COST-EFFECTIVENESS OF FECAL MICROBIOTA TRANSPLANT IN TREATING CLOSTRIDIUM DIFFICILE INFECTION IN CANADA

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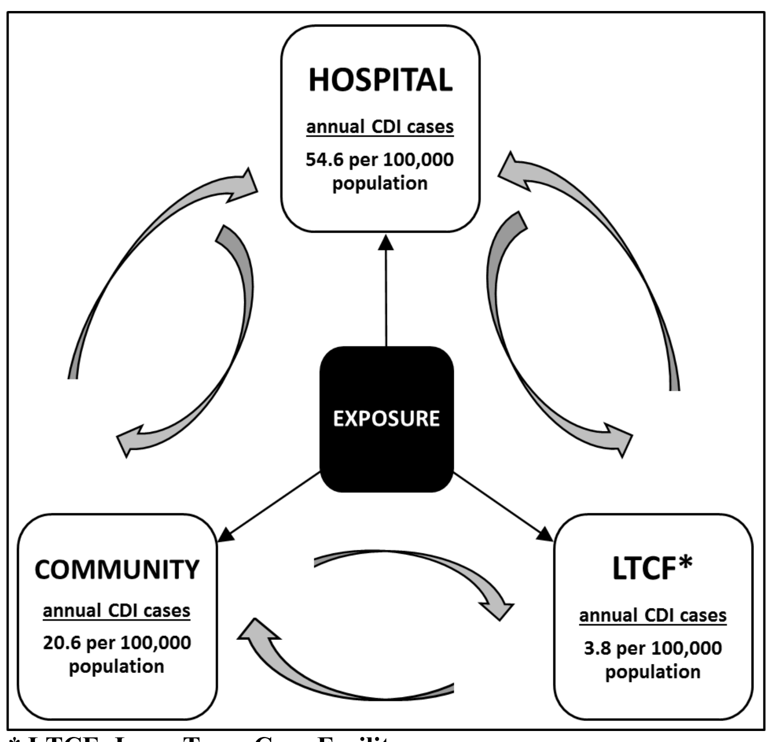
Abstract

Objectives: To estimate the cost-effectiveness of Fecal Microbiota Transplant (FMT) for Clostridium difficile infection (CDI) as compared to current practice comprising of antibiotic treatments.
Methods: We developed a decision analytic model to compare strategies for the management of CDI, by age, gender, and three major subpopulations: hospitals, communities, and long-term care facilities (LTCFs). We performed validation analyses to demonstrate that the predicted CDI rates were a reasonable representation of the selected actual rates. Mortality rates were stratified by age. A probabilistic sensitivity analysis (PSA) was performed to account for the effect of uncertainty in the model parameters.
Results: For the current practice, we estimated that annually 75% of CDI cases are new infections; the rest are recurrences; 40% of CDI occurs among individuals aged 80+, 41% among 60-79, and 19% among those below 60; hospital-based CDI accounted for 69 % of all CDI, while community and LTCF based CDI accounted for 26% and 5% of all CDI, respectively. The recurrence rates for current antibiotic treatment were estimated at 25.3% and 35.9% for first and second recurrences, respectively. The recurrence rate for FMT was estimated at 10.4%. For the base case, we estimated 79.0 and 64.9 per 100,000 population cases of CDI for current practice and FMT, respectively. The number of deaths is estimated at 5.8 and 4.7 per 100,000 population for current practice and FMT, respectively. The results of the cost-effectiveness analysis indicate that in the base case, FMT is a dominant strategy. The results of the PSA reveal that for the majority of simulations, FMT is dominant (positive incremental QALYs and negative incremental cost).
Conclusions: The results of the cost-effectiveness analysis indicate that FMT appears to be the dominant strategy, with lower costs and better outcomes than the existing antibiotic treatments.

Figure 1: Model of CDI transmission across three major subpopulations



* LTCF: Long-Term Care Facility

Background

Clostridium difficile infection (CDI) is the leading cause of health care associated infectious diarrhea in hospitals, ranging from a mild to a severe, life threatening, colitis. CDI has mainly been considered to be a hospital associated infection (HA-CDI), and most simulation models have been restricted to HA-CDI. With the prevalence of CDI increasing; CDI is now appearing in the community and long-term care facilities (LTCFs), where up to 80% of the elderly are colonized. Efforts to model CDI transmission between hospital, community, and LTCF settings have been limited. Little information is available on the effects of age (advanced age has been identified as an important risk factor for CDI) and gender on clinical responses to CDI. In 2005, 28% of CDI in Canada were among the population aged 80+. In 2011, 40% of infections occurred among patients aged 80+. Elderly patients experience more severe episodes of CDI, and almost twice the recurrence rate compared with younger populations.

Objectives

The aim of this study is to estimate the cost-effectiveness of Fecal Microbiota Transplant (FMT) for Clostridium difficile infection (CDI) as compared with current practice comprising of antibiotic treatment with Metronidazole and Vancomycin.

Methods

We developed a decision analytic Monte Carlo computer simulation model to compare FMT to the current practice comprising of antibiotic treatment with Metronidazole and Vancomycin for the management of recurrent CDI by age, gender and three major subpopulations in Canada: hospitals (HA-CDI), communities (CA-CDI), and LTCFs (LTCF-CDI) **(Figure 1)**. To estimate the number of CDI incidences in Canada, stratified by age and gender, by three major subpopulations, and by primary vs. recurrent infections, we conducted a systematic analysis of all provincial and federal CDI data in Canada. The most recent data from four provinces, Quebec, Ontario, British Columbia, and Manitoba were considered to be relevant for the estimation of stratified CDI rates for Canada, as their combined populations represent over 75% of Canada's population. Based on the provincial reports, the incidence and recurrence rates, stratified by age, gender and the three subpopulations were estimated for Canada as a whole **(Figures 2-6)**.

Individual regression analyses were used to estimate the HA-CDI, CA-CDI and LTCF-CDI rates by age and gender. These were estimated using spline interpolation, consisting of smooth polynomial functions, piecewise defined for the younger and older age groups. Extrapolation of predicted estimates was bounded by the observed data. We calibrated the results of the regression analyses using selected provincial data. Goodness of fit measures was applied to all sets of predictive equations. We performed rigorous validation analyses to demonstrate that the predicted CDI rates are a reasonable representation of the selected actual rates for Canada. A series of independent validations were performed by comparing model estimates to selected data reported by the Canadian Nosocomial Infection Surveillance Program (CNISP), the Institute for Clinical Evaluative Sciences (ICES) and the Ontario Ministry of Health and Long-Term Care selected databases, Goodness of fit tests across nine age groups show a high degree of association between estimated and observed CDI rates.

The time horizon for the model was 1 year. The input parameters for the model included the recurrence rates for FMT and current practice, mortality rates, quality of life, and hospital costs, as well as the distribution parameters for each variable **(Table 1)**. Infected patients had probabilities of successful treatment and of CDI recurrence, with two possible recurrences for antibiotic treatment and one recurrence for FMT. The base case recurrence rates for antibiotic treatment were estimated at 25.3% and 35.9% for first and second recurrences, respectively. The base case recurrence rate for FMT was 10.4%. Patients 60 years and older were assumed to have 1.75 (hazard ratio) times the rate of recurrence than patients 18-59 years. Treatment failures at any point in the model would progress to more serious CDI or death. Mortality rates for CDI patients were based on age, and could occur during the initial CDI episode and recurrences. Effectiveness was measured in quality-adjusted life years (QALYs) where patients contributed person-time in 1 of 3 health states: initial CDI episode, recurrent CDI, or death, calculated on a 4 month cycle over one year. Total annual hospital costs were calculated as the product of the estimated annual number of stratified CDI cases (initial episodes and recurrences) and the age-based hospital cost for CDI. The base case hospital cost, hazard ratio, quality of life, and mortality rates were assumed to be the same for current practice and FMT. Results were expressed as incremental cost-effectiveness ratios (ICERs). A probabilistic (Monte Carlo) sensitivity analysis (PSA) was performed to account for the effect of uncertainty regarding the model inputs **(Table 1)**.

Results

We estimated 79 per 100,000 population annually of CDI in Canada in 2011, with 86 per 100,000 population CDI cases for females (55%), and 71 per 100,000 population for males. Of these cases, 75% or 58.8 per 100,000 population were new infections (incidences), and 20.3 per 100,000 were recurrences. There were annually 638.3 cases per 100,000 population of CDI for ages 80 years and older, 158.4 per 100,000 for 60-79 years, and 20.1 per 100,000 for 18-59 years, representing 40%, 41%, and 19% of CDI cases, respectively. We estimated 54.6 per 100,000 population annual HA-CDI cases across all ages, 20.6 per 100,000 population cases of CA-CDI, and 3.8 per 100,000 population cases of LTCF-CDI, representing 69%, 25%, and 5% of CDI cases, respectively. In Canada, the number of deaths due to CDI is estimated at 5.8 per 100,000 and 4.7 per 100,000 population for current practice and FMT, respectively. For patients 80 years and older, the number of deaths due to CDI is estimated at 72.5 and 58.3 per 100,000 population for current practice and FMT, respectively.

The total hospital cost in Canada for CDI patients treated with FMT have been estimated at $253M (95% CI: $217M-$290M), compared with the cost of $309M ($263M-$359M) for patients treated with antibiotics **(Table 2)**. By the three major subpopulations, HA-CDI accounted for 70%, CA-CDI accounted for 25%, and LTCF-CDI accounted for 5% of the total hospital cost. The incremental cost savings were estimated at $56M ($117M to -$3M); 50% of the cost savings in patients 80 years and older, and 41% in patients 60-79 years. FMT appears to be dominant for all three age groups, that is, has a lower cost and better outcomes than the existing treatment strategy. The results of the 20,000 PSA simulations are presented in **Figure 7**. For 96.7% of simulations, FMT is dominant (positive incremental QALYs and negative incremental cost). Across age groups, for 87.3%, 97.9%, and 96.7% of the simulations, FMT is dominant for ages 18-59, 60-79, and 80 years and older, respectively.

Conclusions

FMT has emerged as a highly effective therapy for CDI because of high cure rates and low rates of recurrence. The results of the cost-effectiveness analysis indicate that FMT appears to be the dominant strategy for treating CDI, with lower costs and better outcomes than the existing antibiotic treatments. FMT appears to be a rational, and acceptable treatment option for patients with recurrent CDI.

Figure 2: Current Practice vs. FMT: CDI cases by age, gender, and three major subpopulations, Canada

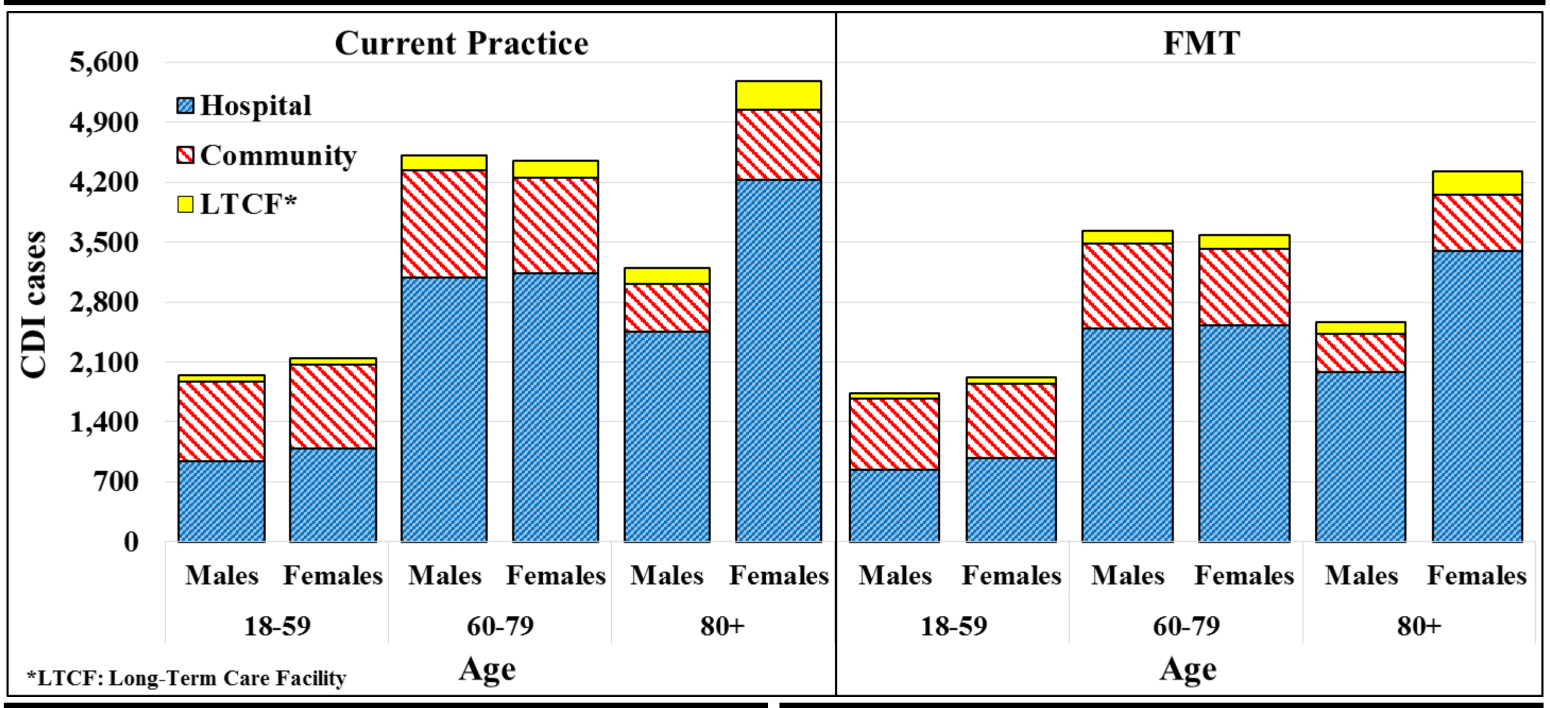


Figure 3: Current Practice vs. FMT: CDI cases by age, Canada

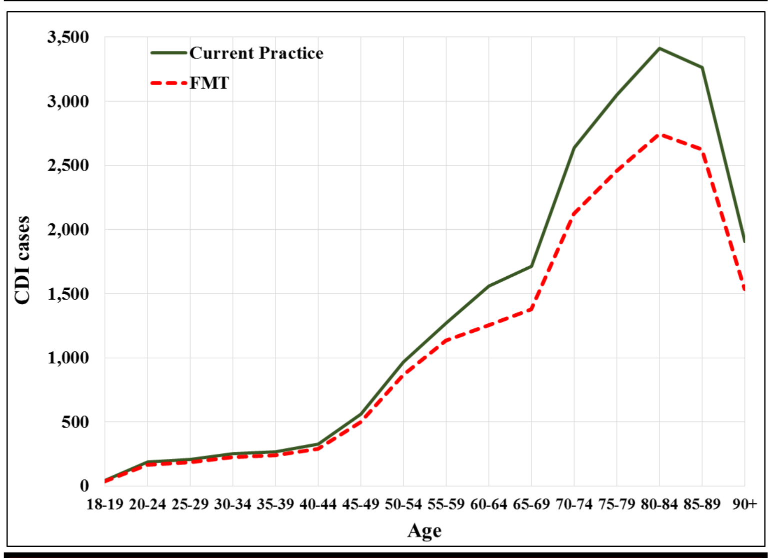


Figure 4: Current Practice vs. FMT: CDI cases per 100,000 population by age, Canada

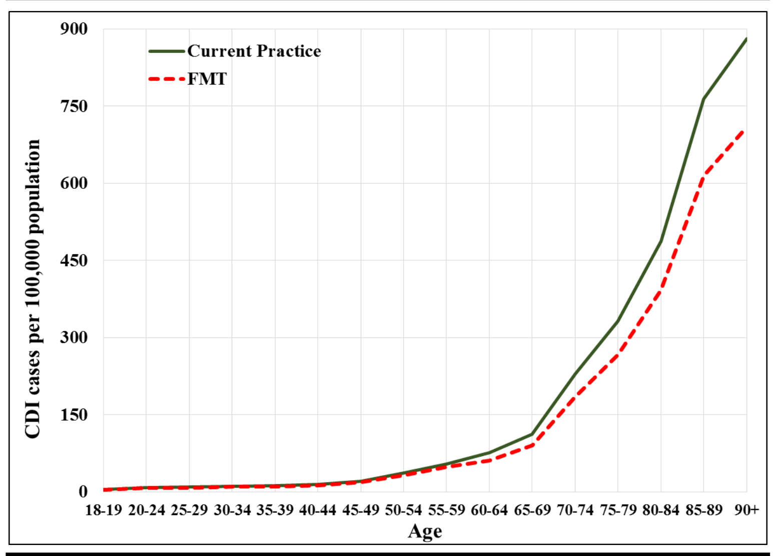


Figure 5: Current Practice vs. FMT: Recurrent CDI cases by age, Canada

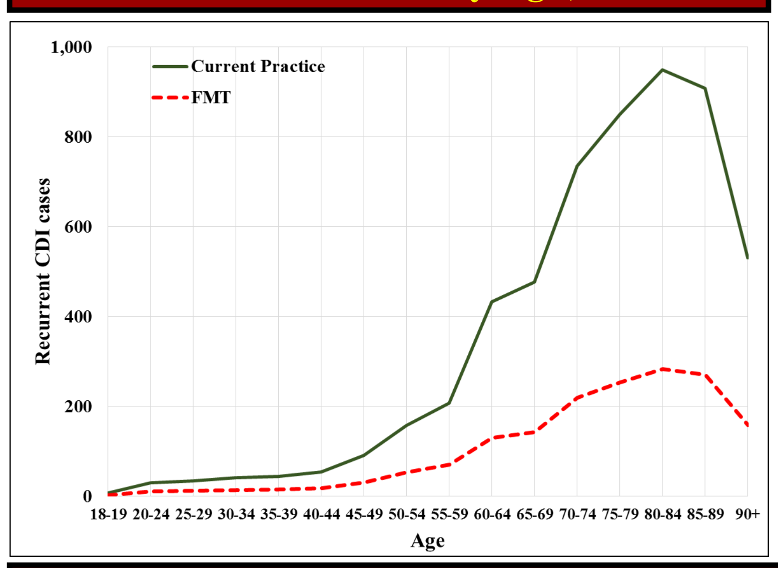


Figure 6: Current Practice vs. FMT: Recurrent CDI cases per 100,000 population by age, Canada

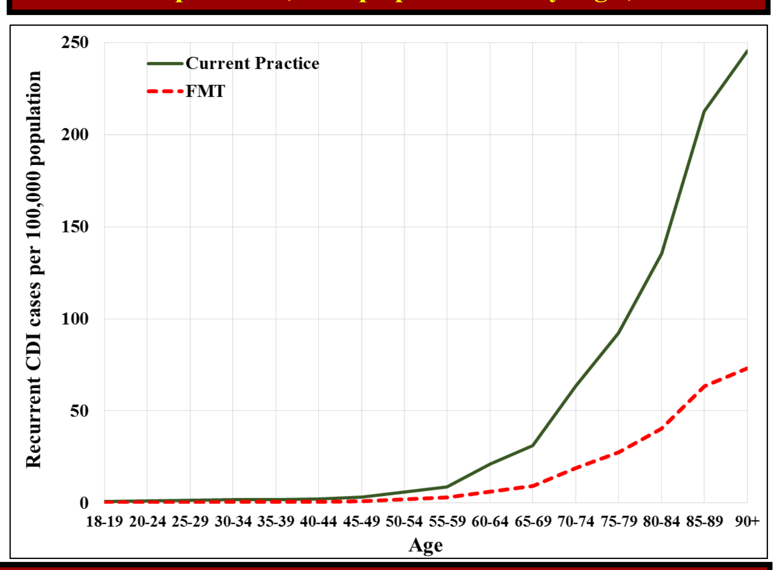


Table 1: CDI decision model: transition probabilities, costs, utilities, and distributions

	Base Case	Range	Distribution
Probabilities			
FMT (recurrence)	10.4%	5% - 19%	Beta (0.104; SD 0.017)
Current Practice (first recurrence)	25.3%	16% - 37%	Beta (0.253; SD 0.027)
Current Practice (second recurrence)	35.9%	25% - 47%	Beta (0.359; SD 0.027)
Mortality (age 18 - 59 y)	2.5%	0.2% - 8.6%	Beta (0.025; SD 0.010)
Mortality (age 60 - 79 y)	5.7%	1.9% - 12.1%	Beta (0.057; SD 0.013)
Mortality (age ≥ 80 y)	11.3%	6.1% - 18.2%	Beta (0.113; SD 0.015)
Hazard ratio			
Recurrence rate (age ≥ 60 y)	1.75	1.11 - 2.65	Log Normal (1.75,0.2)
Utilities			
Initial CDI (age 18–59 y)	0.92	0.81 - 0.98	Beta (0.92; SD 0.021)
Initial CDI (age ≥60 y)	0.79	0.66 - 0.89	Beta (0.79; SD 0.028)
Recurrent CDI	0.52	0.33 - 0.72	Beta (0.52; SD 0.047)
CDI: Costs ($CAN 2011)			
age 18–59 y	$11,878	$8,604 - $15,447	Gamma ($11,878; SD $824)
age 60-79 y	$13,146	$9,531 - $16,974	Gamma ($13,146; SD $951)
age ≥ 80 y	$16,583	$11,898 - $23,316	Gamma ($16,583; SD $1,314)

Table 2: Current Practice vs. FMT: Cost-effectiveness analysis

	Cost (Millions)			QALY			ICER (Thousands)		
Scenario	Baseline	Lower 95% CI	Upper 95% CI	Baseline	Lower 95% CI	Upper 95% CI	Baseline	Lower 95% CI	Upper 95% CI
Current Practice (age ≥ 18y)	$309	$263	$359	11,410	10,625	12,121			
FMT (age ≥ 18y)	$253	$217	$290	11,941	11,151	12,646	-$105.6	-$246.4	$6.6
Current Practice (age 18-59y)	$49	$42	$56	2,928	2,758	3,068			
FMT (age 18-59y)	$43	$38	$49	3,016	2,847	3,152	-$59.1	-$179.3	$50.7
Current Practice (age 60-79y)	$118	$101	$137	4,480	4,122	4,809			
FMT (age 60-79y)	$95	$82	$109	4,695	4,327	5,026	-$107.2	-$245.2	-$4.1
Current Practice (age ≥ 80y)	$142	$120	$167	4,002	3,667	4,320			
FMT (age ≥ 80y)	$114	$97	$133	4,230	3,891	4,547	-$122.1	-$285.8	$9.0

Figure 7: Current Practice vs. FMT: Probabilistic Sensitivity Analysis