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ORIGINAL RESEARCH ARTICLE

# Cost-Effectiveness Analysis of Antimicrobial Prescribing in the Treatment of Clostridioides Difficile Infection in England

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## Abstract

**Background** An economic model was developed with guidance from the National Institute for Health and Care Excellence (NICE) 'Managing Common Infections' (MCI) Committee to evaluate the cost effectiveness of different antibiotic treatment sequences for treating Clostridioides difficile infection (CDI) in England.

**Methods** The model consisted of a 90-day decision tree followed by a lifetime cohort Markov model. Efficacy data were taken from a network meta-analysis and published literature, while cost, utility and mortality data were taken from published literature. A treatment sequence was defined as a first-line intervention or a different second-line intervention, and used constant third- and fourth-line interventions. The possible first- and second-line interventions were vancomycin, metronidazole, teicoplanin and fidaxomicin (standard and extended regimens). Total costs and quality-adjusted life-years (QALYs) were calculated and were used to run a fully incremental cost-effectiveness analysis. Threshold analysis was conducted around pricing.

**Results** Sequences including teicoplanin, fidaxomicin (extended regimen) and second-line metronidazole were excluded based on recommendations from the committee. The final pairwise comparison was between first-line vancomycin and second-line fidaxomicin (VAN-FID), and the reverse (FID-VAN). The incremental cost-effectiveness ratio for FID-VAN compared with VAN-FID was £156,000 per QALY gained, and FID-VAN had a 0.2% likelihood of being cost effective at a £20,000 threshold.

**Conclusion** First-line vancomycin and second-line fidaxomicin was the most cost-effective treatment sequence at the NICE threshold for treating CDI in England. The main limitation of this study was that the initial cure and recurrence rates of each intervention were applied constantly across each line of treatment and each round of recurrence.

## 1 Introduction

Clostridioides difficile (C. difficile) is a bacterium that can infect the bowel. The infection can cause symptoms ranging from mild diarrhoea and abdominal pain to the possibility of fulminant colitis and eventually death. There were 12,273 cases of C. difficile infection (CDI) reported in the 2020–2021 financial year in the UK [1]. In the same period, there were 1825 all-cause fatalities in patients who had a

**Key Points for Decision Makers**

This evaluation was part of an update to the National Institute for Health and Care Excellence (NICE) Clostridioides difficile infection (CDI) antimicrobial prescribing guideline and was developed with guidance from the NICE 'Managing Common Infections' Committee.

The cost-effectiveness model compared different sequences of interventions for the treatment of CDI in the UK and, after certain sequences were excluded by the committee, found that vancomycin followed by fidaxomicin was the most cost-effective sequence.

Following the consideration of this analysis by the NICE 'Managing Common Infections' Committee, NICE recommendations effectively led to a change in practice in England, as metronidazole is no longer recommended for routine use in first- and/or second-line CDI treatment.

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CDI diagnosis. This demonstrates the high level of mortality associated with CDI (a case-fatality rate of 14.9%). Alongside poor clinical outcomes, CDI also represents a substantial economic burden on healthcare. One reason for this is the high level of recurrence associated with CDI, either as a relapse occurring up to 12 weeks following an initial resolution or as a re-infection after that. There is a high cost of hospitalisation for CDI (in the UK this is estimated to be £8173 per patient [2]) and a possibility of numerous recurrences. These factors, along with the risk of progression into fulminant colitis that necessitates either a colectomy or additional medical treatment, mean that treatment per patient can become expensive.

CDI can be treated with numerous interventions, including a variety of antibiotics and a faecal microbiota transplant (FMT). Antibiotics licensed for the treatment of CDI in England include vancomycin, fidaxomicin, metronidazole and teicoplanin. Vancomycin and teicoplanin are both glycopeptide antibiotics that have been clinically available in Europe for over 30 years [3–6]; metronidazole is a nitroimidazole that has been available in Europe for a similarly long amount of time [7, 8]; and fidaxomicin is an antibiotic in the tiacumicin family (macrocyclic antibacterials) that was approved by the European Medicines Agency (EMA) more recently than the other three antibiotics (2011) [9, 10]. Bezlotoxumab, a human monoclonal antitoxin antibody, is able to be administered alongside an antibiotic to reduce the risk of recurrence. This model set out to find the most cost-effective sequence of antibiotic treatment options for a population with characteristics of the 'average' CDI patient. The model was developed with guidance from the National Institute for Health and Care Excellence (NICE) 'Managing Common Infections' (MCI) Committee.

## 2 Materials and Methods

### 2.1 Model Structure

A de novo model was developed in Microsoft Excel [11] to determine the most cost-effective treatment strategy in the setting for CDI patients (the model has been provided as electronic supplementary material). A UK National Health Service (NHS) and Personal Social Services (PSS) perspective was used. The model was constructed with two distinct parts to accurately capture the short- and long-term cost and benefits. Short-term outcomes were determined by a series of four linked decision trees, while long-term outcomes were determined by both the decision trees and a Markov model.

The short-term model used a time horizon of 90 days, which represented the time period in which a recurrence in CDI is considered a relapse. Ninety days was the maximum time period used to measure recurrence in any of the randomised controlled trials (RCTs) included in the network meta-analysis (NMA) that was used for the baseline characteristics and antibiotic efficacy [12]. The short-term model comprised four decision-tree components, as shown in Fig. 1.

The first tree represented treatment of the initial infection. Patients could receive up to four lines of treatment in this initial infection period. If an intervention was unsuccessful, then the patients would be at risk of fulminant colitis and would either move onto the next line of the treatment sequence or move into the fulminant colitis tree. Acute mortality from CDI was limited to the first decision tree in the model. The 30-day all-cause acute mortality rate was split into three scenarios; death could occur straight after diagnosis, after an unsuccessful first-line treatment, or after an unsuccessful second-line treatment.

Patients treated successfully in the initial treatment tree then moved to the second and third trees, at which point CDI either recurred or did not recur. Those for who CDI did not recur moved to the 'successful treatment' endpoint. For those with CDI recurrence, the tree was then identical in structure to the first tree. The fourth tree was populated by the cohort of patients who had developed fulminant colitis in any of the other trees. Each patient in this tree was treated with either a colectomy or additional medical treatment specific to fulminant colitis. The proportion of patients receiving each treatment was fixed. Since fulminant colitis is fatal if not successfully cured by treatment, it was recommended by the committee that if treatment was unsuccessful, it should be assumed that the patient died. The possible interventions for each line of treatment are shown in Table 1.

The antibiotic interventions were the same across the first- and second-line treatments with the exception of fidaxomicin (extended regimen), which is an unlicensed dosing variation of fidaxomicin. The committee advised that it would not be administered as a first-line intervention. Only one drug from each line was able to be selected per sequence; the second-line treatment was not able be the same drug as the first-line treatment. Since the focus of the model was the sequencing of antibiotics, the third- and fourth-line treatments were fixed across all sequences. Third-line treatment was split between the use of vancomycin taper pulse (VTP) and FMT, and all patients reaching the fourth-line treatment received FMT.

Each terminal node of the overall decision tree corresponded with a starting health state in the Markov model. The cohort Markov model used a lifetime time horizon with 1-year cycles. The Markov model included four health states:

1. Successfully treated CDI.
2. Survived fulminant colitis after a colectomy (post-colectomy).

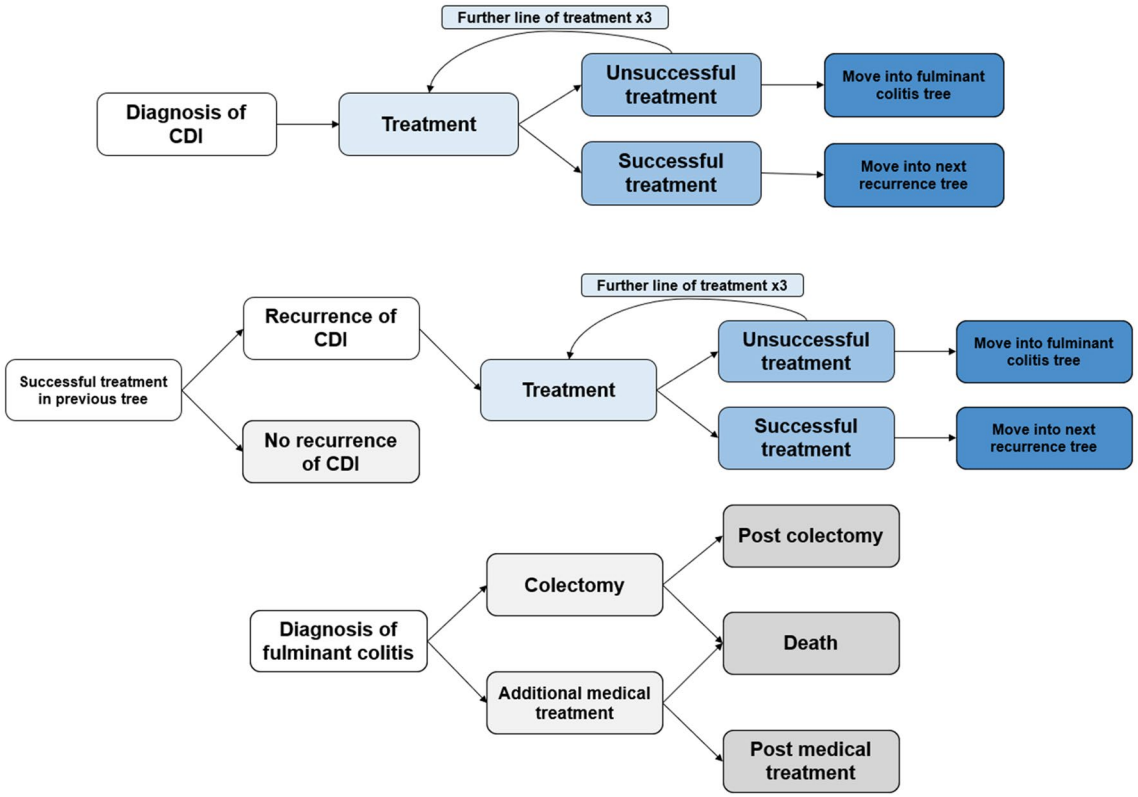


**Fig. 1** Decision tree structure. In order: first tree (initial treatment), second and third trees (recurrence round one and recurrence round two), fourth tree (fulminant colitis tree). *CDI* Clostridioides difficile infection

3. Survived fulminant colitis after additional medical treatment (post-medical treatment).
4. Dead.

Patients could not transition between the three 'alive' health states, and could only progress from their original health state to 'dead'. The transition probability from each state to 'dead' was the background mortality rate associated with the age of the patient. Each health state had an associated cost and health-related quality-of-life utility. These were tracked as the model progressed and were summed at the end of the model to find the total costs and QALYs for the entire cohort.

## 2.2 Model Set-Up

The model follows a hypothetical cohort diagnosed with CDI. The cohort enters the model at a starting age of 63 years, which was determined by the baseline characteristics of the RCT studies included in the NMA conducted by Beinortas et al [12]. In the absence of quantitative data, the committee advised that 50% of patients would move straight to the second-line treatment in recurrence. The model set-up inputs are shown in Table 1.

## 2.3 Treatment Effectiveness and Clinical Data

Odds ratios for the initial cure rate ('resolution of diarrhoea, per individual trial criteria') and the recurrence rate ('recurrence of diarrhoea or death within the follow-up period of each trial') (Table 2) were adapted from the NMA reported by Beinortas et al. [12]. These odds ratios compared the efficacy of each antibiotic with the efficacy of vancomycin.

The absolute efficacy of vancomycin was also adapted from the study by Beinortas et al. [12] and is also shown in Table 2. Data for the absolute initial cure rate and absolute recurrence rate of vancomycin were pooled from each RCT featured in the NMA. Specifically, events (i.e., patients cured or recurrences) and sample sizes in the vancomycin arm of each trial were each weighted by sample size and summed. The total events were then divided through by the total sample size to find the absolute rate.

The relative odds ratio data and the absolute vancomycin data were combined to find the absolute initial cure rates and absolute recurrence rates of each of the antibiotics. The odds ratios were transformed into relative risk values that were then applied to the absolute vancomycin rates. The relative risk for recurrence with bezlotoxumab was also taken from the Beinortas et al. [12] NMA. This relative risk was applied

**Table 1** Model set-up inputs

| Category | Parameter | Value | Source |
|---|---|---|---|
| Patient starting age | Base-case population | 63 | [12] |
| | 'At increased risk' | 71 | [13] |
| | 'At decreased risk' | 55 | Assumption based on committee recommendation |
| Discount rate | Costs | 3.5% | [14] |
| | QALYs | 3.5% | |
| Percentage of patients straight to second-line in recurrence | Base case | 50% | Clinical advice |
| Percentage split of FMT versus VTP in third line | Base case | 50% | |
| Possible interventions at each line of treatment | First line | Vancomycin<br>Metronidazole<br>Teicoplanin<br>Fidaxomicin (standard regimen) | Interventions were decided by the committee |
| | Second line | Vancomycin<br>Metronidazole<br>Teicoplanin<br>Fidaxomicin (standard regimen)<br>Fidaxomicin (extended regimen) | |
| | Third line | FMT<br>VTP | |
| | Fourth line | FMT | |

*FMT* faecal microbiota transplant, *QALY*s quality-adjusted life-years, *VTP* vancomycin taper pulse

to the final absolute recurrence rate of the chosen first-line treatment. Based on the findings from the clinical review, it was assumed that bezlotoxumab had no impact on the initial cure rate.

The absolute initial cure rates and absolute recurrence rates associated with FMT and VTP as third-line treatments were taken from published models. The usage split between these two treatments was assumed to be 50% in the base case, based on the clinical advice from the committee. For the fourth-line treatment, FMT was set to a 100% absolute initial cure rate with the same recurrence rate that was used in the third line. This simplifying assumption was used to ensure the entire cohort was in a defined post-treatment health state upon entering the Markov model. This simplifying assumption only affected a small proportion (approximately 1%) of the hypothetical cohort and did not have a material effect on the results of the model. The above rates are shown in Table 3.

The proportion of recurrences that required hospital admission was determined using three separate parameters:

**Table 2** Antibiotic efficacy inputs

| Input type | Antibiotic | Odds ratio | Source |
|---|---|---|---|
| Initial cure rate efficacy | Metronidazole | 0.72 | [12] |
| | Vancomycin | 1.00 | |
| | Teicoplanin | 2.19 | |
| | Fidaxomicin standard regimen | 0.96 | |
| | Fidaxomicin extended regimen | 0.83 | |
| Recurrence rate efficacy | Metronidazole | 1.17 | |
| | Vancomycin | 1.00 | |
| | Teicoplanin | 0.38 | |
| | Fidaxomicin standard regimen | 0.50 | |
| | Fidaxomicin extended regimen | 0.20 | |
| Absolute efficacy rates for vancomycin | Absolute initial cure rate | 79.6% | |
| | Absolute recurrence rate | 18.8% | |

- the percentage of severe recurrences that required hospital admission [17];
- the percentage of non-severe recurrences that required hospital admission [17];
- the proportion of recurrences that were severe versus non-severe [13].

An average of the former two parameters was weighted by severity with the latter parameter to find the rate for the base-case population. The parameters are also shown in Table 3.

The prevalence of fulminant colitis, which was applied after an unsuccessful treatment, was taken from a published model by Varier et al. [18]. To prevent overestimating the prevalence rate in the decision trees, the rate was split depending on the number of possible unsuccessful treatments a patient could receive. All patients in the first decision tree (initial treatment) could receive up to three unsuccessful treatments. This meant that the prevalence rate was split into three and was applied after each unsuccessful treatment. Patients who started with first-line treatment in the recurrence round one and round two decision trees could also receive up to three unsuccessful treatments and the same multiplier was applied. In contrast, patients who skipped first-line treatment in these could only receive up to two lines of unsuccessful treatment. This meant that the prevalence rate for this cohort of patients was only split into two and was only applied after an unsuccessful second- and third-line treatment.

The proportion of people receiving a colectomy versus additional medical treatment after a fulminant colitis diagnosis was determined by advice from the committee. The efficacy and mortality rate associated with each fulminant colitis treatment was taken from a published study by Sailhamer et al. [19]. The parameters for fulminant colitis are shown in Table 4.

## 2.4 Costs, Resource Use and Health-Related Quality of Life

The cost per pack of the majority of antibiotics was taken from the NHS electronic market information tool (eMIT) database [20], although the cost per pack of fidaxomicin came from the NHS Electronic Drug Tariff [21] since fidaxomicin had no eMIT cost. The final cost of each drug was based on the number of necessary doses and pack size. For the cost of bezlotoxumab, the average weight of men and women in the general population was calculated (87.89 kg for men and 74.43 kg for women) and then the appropriate number of vials for that body weight was determined; this was determined to be one vial. This method led to a conservative estimate for the resource use of bezlotoxumab since a certain proportion of the population who were above the average weight would need more than one vial, while no one from the population could receive less than one vial. The cost per vial was taken from the British National Formulary (BNF) [22]. The regimen associated with each treatment was the licensed dosing information given by the NICE, and is shown in Table 5 along with the final cost per course of each antibiotic.

All of the unit cost figures that were not in 2019 prices were inflated using the Personal Social Services Research Unit (PSSRU) Inflation Index [23]. The cost and future cost per year of a colectomy were taken from an NICE costing statement on ulcerative colitis [24], and the recurrence hospitalisation cost was taken from the published study by Wilcox et al [2]. The cost of additional medical treatment was an average of four NHS non-elective tariff codes for inflammatory bowel disease [25], while the cost of FMT was an average between two methods from the study by Abdali et al. [26] that had been micro-costed using the BNF, PSSRU, NHS reference costs, expert opinion and British Society of Gastroenterology

**Table 3** Additional efficacy rates and inputs for the proportion of recurrences that required hospital admission

| Category | Parameter | Value | Source |
|---|---|---|---|
| Absolute third-line intervention efficacy | Faecal microbial transplant | 76.1% | [15] |
| | Vancomycin taper pulse | 69.0% | [16] |
| Absolute fourth-line intervention efficacy | Faecal microbial transplant | 100% | Assumption |
| Recurrence relative risk | Bezlotoxumab | 0.620 | [12] |
| Absolute third-line intervention recurrence rate | Faecal microbial transplant | 9.1% | [16] |
| | Vancomycin taper pulse | 27.4% | [16] |
| Absolute fourth-line intervention recurrence rate | Faecal microbial transplant | 9.1% | [16] |
| Percentage of recurrences that are severe | – | 9.9% | [13] |
| Percentage of recurrences hospitalised | Severe | 100.0% | [17] |
| | Non-severe | 67.0% | [17] |
| Proportion of recurrences that required hospital admission | Base-case population | 70.3% | Calculation |

and Healthcare Infection Society guidelines [26]. These parameters are shown in Table 6.

Baseline utility general population norms for the UK, by age, were taken from an analysis of Health Survey for England data (self-assessed EQ-5D-3L data from 25,320 UK adults) by Love-Koh et al. [27], and the utility associated with CDI was taken from the study by Wilcox et al. [2], who collected self-assessed EQ-5D-3L utility scores of 30 patients treated for CDI in UK hospitals. The decrement for CDI was applied for 15 days per line of treatment (the length of time each line of treatment generally takes). The utilities associated with a colectomy and the additional medical treatment were taken from the study by Konijeti et al. [16], and the decrements were applied for 30 days. The post-colectomy health state decrement applied in the Markov model was also taken from this study and was applied every cycle. These utility parameters are shown in Table 7.

## 2.5 Mortality

Acute mortality for the decision tree was taken from the Public Health England (PHE) 30-day all-cause fatality rate for CDI [28]. No FMT-related mortality was included in the decision tree. Although some data on the mortality rate associated with FMT were found, the committee decided the data were not robust enough to be used.

The background mortality rates for the Markov model were taken from the Office for National Statistics (ONS) National Life Tables [29], with a weighted average used to find the general rate by age to account for differences in the number of men and women.

## 2.6 Outcomes

The following outcomes were generated in each treatment sequence of the model and the difference between the sequences was calculated:

- total costs per patient;
- total QALYs per patient.

These 'per patient' values were then used to perform incremental cost-effectiveness analysis between all possible sequences.

## 2.7 Sensitivity Analyses

Probabilistic sensitivity analysis (PSA) was performed for the most relevant pairwise sequence. The model used a sample of 10,000 iterations since the net monetary benefit trace stabilised at 8000 iterations for test analyses. Each iteration used a different set of values for the inputs. The distributions of the odds ratios associated with each pharmaceutical were sampled independently rather than using covariances.

To generate the input values for each iteration, distributions were fitted to uncertain parameters within the model. The distribution fitted to each parameter is included in Table 8.

**Table 4** Fulminant colitis inputs

| Category | Parameter | Value | Source |
|---|---|---|---|
| Fulminant colitis prevalence after unsuccessful treatment | Base case | 16.0% | [18] |
| Percentage of split colectomy vs. additional medical treatment | Base case | 10.0% | Clinical advice |
| Absolute fulminant colitis treatment efficacy | Colectomy | 68.0% | [19] |
| | Additional medical treatment | 63.7% | |

**Table 5** Regimen and cost per pack for pharmaceuticals used in the model

| Drug | Regimen | Packs necessary | Cost (£) | Cost per pack (£) | Source |
|---|---|---|---|---|---|
| Metronidazole (400 mg) | 400 mg every 8 h for 10 days | 2 | 1.04 | 0.52 | [20] |
| Vancomycin (125 mg) | 125 mg every 6 h for 10 days | 2 | 103.38 | 51.69 | |
| Teicoplanin (200 mg) | 200 mg twice daily for 10 days | 20 | 69.00 | 3.45 | |
| Vancomycin taper pulse (125 mg) | 125 mg every 6 h for 10 days, then 125 mg once every 2–3 days for 3 weeks | 2 | 103.38 | 51.69 | |
| Fidaxomicin standard regimen (200 mg) | 200 mg every 12 h for 10 days | 1 | 1350.00 | 1350.00 | [21] |
| Fidaxomicin extended regimen (200 mg) | 200 mg every 12 h for 5 days, then 200 mg once every 2 days for 20 days | 1 | 1350.00 | 1350.00 | |
| Bezlotoxumab (1 g vial) | One dose dependent on patient weight: 10 mg/kg | 1 | 2470 | 2470.00 | [12] |

**Table 6** Procedural cost inputs

| Category | Parameter | Value (£) | Source |
|---|---|---|---|
| FMT costs | Colonoscopy method cost | 3006.17 | [26] |
| | Nasogastric tube method cost | 740.16 | |
| | Percentage split | 50% | Clinical advice |
| | Final cost per patient | 1873 | Calculated |
| Event costs | Recurrence hospitalisation cost | 8173 | [2] |
| | Colectomy | 13,652 | [24] |
| | Medical treatment | 5135[a] | [25] |
| Health state costs | Successfully treated CDI | 0 | Clinical advice |
| | Post-colectomy | 2428 | [24] |
| | Post-medical treatment | 0 | Clinical advice |

*FMT* faecal microbiota transplant, *CDI* Clostridioides difficile infection, *NHS* National Health Service

[a]Average of four NHS non-elective spell tariff codes:

FZ37K Inflammatory Bowel Disease with Multiple Interventions, with CC Score 3+

FZ37L Inflammatory Bowel Disease with Multiple Interventions, with CC Score 0–2

FZ37M Inflammatory Bowel Disease with Single Intervention, with CC Score 4+

FZ37N Inflammatory Bowel Disease with Single Intervention, with CC Score 0–3

**Table 7** Utility inputs

| Category | Parameter | Value | Source |
|---|---|---|---|
| Event utility | CDI utility value | 0.420 for 15 days | [2] |
| | Colectomy utility value | 0.610 for 30 days | [16] |
| | Medical treatment | 0.710 for 30 days | |
| Health state disutility | Colectomy | 0.002 | |
| | Additional medical treatment | 0.000 | Clinical advice |
| Age-specific population norms, years | 0–15 | 1.000 | [27] |
| | 16–24 | 0.928 | |
| | 23–34 | 0.915 | |
| | 35–44 | 0.877 | |
| | 45–54 | 0.844 | |
| | 55–64 | 0.799 | |
| | 65–74 | 0.795 | |
| | 75+ | 0.723 | |

*CDI* Clostridioides difficile infection

Due to the large number of pairwise comparisons in the model, the main form of deterministic sensitivity analysis (DSA) conducted was the threshold analysis. The threshold analysis established the level that certain model parameters would have to be for a treatment sequence to be cost effective versus a comparator in a certain population. To represent the NICE threshold, results were reported at both a £20,000 and £30,000 threshold. Three parameters were varied as part of this analysis:

- the absolute recurrence rate of vancomycin;
- the price of fidaxomicin;
- the price of bezlotoxumab.

## 3 Results

Four of the six treatment sequences that included first-line teicoplanin were the least costly and also produced higher QALYs. However, the committee advised that the clinical evidence from the RCTs that included teicoplanin used low-quality data, which led to the presentation of results with teicoplanin excluded.

The committee also advised that it was unlikely that metronidazole would be used as a second-line treatment in a clinical setting due to its lower relative effectiveness. The committee reasoned that the majority of patients who could have successfully been treated with metronidazole would

likely have already responded to the more effective first-line treatments. This led to the presentation of results with both second-line metronidazole and first- and second-line teicoplanin excluded.

Finally, the committee highlighted that the fidaxomicin extended regimen was not a licensed dosage regimen for the UK and was not commonly used in NHS hospitals. This led to the exclusion of first- and second-line fidaxomicin (extended regimen) and teicoplanin, and second-line metronidazole.

For ease of notation, strategies are written with the antibiotics abbreviated as first–second (i.e., teicoplanin as the first-line treatment and vancomycin as the second-line treatment will be written as TEIC–VAN).

- VAN: vancomycin
- MET: metronidazole
- TEIC: teicoplanin
- FID: fidaxomicin standard regimen
- FIDEX: fidaxomicin extended regimen
- B: Bezlotoxumab

### 3.1 Full Base-Case Results

Table 9 shows the results and incremental analysis for all possible sequences (excluding bezlotoxumab). TEIC–VAN dominated (lower cost per patient and higher health benefit per patient) all other sequences except TEIC–FID. TEIC–FID had a greater health benefit, although this was small in magnitude and led to an incremental cost-effectiveness ratio (ICER) that exceeded £200,000 per QALY gained.

### 3.2 Results with Teicoplanin Excluded

Table 10 shows the base-case results when teicoplanin was excluded. VAN–MET became the comparator and dominated every other strategy that also included metronidazole. VAN–FIDEX was considered plausibly cost effective at the NICE threshold versus VAN–MET, making it the comparator in the following table (Table 11).

### 3.3 Results with Teicoplanin and Second-Line Metronidazole Excluded

Table 11 shows that once second-line metronidazole was removed, VAN–FIDEX was the cost-effective option at the NICE threshold since when VAN–FID was directly compared with VAN–FIDEX, the ICER was above the NICE threshold.

### 3.4 Results with Teicoplanin, Second-Line Metronidazole and Fidaxomicin (Extended Regimen) Excluded

Once fidaxomicin (extended regimen) was also excluded and the dominated strategies were removed, there were only two sequences to compare. Table 12 shows that while FID–VAN had greater health benefits, the ICER was above the NICE cost-effectiveness threshold. This means that based on the assumptions in our model and a NICE threshold of £20,000–£30,000, VAN–FID was the optimum strategy since no other sequence was cost effective versus at the NICE threshold.

### 3.5 Probabilistic Sensitivity Analysis

When VAN–FID and FID–VAN were directly compared, FID–VAN had a 0.4% likelihood of being cost effective versus VAN–FID at a £20,000 threshold, and a 2.3% likelihood at a £30,000 threshold.

VAN–FID and VAN–FIDEX were also directly compared because they had similar costs per patient and health benefits per patient. In the base-case population, VAN–FID had a 31.6% likelihood of being cost effective versus VAN–FIDEX at a £20,000 threshold, and a 34.9% likelihood at a £30,000 threshold.

**Table 8** Probabilistic sensitivity analysis distributions

| Parameter or parameter group | Distribution | Justification | Source |
|---|---|---|---|
| Odds ratios for efficacy | Log-normal | The parameter is always positive | [30] |
| Absolute efficacy rates | Beta | The parameter is bound by 0 and 1 | |
| Relative risk for bezlotoxumab | Log-normal | The parameter is always positive | |
| Costs | Gamma | The parameter will always be a value $\geq 0$ | |
| Utility values | Beta | The parameter is bound by 0 and 1 | |
| Disutility values | Gamma | The parameter will always be a value $\geq 0$ | |
| Patient starting age | Gamma | The parameter will always be a value $\geq 0$ | |
| Clinical guidance on percentage splits of treatment, etc. | Beta | The parameter is bound by 0 and 1 | |
| Prevalence of fulminant colitis | Beta | The parameter is bound by 0 and 1 | |

**Table 9** Initial results

| First-line drug | Second-line drug | Cost per patient (£) | QALYs per patient | Incremental cost | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| TEIC | VAN | 744 | 10.7801 | | | Reference |
| TEIC | MET | 761 | 10.7769 | | | Dominated |
| TEIC | FIDEX | 828 | 10.7800 | | | Dominated |
| TEIC | FID | 863 | 10.7806 | £119 | 0.0005 | £238,000 |
| VAN | TEIC | 1309 | 10.7533 | | | Dominated |
| MET | TEIC | 1324 | 10.7361 | | | Dominated |
| VAN | MET | 1586 | 10.7336 | | | Dominated |
| MET | VAN | 1621 | 10.7202 | | | Dominated |
| VAN | FIDEX | 1715 | 10.7408 | | | Dominated |
| VAN | FID | 1792 | 10.7420 | | | Dominated |
| MET | FIDEX | 1822 | 10.7210 | | | Dominated |
| MET | FID | 1918 | 10.7222 | | | Dominated |
| FID | TEIC | 2178 | 10.7566 | | | Dominated |
| FID | VAN | 2412 | 10.7461 | | | Dominated |
| FID | MET | 2448 | 10.7403 | | | Dominated |

*ICER* incremental cost-effectiveness ratio, *FID* fidaxomicin standard regimen, *FIDEX* fidaxomicin extended regimen, *MET* metronidazole, *QALYs* quality-adjusted life-year, *TEIC* teicoplanin, *VAN* vancomycin

**Table 10** Base-case results with teicoplanin excluded

| First-line drug | Second-line drug | Cost per patient (£) | QALYs per patient | Incremental cost (£) | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| VAN | MET | 1586 | 10.7336 | | | Reference |
| MET | VAN | 1621 | 10.7202 | | | Dominated |
| VAN | FIDEX | 1715 | 10.7408 | 129 | 0.0072 | £17,917 |
| VAN | FID | 1792 | 10.7420 | 206 | 0.0084 | £24,524 |
| MET | FIDEX | 1822 | 10.7210 | | | Dominated |
| MET | FID | 1918 | 10.7222 | | | Dominated |
| FID | VAN | 2412 | 10.7461 | 826 | 0.0125 | £66,080 |
| FID | MET | 2448 | 10.7403 | | | Extended dominated |

*ICER* incremental cost-effectiveness ratio, *FID* fidaxomicin standard regimen, *FIDEX* fidaxomicin extended regimen, *MET* metronidazole, *QALYs* quality-adjusted life-years, *VAN* vancomycin

**Table 11** Base-case results with teicoplanin and second-line metronidazole excluded

| First-line drug | Second-line drug | Cost per patient (£) | QALYs per patient | Incremental cost (£) | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| VAN | FIDEX | 1715 | 10.7408 | | | Reference |
| VAN | FID | 1792 | 10.7420 | 77 | 0.0011 | £70,000 |
| MET | FIDEX | 1822 | 10.7210 | | | Dominated |
| MET | FID | 1918 | 10.7222 | | | Dominated |
| FID | VAN | 2412 | 10.7461 | 697 | 0.0052 | £134,038 |

*ICER* incremental cost-effectiveness ratio, *FID* fidaxomicin standard regimen, *FIDEX* fidaxomicin extended regimen, *MET* metronidazole, *QALYs* quality-adjusted life-years, *VAN* vancomycin

To explore the likelihood that a sequence including bezlotoxumab was cost effective versus its counterpart sequence at the NICE threshold, VAN–B–FID was compared with VAN–FID. In the base-case population, VAN–B–FID had no likelihood of being cost effective versus VAN–FID at either a £20,000 or £30,000 threshold.

### 3.6 Scenario analysis

#### 3.6.1 Absolute Recurrence Rate of Vancomycin

Threshold analysis around the absolute recurrence rate for vancomycin was conducted for FID–VAN versus VAN–FID. The base-case absolute recurrence rate for vancomycin was 18.76%. At a £20,000 threshold, the recurrence rate would have to be 43.97%, a 25.2% incremental increase, for FID–VAN to be cost effective versus VAN–FID. At a £30,000 threshold, this rate would only have to be 38.41%, a 19.65% incremental increase, for FID–VAN to be cost effective versus VAN–FID.

#### 3.6.2 Price of Fidaxomicin

It is possible that patient access schemes with Clinical Commissioning Groups (CCGs) may reduce the cost per pack of fidaxomicin. In the base-case population, for FID–VAN to be cost-effective at a £20,000 threshold versus VAN–FID, there would need to be a 51% pricing discount. At a £30,000 threshold, there would need to be a 47.1% discount.

#### 3.6.3 Price of Bezlotoxumab

It is possible that patient access schemes with CCGs may reduce the cost per vial of bezlotoxumab. In the base-case population, for VAN–B–FID to be cost effective at a £20,000 threshold versus VAN–FID, there would need to be a 78.8% pricing discount; at a £30,000 threshold, there would have to be a 76.5% discount.

## 4 Discussion

The results indicated that teicoplanin as the first-line treatment and vancomycin as the second-line treatment was the cost-effective option to treat CDI in the NHS at the NICE threshold versus other pharmaceutical combinations. However, the paucity of data on teicoplanin created material uncertainty about the results of that analysis. It is recommended that this analysis should be run again if new evidence about the clinical efficacy of teicoplanin becomes available.

The committee advised that the teicoplanin studies used in the clinical efficacy NMA were poor quality with low participant numbers, which created bias in the results. In addition, the committee advised that using a less efficacious treatment in the second line would not make clinical sense. Finally, the committee decided that there was insufficient evidence of the benefits from fidaxomicin (extended regimen) to justify recommending the off-label regimen over the licensed, standard regimen. For this reason, all strategies that included teicoplanin or fidaxomicin (extended regimen) at either line, or second-line metronidazole, were excluded from the analysis.

The final pairwise comparison was FID–VAN versus VAN–FID as the comparator, with the cost per QALY gained that exceeded the NICE threshold. In the base case, FID–VAN had only a 0.4% likelihood of being cost effective versus VAN–FID at a £20,000 per QALY gained threshold, and a 2.3% likelihood at a £30,000 per QALY gained threshold.

It is worth noting that following the committee consideration of this analysis, NICE recommendations effectively led to a change in practice in England, as metronidazole is no longer recommended for routine use in first- and/or second-line CDI treatment.

It should also be noted that these results are highly specific to the UK due to the contributions of the NICE committee in deciding the current clinical practice in the UK and which antibiotics should be included in the final incremental analysis. Any generalisations to other countries or perspectives should be made with caution.

### 4.1 Model Limitations

One assumption made about the clinical data used in the model was that the initial cure rate and recurrence rate of each antibiotic would remain constant for both lines of treatment and across each round of recurrence. While there were no clinical data to contradict this assumption, real-world efficacy may show that the cure rate changes with recurrence. This meant that it is possible that the model overestimated

**Table 12** Base-case results with teicoplanin, second-line metronidazole and fidaxomicin extended regimen excluded

| First-line drug | Second-line drug | Cost per patient (£) | QALYs per patient | Incremental cost (£) | Incremental QALYs | ICER |
|---|---|---|---|---|---|---|
| VAN | FID | 1792 | 10.7420 | | | Reference |
| FID | VAN | 2412 | 10.7461 | 620 | 0.0041 | £151,220 |

*ICER* incremental cost-effectiveness ratio, *FID* fidaxomicin standard regimen, *QALYs* quality-adjusted life-years, *VAN* vancomycin

second-line efficacy at different rates for each intervention, causing bias. A similar argument to this can be made about using less efficacious drugs as first- or second-line treatments in the two rounds of recurrence. Patients less likely to be cured may be more likely to experience a recurrence, therefore the efficacy of each antibiotic in the recurrence rounds may be reduced. The rate at which the efficacy reduced could be different, and the results did not account for this nor explore the possibility.

In terms of treatment options, this model was limited in scope to first- and second-line antibiotic treatment options, with no option to explore which third-line treatment option would be more cost effective versus the other.

When looking at the assumptions made for costs, bezlotoxumab and fidaxomicin are still currently on patent therefore the full BNF/tariff price was used. The main results and subsequent committee recommendations did not take the possibility of patient access schemes for CCGs into account.

Another limitation was that certain costs were excluded from the model. Teicoplanin and fidaxomicin can both be administered using an injection. Clinical advice was received that these are usually administered orally for CDI, therefore the cost of injection was not explicitly included. If they are administered in secondary care, the cost for the injection is included in the reference cost. However, the reference cost for teicoplanin and fidaxomicin in the primary care setting does not capture the costs for administering the injection (e.g. health care professional time and equipment). These were therefore omitted from the model. If included, these costs would likely increase the cost per QALY associated with each sequence that included teicoplanin or fidaxomicin.

While the utility inputs for the general population norms and CDI were highly applicable to the study population, the source for the colectomy and post-colectomy utility and disutility values did not state the population or elicitation methods used; hence, the applicability of these inputs to the study population cannot be commented on.

The starting age of the model (63 years) was chosen since this was the average age of all patients included in the meta-analysis that informed the model efficacy inputs. The NICE committee agreed that this was appropriate to use as a starting age for a UK population with recurrent CDI. However, generalising the results of the model to an older cohort of patients is cautioned because the risk of CDI recurrence changes over age; age over 65 years is a significant factor of increased risk of CDI recurrence [31].

Finally, the model does not address pertinent current issues such as the increasing rate of antimicrobial resistance (AMR). AMR may mean the efficacy of certain antibiotics in the model could be reduced. This would reduce the health benefits associated with each antibiotic, and could be at different relative rates depending against which antibiotics the C. difficile bacteria develop resistance.

## 5 Conclusion and Policy Implications

The results indicated that first-line teicoplanin and second-line vancomycin was the most cost-effective option to treat CDI in the NHS, at the NICE threshold, versus other pharmaceutical combinations; however, the paucity of data on teicoplanin created material uncertainty regarding the results of that analysis.

Following committee advisement in the removal of teicoplanin as an intervention, second-line metronidazole, or strategies including fidaxomicin (extended regimen), the final pairwise comparison was FID–VAN versus VAN–FID as the comparator. VAN–FID had a higher probability of being cost effective. Threshold analysis demonstrated that significant price discounting (approximately 50%) was needed to reverse this.

It is recommended that this analysis should be run again if new evidence about the clinical efficacy of teicoplanin becomes available. Furthermore, this analysis did not consider the possibility of FMT as a first- or second-line intervention. Currently, only weak clinical evidence is available [32] since FMT is a relatively new intervention for CDI, but it is a potentially efficacious treatment option. While FMT has recently been recommended as a third-line intervention in the UK [32], this analysis should be run again if new evidence for first- or second-line efficacy is collected.

**Supplementary Information** The online version contains supplementary material available at https://doi.org/10.1007/s41669-023-00420-3.

## Declarations

**Disclaimer** The guideline referred to in this article was produced by the NICE. The views expressed in this article are those of the authors and not necessarily those of NICE (2021; Clostridioides difficile infection: antimicrobial prescribing. Available at https://www.nice.org.uk/guidance/ng199).

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**Ethics approval** Not applicable.

**Consent to participate** Not applicable.

**Consent for publication** Not applicable.

**Availability of data and materials** The efficacy data used to inform the model parameters have been previously published by Beinortas et al. [12]. The health economic model has been shared as part of the electronic supplementary material.

**Code availability** Not applicable.

**Authors' contributions** TB, HH and JP conceptualised the model and wrote the model protocol. TB and HH built and finalised the model. JP and HH reviewed and critiqued the final model and its associated results. LC and SW wrote the manuscript, with review and input from TB, HH and JP.



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