Economic evaluation of the treatment of Acute Bacterial Skin and Skin Structure Infections (ABSSSIs) from the national payer perspective: introduction of a new treatment to the patient journey. A simulation of 3 European Countries

ABSTRACT

Background: The aim of this study was to develop a spending predictor model to evaluate the direct costs associated with the management of ABSSSIs from the National healthcare provider's perspective of Italy, Romania and Spain.

Methodology: A decision-analytic model was developed to evaluate the diagnostic and clinical pathways of hospitalized ABSSSI patients based on scientific guidelines and real-world data. A Standard of Care (SoC) scenario was compared with a dalbavancin scenario in which the patients could be discharged early. The epidemiological and cost parameters were extrapolated from national administrative databases (i.e., hospital information system). A probabilistic sensitivity analysis (PSA) and one-way sensitivity analysis (OWA) were performed.

Results: Overall, the model estimated an average annual number of patients with ABSSSIs of approximately 50,000 in Italy, Spain and Romania. On average, the introduction of dalbavancin reduced the length of stay by 3.3 days per ABSSSI patient. From an economic perspective, dalbavancin did not incur any additional cost from the NHS perspective, and the results were consistent among the countries. The PSA and OWA demonstrated the robustness of these results.

Conclusion: This model represents a useful tool for policymakers by providing information regarding the economic and organisational consequences of an early discharge approach in ABSSSI management.

Keywords: ABSSSIs; dalbavancin; economic evaluation; Italy; Spain; Romania

JEL codes: I15

Key point:

1. Acute Bacterial Skin and Skin Structure Infections (ABSSSI) impose a significant economic burden on the healthcare systems due to the associated inpatient management, surgical procedures and parenteral antibiotic therapy.
2. The present study aimed to develop a predictor model to evaluate the direct costs associated with the management of ABSSSIs. We collected data of hospital management in three European countries, namely, Italy, Romania and Spain and compared drug costs related to therapy-related adverse events, administration costs, diagnosis-related groups (DRG) and service-related resources associated with standard of care (SoC) and dalbavancin.
3. the introduction of dalbavancin reduced the length of stay by 3.3 days per ABSSSI patient and from an economic perspective, dalbavancin did not incur in any additional cost from the NHS perspective of all the included countries. Considering the costs from a hospital perspective according to the probabilistic analysis, dalbavancin could decrease the total economic burden with a significant difference.

INTRODUCTION

In 2013, the US Food and Drug Administration (FDA) coined the acronym “ABSSSIs” (Acute Bacterial Skin and Skin Structure Infections) to include all complicated infections of the skin and soft tissues [1]. ABSSSIs include severe skin and soft tissue infections, such as cellulitis, erysipelas, cutaneous abscesses, infected wounds and ulcers, that usually require inpatient management, surgical procedures and parenteral antibiotic therapy.

Inpatient treatment of ABSSSIs imposes a significant economic burden on the healthcare system. In the United States, over 750,000 patients per year are admitted to the hospital for ABSSSI, incurring an estimated cost of >6 billion dollars [2]. Nearly 10 % of all US hospital admissions are attributed to ABSSSIs[3], while in Europe ABSSSIs may account up to 15% of all infections treated in hospitals [4].

ABSSSIs are primarily caused by Gram-positive pathogens, mainly *Staphylococcus aureus* and *Streptococcus pyogenes*, but are also caused by Gram-negative and anaerobic bacteria, particularly in polymicrobial infections [5].

S. aureus has historically been the leading cause of ABSSSIs, although its clinical relevance has rapidly increased over the previous 15 years due to the emergence of methicillin-resistant S. aureus (MRSA) [6]. *S. aureus* is considered the predominant pathogen in all regions across North America, Latin America and Europe. The rates of MRSA vary among these continents, and the highest proportion is observed in the Americas [6-8]. *Staphylococcus aureus* is also the most common cause of complicated Skin and Soft Tissue infections (cSSTIs) in Europe. According to a study investigating more than 3000 cSSTI-associated isolates sampled from 19 countries in and around Europe between 2008 and 2009, nearly one-third of the isolates were *S. aureus*, and of these isolates, approximately one-half were MRSA [7, 8].

In Europe, the incidence of MRSA has changed over the previous 10 years; however, in the European Community, MRSA accounts for 16.7% of all *Staphylococcus aureus* isolates. In ten countries, the incidence of MRSA in infections sustained by *Staphylococcus aureus* was 10-25%. Although, an incidence of MRSA >25% was reported in Italy and Spain, and accounted almost for 50% of *S. aureus* isolates in Romania [9].

Due to the emerging incidence of bacterial resistance to multiple antibiotics, ABSSSIs are increasingly challenging to treat [10]. Furthermore, the choice of treatment is often complicated by the urgency to treat with an antibiotic therapy before having obtained a confirmed microbiological diagnosis.

Due to the increasing incidence of MRSA, particularly in community-acquired infections, vancomycin, which is the standard therapy for documented MRSA infections, is often the treatment of choice if MRSA is suspected. However, the use of this agent is associated with suboptimal outcomes [11-13].

The guidelines of the Infectious Diseases Society of America recommend therapy with β-lactam or clindamycin for mild/moderate ABSSSIs and non-purulent ABSSSI and vancomycin plus piperacillin/tazobactam for severe, non-purulent ABSSSI [5]. The empirical treatment of purulent ABSSSIs should cover MRSA with doxycycline or trimethoprim/sulfamethoxazole (TMP/SMX) in moderate cases and vancomycin, daptomycin, linezolid, telavancin, or ceftaroline in severe cases [14]. However, clinical MRSA isolates have progressively shown a decreasing susceptibility or resistance to these drugs [15]. Consequently, the treatment of ABSSSIs currently requires a greater need for hospitalization, which is associated with a net increase in costs [16].

Dalbavancin is a novel long-acting lipoglycopeptide that was approved by the FDA in May 2014 and the European Medicines Agency (EMA) in February 2015 for the treatment of

ABSSSIs caused by susceptible Gram-positive organisms. It is active against gram-positive pathogens, including methicillin-resistant *Staphylococcus aureus* (MRSA), and minimum inhibitory concentrations (MICs) are consistently <0.125 μg/ml, lower than most other anti-MRSA agents. In vitro data against MRSA, suggest that dalbavancin is 4–8 times more potent than vancomycin. Moreover, dalbavancin has a β half-life (elimination half life) of >8 days (~200 hours) and a terminal half-life of >14 days (~346 hours), allowing for clinical safety and efficacy assessment using a once-weekly dosing regimen of 1000 mg on day1 and 500 mg on day 8 [17, 18].

Due to its long-acting bactericidal activity and unique dosing schedule, dalbavancin allows clinicians to endorse early discharge (ED) programmes, enabling patients to complete the treatment after hospital discharge. ED programmes have been shown to significantly reduce the use of hospital resources [19] in the management of MRSA infections, particularly complicated skin and skin structure infections [19, 20].

The first objective of this study was to develop a spending predictor model to evaluate the direct costs associated with the hospital management of ABSSSIs from the perspective of the National Health Service (NHS). The second objective was to collect data of the direct costs of hospital management of ABSSSIs in three European countries, namely, Italy, Romania and Spain. Finally, the third objective was to apply country-specific cost inputs to the spending predictor model to compare the estimated direct costs of the hospital treatment of ABSSSIs between patients treated with standard antibiotics therapy and those treated with dalbavancin.

METHODS

Authors followed methodological indications of the ISPOR Budget Impact Analysis—Principles of Good Practice [21]. Due to the lack of data availability and as advised by the above-mentioned article, whenever data from the clinical trials and/or the official administrative databases were not accessible, clinical experts' opinions were used as data source [21].

Health care systems and perspective

A decision-analytic model was built based on the current clinical practices in three European countries to simulate the hospital management of ABSSSI patients receiving empiric treatment with antibiotics (Figure 1).

The choice of the countries was based on access to healthcare and public spending per capita data. Most of 28 Countries in the European Community have a publicly directly or indirectly funded National system that provides universal access to healthcare. However, national expenditures on healthcare widely vary around the EU28 mean value (€ 2,323 per capita) [22]. Based on the relevance of incremental costs/savings to the public budget, the simulation included the two EU25 countries closest to the mean (Italy, € 2,339, and Spain, € 2,199) and the country with the lowest per capita annual expenditure (Romania, € 809).

The model was generated from the perspective of the National healthcare provider.

Eligible population

An algorithm consistent with the IDSA guidelines published in 2014 [14] was used to identify severe purulent and non-purulent patients requiring observation for over 72 hours. The eligible patients were identified using the national administrative databases of each country (Appendix A). The algorithm included all acute inpatient admissions. The longest data collection period per country was selected based on the available data as follows:

between January 1, 2006 and December 31, 2010 in Italy, January 1, 2010 and December 31, 2013 in Romania, and January 1, 2006 and December 31, 2015 in Spain.

Intervention comparison and model structure

The decisional tree was designed to follow IDSA guidelines and as illustrated in Figure 1: in the model, all ABSSSI patients can be hospitalized for purulent or non-purulent ABSSSIs (first probabilistic node). The patients initially received an empirical antibiotic treatment to cover both Gram-positive and Gram-negative infections.

The model considers that the patients could receive vancomycin, intravenous linezolid or teicoplanin as Gram-positive therapy plus piperacillin tazobactam as Gram-negative therapy (current intervention or Standard of Care, SoC) or the new intervention of dalbavancin as the Gram-positive therapy of choice in addition to piperacillin tazobactam. The choice of antibiotic combination therapy (antibiotic for gram-positive plus piperacillin tazobactam) was made according to the IDSA guidelines on the treatment of severe ABSSIs [5].

After receiving the first dose of the empirical antibiotic therapy, the patients may progress to one of the following treatment pathways (branch of possible events): purulent surgical eligible for early discharge (ED), purulent surgical not eligible for ED, purulent not surgical, non-purulent Gram-positive, non-purulent Gram-negative, non-purulent indeterminate or polymicrobial. Each pathway (except for purulent surgical not eligible for ED) includes the following states: discharge on day 4, observation up to day 8, discharge on day 9, or observation up to the clinical evaluation. The transition probabilities change according with the treatment (SoC or dalbavancin) administered on day 0 (tree's decision node).

Non-monetary inputs to the model

The input value of the probabilistic nodes is reported in Table 1.

The purulent and non-purulent occurrence rates and the time to discharge in the SoC scenario were estimated based on data obtained from the real-world databases of each country (details are provided in Appendix), while the discharge probabilities in the dalbavancin scenario were estimated based on the opinion consensus of experts (co-author of this work). However, the transition probabilities in Spain were assumed to be the same as those applied to Italy due to the lack of country-specific data.

The cut-offs for the eligibility to early discharge (ED) were set based on the distribution of the length of stay of the included patients stratified as purulent or non-purulent. For both purulent and non-purulent infections, eligibility for early discharge was attributed to patients with a length of stay >4, considering the differences in medical treatments as suggested by clinical experts.

All purulent infections were considered sustained by *S. aureus*, while the distribution of the bacteria responsible of the non-purulent infections was estimated based on the consensus among the experts. The treatment undergone by patients with purulent and non-purulent infections and the discharge probabilities in the SoC scenario were based on real-world data obtained from the administrative databases of each Country. For the sake of avoiding an overcomplication of the decisional tree, all the therapies included in the model were assumed to have 100% efficacy.

Table 1 - Transition probabilities: SoC (real-world data) vs. Dalbavancin (expert opinion)

Number of patients with ABSSSIs	*ITALY*	*ROMANIA*	*SPAIN*	*References*
Non-purulent patients - Sort of bacteria		*Model value*		
Indeterminate	71%	18%	70%	Expert opinion
Polymicrobial	17%	18%	10%	
Gram-negative	7%	9%	7%	
Gram-positive	6%	56%	13%	
Purulent patients - Sort of origin		*Model value*		
Surgical	26%	95%	70%	Expert opinion
Non-surgical	74%	5%	30%	
Surgical eligible for ED	50%	30%	50%	
Surgical not eligible for ED	50%	70%	50%	
Discharge distribution with dalbavancin				***References***
Non-purulent patients: Indeterminate or polymicrobial		*Model value*		
Discharge (4 day)	50%	60%	60%	Expert opinion
Discharge (8 day)	70%	70%	70%	
Non-purulent patients: Gram-positive		*Model value*		
Discharge (4 day)	70%	70%	70%	Expert opinion
Discharge (8 day)	80%	90%	90%	
Purulent patients: Surgical		*Model value*		
Discharge (4 day)	70%	70%	50%	Expert opinion
Discharge (8 day)	80%	80%	70%	
Purulent patients: Non-surgical		*Model value*		
Discharge (4 day)	70%	65%	40%	Expert opinion
Discharge (8 day)	80%	80%	70%	
Discharge distribution with standard therapy				***References***
Non-purulent patients: Indeterminate or polymicrobial		*Model value*		
Discharge (4 day)	11%	10%	11%	Data from administrative databases
Discharge (8 day)	42%	35%	42%	
Non-purulent patients: Gram-positive		*Model value*		
Discharge (4 day)	11%	31%	11%	Data from administrative databases
Discharge (8 day)	58%	55%	58%	
Purulent patients: Surgical		*Model value*		
Discharge (4 day)	11%	55%	11%	Data from administrative databases
Discharge (8 day)	50%	65%	50%	
Purulent patients: Non-surgical		*Model value*		
Discharge (4 day)	12%	33%	12%	Data from administrative databases
Discharge (8 day)	57%	67%	57%	

* in the table are shown the percentage of discharge at each decision point of the analytic model that has been used to describe patients' pathway. Each pathway (except for purulent surgical not eligible for ED) includes the following states: discharge on day 4, observation up to day 8, discharge on day 9, or observation up to the clinical evaluation. Full distribution is shown in appendix B in table 2.

Cost inputs to the model

The inputs used to inform the model were based on a literature review and expert clinical opinion [23]. The following cost assumptions were used to inform the model based on a consensus of expert opinion.

- **Hospitalization cost**: Consistent with the perspective of the study, the hospitalization costs were determined exclusively based on National Diagnosis-Related Group (DRG) tariffs. Consequently, from the perspective of the payer, the patient's length of stay (LoS) at a hospital is irrelevant to the cost of hospitalization. However, a length of stay >8 days implies additional risks to the patient, which could bear incremental costs to the payer as follows:
    - **Additional risks**: The model assumes that if a patient is not discharged by day 8, an increased possibility of adverse events is associated with the length of hospital stay.
    - **Incremental costs:** The incremental costs were estimated as the difference between the direct costs associated with a patient LoS <9 days and the cost incurred by patients with a LoS ≥9 days.
- A systematic review of the existent literature was performed to identify the direct costs associated with each state of the model. Table 2 shows the inputs used to inform the cost estimate of each intervention. Consistent to Summary of Product Characteristics (SmPC) of each medicament included in the analysis and clinical practice, all the costs relative to treatments' adverse events were considered not sensitive, with the only exception of the renal adverse event concomitant to vancomycin administration that requires a medical treatment in addition of therapy's withdrawal. The inputs used to evaluate the additional costs incurred with vancomycin are summarized in Appendix B.

Table 2 – Costs inputs for each country included in the analysis

Drug therapy	*ITALY*	*ROMANIA*	*SPAIN*	References *Italy*	*Romania*	*Spain*
Dalbavancin (1+1 dose)	€ 773	€ 670*	€ 844	[24]	[25]	[26]
Dalbavancin (3 doses)	€ 387	€ 335*	€ 422			
Vancomycin (daily cost of administration)	€ 19	€ 23	€ 14			
Teicoplanin (daily cost of administration)	€ 45	€ 24	€ 22			
Linezolid (daily cost of administration)	€ 76	€ 50	€ 72			
% who received vancomycin	35%	59%	*54%*	Expert opinion	Expert opinion	Expert opinion
% who received teicoplanin	35%	11%	*7%*			
% who received linezolid	30%	30%	*39%*			
Gram-positive therapy (daily administration)	€ 45	€ 31	€ 37	[24]	[25]	[26]
Piperacillin tazobactam	€ 23	€ 26	€ 5			
Oral therapy (Amoxicillin Clavulanate)	€ 5	€ 3	€ 3			
Hospitalization						
Incremental cost due to an average length of hospital stay >9 days (purulent)	€ 884	€ 310	€ 884	Data from administrative databases	Data from administrative databases	Assumed to be equal to Italy
Incremental cost due to an average length of hospital stay >9 days (non-purulent)	€ 870	€ 654	€ 870			
Diagnostic tests						
Swab	€ 8.80	€ 3	€ 7	[27]	Database from The National Institute for Infectious Diseases Prof. dr. Matei Bals	[28]
Ultrasound	€ 50	€ 6	€ 20			
CAT	€ 48	€ 40	€ 86			
MRI	€ 160	€ 156	€ 126			
Specialist service						
Examination	€ 21	€ 5	€ 37	[27]	Database from The National Institute for Infectious Diseases Prof. dr. Matei Bals	[28]
Placement of PICC and other related costs						
Placement of peripherally inserted central catheter (PICC)	€ 383	€ 267	€ 495	[29]	Database from The National Institute for Infectious Diseases Prof. dr. Matei Bals	[28]
Thrombophlebitis	€ 306	€ 960	€ 498	[29]		[28]
Malposition	€ 236	€ 134	€ 248	[29]		[28]
Malfunction	€ 383	€ 267	€ 495	[29]		[28]
PICC-related infection	€ 1,263	€ 1,038	€ 945	Difference between DRG 277 (with CC) and DRG 278 (without CC)	Difference between DRG 277 (with CC) and DRG 278 (without CC)	Difference between DRG 277 (with CC) and DRG 278 (without CC)
PICC dressing patch costs	€ 6	€ 10	€ 7	Appendix B	Appendix B	Appendix B
Additional costs due to vancomycin						
EA dialysis	€ 6	€ 19	€ 13	Appendix B	Appendix B	Appendix B
EA nephrotoxicity	€ 1	€ 3	€ 4			
Monitoring	€ 50	€ 46	€ 185			
PICC Risk						
Risk of thrombophlebitis (daily)	0.8%	0.8%	0.8%	[30]	[30]	[30]
Risk of infection (daily)	0.2%	0.2%	0.2%			
Risk of malposition	9.3%	9.3%	9.3%			
Risk of malfunction (daily)	0.8%	0.8%	0.8%			

** Estimated cost*

Statistical analysis

The results are presented as the net difference between the direct costs incurred by the SoC treatment and those incurred by the dalbavancin treatment.

A probabilistic sensitivity analysis (PSA) and one-way deterministic sensitivity analysis (OSA) were performed to estimate the intrinsic variability in the inputs used to inform the model.

The probabilistic distribution used for the PSA was obtained by applying generally reported development of economic evaluation models and distinguishing between costs (gamma distribution) and epidemiological parameters (beta distribution) [31]; the details are provided in Appendix B.

In total, 5,000 Monte Carlo simulations were performed.

The uncertainty imposed by the inputs on the results of the analysis was estimated by performing a OSA. In this analysis, the inputs varied within an uncertainty range, and the impact on the final result was represented by a tornado graph.

In particular, the impact of the variation in the following parameters was analysed:

1. Efficiency of dalbavancin (-10% to +10%) - representing the efficacy on early discharging compared to the SoC;
2. Frequency of adverse events (-10% to +10%);
3. Additional hospitalization cost (-10% to +10%);
4. Administration cost (PICC) (-10% to +10%);

5. Daily cost in the hospital (€ 0-Max), where the maximum is equal to € 732 in the Italian NHS [32],€ 601 Spanish NHS [33] and € 100 in the Romanian NHS [25]; and
6. Length of stay (LoS) (-10% to +10%).

RESULTS

The model included approximately 50,000 patients admitted annually with a main diagnosis of ABSSSI in Italy, Romania and Spain. Figure 2 shows the number and stratification by state of the ABSSSI patients in each country. In Italy, 19,034 patients were included in the analysis as follows: 79.5% (15,131) of the patients were affected by severe ABSSSIs, 54% of the patients had a diagnosis of non-purulent ABSSSIs and 46% of the patients had a diagnosis of purulent ABSSSIs. The average age of the patients with non-purulent ABSSSIs was 63.8 years, and that of the purulent ABSSSI patients was 59.4 years. In Romania, 30,997 patients were included, and 70.3% (21,793) of these patients were severe (61.2% had a diagnosis of non-purulent ABSSSIs, and 38.8% had a diagnosis of purulent ABSSSIs). The Romanian patients were on average 10 years younger than the Italian patients (average age of 56.0 years among the non-purulent patients and 47.5 among the purulent patients). In the Spanish cohort, determining the accurate stratification by severity, infection type and characteristics of the patients was impossible. This issue was resolved by applying the Italian stratification of the ABSSSI patients to the Spanish population as described in the “Methods” section. In total, 17,997 ABSSSI patients were estimated, and 78% (14,027) of the patients were considered to have severe infections (54% with a diagnosis of non-purulent ABSSSI and 46% with a diagnosis of purulent ABSSSI).

Table 3 - PSA results: length of stay (LoS) per patient

Italy			
LoS	**SoC**	**dalbavancin**	**Difference**
Non Purulent *(Min-Max)*	11,4 *(10,89 - 11,85)*	7,8 *(7,41 - 8,29)*	-3,5 *(-4,11 - -2,93)*
Purulent *(Min-Max)*	11,7 *(11,25 - 12,21)*	6,8 *(6,42 - 7,26)*	-4,9 *(-5,46 - -4,33)*
Total ***(Min-Max)***	**11,5** ***(11,19 - 11,87)***	**7,4** ***(7,07 - 7,69)***	**-4,15** ***(-4,57 - -3,74)***
Romania			
LoS	**SoC**	**dalbavancin**	**Difference**
Non Purulent *(Min-Max)*	10,4 *(10,03 - 10,67)*	6,6 *(6,27 - 6,84)*	-3,8 *(-4,17 - -3,41)*
Purulent *(Min-Max)*	9,8 *(9,44 - 10,07)*	9,3 *(8,95 - 9,61)*	-0,5 *(-0,68 - -0,27)*
Total ***(Min-Max)***	**10,1** ***(9,89 - 10,35)***	**7,6** ***(7,37 - 7,86)***	**-2,50** ***(-2,78 - -2,23)***
Spain			
LoS	**SoC**	**dalbavancin**	**Difference**
Non Purulent *(Min-Max)*	11,4 *(10,91 - 11,82)*	7,1 *(6,7 - 7,54)*	-4,3 *(-4,81 - -3,69)*
Purulent *(Min-Max)*	12,1 *(11,69 - 12,61)*	9,7 *(9,33 - 10,1)*	-2,4 *(-2,78 - -2,08)*
Total ***(Min-Max)***	**11,7** ***(11,4 - 12,05)***	**8,3** ***(8 - 8,62)***	**-3,4** ***(-3,76 - -3,06)***

On average, the dalbavancin treatment reduced the in-hospital length of stay by 4.15 days (95% CI: -4.57 to -3.74 days) per Italian ABSSSI patient, 2.5 days (95% CI: -2.78 to -2.23 days) per Romanian patient and 3.4 days (95% CI: -3.76 to -3.06) per Spanish patient (Table 3).

Table 4 - PSA results: annual costs (95% CI: Min-Max)

Cost Items	**Nonpurulent ABSSSI patients (€ milions)**								
	SoC			**dalbavancin**			**Difference dalbavancin - SoC**		
	Italy	**Romania**	**Spain**	**Italy**	**Romania**	**Spain**	**Italy**	**Romania**	**Spain**
Drugs	€ 5,37	€ 5,77	€ 2,88	€ 10,82	€ 13,50	€ 9,28	€ 5,45	€ 7,73	€ 6,41
(Min-Max)	*(€4.77-€6.01)*	*(€5.24-€6.33)*	*(€2.48-€3.3)*	*(€9.7-€12)*	*(€12.28-€14.79)*	*(€8.27-€10.35)*	*(€4.53 to €6.36)*	*(€6.64 to €8.82)*	*(€5.48 to €7.33)*
Specialist service	€ 5,31	€ 7,11	€ 6,11	€ 2,59	€ 3,25	€ 2,49	-€ 2,71	-€ 3,85	-€ 3,62
(Min-Max)	*(€4.6-€6.06)*	*(€6.46-€7.79)*	*(€5.39-€6.87)*	*(€2.07-€3.17)*	*(€2.87-€3.67)*	*(€2.05-€2.97)*	*(-€2.79 to -€2.13)*	*(-€1.05 to -€0.73)*	*(-€2.72 to -€2.01)*
Hospitalization	€ 2,64	€ 3,72	€ 2,35	€ 1,14	€ 0,90	€ 0,80	-€ 1,50	-€ 2,82	-€ 1,55
(Min-Max)	*(€2.17-€3.16)*	*(€3.23-€4.24)*	*(€1.94-€2.8)*	*(€0.88-€1.44)*	*(€0.72-€1.11)*	*(€0.61-€1.02)*	*(-€1.96 to -€1.05)*	*(-€3.25 to -€2.39)*	*(-€1.94 to -€1.17)*
AE	€ 0,86	€ 1,74	€ 0,92	€ 0,15	€ 0,19	€ 0,14	-€ 0,70	-€ 1,54	-€ 0,79
(Min-Max)	*(€0.76-€0.95)*	*(€1.56-€1.91)*	*(€0.82-€1.03)*	*(€0.12-€0.18)*	*(€0.16-€0.23)*	*(€0.11-€0.16)*	*(-€0.79 to -€0.62)*	*(-€1.7 to -€1.39)*	*(-€0.88 to -€0.7)*
Total	**€ 14,18**	**€ 18,33**	**€ 12,26**	**€ 14,70**	**€ 17,85**	**€ 12,71**	**€ 0,52**	**-€ 0,48**	**€ 0,45**
(Min-Max)	***(€12.7-€15.73)***	***(€16.94-€19.79)***	***(€10.98-€13.62)***	***(€13.18-€16.3)***	***(€16.37-€19.39)***	***(€11.37-€14.12)***	***(-€0.55 to €1.6)***	***(-€1.61 to €0.65)***	***(-€0.51 to €1.4)***

Cost Items	**Purulent ABSSSI patients (€ milions)**								
	SoC			**dalbavancin**			**Difference dalbavancin - SoC**		
	Italy	**Romania**	**Spain**	**Italy**	**Romania**	**Spain**	**Italy**	**Romania**	**Spain**
Drugs	€ 3,42	€ 2,33	€ 2,78	€ 7,70	€ 4,54	€ 6,36	€ 4,28	€ 2,21	€ 3,58
(Min-Max)	*(€2.98-€3.89)*	*(€1.99-€2.69)*	*(€2.35-€3.25)*	*(€6.79-€8.67)*	*(€3.97-€5.15)*	*(€5.58-€7.19)*	*(€3.52 to €5.04)*	*(€1.81 to €2.62)*	*(€2.94 to €4.21)*
Specialist service	€ 4,54	€ 4,53	€ 5,22	€ 2,08	€ 3,64	€ 2,86	-€ 2,46	-€ 0,89	-€ 2,36
(Min-Max)	*(€3.91-€5.22)*	*(€4.01-€5.09)*	*(€4.55-€5.94)*	*(€1.64-€2.58)*	*(€3.2-€4.11)*	*(€2.39-€3.38)*	*(-€2.79 to -€2.13)*	*(-€1.05 to -€0.73)*	*(-€2.72 to -€2.01)*
Hospitalization	€ 2,64	€ 3,72	€ 2,35	€ 0,67	€ 0,64	€ 1,47	-€ 1,97	-€ 3,08	-€ 0,89
(Min-Max)	*(€2.17-€3.16)*	*(€3.23-€4.24)*	*(€1.94-€2.8)*	*(€0.52-€0.85)*	*(€0.52-€0.78)*	*(€1.22-€1.73)*	*(-€2.52 to -€1.42)*	*(-€3.63 to -€2.52)*	*(-€1.45 to -€0.33)*
AE	€ 0,86	€ 1,74	€ 0,92	€ 0,11	€ 0,74	€ 0,33	-€ 0,74	-€ 1,00	-€ 0,59
(Min-Max)	*(€0.76-€0.95)*	*(€1.56-€1.91)*	*(€0.82-€1.03)*	*(€0.09-€0.14)*	*(€0.63-€0.86)*	*(€0.27-€0.4)*	*(-€0.84 to -€0.64)*	*(-€1.21 to -€0.78)*	*(-€0.73 to -€0.46)*
Total	**€ 11,16**	**€ 8,60**	**€ 11,22**	**€ 10,58**	**€ 9,56**	**€ 11,02**	**-€ 0,58**	**€ 0,96**	**-€ 0,20**
(Min-Max)	***(€9.9-€12.49)***	***(€7.66-€9.6)***	***(€9.94-€12.58)***	***(€9.34-€11.89)***	***(€8.55-€10.63)***	***(€9.79-€12.32)***	***(-€1.39 to €0.22)***	***(€0.69 to €1.24)***	***(-€0.74 to €0.34)***

Cost Items	**Total ABSSSI patients (€ milions)**								
	SoC			**dalbavancin**			**Difference dalbavancin - SoC**		
	Italy	**Romania**	**Spain**	**Italy**	**Romania**	**Spain**	**Italy**	**Romania**	**Spain**
Drugs	€ 8,79	€ 8,10	€ 5,66	€ 18,52	€ 18,04	€ 15,64	€ 9,73	€ 9,95	€ 9,98
(Min-Max)	*(€8.14-€9.48)*	*(€7.51-€8.72)*	*(€5.03-€6.33)*	*(€17.28-€19.81)*	*(€16.84-€19.29)*	*(€14.54-€16.78)*	*(€8.35 to €11.11)*	*(€8.71 to €11.18)*	*(€8.77 to €11.2)*
Specialist service	€ 9,85	€ 11,64	€ 11,33	€ 4,67	€ 6,90	€ 5,35	-€ 5,17	-€ 4,74	-€ 5,98
(Min-Max)	*(€8.81-€10.95)*	*(€10.87-€12.43)*	*(€10.37-€12.34)*	*(€3.8-€5.64)*	*(€6.3-€7.52)*	*(€4.6-€6.17)*	*(-€5.67 to -€4.68)*	*(-€5.17 to -€4.32)*	*(-€6.52 to -€5.44)*
Hospitalization	€ 5,09	€ 4,45	€ 4,72	€ 1,81	€ 1,55	€ 2,27	-€ 3,27	-€ 2,91	-€ 2,45
(Min-Max)	*(€4.54-€5.67)*	*(€3.98-€4.96)*	*(€4.25-€5.21)*	*(€1.52-€2.13)*	*(€1.33-€1.77)*	*(€1.98-€2.57)*	*(-€3.82 to -€2.73)*	*(-€3.34 to -€2.48)*	*(-€2.86 to -€2.04)*
AE	€ 1,60	€ 2,74	€ 1,77	€ 0,27	€ 0,93	€ 0,47	-€ 1,34	-€ 1,81	-€ 1,30
(Min-Max)	*(€1.49-€1.72)*	*(€2.53-€2.96)*	*(€1.65-€1.9)*	*(€0.23-€0.3)*	*(€0.81-€1.05)*	*(€0.4-€0.54)*	*(-€1.44 to -€1.24)*	*(-€1.97 to -€1.65)*	*(-€1.41 to -€1.2)*
Total	**€ 25,33**	**€ 26,93**	**€ 23,48**	**€ 25,28**	**€ 27,42**	**€ 23,73**	**-€ 0,06**	**€ 0,48**	**€ 0,25**
(Min-Max)	***(€23.89-€26.82)***	***(€25.76-€28.13)***	***(€22.16-€24.84)***	***(€23.67-€26.94)***	***(€26.12-€28.74)***	***(€22.37-€25.12)***	***(-€1.73 to €1.61)***	***(-€0.87 to €1.83)***	***(-€1.15 to €1.64)***

The estimated budget impact of the new intervention (dalbavancin) by country and cost type (drug, hospitalization, specialist services and A&E) is reported in Table 4. From the Italian NHS perspective, a total expenditure of € 25.33 million (PSA 95% CI: € 23.89-26.82 million) was estimated and included in the analysis. The new intervention (dalbavancin) increased the drug cost by 37% compared to SoC. However, the incremental cost of the drug was completely offset by the decrease in resources required for the treatment (-38.5%), and the total impact was approximately neutral (-€ 0.06 million).

In the Romanian setting, a total expenditure of € 26.9 million (PSA 95% CI: € 22.93-28.13 million) was estimated for the treatment of all ABSSSI patients with SoC. Dalbavancin reduces the in-hospital length of stay by approximately 2.5 days (PSA 95% CI: -2.78 to -2.23 days) per patient (Table 4). The increase in the cost of the drugs (+37.1%) was partially compensated for by the decrease in the other costs (-35.1%). Compared to SoC, the total impact of the new intervention on the hospital budget was a negligible increase of 0.1% (€ 0.26 mill).

From the Spain NHS perspective, the model estimated a total expenditure of € 23.5 million (95% CI: € 22.16-24.84 million) for the treatment of all ABSSSI patients with SoC. Dalbavancin reduces the in-hospital length of stay by approximately 3.2 days (PSA 95% CI: -3.76 to -3.06 days) per patient (Table 4). The increase in the cost of the drugs (+42.3%) was partially compensated for by the decrease in the other costs (-41.4%). Compared to SoC, the total impact of the new intervention on the hospital budget was a negligible increase of 1% (€ 0.25 million).

The figure 3 shows the OWA results. In all three settings, the three most influential parameters were the assumptions considered for the daily cost of the hospital stay, the effectiveness estimated for dalbavancin and the cost of administration. If we consider the minimum cost in each country per hospitalization day (base-case analysis assuming the only DRG tariff is a unique cost parameter independent of the length of stay), dalbavancin could decrease

the total economic burden by several million euros in Italy, Romania and Spain. The efficacy of dalbavancin is the second most important parameter.

DISCUSSION

Considering the costs from a hospital perspective (i.e., meals, laundry services, etc.), according to the probabilistic analysis, dalbavancin could decrease the total economic burden with a significant difference.

The advantages of the dalbavancin administration scheme and currently reported tolerability data may be represented by the following:

- Reduction in hospital LoS, and
- Reduction in the following risks:
    - *Peripherally inserted central catheter (PICC)-related adverse events—not necessary in the dalbavancin administration scheme, and*
    - *Reported drug-related adverse events compared to vancomycin.*

The reduction in the length of stay reduces the exposure to additional risk, such as Hospital Acquired Infections (HAIs), although these infections were not considered in the present analysis.

In performing pharmacoeconomic evaluations, only the direct price of purchasing medications is customarily considered. However, to assess the total costs of intravenous (IV) drug therapy, other costs associated with preparation, administration and monitoring of IV antibiotic therapy must be evaluated. Gaining insight into all factors that contribute to the actual total overall costs of drug therapy may help increase awareness of the drivers of the costs of hospital services and identify opportunities for cost savings [34].

Hospital LoS is commonly considered by several authors the most important variable driving total healthcare costs in patients with different health conditions [35-37]; even if national healthcare providers usually pay hospitals through DRGs to standardize the financial contributions for the treatment of the same health conditions, over the threshold LoSs frequently occur due to adverse events, contributing to a further increase in the economic healthcare burden [38]. The

analysis presented in this manuscript predicted the possibility of an increased hospital LoS based on a statistical distribution of over a threshold analysis to enhance our understanding of how in-dwelling can affect total healthcare costs in a DRG-based system.

Intravenous drug infusion and catheter usage are important tools in in-hospital patient care but may be associated with serious catheter-related morbidity and discomfort. PICCs function as central catheters, allowing both drug infusion and blood sampling, and lessen the risk of central venous catheter insertion. Nevertheless, Periard and colleagues showed that even if PICCs are efficient and appreciated catheters in hospitalized patients, one-fifth of patients with PICC develop adverse events attributable to the inserted medical device, indicating that PICCs should not be used as the first-choice option in all hospitalized patients [39].

Vancomycin is active against Gram-positive bacteria, including MRSA, and is regularly used as an armamentarium for the treatment of ABSSSIs and other infectious diseases. The guidelines for vancomycin therapeutic monitoring by the IDSA suggest targeting vancomycin with concentrations of 10 mg/L to avoid the development of resistant strains and concentrations of 15-20 mg/L to improve tissue penetration, which increases the probability of achieving optimal target serum concentrations and improving clinical outcomes. Nephrotoxicity, which is usually reversible, is the most serious common adverse effect of vancomycin and is strictly linked to its plasma concentrations. While the average daily cost of vancomycin is relatively low, a comprehensive account of the cost of vancomycin use should include the direct costs associated with measuring the serum concentrations and those associated with the treatment of adverse reactions, such as nephrotoxicity [40]. Dalbavancin has a better potential tolerability profile than other therapies for ABSSSIs, and it has been recommended by a recently published meta-analysis [41].

Although not within the scope of the present analysis, cross-bacterial colonization can increase with prolonged LoS and is mainly caused by MRSA. Clinicians should consider colonization

in assessments of discharging patients from the hospital, particularly if the clinical conditions are improved and stable [42, 43].

Common to most economic models, this study has various limitations, and we attempted to control these limitations. First, the model was constructed by combining data obtained from multiple randomized clinical trials involving homogeneous populations, but heterogeneous populations existed among the studies considered. To date, the lack of sufficient information for performing an adequate meta-analysis and the inability to appropriately compare the data prevent achieving better estimates. However, all clinical information and modelling assumptions were validated and discussed with key opinion leaders, who identified adequate uncertainty parameters that were used to perform the deterministic sensitivity analysis.

Second, consulting with a panel of experts was the only way to identify the advantages associated with the dalbavancin treatment of patients suffering from ABSSSIs. However, for explanatory purposes, the constant rate of increases and decreases in the cost of items is based on scenarios designated by the panel of clinical experts.

Moreover, in Italy and Spain, the tariffs can vary among the regions due to the delocalization of the NHS, but costs from only 1 region perspective were used, further limiting the analysis. Moreover, in Romania, hospitals purchase most antibiotic therapies directly from wholesalers, and the purchase price of dalbavancin used in the analysis was estimated.

Additionally, assessment period for each country are not perfectly comparable due to the different data availability and the transition probabilities in Spain were assumed to be the same as those applied to Italy. However, all these limitations were considered in the deterministic and probabilistic SA.

Finally, in the model, the cost of a 4-day LoS hospitalization was assumed to be the same as the cost of an 8-day LoS hospitalization. This assumption is a methodological limitation that has

negligible impact on the final estimates since it represents a cost item that is constant in both considered scenarios.

The results of this analytic model are consistent with other published studies comparing SoC treatment for ABSSSIs with newer therapies, different therapeutic administration settings, such as outpatient parenteral antimicrobial therapy (OPAT), or avoiding PICC lines for treatment infusion. In a recent article, Browne, Muszbek [44] estimated the cost consequences of using daptomycin compared with those of using vancomycin as the first-line treatment in patients with proven MRSA-induced bacteraemia-infective endocarditis. Daptomycin required fewer therapeutic switches and a shorter length of stay. When the length of stay was reduced from 42 days to 28 days, daptomycin saved £ 4037 per person compared with vancomycin. Stephens, Gao [45] compared the cost of oral linezolid therapy with the cost of vancomycin or daptomycin regimens and concluded that using linezolid has a potential economic benefit over traditional OPAT considering the total inpatient and outpatient medical costs. PICCs are commonly used to administer antibiotics or other medications, particularly in patients requiring hospital in-dwelling; in a study evaluating the cost offsets of treating Gram-positive ABSSSIs with varied hospital LoSs, a sensitivity analysis comparing the inpatient and outpatient cost breakdown revealed that a key outpatient cost driver was the PICC cost, with an average per patient cost of $873 for placement and $205 for complications [46].

CONCLUSION

This economic analysis suggests that the use of dalbavancin could generate a significant reduction in the length of stay with no statistically significant incremental costs from a National healthcare provider perspective. The validity of this conclusion should better be tested in a “real-life” setting, though, it has been further strengthen by the convergence of the results reported

from all three European Countries with different discharge probabilities, cost inputs and budget constraints. In conclusion, the use of dalbavancin would allow an early discharge approach in ABSSSI management, providing the option to significantly reduce patients' exposure to additional risks associated with prolonged hospitalisation at no incremental cost for the National healthcare providers. This model could represent a useful tool for clinicians and policy makers to inform their decision about optimal treatment pattern of ABSSSIs in the hospital setting.

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Ethics approval

Institutional ethics committee approval and informed consent were not required.

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FIGURE LEGENDS

Fig. 1 Decision tree model structure

Fig. 2 Average annual admissions due to severity and presence of purulence in Italy (2006-2010), Romania (2010-2013), and Spain (2006-2015)

* Assumed to have the same distribution as the Italian data

Fig. 3 DSA: tornado diagram (total burden)