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Fidaxomicin to prevent recurrent *Clostridioides difficile*: what will it cost in the USA and Canada?

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Importance: Recent changes in guidelines for managing *Clostridioides difficile* infections (CDI) have placed fidaxomicin as a first-line treatment.

Objective: To estimate the net cost of first-line fidaxomicin compared to vancomycin in the American and Canadian healthcare systems and to estimate the price points at which fidaxomicin would become cost saving for the prevention of recurrence.

Data sources and study selection: We identified randomized, placebo-controlled trials directly comparing fidaxomicin with vancomycin that reported on recurrence. Medication costs were obtained from the Veterans Affairs Federal Supply Schedule (US) and the Quebec drug formulary (Canada). The average cost of a CDI recurrence was established through a systematic review for each country.

Data extraction, synthesis and outcome measures: For efficacy, data on CDI recurrence at day 40 were pooled using a restricted maximal likelihood random effects model. For the cost review, the mean cost across identified studies was adjusted to reflect May 2022 dollars. These were used to estimate the net cost per recurrence prevented with fidaxomicin and the price point below which fidaxomicin would be cost saving.

Results: The estimated mean system costs of a CDI recurrence were $15 147USD and $8806CAD, respectively. Preventing one recurrence by using first-line fidaxomicin over vancomycin would cost $38 222USD (95%CI $30 577–$57 332) and $13 760CAD (95%CI $11 008–$20 640), respectively. The probability that fidaxomicin was cost saving exceeded 95% if priced below $1140USD or $860CAD, respectively.

Conclusions and Relevance: An increased drug expenditure on fidaxomicin may not be offset through recurrence prevention unless the fidaxomicin price is negotiated.

Introduction

Clostridioides difficile infection (CDI) is a major cause of healthcare-associated diarrhoea in North America. It is estimated that in 2017 there were nearly 462 000 cases in the USA and in 2012[1] there were approximately 37 900 cases in Canada.[2] Of these, approximately 20%–25% represent recurrent infections.[2,3] The prevention of incident and recurrent episodes of CDI is therefore an important public health goal. Several pharmacologic and nonpharmacologic interventions have been investigated as initial treatment, and more specifically, to reduce risk of recurrence. For much of the twenty-first century, the recommended initial treatment of CDI has been oral metronidazole or vancomycin. In 2011, fidaxomicin was first demonstrated to be non-inferior to oral vancomycin for clinical cure.[4] This has ultimately been shown in two out of three double-blind, randomized,

placebo-controlled trials,[4,5] with all three providing evidence of a reduced risk of recurrence at day 40.[4–6] However, recommendations for fidaxomicin as first-line therapy have lagged in guidelines and formulary uptake has been slow, presumably due to fidaxomicin's higher cost. Issues surrounding affordability were highlighted in the 2017 Infectious Diseases and Healthcare Epidemiology Societies of America (IDSA-SHEA) guidelines[7] and in the 2018 Association of Medical Microbiology and Infectious Diseases of Canada (AMMI) guidelines.[8] Now more than a decade since the initial trial was published, the 2021 update to the IDSA-SHEA *C. difficile* guidelines recommended fidaxomicin as first-line therapy for all patients.[9] At the current pricing, treating all American[10] and Canadian[11] patients with fidaxomicin would cost an estimated $2.06 billion US dollars (USD) and $60 million Canadian dollars (CAD) per year, respectively.

Due to higher drug costs, other groups have attempted to evaluate the costs associated with first-line fidaxomicin in the USA and Canada, with mixed results. In one of the earliest evaluations, Bartsch *et al*. estimated that fidaxomicin would be dominated by other available options.[12] Reveles *et al*. suggested fidaxomicin had similar overall costs to compounded vancomycin and that it might be cost saving in some high-risk populations.[13] By contrast, Rajasingham *et al*. estimated that fidaxomicin would be cost-effective below a willingness-to-pay threshold of $100 000 per quality-adjusted life year (QALY).[14] In Canada, Wagner *et al*. estimated fidaxomicin use would be associated with an overall average cost increase of $13 202 per recurrence prevented, assuming a drug cost of $2200.[15]

Consequently, we believe that whether reductions of recurrent CDI will offset the higher up-front costs of fidaxomicin has not yet been determined. We therefore sought to estimate: (i) the net (added) cost of first-line use of fidaxomicin required to prevent a recurrence as compared to oral vancomycin and compare this with (ii) the estimated cost of a CDI recurrence so that we could determine (iii) the price point where a treatment course with fidaxomicin becomes unequivocally cost saving in the American and Canadian contexts.

Methods

To estimate the comparative efficacy of fidaxomicin versus vancomycin we conducted a meta-analysis of the three double-blind, placebo-controlled, randomized controlled trials identified by IDSA-SHEA[9] wherein fidaxomicin was compared head-to-head with vancomycin.[4–6] We excluded a fourth open-label trial that compared a longer total duration of fidaxomicin (30 versus 10 days in all other included studies).[16] This trial was excluded because the open-label nature of the study could create bias in favour of the treatment group both in terms of patient reported symptoms and subsequent physician testing and treating behaviour. We examined the primary outcome of the first CDI recurrence by day 40, which was the longest common duration reported, and meta-analysed the risk ratio with 95% confidence intervals using a restricted maximum likelihood random effects model in STATA v.17 (StataCorp LP). Using the overall control event rate as the expected baseline rate of recurrence, we then estimated the absolute risk difference, number needed to treat, and associated 95% confidence intervals.

We obtained the US drug costs from the Veterans Affairs Federal Supply Schedule (FSS)[10] by choosing the lowest FSS price. We obtained the Canadian drug costs from the Quebec formulary[11] (the province with the highest rate of CDI). A 10-day course of fidaxomicin was estimated to cost $3845.44USD and $1584 CAD, and that of vancomycin at $23.28USD (capsules) and $208 CAD (capsules). While some jurisdictions use the IV formulation as a PO treatment with consequent lower costs, our comparison is based on commercial products. The difference in estimated costs and the NNT were used to calculate the additional cost per recurrence prevented.

We estimated the cost of a CDI recurrence in USD and CAD through a systematic review of the literature. Is the USA, we assumed cost would apply to an insurer and/or patient, and in Canada, to the public payer. We searched PubMed on 10 July 2022, with the search terms described in Appendix 1. We included studies that were primary research articles, contained a cost-analysis of CDI, included cases of recurrent CDI, and were calculated with cost parameters based on the American or Canadian healthcare systems. Studies were excluded if the population exclusively contained hospitalized patients, as the purpose of this analysis was to evaluate fidaxomicin use in all cases of CDI from mild outpatient to more severe inpatient cases and analyses based only on hospitalized patients might inflate costs and not be representative. Studies of paediatric populations were also excluded. References for all included studies were examined for additional applicable studies. Screening and data extraction was performed in duplicate (D.P., J.S. and T.C.L.) with disagreement resolved by consensus. All costs were converted to the May 2022 dollar rate using the Consumer Price Index Inflation Calculator[17] (USD) and Bank of Canada Inflation Calculator[18] (CAD), respectively. Across included studies, the average 2022 dollar cost was calculated and used for the analysis. We also extracted the cost perspective that was examined in each of the included studies (e.g. public payer, traditional insurers, patient, societal, Medicare, Medicaid or third-party payer).

Finally, we calculated the probability of various effect sizes from the baseline recurrence rate and 95% confidence interval associated with the relative risk. We then identified how probable it was, at a specified price for fidaxomicin (rounded down to nearest $10), that the total cost of treating all patients with fidaxomicin relative to vancomycin would be offset by the cost savings from preventing recurrences (probability of cost equivalence). We created scatter plots of the probability of cost equivalence as a function of fidaxomicin price. For visualization purposes, a smooth line of best fit was generated with curvefit[19] for STATA using a rational estimator. A graphical summary of this analysis is shown in Figure S1 (available as Supplementary data at *JAC-AMR* online).

Results

Fidaxomicin effectiveness

The overall relative risk for recurrence with 10 days of fidaxomicin versus 10 days of vancomycin was 0.58 (95% CI 0.46–0.74; Figure 1). This corresponds to an absolute risk reduction of 10.8% (95% CI 6.7%–14%) or a NNT of 10 (95% CI 8–15) using the pooled control event rate of 25.9%. At the current fidaxomicin and vancomycin prices, the estimated additional cost to prevent one recurrence in the USA was estimated as $38 222USD (95%CI $30 577–$57 332) and in Canada this was estimated at $13 760CAD (95%CI $11,008-$20 640).

Cost of recurrence

The results of the systematic literature review for the cost of a CDI recurrence in the American and Canadian healthcare systems are presented in Table 1. Additional descriptions of each included study are contained in Tables S1 and S2. For the USA, the initial search for the cost of a CDI recurrence yielded 786 results. Of these results, 110 articles were selected for further review. Of the 110 articles, 13 were reviews or meta-analyses, 36 included

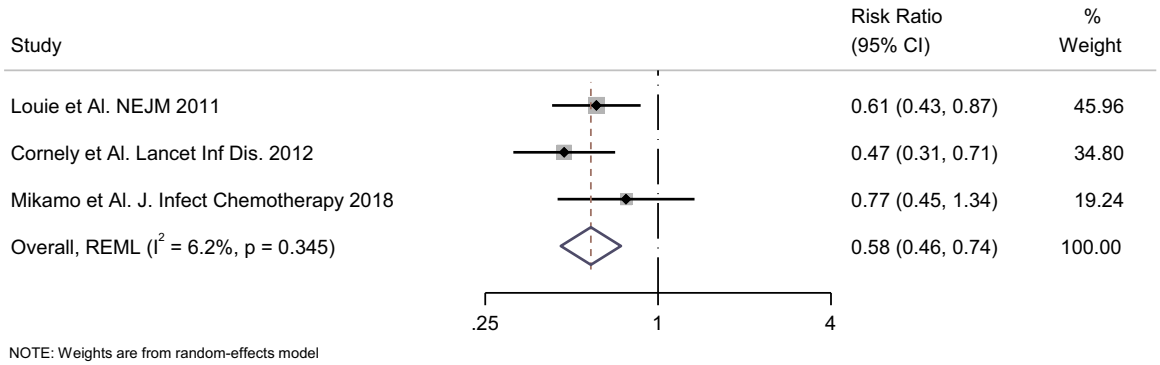

Figure 1. Forest plot of fidaxomicin randomized controlled trials risk of recurrent CDI.

Table 1. Summary of CDI recurrence cost by study

Study	Recurrence cost	May 2022 dollars	Cost perspectives
USA			
McFarland *et al.*[25]	$1914.00	$3405.08	Healthcare perspective; costs obtained from medical billing records and laboratory charges
Desai *et al.*[22]	$9501.74	$11 722.81	Healthcare perspective; study used societal perspective however indirect costs (productivity loss) were excluded from present analysis
Rodrigues *et al.*[21]	$34 104.00	$41 049.68	Payer perspective; most cost values obtained from Centers for Medicare and Medicaid Services, with hospitalization cost from Healthcare Cost Utilization Project Nationwide Inpatient Sample (all-payer hospitalization database)
Zilberberg *et al.*[24], 2017	$12 043.00	$14 495.70	Payer perspective; costs measured as Medicare payments
Zhang *et al.*[23]	$10 580.00	$12 476.42	Healthcare perspective; total healthcare costs were calculated as amount paid by primary and secondary insurers and by patients (i.e. copayment and deductibles) across all claims
Luo *et al.*[20]	$6826.00	$7734.25	Modified third-party payer's perspective (included costs of medications, hospitalizations and any procedures)
Average USA cost		$15 147.32	
Canada			
Wagner *et al.*[15]	$8250.05	$9961.71	Public payer perspective
Levy *et al.*[2]	$8157.89	$9765.04	Public payer perspective; study used a societal perspective however indirect costs were excluded from present analysis
Lapointe-Shaw *et al.*[27]	Metronidazole: $5386.00 Vancomycin: $5929.00	Metronidazole:$6351.97 Vancomycin:$6692.35	Public payer perspective, only vancomycin pathway cost considered
Average Canada cost		$8806.37	

only hospitalized patients, 50 did not calculate the cost of a recurrent CDI episode, three included only a paediatric population, and one was not based in the USA. The seven remaining articles were retained for the final analysis.[20–26] One article was subsequently excluded because it calculated the 12-month all-cause medical costs (as opposed to the attributable cost) of patients with recurrent CDI episodes.[26] Additionally, Luo *et al.* calculated the cost of recurrent CDI based on differing treatment strategies; the cost of the treatment with fidaxomicin was excluded from the overall average.[20]

The search for the cost of a recurrence in Canada yielded 123 results, of which 18 articles were reviewed based on the title and abstract. Of these 18 studies, 14 studies were excluded: five studies did not include cases of recurrent CDI, four studies did not measure the cost of CDI, four studies were literature reviews, and one study measured the cost of readmission to hospital due to CDI without specifying whether it was for first episode or recurrence. Four remaining studies included cases of recurrent or relapsed CDI and their cost.[2,15,27,28] One study that included cases of recurrent CDI was subsequently excluded as it presented the cost in median ($1812CAD) instead of mean.[28] This left three studies that were included in the Canadian analysis for the cost of recurrence.

The estimated mean 2022 systemic costs for a recurrence of CDI in the American and Canadian healthcare systems,

respectively, were $15 147USD and $8806CAD. In the USA, cost perspectives included payer and healthcare system perspectives, calculated using Medicare, third-party payers, and traditional insurers. In Canada, all studies reported costs based on a public payer perspective.

Cost equivalence

With respect to the USA, at the quoted price for 10 days of fidaxomicin and for 10 days of vancomycin capsules, there is a 0% chance that fidaxomicin will be cost equivalent by preventing the first CDI recurrence (Figure 2). At a price of approximately $1650 ($1630 more than the current cost of 10-day course of vancomycin) the probability of cost equivalence rises to 50% and at approximately $1140 ($1120 more than vancomycin) the probability rises to 95%. Therefore, fidaxomicin is very likely to be cost saving if priced below $1140 in the USA.

For Canada, at the current 10-day price of $1580 CAD for fidaxomicin and $208 CAD for vancomycin, there is less than a 0.25% chance that fidaxomicin will be cost equivalent by preventing the next CDI recurrence (Figure 3). At a fidaxomicin price of approximately $1150 CAD ($950 more than the current cost of a 10-day course of vancomycin) the probability of cost equivalence rises to 50% and at approximately $860 CAD ($660 more than vancomycin) the probability rises to 95%. In Canada, at any price below $860 CAD, fidaxomicin is likely to be cost saving.

Discussion

From our detailed review of the literature and associated calculations, we found that for both the USA and Canada, the use of fidaxomicin as first-line treatment for CDI will cost substantially more to both the public payer in Canada and to US payers compared with potential cost savings realized through recurrence reduction. We identified price points of approximately $1140 USD and $860 CAD at or below which the use of fidaxomicin is highly probable to be cost equivalent or cost saving. Despite double-blind, randomized, placebo-controlled trial evidence that 10 days of fidaxomicin is superior to 10 days of vancomycin for the secondary outcome of prevention of first recurrence at day 40, this efficacy has not translated into a meaningful uptake of fidaxomicin that we hypothesize is due to this very high financial impact. In Canada, individual provinces have their own drug plans, and negotiation with the manufacturer to obtain a more cost-equivalent price point is possible, which could facilitate a financially viable practice change. In the USA, such negotiations are generally not currently permitted by Medicare by law; however, negotiation of pricing could save the USA billions per year for all drugs, including fidaxomicin.[29] Individual US insurance companies, particularly ones with large formulary budgets may have negotiating power to reduce costs.

Previous economic analyses in the North American context have yielded conflicting results regarding the cost-benefit of fidaxomicin. Bartsch *et al.* used a decision-analytic model to compare fidaxomicin versus no fidaxomicin and estimated that vancomycin would be dominated unless the cost was reduced to below $150 without strain typing (and $400 with strain typing).[12] A decision-analytic model comparing fidaxomicin to vancomycin by Reveles *et al.* for hospitalized patients yielded similar overall treatment costs per patient ($14 442 for fidaxomicin versus $14 179 for vancomycin), using fidaxomicin cost of $2350.[13] By contrast, Rajasingham used a Markov model approach and found fidaxomicin to be cost-effective with a cost of $31 751/QALY assuming a fidaxomicin cost of $1767.20.[14] In Canada, Wagner *et al.* estimated fidaxomicin use would be

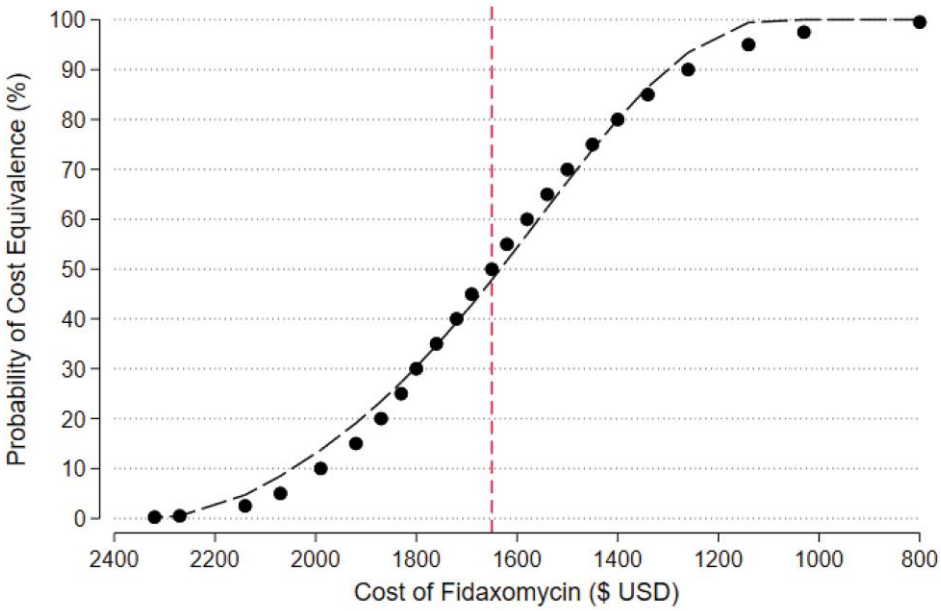

Figure 2. Probability of fidaxomicin cost equivalence—USA.

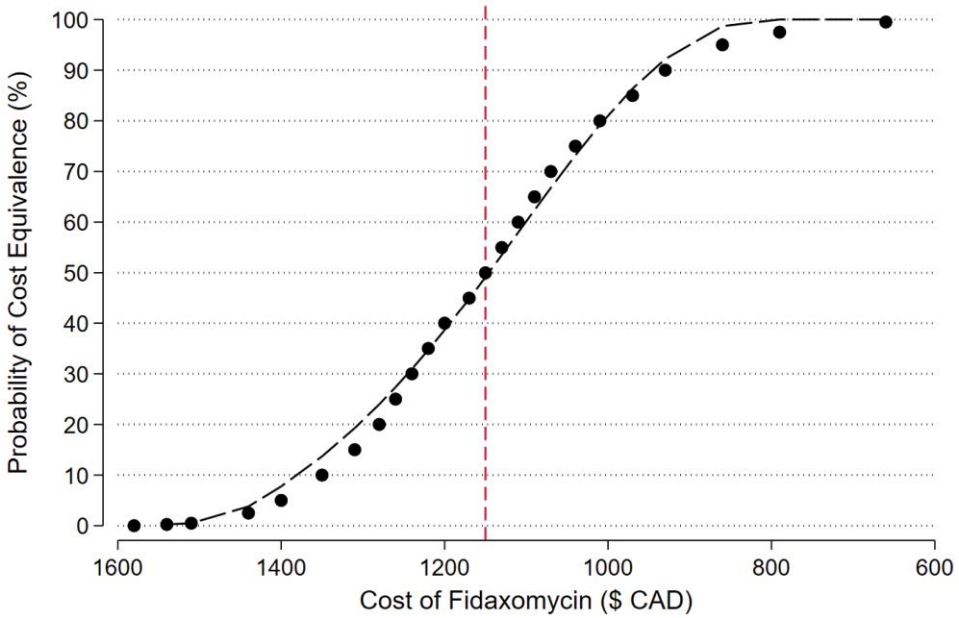

Figure 3. Probability of fidaxomicin cost equivalence—Canada.

associated with an overall average cost increase of $13 202 per recurrence prevented assuming a drug cost of $2200 and accounting for CDI-related admissions to hospital.[15]

In terms of observational studies with paired economic analyses, McDaniel *et al.*[30] conducted a retrospective single-centre study using electronic medical record data. Comparing pre- versus post-implementation of a treatment pathway favouring fidaxomicin for first and second episodes of *C. difficile*, they found 30-day *C. difficile* recurrence rates fell from 18.0% to 6.3% with lower total costs post-intervention for index admissions ($2588.63) and 30-day readmissions ($4738.62). However, metronidazole was used in 48% of cases pre-implementation falling to 1.6% post, suggesting the results may reflect comparisons with metronidazole as much as they do vancomycin. Further, while fidaxomicin was independently associated with a sustained response in a multivariable model (odds ratio 1.96; 95% CI 1.03–3.72), this did not represent a direct comparison between vancomycin and fidaxomicin. Another retrospective analysis by Gallagher *et al.*[31] evaluated a protocol which encouraged fidaxomicin for high-risk patients and compared those who received fidaxomicin and vancomycin. They found that 90-day readmission for *C. difficile* recurrence occurred in 20.4% and 41.3%, respectively, and that at a fidaxomicin cost of $1840, fidaxomicin use saved the hospital $3047 per patient based on lower readmission costs.

These observational studies have several key challenges. Principally, subsequent testing and treating behaviour could be biased by knowledge of fidaxomicin treatment in an open-label context. Second, confounding by indication can be challenging to eliminate, particularly in small studies. Finally, before–after designs may not adequately control for other temporal trends (e.g. changes in dominant strains) and time-series methods are generally preferred in terms of the hierarchy of evidence. Given large and granular enough data sets, a target trial emulation study with adjustment for temporal trends could be an important addition to the literature.

Our analysis has several limitations. At the current price of fidaxomicin, any strategy that increases the efficacy of vancomycin, for example, the use of an up-front decreasing dose taper to prevent recurrence (NCT04138706), would affect our results and would require recalculation. We have presented a best-case scenario for fidaxomicin by comparing it to a 10-day course of vancomycin. Furthermore, the efficacy of fidaxomicin to prevent recurrence at day 56 (the IDSA-SHEA definition of recurrence), or day 90, was not studied in the included randomized trials. Up to 31% of recurrences may occur after day 42[32] and there are no RCT data to allow comparisons including delayed recurrences. Fidaxomicin treatment outcomes have not been properly studied in patients with multiple recurrences, but it is possible that preventing the first recurrence could reduce the risk of subsequent recurrences and therefore be more attractive. Such an evaluation would ideally be conducted with randomized data, which is currently limited. Also, US drug prices are not fully transparent, and the costs borne to different parts of the system (patient, insurance company, hospitals/facilities) are often unclear. We used publicly available data to estimate the costs, but these costs may not reflect the costs to each party. Finally, further reducing the cost of vancomycin through the compounding of generic IV vancomycin into liquid form or reducing the cost of other formulations would increase the break-even price of fidaxomicin, particularly in Canada.

The estimation of CDI recurrence cost through systematic review for each country also has some limitations. The articles from the USA had differing cost perspectives, with half the articles having a payer perspective while the other half had a healthcare perspective. The time frame of both Canadian and US studies also differed, ranging from within 6 weeks of a recurrence to up to 12 months from a recurrence, with some studies having an

unspecified time frame. Another limitation stems from the cost of recurrence calculations in the studies retained. All the Canadian studies used decision models, with resource use and costs being derived from Canadian surveillance programmes, Canadian hospitals, and published literature. Out of the six US studies, four had real-world data, either from observational studies[21,23,24] or a clinical trial.[25] The remaining two studies used decision models.[20,22]

Finally, the aim of our study was to evaluate only direct medical costs from either a payer or healthcare perspective. This study did not look at broader indirect costs, such as costs related to patient time and lost productivity. Only two of the studies included evaluated costs from a broader societal perspective.[2,22] Therefore, additional studies are needed to draw conclusions based on broader societal perspective costs.

A strength of our study is the use of a meta-analytic assessment of the effect size for fidaxomicin from all the placebo-controlled trials, coupled with a systematic estimate of recurrence costs to produce a practical and easily understood comparison. Comparing additional drug costs versus an estimate of the cost of a recurrence is a different analytic perspective than the cost per quality-adjusted life-year point of view. Previous cost-effectiveness studies have been conducted, most showing a fractional difference (e.g. 0.02[33]–0.03[14]) in QALYs. More fundamentally, cost-effectiveness is not the same as cost saving. Cost-effectiveness measures, including cost per QALY and cost per incremental cost-effectiveness ratio, assess added costs by a subjectively perceived threshold of value. Often this is contextualized against the historical price for a year of haemodialysis, which is lifesaving. However, hospitals, patients and governments do not have unlimited budgets and most treatments are not a crucially lifesaving as haemodialysis. Even if an intervention is perceived as valuable, if the cost is unsustainable, cost-effectiveness may be irrelevant whereas cost equivalence or cost saving compared to current effective therapies is always relevant.

CDI causes a major burden to health systems worldwide and reduction of recurrence has value. Yet, health system sustainability requires thoughtful assessment of both current and future costs and benefits. At current pricing, a switch to first-line fidaxomicin will cost billions of excess healthcare dollars to US and Canadian payers and, on the basis of this analysis, these costs will not be recouped through the reduction of recurrent CDI. Assuming vancomycin costs remain the same, and until additional placebo-controlled trials of novel vancomycin or fidaxomicin dosing strategies are available, a reduction of the cost of fidaxomicin to below $1140USD and $860CAD, respectively, would support a substantial change to fidaxomicin prescribing practices.

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Conflicts of interest

EGM and TCL are principal investigators on a Canadian Institutes of Health Research Funded clinical trial looking at alternative vancomycin dosing strategies for the first episode of *C. difficile*.

CRediT author statement

Conceptualization—TCL, DP; methodology—TCL; validation—TCL, DP; formal analysis—TCL, DP; investigation—TCL, DP, JS; resources—TCL; data curation—TCL, DP, JS; writing—original draft—DP, EGM, TCL, JS; writing: review and editing—all authors; visualization—DP, TCL; supervision—TCL; project administration—TCL.

Supplementary data

Figure S1 and Tables S1 and 2 are available as Supplementary data at *JAC-AMR* online.

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