Economic evaluation of *S. boulardii* CNCM I-745 for prevention of antibiotic-associated diarrhoea in hospitalized patients

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Abstract

Interest in administration of probiotics to prevent antibiotic-associated diarrhoea (AAD) in hospitalized patients is increasing. We determined the cost of antibiotic-associated diarrhoea in hospital settings for non-complicated and Clostridium difficile (C.diff) complicated AAD, and performed a health-economic analysis of AAD prevention with S. boulardii CNCM I-745 (*S. boulardii*) from data collected in 1 university and 3 regional hospitals in Flanders. Using a decision tree analytic model, costs and effects of S. boulardii for AAD prevention are calculated. Incremental costs due to AAD, including increased length of hospitalization, were calculated using bottom-up and top-down costing approaches from a hospital, healthcare payer (HCP) and societal perspective. Model robustness was tested using sensitivity analyses. Additional costs per hospitalized patient range from € 277.4 (hospital) to € 2,150.3 (societal) for non-complicated and from € 588.8 (hospital) to € 2,239.1 (societal) for *C. diff.* complicated AAD. Using *S. boulardii* as AAD prevention results in cost savings between € 50.3 (bottom-up) and € 28.1 (top-down) per patient treated with antibiotics from the HCP perspective; and € 95.2 and € 14.7 per patient from the societal and hospital perspectives. Our analysis shows the potential for using S. boulardii as AAD prophylactic treatment in hospitalized patients. Based on 831,655 hospitalizations with antibiotic administration in 2014 and € 50.3 cost saving per patient on antibiotics, generalized use of *S. boulardii* could result in total annual savings up to € 41.8 million for the Belgian HCP. (Acta gastroenterol. belg., **2018**, 81, **269-276).**

Key words : antibiotic associated diarrhoea, *clostridium difficile*, *Saccharomyces boulardii*, prevention, cost, economic evaluation.

Abbreviations : AAD : antibiotic-associated diarrhoea ; CDAAD : Clostridium difficile complicated antibiotic-associated diarrhoea ; C. diff: *Clostridium difficile* ; non-CDAAD : uncomplicated antibiotic associated diarrhoea ; *S. boulardii* : *Saccharomyces boulardii* CNCM I-745

Introduction

Antibiotic-associated diarrhoea (AAD) is a common complication of antibiotic treatment in hospitalized patients. AAD severity ranges from *Clostridium difficile (C. diff)* complicated AAD (CDAAD) to uncomplicated cases (non-CDAAD), with reported prevalence varying from 3.2 % to 29.0% (1). A recently published study in four Belgian hospitals reports an incidence of 9.6% of AAD in adults treated with antibiotics (2).

Many cost studies quantified health care costs related to AAD, in particular to CDAAD (3-14). However, the cost of the more prevalent uncomplicated AAD has not been investigated to the same extent.

Given the high prevalence of AAD in hospitalized patients and the evidence for some probiotic strains to be effective in preventing AAD (15-21), it could be beneficial to administer probiotics preventively to hospitalized patient treated with antibiotics. In a systematic review and meta-analysis, Hempel et al. reported that the preventive use of the non-pathogenic yeast *Saccharomyces boulardii* CNCM I-745 (*S. boulardii*) results in a 52% risk reduction for the development of AAD (22).

Few health economic evaluations have addressed the cost-effectiveness of probiotics in the prevention of AAD (23,24) (literature search details in appendix 1). Moreover, these focus primarily on the costly *C. diff* complicated cases of AAD (CDAAD), leaving out the less costly but more prevalent uncomplicated cases (non-CDAAD).

The present study aims to (1) determine the additional cost of AAD in a Belgian hospital setting, both for non-complicated and *C. diff* complicated AAD; (2) perform a health-economic analysis of AAD prevention with *S. boulardii*.

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Materials and methods

A decision tree analytic model (Fig. 1) is used to examine the effect of AAD preventive treatment with *S. boulardii* on the number of AAD cases and associated costs in an adult hospitalized patient population treated with antibiotics. Costs accrued during the entire episode of AAD whilst hospitalized, including the cost due to increased length of hospitalisation, are included.

Three cost perspectives are considered: the primary perspective is the health care payer perspective, capturing costs relevant for both the patient and (private or public) insurance. The societal perspective additionally includes societal costs resulting from productivity loss due to work absenteeism. Finally, the hospital perspective considers costs specific to the hospital.

The patient population entering the model either receives *S. boulardii* as preventive treatment (intervention arm) or not (comparator arm). Patients subsequently enter one of three health states: they do not develop AAD, they develop uncomplicated AAD (non-CDAAD), or they develop *C. diff* complicated AAD (CDAAD). For patients developing CDAAD, the model optionally includes the cost caused by an additional hospitalization for CDAAD recurrence.

Clinical data sources

A prevalence study was previously performed to determine the absolute risk of AAD in adult hospitalized patients in Belgium. The details of this study are published elsewhere (2). In this study, adult patients treated with antibiotics whilst hospitalized on an internal medicine ward were monitored for AAD in one university hospital and three associated regional hospitals in the northern part of Belgium. Patient screening occurred on eight different observation days, separated by 10-14 day intervals. Patients receiving antibiotics on an observation day were included in the study and screened for the presence of AAD. AAD was observed in 9.6% (71/743 patients) of the patients on antibiotics. Of those patients developing AAD, 5.6% (4/71 AAD patients) experienced a confirmed *C. diff* infection. These results are used in this analysis and are considered as the absolute risk for occurrence of non-CDAAD and CDAAD, respectively.

The risk reduction due to *S. boulardii* prevention in our model was based on the results of a meta-analysis by Hempel et al., reporting that the relative risk for AAD is 48% by administrating *S. boulardii* as preventive probiotic treatment if compared to no probiotics administered (22). As Hempel et al. do not report on the relative risk in uncomplicated AAD and CDAAD separately, we include the same relative risk (48%) for both patient groups. This limitation was addressed by performing a scenario analysis assuming no effect of prevention for CDAAD patients. Moreover, a more recent Cochrane meta-analysis reported a relative risk of 47% for the administration of *S. boulardii* as preventive measure in CDAAD in patients receiving antibiotics (21), supporting the relative risk (48%) used in our base case analysis.

Patients initially cured from a *C. diff* infection may experience recurrent episodes. Reported recurrence rates vary between 12% and 30% (15, 25-27). We included a (single) recurrence rate of 0% in the base case analysis and 15% in a scenario analysis. When included, the risk of recurrence was conservatively assumed not to be influenced by *S. boulardii* preventive treatment.

Cost data sources

The primary cost data source both for non-complicated cases of AAD and C. diff complicated cases of AAD is the aforementioned prevalence study (2). For patients developing AAD, AAD-related investigations and treatments were collected for the entire duration of AAD. Additionally, hospital invoices were collected, including the length of hospitalisation. In order to evaluate the extra workload, extra nursing care related to the diarrhoea was registered using a checklist.

Secondary, a literature search was performed to identify an alternative value for the additional cost of the occurrence of CDAAD in hospitalized patients and for the mean cost of a hospitalization for CDAAD recurrence. The cost of isolation for AAD patients was calculated using both literature and conservative

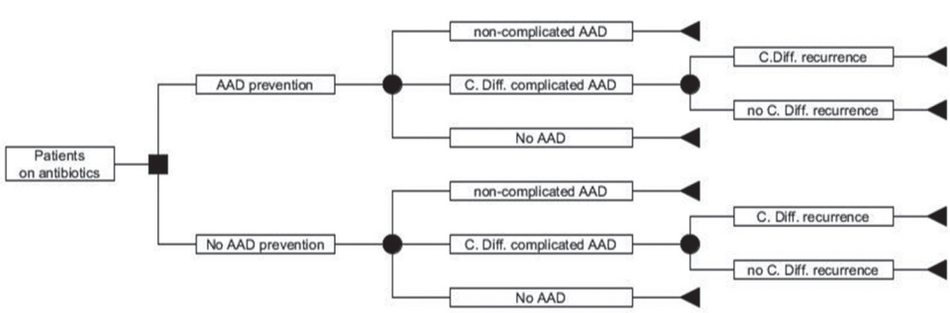

Fig. 1. — Decision tree analytic model

assumptions. Cost data were actualized to 2017 price levels using the appropriate components of the Health Index (28).

Cost Calculations

Health Care Payer Perspective

The cost for preventive treatment was calculated based on a dosage of 500 mg *S. boulardii* daily, for the entire duration of the antibiotic treatment. The incremental cost for non-CDAAD and CDAAD was calculated using a bottom-up and a top-down costing approach. The bottom-up approach calculates the incremental cost of non-CDAAD or CDAAD by multiplying resource use registered in non-CDAAD or CDAAD patients (2) with the corresponding unit costs. Unit costs were derived following the Belgian guidelines on economic evaluations and budget impact (29), based on the official national prices (RIZIV/INAMI) and from the Belgian manual for cost-based pricing of hospital interventions (30).

In the top-down approach, the incremental cost of non-CDAAD or CDAAD is calculated from the price difference between the total average hospital invoice of a non-CDAAD or CDAAD patient and the total hospital invoice of a patient not experiencing AAD. The resulting cost difference was corrected for confounders including age, number of antibiotic treatments, type of ward and known risk factors for the development of diarrhoea using linear regression analysis on the log-transformed variables after exclusion of outlier results.

Additional costs due to increased length of hospitalisation for non-CDAAD or CDAAD patients were included in both the bottom-up and top-down costing analyses. Additional length of hospitalisation was calculated by subtracting the average length of hospitalisation of patients not experiencing AAD from the average duration of hospitalisation of non-CDAAD and CDAAD patients. The resulting length of hospitalisation difference was again corrected for confounders including age, number of antibiotic treatments, type of ward and known risk factors for development of diarrhoea using linear regression analysis on the log-transformed variables after exclusion of outlier results. Its associated cost was calculated according to Belgian guidelines (29).

As the prevalence study included only four patients with *C. diff* infection (2), an additional literature search was performed to validate the incremental cost of CDAAD in hospitalized patients. Ten studies were identified, based on study population, setting and design (3, 4, 6-13). A mean cost of € 8,703.7 (range € 2,706-€ 19,678) was calculated as incremental cost of CDAAD during hospitalization. For the base case analysis, the conservative costs for CDAAD from the prevalence study are used (2). A scenario analysis was conducted using the higher incremental cost for CDAAD reported in literature.

Finally, the cost for (re)hospitalization due to a recurrent *C. diff* episode was calculated based on a supplementary literature search. Four studies were retained, based on study population, setting and design (6,31-33). A mean cost of € 11,868.5 (range € 7,045-€ 14,985) was calculated for a hospitalization for *C. diff* recurrence. For the base case analysis, *C. diff* recurrence was not taken into account. A scenario analysis was performed including the cost for a single recurrence of *C. diff* infection.

Additional cost for the societal perspective

For the societal perspective, an additional cost per day for productivity loss due to work absenteeism was taken into account : € 290.22 per day of productivity loss (29).

Hospital perspective

In the prevalence study, 14.1% of AAD patients were isolated for suspected *C. diff* infection (2). Patients with confirmed *C. diff* infection were isolated for on average 12.5 days (SD 3.90), versus 7 days (SD 2.16) for patients with non-complicated AAD (2). This represents an additional cost for the hospital included in the bottom-up costing approach. To calculate this cost, the process steps and timings (e.g. to prepare the isolation room and patient, to clean the original room, to educate visitors or additional time for nurse and physician contact due to isolation measures) for a typical stay in isolation were derived from literature (34,35). This includes the opportunity cost of a non-occupied bed, calculated based on a 11% versus 89% single versus two-bed room ratio observed in the hospitals from the prevalence study (2) and assuming that 75% of the patients in two-bed rooms were isolated in a single room, while 25% were isolated in their original (two-bed) room. As representative literature sources could not be identified, we conservatively assumed no additional material costs due to isolation, no opportunity costs for lost supplement revenues in case of single room occupancy, no extra cost of cleaning in case of external treatments (e.g. endoscopy), no cost for the administration of antibiotics, etc. Taking into account a mean duration of isolation of 10 days for all AAD patients (2), the mean cost per isolation day was calculated as € 133.89/day.

The additional cost for nurse time spent on AAD related activities included in the bottom-up costing approach was calculated based on the median number of minutes spent on diarrhoea related care as reported in the prevalence study (2). The per minute unit cost for a general nurse (€ 0.63/min) was obtained from Belgian guidelines (29).

Modelling uncertainty

Model robustness was tested using one-way-sensitivity analysis (OWSA) and probabilistic sensitivity analysis (PSA). Four different scenario analyses were conducted.

Table 1. — **Parameters included in the sensitivity analysis**

Parameter	OWSA					PSA
	Deterministic value	Low % of deterministic value	High % of deterministic value	Low Absolute value	High Absolute value	
Bottom-up analysis						
Relative risk for AAD (prevention vs no prevention)	48,0%	70%	130%	33,6%	62,4%	Lognormal
Relative risk for CDAAD (prevention vs no prevention)	48,0%	70%	130%	33,6%	62,4%	Lognormal
Absolute risk for AAD (no prevention)	9,6%	70%	130%	6,7%	12,5%	Beta
Absolute risk for CDAAD in AAD group	5,6%	70%	130%	3,9%	7,3%	Beta
% recurrence of CD	15,0%	70%	130%	10,5%	19,5%	Beta
S. Boulardii dosage for prevention	3650,0	70%	130%	2555,0	4745,0	Gamma
Percentage of (uncomplicated) AAD patients receiving a standard biological test	38,0%	70%	130%	26,6%	49,4%	Gamma
Percentage of (uncomplicated) AAD patients tested for C. Diff. Infection	93%	70%	130%	65%	100%	Gamma
Additional days of hospitalisation (uncomplicated AAD)	3,10	70%	130%	2,17	4,03	Gamma
Percentage of (C. Diff. complicated) AAD patients receiving a standard biological test	38%	70%	130%	27%	49%	Gamma
Additional days of hospitalisation (C. Diff complicated AAD)	3,10	70%	130%	2,17	4,03	Gamma
Top-down analysis						
Total cost for non-AAD hospitalisation	€ 3.290,00	70%	*125%*	€ 2.303,00	€ 4.101,00	Gamma
Total cost for non-CDAAD hospitalization	€ 4.101,00	*80%*	130%	€ 3.290,00	€ 5.331,30	Gamma
Total cost for CDAAD hospitalization	€ 4.101,00	*80%*	130%	€ 3.290,00	€ 5.331,30	Gamma

Table 2. — **Health state costs**

Costing approach		Bottom-up			Top-down	Literature review
Perspective		HCP	Hospital	Societal	HCP	HCP
Cost parameter estimates	Cost for S. Boulardii CNCM I-745 prevention	€ 12,4	€ -	€ 12,4	€ 12,4	*NA*
	Additional cost for AAD	€ 1.250,6	€ 277,4	€ 2.150,3	€ 1.248,7	*NA*
	Additional cost for CDAAD	€ 1.339,5	€ 588,8	€ 2.239,1	€ 1.337,5	€ 8.703,7
	One-off cost for hospitalisation due to C.Diff relapse/reinfection	*NA*	*NA*	*NA*	*NA*	€ 11.868,5

Table 3. — **Base case and scenario analyses settings**

Base case	
	Healthcare payer perspective
	Risk reduction for CDAAD due to prevention = risk reduction for AAD due to prevention
	Cost for CDAAD based on prevalence study registrations
	Cost for non-CDAAD based on prevalence study registrations
	No rehospitalisations for C. Diff. recurrence / reinfection
Scenario 1 (bottom-up costing approach only)	
	Societal perspective
	Risk reduction for CDAAD due to prevention = risk reduction for AAD due to prevention
	Cost for CDAAD based on prevalence study registrations
	Cost for non-CDAAD based on prevalence study registrations
	No rehospitalisations for C. Diff. recurrence / reinfection
Scenario 2 (bottom-up costing approach only)	
	Hospital perspective
	Risk reduction for CDAAD due to prevention = risk reduction for AAD due to prevention
	Cost for CDAAD based on prevalence study registrations
	Cost for non-CDAAD based on prevalence study registrations
	No rehospitalisations for C. Diff. recurrence / reinfection
Scenario 3	
	Healthcare payer perspective
	Risk reduction for CDAAD due to prevention = risk reduction for AAD due to prevention
	Cost for CDAAD based on literature review
	Cost for non-CDAAD based on literature review
	Cost for non-CDAAD based on prevalence study registrations
	Include rehospitalisations for C. Diff. recurrence / reinfection
Scenario 4	
	Healthcare payer perspective
	No risk reduction due to prevention for CDAAD occurrence
	Cost for CDAAD based on literature review
	Cost for non-CDAAD based on literature review
	Cost for non-CDAAD based on prevalence study registrations
	No rehospitalisations for C. Diff. recurrence / reinfection

The OWSA examines the impact of the change of a single model parameter on the model result. Parameters were varied from 70% to 130% of their deterministic value, with the limitation that the total cost for a hospitalization of a patient not experiencing AAD should always be lower than the total cost for a hospitalization of a patient experiencing AAD.

In the PSA a probabilistic value was calculated based on probability distributions determined for each included parameter. This was repeated 5,000 times to assess the impact of the combined uncertainty on the deterministic model results.

Table 1 lists the parameters included in the OWSA and PSA.

Statistical analyses

Statistical analyses were performed in R version 3.1.2 (36). Significance was tested using Mann-Whitney U tests. Significance for length of hospitalisation and hospital invoice cost differences were assessed through regression analysis of the log-transformed variables after removal of outlier results and correction for confounding factors. Outlier detection was performed using boxplot statistics, excluding results which were more than 1.5 (length of hospitalisation) and 3 (hospital invoice cost differences) box lengths from the box. Confounders considered included age, number of antibiotic treatments, type of ward and known risk factors for development of diarrhoea. These were included using stepwise selection.

Results

Table **2** summarizes the additional costs of prevention, the additional cost for non-complicated AAD and CDAAD during hospitalization, and the one-off cost of a (re)hospitalization for *C. diff* recurrence. Table 3 summarizes the base case and scenario analyses settings used in the performed health-economic analysis.

In the base case analysis, by using *S. boulardii* as AAD prevention, between €50.3 (bottom-up analysis) and € 28.1 (top-down analysis) is saved per patient treated on antibiotics (health care payer perspective). This saving takes into account a € 12.4 cost for preventive treatment. In the base case scenario, recurrence of *C. diff* infections is not considered, resulting in an equal cost for the group of patients experiencing CDAAD with or without *C. diff* reinfection.

Cost savings from using *S. boulardii* as prevention for AAD increase to € 95.2 by taking into account productivity loss due to increased length of hospitalisation (societal perspective).

Taking only into account nurse time spent on AAD care and the costs for isolation, a cost saving of € 14.7 is realized (hospital perspective). This does not take into account the cost of prevention, estimated at € 12.4 per patient in our model, as this is a patient cost in the model.

Including the more significant cost for *C. diff* infection from literature and taking into account a single *C. diff* recurrence increases savings to € 76.0 (bottom-up) and € 55.3 (top-down). Assuming the effect of *S. boulardii* prevention in the group of patients experiencing CDAAD to be non-existent decreases savings to € 53.8 (bottom-up) and € 30.2 (top-down).

Sensitivity analyses were performed for the base case healthcare payer perspective. Panels (A) and (B) in Figure 2 show the one way sensitivity analysis results.

For the bottom-up analysis, the parameters to which our model was most sensitive are the absolute risk for development of AAD (higher cost savings for higher occurrence of AAD), increased length of hospitalisation due to AAD (higher cost savings for a more increased length of hospitalisation) and the relative risk of AAD in the prevention group (lower cost savings for a higher relative risk). None of the one way sensitivity analysis analyses resulted in a cost increase, demonstrating the robustness of the model results.

For the top-down analysis, our model is most sensitive to the total hospitalization cost of a patient experiencing uncomplicated AAD (non-CDAAD) and the total hospitalization cost for a patient not experiencing AAD: the closer the cost of a patient experiencing AAD is to the cost of a patient not experiencing AAD, the lower the potential cost savings due to *S. boulardii* prevention. In the unlikely case where the total cost of hospitalization does not differ between a patient experiencing AAD and a patient not experiencing AAD, only the cost of preventive treatment remains (+ € 12.4).

Panels (C) and (D) in Figure 2 show the results of the PSA. The majority of simulations were cost saving (90.1% and 97.8% of simulations for the top-down and bottom-up analyses, respectively).

Finally, a threshold analysis was performed to identify the minimal risk reduction necessary to offset the cost of prevention with *S. boulardii*. From the health care payer perspective, a relative risk of 0.84 to 0.90 (top-down and bottom-up analysis, respectively), corresponding to a risk reduction of 0.16 to 0.10, resulted in a break-even result (€ 0 cost or savings).

Discussion

This study shows that, regardless of the perspective chosen, the administration of *S. boulardii* as preventive treatment in each hospitalized patient on antibiotics results in considerable cost savings. To put this in perspective, antibiotics were administered to 48.5% of all hospitalized patients in Belgium in 2011 (37). Generalizing preventive AAD treatment with *S. boulardii* could thus result in a total annual savings of up to € 41.8 million, based on 831,655 hospitalizations with antibiotic administration in 2014 and a € 50.3 cost saving per patient on antibiotics from the health care payer perspective and the bottom-up costing approach.

Our analysis uses a single source of real-life data for AAD prevalence, associated resource use, duration of isolation and length of hospitalisation (2). The

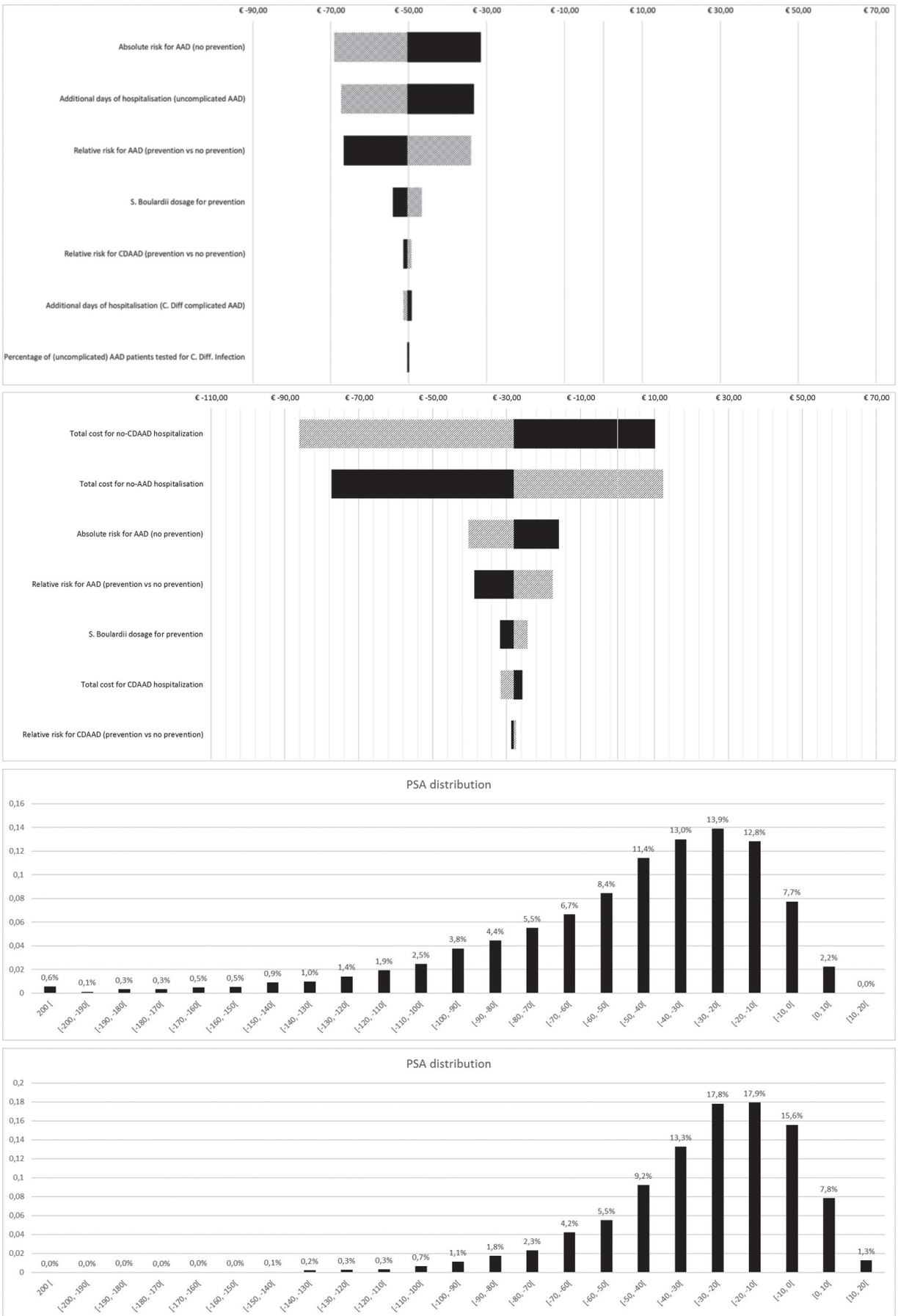

Fig. 2. — Sensitivity analyses : (A) OWSA – bottom-up base case analysis ; (B) OWSA – top-down base case analysis ; (C) PSA – bottom-up base case analysis ; (D) PSA – top down base case analysis.

study conducted by Elseviers et al. (2) was specifically set up within the context of this evaluation. Other health economic evaluations assessing the preventive use of probiotics, include prevalence and resource use estimates based on clinical trials or literature (23) and Delphi panels (24). Particularly the increase in duration of hospitalization due to AAD should not be based on assumptions or estimates (23,24) due to its significant impact on the additional costs associated with AAD. The 9.6% AAD prevalence used in this economic evaluation is conservative in comparison to AAD prevalence estimates used elsewhere : 44.1% (23) and 15% (24), as higher AAD prevalence results in increased cost savings.

Our results show that savings can be achieved when *S. boulardii* is administered in patients on antibiotic treatment as prevention for AAD, including both uncomplicated (less expensive) and C. diff complicated (expensive) cases. Not including CDAAD recurrence in the base case analysis leads to conservative results compared to other health economic evaluations (23,24). A scenario analysis based on reported recurrence rates for *C. diff* infection in literature, shows increased cost savings. The scenario analysis conservatively includes a single CDAAD recurrence and excludes any effect of *S. boulardii* on the risk of recurrence.

The effectiveness of *S. boulardii* in the model is based on a meta-analysis by Hempel et al. (22). Using a meta-analysis is preferred to using only one clinical trial. A limitation of this meta-analysis is that the prevention and treatment of AAD in ambulatory and hospital setting and in different patient populations were al grouped together. We conducted several subgroup analyses to evaluate if the reported result was sensitive to these population differences. The relative risk of a group including only RCT's evaluating the effect of *S. boulardii* in the prevention of AAD in adult hospitalized patients (38–41), which is in line with our study population, did not differ significantly from the relative risk calculated for all 15 *S. boulardii* RCTs included in the meta-analysis. The reported results of health economic analysis are based on the published effectiveness of *S. boulardii* specifically and may thus not be extrapolated to other probiotics.

As Hempel et al. did not report on the relative risk in uncomplicated and *C. diff* complicated patients separately, we include the same relative risk (0.48) for both patient groups. This limitation was addressed by performing a scenario analysis assuming a "no effect" of prevention for CDAAD patients, which resulted in €53.8 saving per patient (bottom-up approach). A recent Cochrane meta-analysis reports a relative risk of 0.47 for *S. boulardii* as preventive measure in *C. diff* associated diarrhoea in patients receiving antibiotics (21), supporting our base case analysis.

Our study uses costs obtained from mostly Belgian sources calculated according to Belgian guidelines (29). Translating our results to different settings will require obtaining costs for those settings and reviewing the cost calculations with local guidelines. Costs induced by potential adverse events of *S. boulardii* are not taken into account in our analysis. These were not reported by Hempel et al. and the Summary of Product Characteristics of *S. boulardii* reports that adverse events occur only very rarely (< 1/10,000 patients).

In conclusion, our analysis shows the potential benefit of a prophylactic administration of *S. boulardii* for the prevention of AAD in hospitalised patients on antibiotic treatment, from three different cost perspectives.

Disclosures

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