin would save the hospital between $1105 and $1150 in a year. This means that despite the higher cost of fidaxomicin, treating as few as 15% of patients with CDI using fidaxomicin instead of vancomycin can be cost-saving for hospitals.

Keywords: Budget impact; *Clostridioides difficile*; Fidaxomicin; Hospital; Recurrence; Vancomycin

Key Summary Points

Why carry out this study?

Clinical trial data have shown that fidaxomicin is as effective as vancomycin in treating *Clostridioides difficile infection* (CDI) but more effective at preventing recurrence

Fidaxomicin's uptake in healthcare settings has been limited by its cost, and its overall value in managing CDI is not well understood

This study assessed the budget impact of introducing fidaxomicin versus vancomycin for the treatment of adults with CDI from a hospital perspective in the USA

What was learned from this study?

Treating with fidaxomicin instead of vancomycin for 15% of patients with an initial or recurrent episode of CDI can result in cost savings over 1 year of $1105 to $1150 at the hospital level, $14 to $74 per treated CDI patient, and $0.11 to $0.12 per admitted patient

The broader benefits of fidaxomicin, beyond its cost, should be considered by healthcare stakeholders and policy makers when making decisions about formulary inclusion

INTRODUCTION

Clostridioides difficile, formerly known as *Clostridium difficile*, is the most common cause of nosocomial infectious diarrhea in adults in the US [1–3]. *C. difficile* infection (CDI) is a national public health concern, with an estimated incidence of 14.2 per 1000 adult non-maternal hospital discharges in 2015 [4]. A population-based survey in the US reported an annual incidence of 453,000 CDI cases, with 83,000 first recurrences and 29,300 deaths, most of which occurred in individuals aged 65 years or older [5]. Multiple risk factors for CDI have been identified including advanced age, previous CDI, antibiotic exposure, immunocompromised status, multiple comorbidities, hospitalization, residence in a long-term care facility, cancer chemotherapy, and gastrointestinal surgery [6–9].

A common hallmark of CDI is an increased risk of recurrence after an initial resolution of symptoms following treatment with antibiotics. Among patients with a primary case of CDI, 25% experience a recurrent episode [10, 11]. The likelihood of recurrence increases with each CDI episode, with the rate rising to 65% after two recurrences [12]. Compared to an initial episode, recurrent CDI is more challenging to treat and is associated with more hospitalizations, increased morbidity and mortality [13], and greater costs [14, 15]. The total costs of CDI

hospital management in the US was $6.3 billion in 2015 [16].

Clinical practice guidelines recommend treating an initial episode of CDI primarily with antibiotics, with recent guidelines suggesting treating with vancomycin or fidaxomicin rather than metronidazole, regardless of severity [3]. Recurrent CDI may be treated with vancomycin using a standard 10-day course (125 mg orally four times daily), vancomycin in a tapered/pulsed regimen, or with fidaxomicin using a standard 10-day course (200 mg orally twice daily).

Fidaxomicin is a macrolide antibiotic licensed in the US since 2011 for the treatment of *C. difficile*-associated diarrhea, also called CDI, in adults [17]. The efficacy and safety of fidaxomicin were established in two phase 3, randomized, controlled, double-blind, clinical trials [18, 19]. Results from a pooled analysis of the two pivotal clinical trials demonstrated that fidaxomicin was similar to vancomycin in achieving > 90% clinical response at the end of therapy [10]. However, among the cohort of patients with no prior CDI episode, CDI recurrence within 28 days occurred less often in those treated with fidaxomicin (11.7%) versus those treated with vancomycin (22.6%). Similarly, among the cohort of patients with a prior CDI episode, CDI recurrence was reported in 19.7% of patients treated with fidaxomicin versus 35.5% of patients treated with vancomycin.

Since fidaxomicin was approved for use, its uptake has been limited by its cost, despite its superior efficacy. Traditionally, antibiotics in a US hospital setting are funded through diagnosis-related groups (DRGs), which classify admissions based on principal diagnosis. Under this system, hospitals are reimbursed at a predetermined rate for healthcare services and drug costs according to the assigned DRG [20]. Often in a hospital setting, prices rather than the broader benefits or cost offsets of therapies are emphasized during selections of drugs to include in a formulary [20]. Therefore, bundling the cost of an antibiotic into a DRG payment can discourage the use of high-cost therapies such as fidaxomicin because of hospital budget constraints.

Although fidaxomicin's cost-effectiveness has been assessed in several studies as reported in a systematic review [21], little information is available about its budget impact. Because fidaxomicin or vancomycin can be used to treat an initial episode or first recurrence of CDI [3], this study assessed the budget impact of introducing fidaxomicin versus vancomycin for the treatment of adults with CDI from a US hospital perspective.

METHODS

Model Overview

A cohort-based decision analytic model was developed in Microsoft® Excel® 365 (Microsoft Corp., Redmond, WA) to determine the budget impact of introducing fidaxomicin versus vancomycin for the treatment of adults with CDI from a US hospital perspective. This budget impact analysis included two scenarios, with (a mix of fidaxomicin and vancomycin) or without fidaxomicin use (vancomycin only). Time horizons ranging from 1 to 5 years have been recommended for budget impact analyses because of short planning horizons by budget holders [22]; a 1-year time horizon was selected as the base case to assess budget impact. This timeframe is consistent and relevant to budget holders who typically evaluate hospital budgets on an annual basis. As is customary in the conduct of budget impact analysis, costs were not discounted due to the short time horizon. All costs were expressed in 2019 US dollars using the Consumer Price Index for medical care. Because no difference was found in the primary endpoint (clinical response) in the pivotal phase 3 trials of fidaxomicin versus vancomycin [18, 19], we used recurrence of CDI episodes during the 28 days following clinical response, the secondary endpoint in the trials, as the clinical endpoint for the model. Since fidaxomicin is associated with fewer CDI recurrences than vancomycin [10], only one CDI recurrence was included in the current analysis, which was considered as a conservative approach.

Model outcomes included cost, payment, and revenue at the hospital level, per treated CDI patient, and per admitted patient. The threshold proportion of days of therapy in a hospital inpatient versus outpatient setting at which the use of fidaxomicin is budget neutral was also assessed. Payment was for both reimbursement for fidaxomicin and vancomycin and for hospital readmission for recurrent CDI. Cost was composed of the drug acquisition cost of fidaxomicin and vancomycin plus the cost of a hospital readmission for recurrent CDI. Cost and payment were stratified by the proportion of days of therapy in the hospital inpatient and outpatient settings.

For scenarios with and without fidaxomicin, revenue was calculated as the difference between total payments received and total costs. The budget impact was then calculated as the difference in total revenue between the two scenarios. A positive budget impact in this analysis indicated higher revenue or cost savings. An overview of the model structure is depicted in Fig. 1.

Model Inputs and Assumptions: Base Case

Target Populations, Treatments, and Management Settings

A hypothetical hospital with 10,000 annual hospitalizations was simulated, with a proportion of adult patients admitted for CDI. The incidence of CDI was assumed to be 1.42% of hospital admissions, based on a reported estimate of 14.2 per 1000 adult nonmaternal hospital discharges in 2015 [4].

Two target patient populations were considered in this model: patients with no prior CDI episode (primary analysis) and patients with one prior CDI episode (additional analysis). For each population, the proportion of patients was sourced from a post hoc analysis of two phase 3 double-blind, randomized, controlled trials [10]. These proportions were calculated as the total number of patients with CDI recurrence in the per-protocol population receiving fidaxomicin or vancomycin divided by the total number of patients enrolled. Demographic characteristics of patients were assumed to be similar to those of the patients in the pooled randomized controlled trials evaluating fidaxomicin versus vancomycin [18, 19].

This model assessed two scenarios for each patient population: with fidaxomicin, representing patients treated with a mix of fidaxomicin (15%) and vancomycin (85%), and without fidaxomicin use, representing 100% of patients treated with vancomycin. No clinical criteria were used to select the 15% of patients receiving fidaxomicin. This uptake estimate was based on an assumed increase in the use of fidaxomicin over the 8% uptake reported in recent US national claims data [23], given the provisional 2020 Infectious Diseases Society of America guideline update recommending the

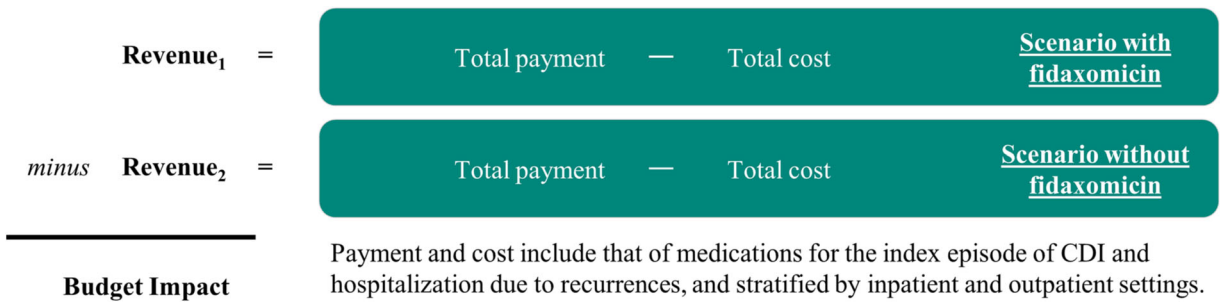

Fig. 1 Budget impact model structure. Scenario with fidaxomicin represents a mix of patients on fidaxomicin (15%) or vancomycin (85%). Scenario without fidaxomicin represents 100% of patients on vancomycin. Payment was for both reimbursement for fidaxomicin and vancomycin and for hospital readmission for recurrent *Clostridioides difficile* infection. Cost was composed of the drug acquisition cost of fidaxomicin and vancomycin plus the cost of a hospital readmission for recurrent *C. difficile* infection

use of fidaxomicin rather than vancomycin for initial or recurrent CDI episodes [24].

In addition, different management settings were considered in the analysis. The model accounted for the proportion of patient days of therapy spent in a hospital inpatient setting (49.8%) and a hospital outpatient setting (50.2%) based on data on fidaxomicin and vancomycin from a recently published analysis by the US Centers for Disease Control and Prevention [25].

Clinical Inputs

The default input parameters included in this model were obtained from published sources and are summarized in Table 1. Ethics committee approval was not required because this study was an economic simulation using data from previously conducted studies and did not involve new studies of human subjects.

Estimates of CDI recurrence for patient populations were based on per-protocol population results from a post-hoc analysis of the efficacy of fidaxomicin and vancomycin aggregated from two pivotal US clinical trials (Table 1) [10]. One recurrence of CDI per patient was considered in the model. It was assumed that not all recurrent CDI would lead to hospitalization. Based on a retrospective cohort study [26], 85.0% of patients with recurrent CDI were readmitted.

Death due to CDI was not taken into account for parsimony. Such simplification is judged appropriate as it has a limited impact on the difference in cost, payment, and revenue between the two scenarios, which is the primary outcome of the current study.

Economic Inputs

Costs were based on the most recent available data at the time of analysis (June 3, 2019) [27]. Drug acquisition costs per patient per day by inpatient and outpatient settings are shown in Table 1. A recommended treatment course of 10 days for fidaxomicin (one 200-mg tablet orally twice daily) [17] and vancomycin (one 125-mg tablet orally four times daily) was assumed [28].

The inpatient drug acquisition costs used in this model were based on fidaxomicin purchased at the discounted price and vancomycin purchased at the catalog price (equivalent to discounted price). The catalog price for fidaxomicin for a 10-day course of therapy was $3865.80, while the discounted cost of fidaxomicin was $2319.48, when assuming a 40% discount, consistent with a previous economic analysis [29]. The catalog and discounted cost of vancomycin was $136.30 for a 10-day course of therapy (assumed to be FIRVANQ™, a commonly used brand in the US). As per clinical practice, a 150 ml bottle of vancomycin hydrochloride, 50 mg/ml solution was used to calculate the cost of vancomycin [28]. Excess product was assumed to be wastage. The model did not account for payment in the inpatient setting as this was bundled within the DRG payment.

Based on expert input, the hospital outpatient setting was stratified into three categories for drug acquisition costs and payments: hospital-owned, non-340B-eligible outpatient pharmacy (15%); hospital-owned, 340B-eligible outpatient pharmacy (20%); and non-hospital-owned, outpatient pharmacy (65%). Drug acquisition costs in a hospital-owned, non-340B-eligible outpatient pharmacy setting could fluctuate; therefore, a conservative assumption of 3.65% less than the respective wholesale acquisition cost was applied to both fidaxomicin and vancomycin. Data from the second quarter of 2019 were used for all base prices of medications in a hospital-owned, 340B-eligible outpatient pharmacy setting [30]. For vancomycin, a minimum 23.1% discount was assumed [30]. In terms of payment for hospital-owned, non-340B-eligible, or 340B-eligible, the average national or general reimbursement for outpatient pharmacy branded drug medication was the wholesale acquisition cost + 2% + $2.00 dispensing fee (the dispensing fee was for the number days of therapy in the outpatient pharmacy).

Cost and payment for a recurrent CDI readmission were estimated based on a retrospective database study by Zilberberg et al. [31]. The study used 2009–2013 data from state inpatient databases [32] and reported the cost of and DRG

Table 1 Budget impact model input parameters

Parameters	Fidaxomicin arm	Vancomycin arm	References
Clinical inputs			
Recurrence rate of CDI (%)			
No prior CDI episode	11.7%	22.6%	[10]
One prior CDI episode	19.7%	35.5%	[10]
Readmission rate of CDI (%)	85.0%	85.0%	[26]
Economic inputs			
Drug acquisition cost per patient, per day ($)			
Inpatient	$231.95	$13.63	[27, 29]
Outpatient hospital-owned, non-340B-eligible pharmacy[a]	$372.47	$13.13	[27]
Outpatient hospital-owned, 340B-eligible pharmacy[b]	$121.03	$10.48	[27, 30]
Outpatient non-hospital-owned pharmacy[c]	$0.00	$0.00	[27]
Cost per patient for 10-day course of therapy ($)[d]			
Hospital inpatient setting	$1894.24	$136.30	
Hospital outpatient setting[c,e]	$800.77	$40.66	
Cost of recurrent CDI readmission ($)	$22,806.06	$22,806.06	[31]
Payment per patient for 10-day course of therapy ($)[d]			
Hospital inpatient setting	$0.00	$0.00	
Hospital outpatient setting[c,e]	$1380.79	$49.34	
Payment of recurrent CDI readmission ($)	$13,173.59	$13,173.59	[31]

CDI, *Clostridioides difficile* infection

[a] To account for fluctuations in cost, a conservative assumption was made to apply 3.65% less than the respective wholesale acquisition cost to both fidaxomicin and vancomycin

[b] Drug acquisition cost was sourced from the customer/hospital, depending on 340B-eligibility. For fidaxomicin, 340B price changes quarterly. For vancomycin, a minimum 23.1% discount was assumed [30]

[c] A proportion of patients administered medication in the outpatient setting may utilize outpatient pharmacies outside the hospital network. This proportion was factored into the model; however, costs specific to this cohort fall outside the hospital system and so are not factored into the model

[d] Drug acquisition costs per patient per day were used to calculate costs and payments for fidaxomicin and vancomycin for a recommended 10-day course of therapy. Costs and payments were proportioned based on patient days of therapy in the hospital inpatient (49.8%) vs. outpatient setting (50.2%)

[e] Drug acquisition costs and payments in the outpatient setting were calculated based on the relative proportions of outpatient pharmacy type applied in the model, i.e., hospital-owned, non-340B-eligible outpatient pharmacy (15%); hospital-owned, 340B-eligible outpatient pharmacy (20%); and non-hospital-owned, outpatient pharmacy (65%)

payment for the top five DRGs for readmissions where CDI was listed as the principal or secondary diagnosis. Our model default values reflected the weighted average cost and DRG payment of the top DRG groups [31]. Using the medical care Consumer Price Index from the Bureau of Labor Statistics (series CUUR0000-SAM) [33], values were inflated from 2009 to

Table 2 Budget impact of fidaxomicin in the treatment of patients with no prior CDI episode and with one prior CDI episode at the hospital level, per treated CDI patient, and per admitted patient

	Scenario A: with fidaxomicin	Scenario B: without fidaxomicin	Difference (Scenario A − Scenario B)
No prior CDI episode (N = 81)			
Budget impact at hospital level			
Cost	$355,007	$362,830	− $7824
Payment	$200,732	$207,451	− $6719
Revenue	− $154,275	− $155,380	
Total potential savings			$1105
Budget impact per treated CDI patient			
Cost	$4369	$4465	− $96
Payment	$2470	$2553	− $83
Revenue	− $1899	− $1912	
Total potential savings			$14
Budget impact per admitted patient			
Cost	$35.50	$36.28	− $0.78
Payment	$20.07	$20.75	− $0.67
Revenue	− $15.43	− $15.54	
Total potential savings			$0.11
One prior CDI episode (N = 16)			
Budget impact at hospital level			
Cost	$105,086	$108,811	− $3725
Payment	$59,869	$62,443	− $2575
Revenue	− $45,218	− $46,368	
Total potential savings			$1150
Budget impact per treated CDI patient			
Cost	$6728	$6966	− $238
Payment	$3833	$3998	− $165
Revenue	− $2895	− $2969	
Total potential savings			$74
Budget impact per admitted patient			
Cost	$10.51	$10.88	− $0.37
Payment	$5.99	$6.24	− $0.26
Revenue	− $4.52	− $4.64	

Table 2 continued

	Scenario A: with fidaxomicin	Scenario B: without fidaxomicin	Difference (Scenario A − Scenario B)
Total potential savings			$0.12

CDI, *Clostridioides difficile* infection

2013 (index = 400.873) to May 2019 (index = 486.886) rates to reflect the price at the time of analysis. The cost of readmission for a recurrent CDI was estimated at $22,806.06, and payment was estimated at $13,173.59. These estimates are in line with recently published literature on the cost/payment associated with recurrent CDI [34, 35].

Costs and payments by CDI management setting are presented in Table 1. Average costs were used to calculate the budget impact for both model scenarios.

Sensitivity Analyses

One-way sensitivity analyses were conducted to determine the effects of uncertainty of model input parameters on the overall budget impact for both patient populations. Parameters used in the base case were varied as follows: proportion of patients admitted (± 20%), uptake of fidaxomicin (10–100%), time horizon (5 years), difference in cost/payment of recurrent CDI hospitalization (± 20%), and cost of fidaxomicin (+ 5%). In addition, while keeping the rate of CDI recurrence for fidaxomicin constant, we varied the rate for vancomycin in patients with no prior CDI episode between 16.9% (i.e., 11.7% + 5.2%) and 28.2% (i.e., 11.7% + 16.5%) based on the 95% confidence interval (− 16.5 to − 5.2) for difference in CDI recurrence between the two treatment arms reported in the post-hoc analysis by Cornely et al. [10]. Similarly, in patients with one prior CDI episode, the rate of CDI recurrence for vancomycin varied between 20.0% and 50.1% [10]. The proportion of days of therapy in the inpatient versus outpatient setting was varied to 50:50. A threshold analysis was conducted to determine the proportion of days of therapy in the hospital inpatient versus outpatient setting at which the use of fidaxomicin was budget neutral. The outpatient pharmacy split (hospital-owned, non-340B-eligible vs. hospital-owned, 340 eligible vs. non-hospital-owned) varied between 10:15:75 and 20:25:55.

RESULTS

Base Case Analysis

For a cohort of 10,000 admitted patients, an estimated 142 patients would present with an episode of CDI. Of these, 81 patients (57.2%) are expected to have no prior CDI episode and 16 patients (11.0%) to have one prior CDI episode. The remainder of patients were expected to have more than one prior CDI episode and were excluded as additional CDI recurrences were not in the scope of the current analysis. In the no prior CDI episode population, 17 patients in the scenario with fidaxomicin and 18 patients in the scenario without fidaxomicin were estimated to present with recurrent CDI. In the one prior CDI episode population, five patients in the scenario with fidaxomicin and six patients in the scenario without fidaxomicin were estimated to present with recurrent CDI.

Although patients treated with fidaxomicin had a higher drug acquisition cost, savings attributed to a reduced rate of CDI recurrence were observed at the hospital level (Table 2). In the primary analysis (no prior CDI episode), for the scenario with fidaxomicin, total costs decreased by $7824 and total payments decreased by $6719 compared with the scenario without fidaxomicin. The difference between payment and cost was − $154,275 in the

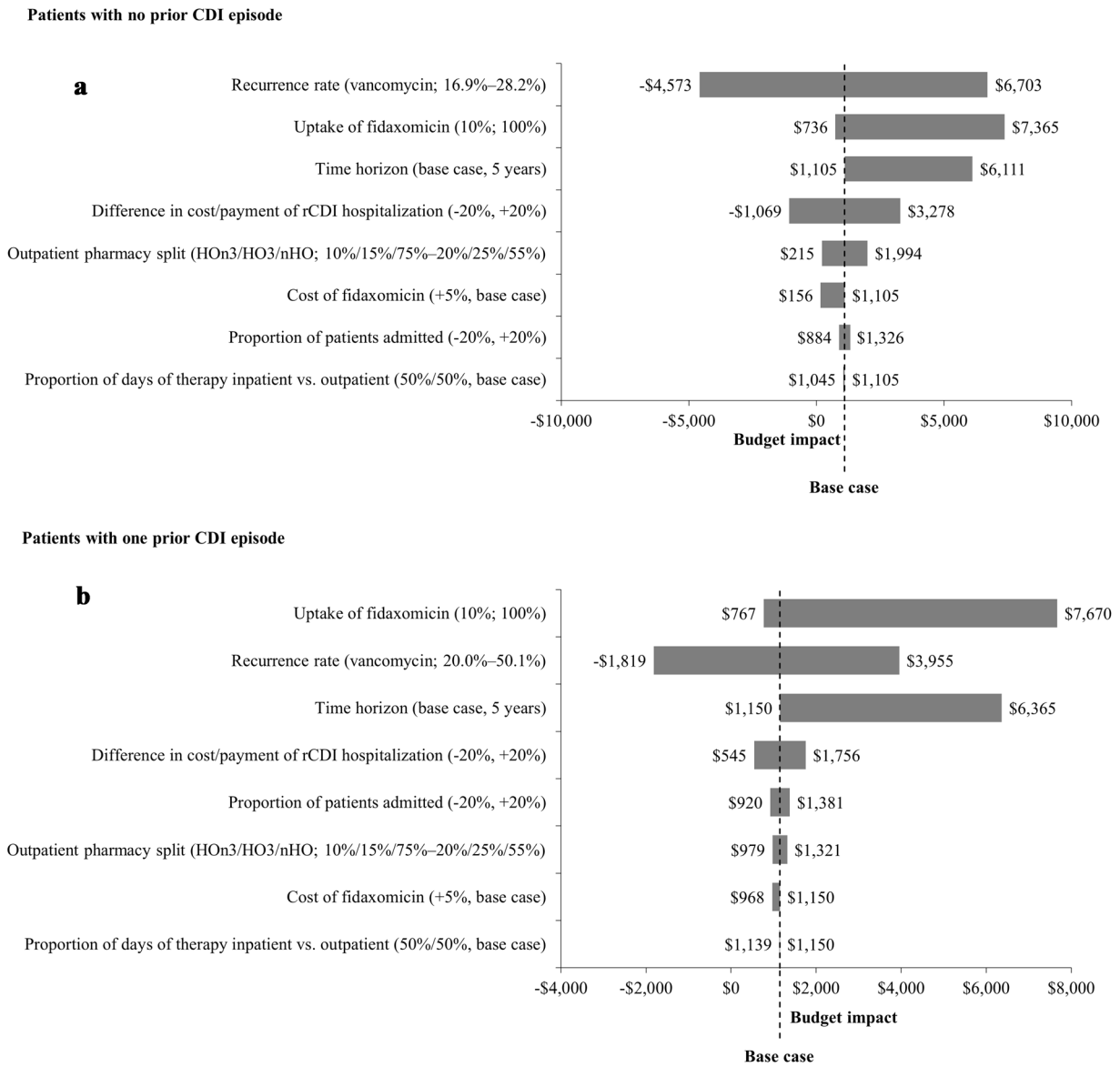

Fig. 2 One-way sensitivity analysis of budget impact of fidaxomicin at the hospital level for patients with no prior CDI episode and one prior CDI episode. CDI, *Clostridioides difficile* infection; HOn3, hospital-owned, non-340B-eligible; HO3, hospital-owned, 340B-eligible; nHO, non-hospital-owned

scenario with fidaxomicin and – $155,380 in the scenario without fidaxomicin. Hence, treatment with fidaxomicin was associated with a total potential savings of $1105 at the hospital level.

Over a 1-year time horizon, the model predicted that total costs would be reduced by $96 and total payments by $83 per treated CDI patient in the scenario with fidaxomicin compared to the scenario without fidaxomicin. The difference between payment and cost was – $1899 in the scenario with fidaxomicin and – $1912 in the scenario without fidaxomicin, resulting in a savings of $14 per treated CDI patient with fidaxomicin use.

Comparing the scenario with fidaxomicin and the scenario without fidaxomicin, the model estimated that total costs would be reduced by $0.78 and total payments by $0.67 per admitted patient. The difference between

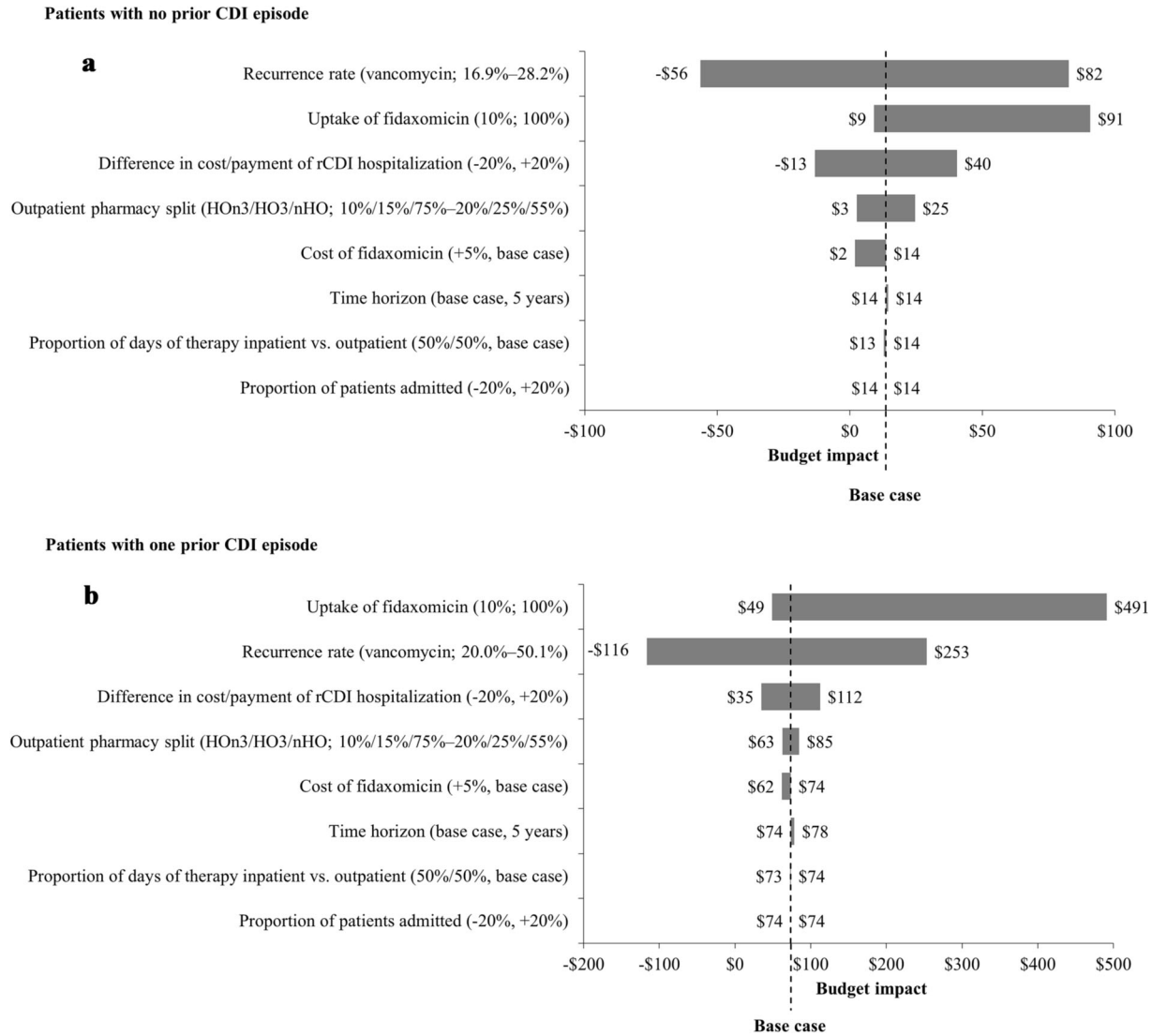

Fig. 3 One-way sensitivity analysis of budget impact of fidaxomicin per treated CDI patient for patients with no prior CDI episode and one prior CDI episode. CDI, *Clostridioides difficile* infection; HOn3, hospital-owned, non-340B-eligible; HO3, hospital-owned, 340B-eligible; nHO, non-hospital-owned

payment and cost was − $15.43 in the scenario with fidaxomicin versus − $15.54 in the scenario without fidaxomicin. A potential savings of $0.11 per admitted patient was projected when fidaxomicin is introduced into a hospital setting.

A similar trend in potential savings with fidaxomicin use was observed at the hospital level, per treated CDI patient, and per admitted patient when analyzed for patients with one prior CDI episode (Table 2). Potential savings was estimated at $1150 at the hospital level, $74 per treated CDI patient, and $0.12 per admitted patient when comparing the scenario with fidaxomicin to the scenario without fidaxomicin.

Sensitivity Analyses

Results from one-way sensitivity analyses for patients with no prior CDI episode showed that fidaxomicin use was associated with an increase in revenue at the hospital level (Fig. 2), per

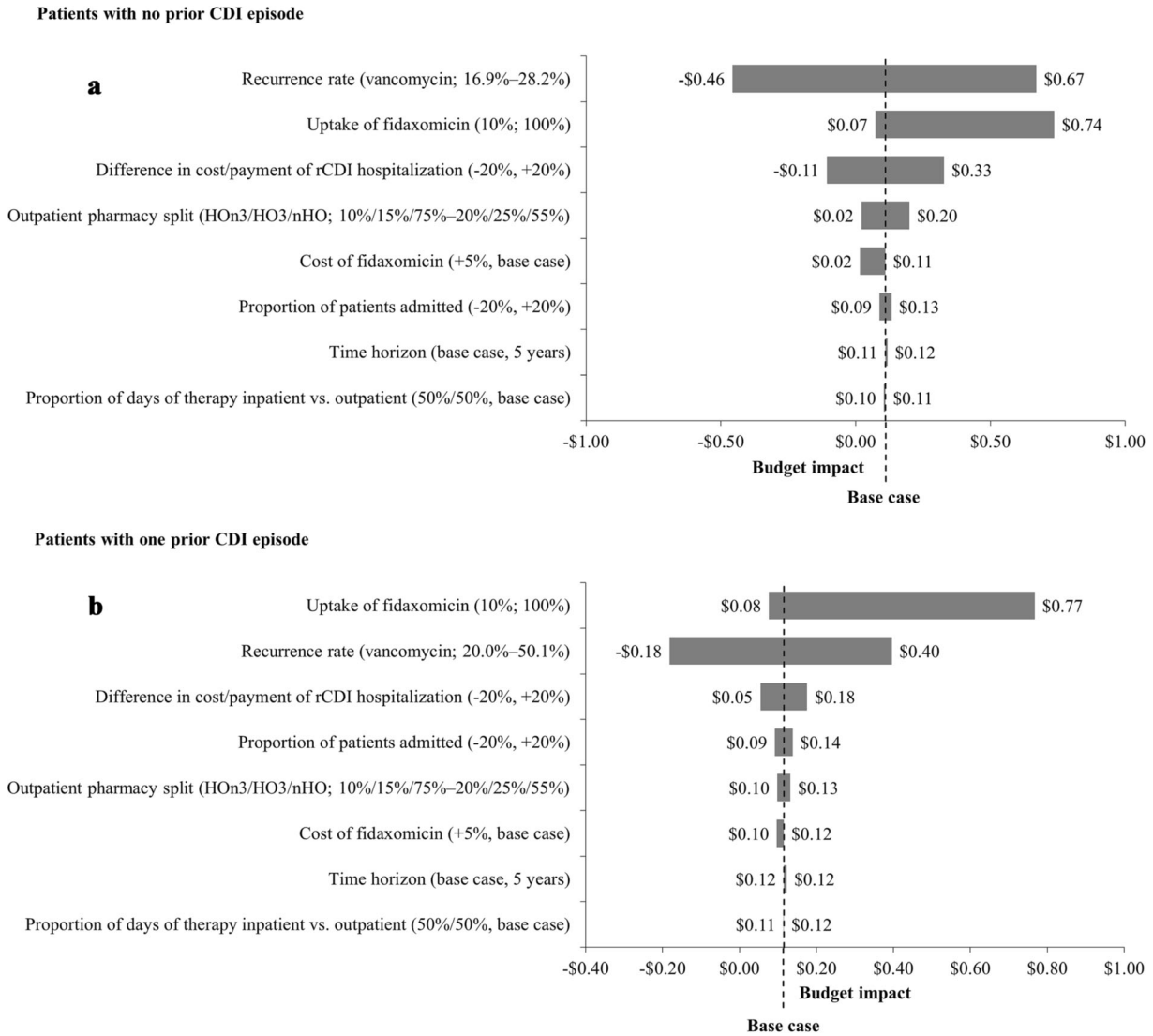

Fig. 4 One-way sensitivity analysis of budget impact of fidaxomicin per admitted patient for patients with no prior CDI episode and one prior CDI episode. CDI, *Clostridioides difficile* infection; HOn3, hospital-owned, non-340B-eligible; HO3, hospital-owned, 340B-eligible; nHO, non-hospital-owned

treated CDI patient (Fig. 3), and per admitted patient (Fig. 4) in most cases tested. The total budget impact for all variables examined ranged from − $4,573 to $7,365 at the hospital level; − $56 to $91 per treated CDI patient level; and − $0.46 to $0.74 per admitted patient level. The budget impact for the hospital level was most sensitive to the rates of CDI recurrence for vancomycin, the uptake of fidaxomicin, and the time horizon. The budget impact per treated CDI patient and per admitted patient were most sensitive to the rates of CDI recurrence for vancomycin, the uptake of fidaxomicin, and the difference in cost/payment of recurrent CDI hospitalization. Similar results were observed for patients with one prior CDI episode (Figs. 2, 3, 4).

The threshold analysis showed that fidaxomicin was budget neutral when the proportion of days of therapy in the hospital inpatient versus outpatient setting was 53.1% for patients

with no prior CDI episode and 67.6% for patients with one prior CDI episode.

DISCUSSION

Fidaxomicin's cost-effectiveness has been examined in several studies [21], but few studies have assessed its budget impact versus vancomycin. This study used an economic model to assess the budget impact of introducing fidaxomicin versus vancomycin for the treatment of adults with CDI, considering clinical outcomes, from a hospital perspective in the US over a 1-year period. The budget impact analysis showed that, although the acquisition cost of fidaxomicin is higher than vancomycin, using fidaxomicin should offer savings at the hospital level, per treated CDI patient, and per admitted patient. In patients who have not had prior CDI episodes, treatment with fidaxomicin instead of vancomycin for 15% of patients resulted in an estimated revenue increase of $1105 at the hospital level, $14 per treated CDI patient, and $0.11 per admitted patient. Similarly, fidaxomicin use was associated with an increase in revenue of $1150 at the hospital level for patients with one prior CDI episode. These savings are due to lower management costs from a reduced rate of CDI recurrence with fidaxomicin treatment, which outweighs the cost of medication.

One-way sensitivity analyses were conducted to verify the robustness of the model results. The use of fidaxomicin resulted in cost savings in most scenarios tested. Key drivers of budget impact at the hospital level were recurrence rates for vancomycin, uptake of fidaxomicin, and time horizon.

Our findings are consistent with previous studies showing hospital savings from treating with fidaxomicin instead of vancomycin [36–38]. Gallagher et al. analyzed the budgetary impact of fidaxomicin versus vancomycin in the treatment of an initial or recurrent CDI episode for patients hospitalized during a 2-year period [36]. They reported that treating with fidaxomicin was associated with cost savings of $3047 per patient. In another study, Watt et al. estimated the budget impact over a 1-year time horizon of fidaxomicin compared with vancomycin in a German hospital setting for patients with an initial CDI episode who had an increased risk of recurrence [37]. Hospitalization costs of initial CDI treatment were lower for patients receiving fidaxomicin versus vancomycin, resulting in an increase in revenue of up to €2438 per patient. A recent retrospective chart review study by Summers et al. found that hospitalization costs were $24,225 lower for patients with severe CDI treated with fidaxomicin than for those treated with vancomycin [38].

Compared to previous published models, our budget impact model was able to better reflect real-world practice by distinguishing between different management settings for fidaxomicin. To our knowledge, no prior budget impact analysis for fidaxomicin has accounted for patients receiving a portion of therapy in an inpatient setting and the remainder in an outpatient setting. Factoring into the analysis the portion of therapy received in an outpatient setting is important for providing a complete assessment of budget impact for hospitals that own or are affiliated with outpatient pharmacies, including those involved in the "meds-to-beds programs" [39, 40].

Limitations

As with most, if not all, budget impact analyses, the construction of the budget impact model and the results derived therefrom require disparate information, expert opinion, and several assumptions. Whenever possible, published data and expert opinion were used to inform the budget impact analysis.

Because the desired outcome of CDI treatment is to achieve a sustained clinical response (i.e., resolution of the initial illness without subsequent recurrence), this modeling study examined patients with an initial and first recurrent episode of CDI. This is especially relevant to the treatment of CDI because each episode of recurrence increases the likelihood of further episodes. The model did not consider subsequent recurrences of CDI, which may have

underestimated the benefits from the use of fidaxomicin.

A potential limitation is that the efficacy estimates used in this analysis were based on a single source, pooled results from a post hoc analysis [10] of two pivotal US clinical trials [18, 19]. This was the only source available that provided efficacy data for the subgroups of interest. The same efficacy estimates were also used in a previous meta-analysis comparing the clinical efficacy of fidaxomicin, vancomycin, and metronidazole [41] and in a study of fidaxomicin's cost-effectiveness [42].

In addition, the price of fidaxomicin or vancomycin used in our analysis does not necessarily reflect actual prices paid by consumers, payers, or the dispenser. The actual price paid by a healthcare system may vary depending on that healthcare system's method of purchase. An institution's drug acquisition cost may vary from those presented in the analysis (e.g., if a different dosing regimen for vancomycin is used).

The data reflected in the model are an estimate of potential budgetary impact; actual financial results may differ based on a variety of factors. Variations in medication utilization patterns, costs, and payments were not accounted for in the model. Determining the budget impact is a challenge because it can vary with price, which, in practice, is determined by several factors including whether a reduction in the list price has been negotiated. Although the results of this model may be accurate to healthcare systems at the national level, they cannot be generalized to healthcare systems at the local level because of differences in healthcare settings. Model outcomes may also vary over time. Assumptions about initial uptake, annual increases, and other variables related to fidaxomicin may vary depending on locality and vagaries of health care market and system conditions. Projected market share estimates for fidaxomicin were intentionally conservative, as is expected for recently approved, as opposed to existing, therapeutic options.

CONCLUSIONS

This budget impact analysis demonstrated that, although the acquisition cost of fidaxomicin is higher than vancomycin, hospital savings can be achieved with fidaxomicin due to its ability to reduce CDI recurrence, leading to a superior sustained clinical response. Using fidaxomicin to treat patients with an initial or recurrent episode of CDI can result in cost savings at the hospital level, per treated CDI patient, and per admitted patient. Our results support considering the broader benefits of fidaxomicin, beyond its cost, when making decisions about formulary inclusion.

ACKNOWLEDGEMENTS

Funding. Sponsorship for this study and Rapid Service Fee were funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Authorship. All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

Medical writing, editorial, and other assistance. Medical writing assistance in the preparation of this article was provided by Julia Zolotarjova, MSc, MWC, and Phillip Leventhal, PhD, of Evidera. Support for this assistance was funded by Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA.

Disclosures. Yiling Jiang is an employee of Merck Sharp & Dohme (UK) Ltd., who may own stock and/or stock options in the company. Eric M Sarpong, Pamela Sears, and Engels N Obi are employees of Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc., Kenilworth, NJ, USA, who may own stock and/or stock options in the company.

Compliance with ethics guidelines. Ethics committee approval was not required because this study was an economic simulation using data from previously conducted studies and did not involve any new studies of human subjects.

Data availability. All data generated or analyzed during this study are included in this published article/as supplementary information files.

Prior presentation. The main findings of this study were presented as a poster at the Virtual International Society of Pharmacoeconomics and Outcomes Research (ISPOR) conference, May 18–20, 2020.

REFERENCES

1. Lessa FC, Gould CV, McDonald LC. Current status of *Clostridium difficile* infection epidemiology. Clin Infect Dis. 2012;55(Suppl 2):S65-70.
2. Reveles KR, Lee GC, Boyd NK, Frei CR. The rise in *Clostridium difficile* infection incidence among hospitalized adults in the United States: 2001–2010. Am J Infect Control. 2014;42:1028–32.
3. McDonald LC, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and society for healthcare epidemiology of America (SHEA). Clin Infect Dis. 2018;66:e1-48.
4. Barrett ML, Owens PL. *Clostridium difficile* hospitalizations, 2011–2015. U.S. Agency for Healthcare Research and Quality; 2018. https://www.hcup-us.ahrq.gov/reports/HCUPCDiffHosp2011-2015Rpt081618.pdf. Accessed 21 Sep 2020.
5. Lessa FC, Mu Y, Bamberg WM, et al. Burden of *Clostridium difficile* infection in the United States. N Engl J Med. 2015;372:825–34.
6. Aslam S, Hamill RJ, Musher DM. Treatment of *Clostridium difficile*-associated disease: old therapies and new strategies. Lancet Infect Dis. 2005;5:549–57.
7. Schroeder MS. *Clostridium difficile*–associated diarrhea. Am Fam Physician. 2005;71:921–8.
8. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for *Clostridium difficile* infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). Infect Control Hosp Epidemiol. 2010;31:431–55.
9. Khanna S, Gupta A, Baddour LM, Pardi DS. Epidemiology, outcomes, and predictors of mortality in hospitalized adults with *Clostridium difficile* infection. Intern Emerg Med. 2016;11:657–65.
10. Cornely OA, Miller MA, Louie TJ, Crook DW, Gorbach SL. Treatment of first recurrence of *Clostridium difficile* infection: fidaxomicin versus vancomycin. Clin Infect Dis. 2012;55(Suppl 2):S154–61.
11. Sheitoyan-Pesant C, Abou Chakra CN, Pepin J, Marcil-Heguy A, Nault V, Valiquette L. Clinical and healthcare burden of multiple recurrences of *Clostridium difficile* infection. Clin Infect Dis. 2016;62:574–80.
12. McFarland LV. Alternative treatments for *Clostridium difficile* disease: what really works? J Med Microbiol. 2005;54:101–11.
13. Kuntz JL, Baker JM, Kipnis P, et al. Utilization of health services among adults with recurrent *Clostridium difficile* infection: a 12-year population-based study. Infect Control Hosp Epidemiol. 2017;38:45–52.
14. Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW. Economic healthcare costs of *Clostridium difficile* infection: a systematic review. J Hosp Infect. 2010;74:309–18.
15. Zhang D, Prabhu VS, Marcella SW. Attributable healthcare resource utilization and costs for patients with primary and recurrent *Clostridium difficile* infection in the United States. Clin Infect Dis. 2018;66:1326–32.
16. Zhang S, Palazuelos-Munoz S, Balsells EM, Nair H, Chit A, Kyaw MH. Cost of hospital management of *Clostridium difficile* infection in United States-a meta-analysis and modelling study. BMC Infect Dis. 2016;16:447.
17. Dificid (fidaxomicin), for oral use. Merck & Co., Inc.; 2019. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/201699s011lbl.pdf. Accessed 21 Sep 2020.
18. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for *Clostridium difficile* infection. N Engl J Med. 2011;364:422–31.
19. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with *Clostridium difficile* in Europe, Canada, and the USA: a double-blind, non-inferiority, randomised controlled trial. Lancet Infect Dis. 2012;12:281–9.

20. Bhatti T, Lum K, Holland S, Sassman S, Findlay D, Outterson K. A perspective on incentives for novel inpatient antibiotics: no one-size-fits-all. J Law Med Ethics. 2018;46:59–65.

21. Burton HE, Mitchell SA, Watt M. A systematic literature review of economic evaluations of antibiotic treatments for *Clostridium difficile* infection. Pharmacoeconomics. 2017;35:1123–40.

22. Foroutan N, Tarride J-E, Xie F, Levine M. A methodological review of national and transnational pharmaceutical budget impact analysis guidelines for new drug submissions. Clinicoecon Outcomes Res. 2018;10:821–54.

23. Clancy CJ, Buehrle D, Vu M, Wagener MM, Nguyen MH. Impact of revised Infectious Diseases Society of America and Society for Healthcare Epidemiology of America clinical practice guidelines on the treatment of *Clostridium difficile* infections in the United States. Clin Infect Dis. 2020;72:1944–9.

24. Johnson S. Focused update on *C. difficile* infection treatment guidelines: fidaxomicin and bezlotoxumab. ID Week 2020 Virtual Meeting; 2020.

25. 2018 annual report for the emerging infections program for *Clostridioides difficile* infection. Centers for Disease Control and Prevention; 2020. https://www.cdc.gov/hai/eip/Annual-CDI-Report-2018.html. Accessed 13 Jan 2021.

26. Olsen MA, Yan Y, Reske KA, Zilberberg M, Dubberke ER. Impact of *Clostridium difficile* recurrence on hospital readmissions. Am J Infect Control. 2015;43:318–22.

27. First DataBank AnalySource® Online. Wholesale acquisition cost (WAC). 2020. http://www.fdbhealth.com/fdb-medknowledge-drug-pricing. Accessed 21 Sep 2020.

28. FIRVANQ™ (vancomycin hydrochloride), for oral solution. CutisPharma; 2018. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/208910s000lbl.pdf. Accessed 21 Sep 2020.

29. Rajasingham R, Enns EA, Khoruts A, Vaughn BP. Cost-effectiveness of treatment regimens for *Clostridioides difficile* infection: an evaluation of the 2018 Infectious Diseases Society of America Guidelines. Clin Infect Dis. 2020;70:754–62.

30. 340B Health. Overview of the 340B drug pricing program. 2019. https://www.340bhealth.org/members/340b-program/overview/. Accessed 21 Sep 2020.

31. Zilberberg MD, Nathanson BH, Marcella S, Hawkshead JJ 3rd, Shorr AF. Hospital readmission with *Clostridium difficile* infection as a secondary diagnosis is associated with worsened outcomes and greater revenue loss relative to principal diagnosis: a retrospective cohort study. Medicine (Baltimore). 2018;97:e12212.

32. HCUP: Healthcare Costs and Utilization Project. Overview of state inpatient databases (SID). Agency for Healthcare Research and Quality; 2019. https://www.hcup-us.ahrq.gov/sidoverview.jsp. Accessed 21 Sep 2020.

33. Bureau of Labor Statistics. Consumer price index. 2019. https://www.bls.gov/cpi/. Accessed 21 Sep 2020.

34. Feuerstadt P, Stong L, Dahdal DN, Sacks N, Lang K, Nelson WW. Healthcare resource utilization and direct medical costs associated with index and recurrent *Clostridioides difficile* infection: a real-world data analysis. J Med Econ. 2020;23:603–9.

35. Duhalde L, Lurienne L, Wingen-Heimann SM, Guillou L, Buffet R, Bandinelli PA. The economic burden of *Clostridioides difficile* infection in patients with hematological malignancies in the United States: a case-control study. Infect Control Hosp Epidemiol. 2020;41:813–9.

36. Gallagher JC, Reilly JP, Navalkele B, Downham G, Haynes K, Trivedi M. Clinical and economic benefits of fidaxomicin compared to vancomycin for *Clostridium difficile* infection. Antimicrob Agents Chemother. 2015;59:7007–10.

37. Watt M, McCrea C, Johal S, Posnett J, Nazir J. A cost-effectiveness and budget impact analysis of first-line fidaxomicin for patients with *Clostridium difficile* infection (CDI) in Germany. Infection. 2016;44:599–606.

38. Summers BB, Yates M, Cleveland KO, Gelfand MS, Usery J. Fidaxomicin compared with oral vancomycin for the treatment of severe *Clostridium difficile*-associated diarrhea: a retrospective review. Hosp Pharm. 2020;55:268–72.

39. Lash DB, Mack A, Jolliff J, Plunkett J, Joson JL. Meds-to-beds: the impact of a bedside medication delivery program on 30-day readmissions. J Am Coll Clin Pharm. 2019;2:674–80.

40. Zillich AJ, Jaynes HA, Davis HB, et al. Evaluation of a "meds-to-beds" program on 30-day hospital readmissions. J Am Coll Clin Pharm. 2020;3:577–85.

41. Cornely OA, Nathwani D, Ivanescu C, Odufowora-Sita O, Retsa P, Odeyemi IA. Clinical efficacy of fidaxomicin compared with vancomycin and metronidazole in *Clostridium difficile* infections: a meta-analysis and indirect treatment comparison. J Antimicrob Chemother. 2014;69:2892–900.

42. Okumura H, Ueyama M, Shoji S, English M. Cost-effectiveness analysis of fidaxomicin for the treatment of Clostridioides (Clostridium) difficile infection in Japan. J Infect Chemother. 2020;26:611–8.

Publisher's Note