Cost-effectiveness analysis of ribotype-guided fecal microbiota transplantation in Chinese patients with severe *Clostridium difficile* infection

Minghuan Jiang¹,²,³,⁴, Nok-hang Leung⁵, Margaret Ip⁶, Joyce H. S. You⁵*

¹ The Department of Pharmacy Administration and Clinical Pharmacy, School of Pharmacy, Xi’an Jiaotong University, Xi’an, Shaanxi, China, ² The Center for Drug Safety and Policy Research, Xi’an Jiaotong University, Xi’an, Shaanxi, China, ³ The Global Health Institute, Xi’an Jiaotong University, Xi’an Jiaotong University, Xi’an, Shaanxi, China, ⁴ Shaanxi Center for Health Reform and Development Research, Xi’an, Shaanxi, China, ⁵ School of Pharmacy, Faculty of Medicine, The Chinese University of Hong Kong, Hong Kong SAR, China, ⁶ Department of Microbiology, Faculty of Medicine, The Chinese University of Hong Kong, Shatin, N.T., Hong Kong SAR, China

*joyceyou@cuhk.edu.hk

Abstract

**Background**

*Clostridium difficile* infection (CDI) caused by ribotype 002 strain is associated with poor outcomes in Chinese patients. Fecal microbiota transplantation (FMT) is an effective but costly treatment for CDI. We aimed to examine potential cost-effectiveness of ribotype-guided FMT in Chinese patients with severe CDI.

**Methods**

A decision-analytic model was designed to simulate outcomes of ribotype 002-guided FMT versus vancomycin treatment in Chinese patients with severe CDI in the hospital setting. Outcome measures included mortality rate; direct medical cost; and quality-adjusted life year (QALY) loss for CDI. Sensitivity analysis was performed to examine robustness of base-case results.

**Results**

Comparing to vancomycin treatment, ribotype-guided FMT group reduced mortality (11.6% versus 17.1%), cost (USD8,807 versus USD9,790), and saved 0.472 QALYs in base-case analysis. One-way sensitivity analysis found the ribotype-guided FMT group to remain cost-effective when patient acceptance rate of FMT was >0.6% and ribotype 002 prevalence was >0.07%. In probabilistic sensitivity analysis, ribotype-guided FMT gained higher QALYs at 100% of simulations with mean QALY gain of 0.405 QALYs (95%CI: 0.400–0.410; p<0.001). The ribotype-guided group was less costly in 97.9% of time, and mean cost-saving was USA679 (95%CI: 670–688; p<0.001).
Conclusions
In the present model, ribotype-guided FMT appears to be a potential option to save QALYs and cost when comparing with vancomycin. The cost-effectiveness of ribotype-guided FMT is subject to the patient acceptance to FMT and prevalence of ribotype 002.

Background
*Clostridium difficile* infection (CDI) is the leading cause of diarrhea and pseudomembranous colitis with high 30-day mortality rate (15–25%) and substantial economic burden to the healthcare system [1]. Vancomycin and fidaxomicin are the recommended antibiotics for severe CDI [2]. Recurrent CDI occurs in 20–30% patients and increases risks of relapses, morbidity, and additional healthcare costs [3].

Fecal microbiota transplantation (FMT) is a procedure to restore the colonic fecal microbial diversity. Clinical findings supported FMT to be safe and effective for treatment of recurrent CDI, with significant higher cure rate than vancomycin [4–6]. The health economic outcomes of FMT for recurrent CDI was examined by decision analyses and the findings suggested FMT to be cost-effective over drug treatment (metronidazole, vancomycin, fidaxomicin) in the many regions [7–11]. Given the clinical efficacy and cost-effectiveness of FMT in patients with recurrent CDI, FMT is a potential treatment option for severe CDI. A retrospective cohort study on 3-month mortality of CDI reported early FMT to be an independent predictor associated with lower odds of mortality in severe CDI, but not in non-severe cases [12]. Nevertheless, serious adverse events including death were reported with the use of FMT [13], and the procedures of FMT preparation and administration are more costly than most drug therapy for CDI. To balance the effectiveness, safety and cost of FMT for treatment of severe CDI, predictors of poor outcome should be considered in the selection of patients for FMT treatment.

It has been reported that some strains of *C. difficile* were associated with poor treatment outcomes of CDI. The hyper-virulent strain ribotype 027 is correlated with enhanced disease severity and recurrence rate in the US and Europe [14,15]. An open prospective study reported that early FMT was associated with reduction of mortality in patients with ribotype 027 infection [16]. Ribotype 017 is increasingly found in Eastern European countries, South America, and Asia, and it is also associated with recurrence and mortality [17,18]. In Hong Kong Chinese patients, the most commonly identified *C. difficile* strain is ribotype 002 [19,20]. An outcome study of CDI in Chinese patients found severe CDI and ribotype 002 were two independent predictors for death [19]. The *C. difficile* ribotype 002 is a potential predictor to select severe CDI cases for early FMT in Chinese patients. Ribotype-guided use of FMT is a possible approach to improve the clinical and economic outcomes of severe CDI. In the present study, we aimed to examine the potential cost-effectiveness of ribotype-guided FMT in Chinese patients with severe CDI from the perspective of healthcare provider.

Methods
Decision-analytic model
A decision-analytic model was designed using TreeAge Pro 2016 software (TreeAge Software Inc., MA, USA) to simulate the outcomes of two therapeutic strategies in a hypothetical cohort of adult patients with severe CDI in the hospital setting. The two strategies were: Vancomycin 125mg four times per day by mouth (Fig 1A) and ribotype-guided FMT (Fig 1B). Inclusion
Fig 1. Vancomycin treatment arm (a) and ribotype-guided FMT arm (b) of decision-analytic model for patients with severe CDI. CDI: Clostridium difficile infection; FMT: fecal microbiota transplantation; ICU: intensive care unit.

https://doi.org/10.1371/journal.pone.0201539.g001
criteria for model entry were adult patients with diagnosis of severe CDI. Severe CDI was defined by leukocytes $>15000$ cells/mL, or serum creatinine $>1.5$ mg/dL [2]. The time horizon of model was 30 days. The primary model outcomes included mortality rate; direct medical cost; and quality-adjusted life year (QALY) loss for CDI.

In the present model, patients in both arms were categorized by C. difficile ribotypes as 002 and non-002. In the vancomycin treatment arm, ribotyping was not performed and all patients received a standard course of oral vancomycin (125mg four times daily) [2]. In ribotype-guided FMT arm, C. difficile PCR-ribotyping was performed for all patients. The non-ribotype 002 cases were treated with the same regimen of vancomycin arm. Patients with ribotype 002 strain were treated with FMT, via lower gastrointestinal (GI) endoscopy, including oral vancomycin (500mg four times daily) 2 days before and 4 days after FMT [12]. Serious adverse events including death might occur to patients who received FMT.

In both study arms, a patient might experience clinical cure (resolution of diarrhea for the duration of therapy), and recurrent CDI might occur after cessation of initial therapy. By the end of model time horizon (30 days), a patient might be in one of the following health states: Global cure (resolution of diarrhea without recurrence), recurrent CDI (relapse of CDI after completion of CDI treatment), refractory CDI (diarrhea did not resolve after completion of CDI treatment) or death. Refractory cases might be admitted to intensive care unit (ICU). Recurrent and refractory CDI (not requiring ICU care) were subsequently treated with a course of FMT via lower endoscopy. Refractory cases at ICU care were treated as fulminant CDI with oral vancomycin and intravenous metronidazole [2].

Clinical inputs

Literature search was conducted on Medline and Scopus over the period of 2000–2018 using keywords “ribotype 002”, “Chinese”, “clostridium difficile infection”, “severe clostridium difficile infection”, “recurrent clostridium difficile infection”, “vancomycin”, “fecal microbiota transplantation”, “adverse events”, “cure” and “mortality”. The selection criteria of clinical trials were: (1) Reports written in English; (2) patients in trials were aged 18 years or above; (3) prevalence of ribotype 002 in Chinese patients and association (if any) between ribotype 002 and treatment outcomes of CDI; (2) cure, recurrent, and mortality rates in 30 days with vancomycin or FMT for severe CDI; and (5) incidence of serious adverse events of FMT. Case reports were excluded. Preferred studies are meta-analyses or randomized controlled trials. If multiple sources were available for a model parameter, the weighted average was used as base-case value and the high/low values formed the range for sensitivity analysis.

Clinical parameters of the model were shown in Table 1. The prevalence of ribotype 002 (12.5%; range 9.4%-22.8%) in Chinese CDI patients were retrieved from a retrospective epidemiology study including 307 cases of CDI from five hospitals (one acute care and four chronic care) [20] and a prospective study in three Hong Kong acute-care hospitals on 100 cases of CDI [19].

The clinical cure rate of vancomycin for severe CDI (86.8%; range: 78.5%-96.8%) and incidence of recurrent CDI (21.2%; range: 7.2%-25.3%) were estimated from the findings of three prospective clinical trials (total 646 cases treated with vancomycin) [21–23]. In a prospective case-control outcome study of CDI (139 cases and 114 controls), the mortality in ribotype 002 cases (47.6%) was higher than those with other ribotypes (12.7%) and ribotype 002 was found to be an independent predictor for mortality (HR 2.8, 95% CI 1.1–7.2; p = 0.03) [19]. The mortality rates of ribotype 002 and non-ribotype 002 cases were adopted by the present model. Ribotype 002 was not identified to associate with refractory or recurrence, and we therefore applied the same cure and recurrent rates to both ribotype 002 and non-ribotype 002 cases.
Table 1. Model inputs.

| Variables | Base-case value | Range | Distribution type | References |
|-----------|-----------------|-------|-------------------|------------|
| **Clinical inputs** | | | | |
| Prevalence of ribotype 002 | 0.125 | 0.094–0.228 | Beta | 19,20 |
| Mortality rate | | | | |
| Ribotype 002 | 0.476 | 0.381–0.571 | Beta | 19 |
| Non-ribotype 002 | 0.127 | 0.102–0.152 | Beta | 19 |
| Vancomycin treatment | | | | |
| Clinical cure rate | 0.868 | 0.785–0.968 | Beta | 21–23 |
| Recurrent rate | 0.212 | 0.072–0.253 | Beta | 21–23 |
| FMT via lower gastrointestinal endoscopy | | | | |
| Clinical cure rate | 0.930 | 0.800–1.000 | Triangular | 25–27 |
| Odds ratio of mortality with early FMT | 0.075 | 0.016–0.34 | Triangular | 12 |
| Incidence of serious adverse event with FMT | 0.061 | 0.0488–0.0732 | Beta | 13 |
| Mortality rate among serious adverse events of FMT | 0.025 | 0.02–0.03 | Beta | 13 |
| CDI-related intensive care unit admission in refractory cases | 0.099 | 0.079–0.119 | Beta | 24 |
| **Duration (days)** | | | | |
| Attributable CDI length of hospitalization | 7 | 5–9 | Uniform | 24,30 |
| Vancomycin treatment course | 12 | 10–14 | Uniform | 2,31 |
| Length of hospitalization for serious adverse event of FMT | 7 | 5–10 | Assumption | |
| **Utility inputs** | | | | |
| Age of patients with initial CDI | 72 | 58–88 | Triangular | 19 |
| Healthy adults aged 58–65 years | 0.92 | - | - | 28 |
| Healthy elderly aged 66–88 years | 0.84 | - | - | 28 |
| Initial CDI | 0.82 | 0.72–0.84 | Triangular | 7 |
| Recurrent CDI | 0.82 | 0.72–0.84 | Triangular | 7 |
| Refractory CDI | 0.71 | 0.5–0.72 | Triangular | 7 |
| Disutility of intensive care unit | -0.34 | -(0.27–0.41) | Triangular | 29 |
| Serious adverse event of FMT | -0.34 | -(0.27–0.41) | Triangular | Assumption |
| **Cost inputs (USD)** | | | | |
| Daily cost of vancomycin (125mg four times daily by mouth) | 2.9 | 2.3–3.6 | Uniform | Local cost |
| Daily cost of antibiotic treatment for fulminant CDI | | | | |
| Vancomycin 500mg four times daily by mouth | 12 | 9–14 | Uniform | Local cost |
| Metronidazole 500mg every 8 hours intravenously | 1.2 | 0.9–1.4 | Uniform | Local cost |
| Daily cost of general medical ward | 654 | - | - | Local cost |
| Daily cost of intensive care unit | 3,128 | - | - | Local cost |
| Cost of *Clostridium difficile* toxin | 26 | 21–32 | Uniform | Local cost |
| Cost of ribotyping test | 128 | 103–154 | Uniform | Local cost |
| Cost of management for serious infection of FMT | 8,305 | 1,886–62,992 | Triangular | 33 |
| Number of FMT received | 1 | 1–3 | Triangular | 12 |
| **Cost of FMT** | | | | |
| Donor tests | 525 | 420–630 | Uniform | Local cost |
| Recipient tests | 118 | 94–142 | Uniform | Local cost |
| FMT preparation | 65 | 52–78 | Uniform | Local cost |
| Bowel preparation | 12 | 10–14 | Uniform | Local cost |
| Vancomycin before and after FMT | 18 | 14–22 | Uniform | Local cost |
| Lower gastrointestinal endoscopy | 640 | 512–768 | Uniform | Local cost |

CDI: *Clostridium difficile* infection; FMT: fecal microbiota transplantation

https://doi.org/10.1371/journal.pone.0201539.t001
The CDI-related ICU admission rate (9.9%) for refractory cases was retrieved from a retrospective case-control outcome study on events attributable to CDI in hospitalized patients (161 cases and 656 control) [24].

The cure rate of FMT via lower GI endoscopy (93%; range: 80%-100%) was estimated from data reported in two systematic reviews and an comparative study on effectiveness of FMT by route of administration [25–27]. The odds ratio of 3-month mortality with early FMT (via lower GI route) versus antibiotic treatment (0.075; 95%CI 0.016–0.34; p = 0.001) was reported in a retrospective outcome study of severe CDI patients (n = 111) [12]. The serious adverse event rate of FMT via lower GI routes (6.1%; range: 4.9%-7.3%) and the mortality rate among serious events (2.5%; range: 2%-3%) were retrieved from a systematic review including 50 publications on adverse events of FMT [13].

Utility inputs

The QALY loss for CDI-associated health states (CDI, recurrent CDI, refractory CDI, serious adverse event of FMT if occurred) in each patient was estimated by loss of utility and the patient-time spent in each state. The loss of utility was approximated by age-specific utility for healthy individual minus health state-specific utility. The base-case value of patient age in the present model was 72 year (range 58–88 years), adopted from the mean age of 139 CDI patients in a local prospective outcome study [19]. Age-specific utility scores of healthy individuals aged 18–64 years (0.92) and aged ≥65years (0.84) were retrieved from a US national health-related quality of life study [28]. Disease-specific utility values for CDI, recurrent CDI and refractory CDI were adopted from the model input values of a cost-effectiveness analysis on four management strategies for CDI treatment [7]. The utility value for refractory cases managed in ICU was further lower by disutility of ICU care (-0.34) [29]. Serious adverse events of FMT via lower GI routes included a broad spectrum of 44 events [13]. Whilst the clinical model input for serious adverse event rate was an estimated value including a variety of events, severe infection requiring ICU care was used as the index event for estimation of QALY loss and cost of serious adverse event in our model. Duration of CDI illness (as time-spent for antibiotic treatment and FMT treatment) were estimated from clinical trials and treatment guidelines [2,12,24,30,31]. The length of treatment for serious adverse event of FMT was assumed to be 7 days (range 5–10 days). The QALYs loss from death was calculated by using age-specific utility score and time loss for death. Time loss for death was retrieved from projected age-specific life expectancy reported by Hong Kong Census and Statistics Department [32]. QALYs loss for death was discounted to year 2018 with an annual rate of 3%.

Cost inputs

The cost analysis was conducted from the perspective of healthcare provider in Hong Kong using direct medical costs at year 2018. Cost of FMT (from universal stool bank) was estimated using local pricing, including FMT preparation, bowel preparation, 6-day vancomycin pre- and post-FMT, donor and recipient testing. The attributable CDI length of hospitalization was estimated from outcome analyses of CDI in the hospital setting [24,30]. The cost of ribotyping test was estimated from a microbiology laboratory in a public hospital of Hong Kong. The management cost of serious infection (as index serious adverse event of FMT) was derived from a health economic study in Hong Kong [33].

Cost-effectiveness analysis, sensitivity analysis, and scenario analysis

Expected mortality, direct medical cost and QALY loss were calculated for each study arm in base-case analysis. When ribotype-guided FMT gained higher QALYs at additional cost, the
incremental cost-effectiveness ratio (ICER) was calculated using the following equation:

\[
\text{ICER} = \frac{(\text{Cost}_{\text{ribotype-guided FMT}} - \text{Cost}_{\text{vancomycin treatment}})}{\left(\text{QALY loss}_{\text{vancomycin treatment}} - \text{QALY loss}_{\text{ribotype-guided FMT}}\right)}
\]

The World Health Organization suggested a strategy to be considered as highly cost-effective if the ICER was lower than $1 \times$ gross domestic product (GDP) per capita of the jurisdiction [34]. The GDP per capita in Hong Kong was USD43,530 (USD1 = HKD7.8) in 2016, and was adopted as the willingness-to-pay (WTP) threshold [35]. Ribotype-guided FMT was considered as the preferred option if it saved QALYs at lower cost, or it saved QALYs at higher cost with ICER lower than 43,530 USD/QALY.

Sensitivity analysis was performed by TreeAge Pro 2016 software (TreeAge Software Inc., MA, USA) and Microsoft Excel 2016 (Microsoft Corporation, WA, USA) to examine the robustness of base-case results. One-way sensitivity analysis was conducted on all model inputs over the ranges listed in Table 1. To evaluate the impact of uncertainty of all variables simultaneously, probabilistic sensitivity analysis was performed using Monte Carlo simulation. Direct cost and QALY loss of both study arms were recalculated 10,000 times by randomly drawing each model input from the probability distribution indicated in Table 1.

In base-case analysis, we assumed 100% patients with ribotype 002 in the ribotype-guided FMT arm to accept FMT treatment. A scenario analysis was performed to examine the impact of acceptance rate of FMT treatment (over wide range of 0%-100%) and to identify the threshold acceptance rate for ribotype-guided FMT to be cost-effective.

Results

Base-case analysis

The results of base-case analysis were shown in Table 2. Comparing with vancomycin treatment, the ribotype-guided FMT arm reduced mortality by 32.2% (11.6% versus 17.1%), saved 0.472 QALYs and reduced cost per patient by 10.0% (USD8,807 versus USD9,790). Ribotype-guided FMT was therefore the preferred option in the base-case analysis. The number needed to treat to prevent one death was 18.

Sensitivity analysis and scenario analysis

One-way sensitivity analysis found the base-case results to be robust and no threshold value was identified throughout variation of all model parameters. The results of scenario analysis showed that ribotype-guided FMT remained to save QALYs throughout the variation of patient acceptance to FMT (from >0% to 100%) (Fig 2A). The QALY loss in both arms were identical when the patient acceptance was 0%. Ribotype-guided FMT arm was less costly than vancomycin group when patient acceptance exceeded 11.5% (Fig 2B). When patient acceptance varied between 0.6%-11.5%, the ribotype-guided FMT saved QALYs at higher cost with ICER below WTP threshold (43,497 USD/QALY) and was therefore the preferred option. When the patient acceptance rate was lower than 0.6%, the ICER of ribotype-guided FMT exceeded the WTP threshold and vancomycin treatment became the preferred option.

To examine the impact of ribotype 002 testing on the cost-effectiveness analysis, one-way sensitivity analysis was further conducted with extended ranges of ribotype 002 prevalence.

Table 2. Base-case results of expected mortality, cost, and quality-adjusted life-year (QALY) loss.

| Strategy           | Mortality | Cost (USD) | QALY loss |
|--------------------|-----------|------------|-----------|
| Ribotype-guided FMT| 0.116     | 8,807      | 0.998     |
| Standard treatment | 0.171     | 9,790      | 1.470     |

CDI: Clostridium difficile infection; QALY: quality-adjusted life-years

https://doi.org/10.1371/journal.pone.0201539.t002
and ribotyping cost (USD103-USD500). Ribotype-guided FMT saved QALYs when ribotype 002 prevalence ranged between >0% to 100% (Fig 3A), and it became more costly than vancomycin treatment at prevalence <1.44% (Fig 3B). The ICER of ribotype-guide FMT was lower than the WTP threshold at ribotype 002 prevalence 0.07%-1.44%, and it exceeded the WTP threshold when the prevalence was lower than 0.07%. Ribotype-guided FMT remained to be cost-saving over the extended range of ribotype cost.

Probabilistic sensitivity analysis was performed by 10,000 Monte Carlo simulations. Fig 4 showed a scattered plot of incremental total cost versus QALYs saved by ribotype-guided FMT comparing to vancomycin treatment. Ribotype-guided FMT gained higher QALYs in 100% of simulations and the mean QALYs saved was 0.405 QALYs (95%CI: 0.400–0.410; p<0.001). The ribotype-guided group was cost-saving in 97.9% of time. In 2.1% simulations, the
ribotype-guided FMT group saved QALYs at higher cost, with ICERs (median 261 USD/QALY; range: 0.5–6,286 USD/QALY) below the WTP threshold. The mean cost saving in 10,000 simulations was USD679 (95%CI: 670–688; \( p < 0.001 \)).

### Discussion

This is the first cost-effectiveness analysis of ribotype-guided use of FMT for patients with severe CDI. Base-case analysis found ribotype-guided FMT to be the preferred strategy with QALYs saved at lower cost when compared to vancomycin therapy. The findings of probabilistic sensitivity analysis supported ribotype-guided FMT to be the preferred option in 100% of 10,000 Monte Carlo simulations (97.9% simulations were effective and cost-saving and 2.1% were cost-effective with ICER < WTP threshold (USD 43,497 USD/QALY)).
A previous study examining patients’ attitude on FMT reported that FMT was not appealing in 75% patients [36]. The patient acceptance to FMT could potentially reduce the cost-effectiveness of ribotype-guided FMT treatment approach. In base-case scenario, we assumed 100% patients with ribotype 002 to accept FMT, and ribotype-guided FMT was more effective at lower cost compared to vancomycin treatment. In the scenario analysis, the acceptance of FMT was examined over 0%-100%. The effectiveness of ribotype-guided FMT was highly robust that it saved QALYs if the acceptance to FMT was above 0%. The cost-saving of ribotype-guided FMT reduced when the acceptance rate declined, yet it remained highly cost-effective (ICER < 1xGDP per capita of Hong Kong) between acceptance rate of 0.6%-11.5%. At acceptance rate less than 0.6%, nearly all patients in the ribotype-guided arm received vancomycin treatment. The QALYs saved by FMT in few cases did not offset the cost of ribotyping test in all patients.

The impact of ribotyping cost on the base-case results was further examined with higher upper limit (USD500) and no threshold value was identified. Extended sensitivity analysis on prevalence of ribotype 002 found that the ribotype-guided FMT remained effective and cost-saving at ribotype 002 prevalence above 1.44%. At extremely low prevalence of ribotype 002 (0.07%-1.44%), the ribotype-guided FMT was effective at higher cost, yet still accepted as cost-effective per WTP threshold.

A previous cost-effectiveness study examined the cost and QALYs of universal FMT versus vancomycin in patients with initial CDI (including both severe and non-severe CDIs) from the perspective of US healthcare payer [37]. Donor stool was administered to all patients in FMT-treated arm. The reported findings suggested that universal FMT was less costly than universal vancomycin for initial CDI by USD221. The cost-saving was mostly generated from the lower cost input of FMT treatment (USD1086) versus vancomycin treatment (USD1347) in this prior analysis. In Hong Kong, the drug treatment with oral vancomycin was much lower, and the total cost input (USD1378) of FMT via lower GI route was nearly 40-fold higher than the cost input (USD2.9 per day for 12 days: USD35) of oral vancomycin treatment course in our analysis. In the present model, we included ribotype 002 for selection of severe CDI cases with high risk for mortality to receive FMT in Chinese patients. Our findings were

![Fig 4. Scatter plot of incremental cost against incremental QALYs of ribotype-guided FMT versus vancomycin treatment.](https://doi.org/10.1371/journal.pone.0201539.g004)
consistent with the previously reported study that the FMT group had higher gain in QALYs. By ribotype-guided selection of high-risk cases, both cost and QALY saving were balanced and cost-effective use of FMT was achieved in the present model.

CDI is a major burden to the healthcare system with extended hospitalization and rehabilitation [38]. FMT is recommended as an option for those who failed standard treatment, especially patients with recurrent CDI. Due to the less appealing procedure, patients’ attitude and acceptance might influence the selection of treatment regimen. The ribotyping results might assist patients in the process of informed decision-making on acceptance of FMT. Selecting severe CDI cases with high-risk ribotype (demonstrated with strong association to severe outcomes such as ICU admission and death) for FMT is a potential approach in CDI management. The results of present study provided insights on application of \textit{C. difficile} ribotype information for cost-effective use of FMT in patients with severe CDI. Ribotype 002 is the \textit{C. difficile} strain associated with poor outcomes in Hong Kong Chinese patients, whilst the association between ribotype 027 (the prominent strain with major outbreaks and serious infections in North America and Europe) and severe outcomes was controversial [39]. Despite that, the model framework developed in the present study is readily to be adopted by healthcare systems in other parts of the world, using system-specific practice and costs of healthcare resources, region-specific high-risk ribotype and the corresponding prevalence. Our findings supported prospective randomized clinical trials to examine the outcomes of applying \textit{C. difficile} ribotype 002 information to guide the selection of severe CDI cases to offer FMT treatment. Further studies to investigate the efficacy, safety and cost-effectiveness of FMT for treatment of all cases of severe CDI in Chinese patients are also warranted to generate important data to inform clinical practice as well as decision-analytic models for robust translation to cost-effective treatment approach.

There are several limitations in the present study. Model-based analyses are generally subject to the uncertainty of model inputs. International pharmacoeconomic guidelines on data transferability consider relative treatment effect to have high transferability even if derived from clinical trials conducted in a population different from the local population. Baseline prevalence is considered to have low transferability and should be sourced from jurisdiction of interest or similar locations. Healthcare resources utilization and unit costs of healthcare resources are also considered to have low transferability, and local data and pricing should be used [40]. The clinical inputs of FMT were retrieved from studies reported in overseas due to limited data available in Chinese patients. Many of the patients in these studies were treated for recurrent CDI, and we assumed the clinical cure rate of FMT in patients with severe CDI was similar to patients with recurrent CDI. The uncertainty in clinical inputs of FMT might over or under estimate the benefits of FMT in the present hypothetical cohort. Rigorous sensitivity analyses was therefore performed to examine the impact of uncertainty of all variables on the robustness of model outcomes. The turn-around-time of ribotyping test is a critical factor on the feasibility of adopting ribotyping into the treatment strategy in clinical trials. The approximated laboratory run time of \textit{C. difficile} ribotyping test was reported to be 6.8 hours [20,41], yet the turn-around-time of ribotyping test was subject to the operational and administration procedures of microbiology laboratory in different hospital settings. The cost of ribotyping in Hong Kong was estimated to be USD128. Introduction of improved and low-cost (<USD10) technology of ribotyping [42] to Hong Kong could reduce the testing cost and further increase the cost-saving of ribotype-guided treatment. The present model assumed the stool are readily available in stool bank from healthy volunteers. In the healthcare setting without access to stool bank, FMT using patient directed donor is more time- and cost-consuming and might therefore affect the cost-effectiveness of FMT. Fidaxomicin is another recommended treatment option for severe CDI, yet it is not marketed in Hong Kong. The present
model therefore did not include fidaxomicin. The cost analysis was conducted with direct medical cost from the perspective of healthcare provider. Indirect cost (loss of productivity in patients and care-takers) was not included, and the cost analysis might therefore underestimate the economic benefits of ribotype-guided FMT.

Conclusions

In the present model, ribotype-guided FMT appears to be a potential option to save QALYs and cost when comparing with vancomycin. The cost-effectiveness of ribotype-guided FMT is subject to the patient acceptance to FMT and prevalence of ribotype 002.

Author Contributions

Conceptualization: Margaret Ip, Joyce H. S. You.

Formal analysis: Minghuan Jiang, Nok-hang Leung, Joyce H. S. You.

Methodology: Minghuan Jiang, Nok-hang Leung, Margaret Ip, Joyce H. S. You.

Project administration: Joyce H. S. You.

Software: Joyce H. S. You.

Supervision: Joyce H. S. You.

Validation: Joyce H. S. You.

Writing – original draft: Minghuan Jiang, Joyce H. S. You.

Writing – review & editing: Margaret Ip, Joyce H. S. You.

References

1. Zimlichman E, Henderson D, Tamir O, Franz C, Song P, Yamin CK, et al. Health care-associated infections a meta-analysis of costs and financial impact on the US health care system. JAMA Intern Med 2013; 173:2039–2046. https://doi.org/10.1001/jamainternmed.2013.9763 PMID: 23999949

2. McDonald LC, Gerding DN, Johnson S, Bakken JS, Carroll KC, Coffin SE, 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–e48. https://doi.org/10.1093/cid/cix1085 PMID: 29462280

3. Shah DN, Aitken SL, Barragan LF, Bozorgui S, Goddu S, Navarro ME, et al. Economic burden of primary compared with recurrent Clostridium difficile infection in hospitalized patients: a prospective cohort study. J Hosp Infect 2016; 93:286–289. https://doi.org/10.1016/j.jhin.2016.04.004 PMID: 27209056

4. van Nood E, Vrieze A, Nieuwdorp M, Fuentes S, Zoetendal EG, de Vos WM, et al. Duodenal infusion of donor feces for recurrent Clostridium difficile. N Engl J Med 2013; 368:407–415. https://doi.org/10.1056/NEJMoa1205037 PMID: 23323867

5. Kelly CR, Khoruts A, Staley C, Sadowsky MJ, Abd M, Alani M, et al. Effect of Fecal Microbiota Transplantation on Recurrence in Multiply Recurrent Clostridium difficile Infection: A Randomized Trial. Ann Intern Med 2016; 165:609–616. https://doi.org/10.7326/M16-0271 PMID: 27547925

6. Lee CH, Steiner T, Petrof EO, Smieja M, Roscoe D, Nemataliah A, et al. Frozen vs Fresh Fecal Microbiota Transplantation and Clinical Resolution of Diarrhea in Patients With Recurrent Clostridium difficile Infection: A Randomized Clinical Trial. JAMA 2016; 315:142–9. https://doi.org/10.1001/jama.2015.18098 PMID: 26757463

7. Konijeti GG, Sank J, Shriime MG, Gupta M, Ananthakrishnan AN. Cost-effectiveness of competing strategies for management of recurrent Clostridium difficile infection: a decision analysis. Clin Infect Dis 2014; 58:1507–1514. https://doi.org/10.1093/cid/ciu128 PMID: 24692533

8. Baro E, Galperine T, Denies F, Lannoy D, Lenne X, Odoi P, et al. Cost-effectiveness analysis of five competing strategies for the management of multiple recurrent community onset clostridium difficile infection in France. PLoS One 2017; 12:e0170258. https://doi.org/10.1371/journal.pone.0170258 PMID: 28103289
9. Lapointe-Shaw L, Tran KL, Coyte PC, Hancock-Howard RL, Powis J, Poutanen SM, et al. Cost-effectiveness analysis of six strategies to treat recurrent clostridium difficile infection. PLoS One 2016; 11: e0149521. https://doi.org/10.1371/journal.pone.0149521 PMID: 26901316

10. Merlo G, Graves N, Brain D, Connelly LB. Economic evaluation of fecal microbiota transplantation for treatment of recurrent Clostridium difficile infection in Australia. J Gastroenterol Hepatol 2016; 31:1927–1932. https://doi.org/10.1111/jgh.13402 PMID: 27043242

11. Varier RU, Biltaji E, Smith KJ, Roberts MS, Kyle Jensen M, LaFleur J, et al. Cost-effectiveness analysis of fecal microbiota transplantation for Clostridium difficile infection. Infect Control Hosp Epidemiol 2015; 36:438–444.

12. Hocquart M, Lagier JC, Cassir N, Saidani N, Eldin C, Kerbaj J, et al. Early fecal microbiota transplantation improves survival in severe Clostridium difficile infections. Clin Infect Dis 2018; 66:645–650. https://doi.org/10.1093/cid/ciy762 PMID: 29020328

13. Wang S, Xu M, Wang W, Cao X, Piao M, Khan S, et al. Systematic Review: Adverse Events of Fecal Microbiota Transplantation. PLoS One 2016; 11:e0161174. https://doi.org/10.1371/journal.pone.0161174 PMID: 27529553

14. Rao K, Micic D, Natarajan M, Winters S, Kiel MJ, Walk ST, et al. Clostridium difficile ribotype 027: relationship to age, detectability of toxins A or B in stool with rapid testing, severe infection, and mortality. Clin Infect Dis 2015; 61:233–41. https://doi.org/10.1093/cid/civ254 PMID: 25828993

15. Marsh JW, Arora R, Schlackman JL, Shutt KA, Curry SR, Harrison LH. Association of relapse of Clostridium difficile disease with BI/NAP1/027. J Clin Microbiol 2012; 50:4078–82.

16. Lagier JC, Delord M, Million M, Parola P, Stein A, Brouqui P, et al. Dramatic reduction in Clostridium difficile disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ 2005; 173:1037–42. https://doi.org/10.1503/cmaj.050978 PMID: 16179431

17. Goorhuis A, Debast SB, Dutilh JC, van Kinschot CM, Harmanus C, Cannegieter SC, et al. Type-specific risk factors and outcome in an outbreak with 2 different Clostridium difficile types simultaneously in 1 hospital. Clin Infect Dis 2011; 53:860–869. https://doi.org/10.1093/cid/cir549 PMID: 21914851

18. Kim J, Seo MR, Kang JO, Kim Y, Hong SP, Pai H. Clinical characteristics of relapses and re-infections in Clostridium difficile infection. Clin Microbiol Infect 2014; 20:1198–1204. https://doi.org/10.1111/1469-0691.12704 PMID: 24894547

19. Wong SH, Ip M, Hawkey PM, Lo N, Hardy K, Manzoor S, et al. High morbidity and mortality of Clostridium difficile infection and its associations with ribotype 002 in Hong Kong. J Infect 2016; 73:115–122. https://doi.org/10.1016/j.jinf.2016.05.010 PMID: 27246801

20. Cheng VCC, Yam WC, Lam OTC, Tsang JL, Tse EY, Siu GK, et al. Clostridium difficile isolates with increased sporulation: emergence of PCR ribotype 002 in Hong Kong. Eur J Clin Microbiol Infect Dis 2011; 30:1371–1381. https://doi.org/10.1007/s10096-011-1231-0 PMID: 21486885

21. Zar FA, Bakkaganagi SR, Moorthy KMLST, Davis MB. A comparison of vancomycin and metronidazole for the treatment of Clostridium difficile—associated diarrhea, stratified by disease severity. Clin Infect Dis 2007; 45:302–307. https://doi.org/10.1086/519265 PMID: 17599306

22. Louie TJ, Miller MA, Mullane KM, Weiss K, Lentnek A, Golan Y, et al. Fidaxomicin versus vancomycin for Clostridium difficile infection. N Eng J Med 2011; 364:422–31.

23. Johnson S, Louie TJ, Gerdning DN, Comely OA, Chasan-Taber S, Fitts D, et al. Vancomycin, metronidazole, or tolevamer for Clostridium difficile infection: Results from two multinational, randomized, controlled trials. Clin Infect Dis 2011; 53:345–54. https://doi.org/10.1093/cid/ciu313 PMID: 22479326

24. Pépin J, Valiquette L, Cossette B. Mortality attributable to nosocomial Clostridium difficile-associated disease during an epidemic caused by a hypervirulent strain in Quebec. CMAJ 2005; 173:1037–42. https://doi.org/10.1503/cmaj.050978 PMID: 16179431

25. Cammarota G1, Masucci L, Ianiro G, Bibbo S, Dinoi G, Costamagna G, et al. Randomised clinical trial: faecal microbiota transplantation by colonoscopy vs. vancomycin for the treatment of recurrent Clostridium difficile infection. Aliment Pharmacol Ther. 2015 May; 41:835–43. https://doi.org/10.1111/1365-2036.13144 PMID: 25728808

26. Drekonja D, Reich J, Gezahegn S, Greer N, Shaukat A, MacDonald R, et al. Fecal microbiota transplantation for Clostridium difficile infection: A systematic review. Ann Intern Med 2015; 162:630–8. https://doi.org/10.7326/M14-2693 PMID: 25938992

27. Gundacker ND, Tamhane A, Walker JB, Morrow CD, Rodriguez JM. Comparative effectiveness of faecal microbiota transplant by route of administration. J Infect 2017; 96:349–52.

28. Gold MR, Franks P, McCoy KL, Fryback DG. Toward consistency in cost-utility analyses—using national measures to create condition-specific values. Med Care 1998; 36:778–792. PMID: 9630120
29. Ridley S, Morris S. Cost effectiveness of adult intensive care in the UK. Anaesthesia 2007; 62:547–54. https://doi.org/10.1111/j.1365-2044.2007.04997.x PMID: 17506731

30. Forster AJ, Taljaard M, Oake N, Wilson K, Roth V, van Walraven C. The effect of hospital-acquired infection with Clostridium difficile on length of stay in hospital. CMAJ 2012; 184:37–42. https://doi.org/10.1503/cmaj.110543 PMID: 22143235

31. Surawicz CM, Brandt LJ, Binion DG, Ananthakrishnan AN, Curry SR, Gilligan PH, et al. Guidelines for diagnosis, treatment, and prevention of Clostridium difficile infections. Am J Gastroenterol 2013; 108:478–498. https://doi.org/10.1038/ajg.2013.4 PMID: 23439232

32. Hong Kong Life Tables 2009–2064, Census and Statistics Department, The government of Hong Kong SAR. Accessed on 5 March 2018: http://www.statistics.gov.hk/pub/B1120016062015XXXXB0100.pdf

33. You JH, Wong WC, Ip M, Lee NL, Ho SC. Cost-effectiveness analysis of influenza and pneumococcal vaccination for Hong Kong elderly in long-term care facilities. J Epidemiol Community Health 2009; 63:906–911. https://doi.org/10.1136/jech.2008.081885 PMID: 19608558

34. The world health report 2002: reducing risks, promoting healthy life. Geneva: World Health Organization; 2002.

35. Census and Statistics Department, the Government of Hong Kong. National income. Accessed on 7 March 2018: http://www.censtatd.gov.hk/hkstat/sub/sp250.jsp?tableID=030&ID=0&productType=8

36. Zipursky JS, Sidorsky TJ, Freedman CA, Sidorsky MN, Kirkland KB. Patient attitudes toward the use of fecal microflora transplantation in the treatment of recurrent Clostridium difficile infection. Clin Infect Dis 2012; 55:1652–1658. https://doi.org/10.1093/cid/cis809 PMID: 22990849

37. Varier RU, Biltaji E, Smith KJ, Roberts MS, Jensen MK, LaFleur J, et al. Cost-effectiveness analysis of treatment strategies for initial Clostridium difficile infection. Clin Microbiol Infect 2014; 20:1343–51. https://doi.org/10.1111/1469-0691.12805 PMID: 25363338

38. Ghantoji SS, Sail K, Laison DR, DuPont HL, Garey KW. Economic healthcare costs of Clostridium difficile infection: a systematic review. J Hosp Infect 2010; 74:309–318. https://doi.org/10.1016/j.jhin.2009.10.016 PMID: 20153547

39. Aitken SL, Alam MJ, Khaleduzzaman M, Walk ST, Musick WL, Pham VP, et al. In the endemic setting, Clostridium difficile ribotype 027 is virulent but not hypervirulent. Infect Control Hosp Epidemiol. 2015; 36:1318–23. https://doi.org/10.1089/ic.2014.0074 PMID: 26288985

40. Barbieri M, Drummond M, Rutten F, Cook J, Glick HA, Lis J, et al. What do international pharmaco-economic guidelines say about economic data transferability? Value in Health 2010; 13:1028–1037. https://doi.org/10.1111/j.1524-4733.2010.00771.x PMID: 20667054

41. Bidet P, Lalande V, Salauze B, Burghoffer B, Avesani V, Delmée M, et al. Comparison of PCR-ribotyping, arbitrarily primed PCR, and pulsed-field gel electrophoresis for typing Clostridium difficile. J Clin Microbiol 2000; 38:2484–2487. PMID: 10878030

42. Martinson JN, Broadaway S, Lohman E, Johnson C, Alam MJ, Khaleduzzaman M, et al. Evaluation of portability and cost of a fluorescent PCR ribotyping protocol for Clostridium difficile epidemiology. J Clin Microbiol 2015; 53:1192–7. https://doi.org/10.1128/JCM.03591-14 PMID: 25631804