Savings from the use of a probiotic formula in the prophylaxis of antibiotic-associated diarrhea
Kamdeu Fansi AA, Robert Guertin J, Lelorier J

Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

CRD summary
The study examined the clinical and economic impact of probiotic formula for management of antibiotic-associated diarrhoea, particularly *Clostridium difficile*-associated diarrhoea, in hospitalised patients receiving antibiotic therapy. A strategy based on two doses of probiotic formula was the most effective and least expensive option for this patient population. The analysis was based on a cost-consequences and relied almost entirely on a single published source of evidence. Nevertheless, the authors’ conclusions appear robust, as shown in the sensitivity analyses.

Type of economic evaluation
Cost-effectiveness analysis

Study objective
The study examined the clinical and economic impact of two different doses of probiotic formula for the management of antibiotic-associated diarrhoea and particularly *Clostridium difficile*-associated diarrhoea (CDAD), in hospitalised patients who received antibiotic therapy.

Interventions
The intervention under examination was a probiotic formula that consisted of Bio-K+ *Lactobacillus acidophilus* CL1285 and *Lactobacillus casei* LBC80R for prophylaxis of antibiotic-associated diarrhoea and CDAD. The two strategies under examination were two doses (two probiotic formula capsules containing 50 billion colony-forming units per day) and one dose of probiotic formula.

The comparator was no prophylactic treatment.

Location/setting
Canada. Primary care.

Methods
Analytical approach:
The analysis was based on a decision tree with a short-term horizon (duration of hospitalisation and three weeks of further follow-up). The authors stated that the analysis took the perspective of a single payer system.

Effectiveness data:
It appeared that a selective approach was used to identify relevant sources of evidence. Most clinical data, especially for treatment effect, came from a recently published randomised double-blind dose response placebo-controlled trial that enrolled 225 patients (86 in the two-dose group, 85 in the one-dose group and 84 in the placebo group). No information was provided on other sources of data used to estimate the incidence of reinfection with CDAD at two months and the effect of anti-CDAD antibiotics.

The main endpoint of the analysis was the incidence of disease with and without the probiotic formulas.

Monetary benefit and utility valuations:
Not considered.

Measure of benefit:
This economic evaluation was a cost-consequences analysis. Incidence of antibiotic-associated diarrhoea and CDAD was the primary endpoint of the clinical analysis.

Cost data:
The economic analysis included three types of hospital costs: costs of microbiological testing to identify bacteria, costs of pharmaceutical agents (probiotic formula and antibiotics) and hospitalisation stay. Drug costs were based on average wholesale prices. Hospitalisation costs and testing costs were taken from previously published studies. Some assumptions were made on duration of hospitalisation which was set equal to the duration of an antibiotic-associated diarrhoea episode. Costs were in US dollars ($). The price year was 2009.

Analysis of uncertainty:
A probabilistic analysis was carried out by varying simultaneously all inputs of the model in a Monte Carlo simulation. Conventional probability distributions were used for groups of parameters. A hospital pharmacy perspective was adopted in an alternative scenario. A deterministic sensitivity analysis assessed the impact of variations in the incidence of antibiotic-associated diarrhoea and CDAD using an alternative source of data.

Results
Incidence of antibiotic-associated diarrhoea was 44.1% with placebo, 28.2% with one-dose formula and 15.5% with two-dose formula. Incidence of CDAD was 23.8% with placebo, 9.4% with one-dose formula and 1.2% with two-dose formula.

Total cost per patient was $2,813 in the placebo group, $845 in the one-dose group and $152 in the two-dose group. Differences held in the multivariate sensitivity analyses when considering both mean and median values. The cost of the probiotic formula was totally offset by the reduction in costs of the disease.

The most influential inputs were incidence of CDAD in the placebo group and length of hospital stay in the placebo group. Both one- and two-dose probiotic formulas remained cost-saving in all options. Probabilistic sensitivity analysis showed that two-dose probiotic formula was cost-saving in 100% of simulations and the one-dose formula was cost-saving compared to placebo in 97.7% of cases.

From the hospital pharmacy perspective, choice of antibiotics affected the size of the cost-savings associated with probiotic formula.

Authors' conclusions
The authors concluded that a strategy based on two doses of probiotic formula was the most effective and least expensive option for management of hospitalised patients taking antibiotics. Substantial cost-savings were observed due to the significant reduce of disease incidence.

CRD commentary
Interventions:
The selection of the comparators was appropriate. The interventions were included in the clinical trial that was used to derive most clinical inputs. The authors stated that the choice of placebo as the background comparator was justified as no other alternative drug was currently and universally accepted for prophylaxis.

Effectiveness/benefits:
Clinical data were mainly taken from a double-blind placebo-controlled clinical trial which should ensure high internal validity. The authors acknowledged that the results of this trial in terms of reduction of disease incidence might not accurately reflect the North American context. Extensive sensitivity analysis was conducted on this parameters and the results appeared quite robust. Fewer details were given on other sources of clinical estimates that were also tested in the sensitivity analysis. This was a cost-consequences analysis so no summary benefit measure was used.

Costs:
The economic analysis was consistent with the perspective stated by the authors. A narrower viewpoint was adopted in a sensitivity analysis. Appropriate cost categories were included in the analysis and key details of unit costs and quantities of resources used were reported, which enhanced the transparency of the economic analysis. Data sources were from...
the North America setting except for duration of hospitalisation. The authors stated that the length of stay used in the analysis was likely to be lower than that in North America and could be considered conservative and the probiotic formulas could have provided even more savings due to reductions in hospitalisations. The price year was reported, which enabled reflation exercises in other time periods. Variations in economic data were taken into account in the sensitivity analyses.

Analysis and results:
The study results were reported clearly. There was no synthesis of costs and benefits because of the cost-consequences framework of this economic evaluation. An appropriate approach was used to deal with the issue of uncertainty and these methods and results were clearly provided. The study results appeared robust. Key details of the decision-analytic model were reported. The study results refer to a population of hospitalised patients aged between 50 and 70 years and it was unclear whether the results would be relevant to other patient populations. Findings were specific to the North American context and might be transferable only in settings with similar drug costs and epidemiology.

Concluding remarks:
The analysis was based on a cost-consequences and relied almost entirely on a single published source of evidence. Nevertheless, the authors’ conclusions appear robust, as shown in the sensitivity analyses.

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