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ORIGINAL RESEARCH

Estimating the Clinical and Economic Impact of Introducing a New Antibacterial into Greek Clinical Practice for the Management of Hospital-Acquired Infections with Limited Treatment Options

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ABSTRACT

Introduction: Hospital-acquired infections (HAIs) and growing antimicrobial resistance (AMR) represent a significant healthcare burden globally. Especially in Greece, HAIs with limited treatment options (LTO) pose a serious threat due to increased morbidity and mortality. This study aimed to estimate the clinical and economic value of introducing a new antibacterial for HAIs with LTO in Greece.

Methods: A previously published and validated dynamic model of AMR was adapted to the Greek setting. The model estimated the clinical and economic outcomes of introducing a new antibacterial for the treatment of HAIs with LTO in Greece. The current treatment pathway was compared with introducing a new antibacterial to the treatment sequence. Outcomes were assessed from a third-party payer perspective, over a 10-year transmission period, with quality-adjusted life years (QALYs) and life years (LYs) gained considered over a lifetime horizon.
Results: Over the next 10 years, HAIs with LTO in Greece account for approximately 1.4 million hospital bed days, hospitalisation costs of more

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than €320 million and a loss of approximately 403,000 LYs (319,000 QALYs). Introduction of the new antibacterial as first-line treatment provided the largest clinical and economic benefit, with savings of up to 93,000 bed days, approximately €21 million in hospitalisation costs and an additional 286,000 LYs (226,000 QALYs) in comparison to the current treatment strategy. The introduction of a new antibacterial was linked to a monetary benefit of €6.8 billion at a willingness to pay threshold of €30,000 over 10 years.

Conclusion: This study highlights the considerable clinical and economic benefit of introducing a new antibacterial for HAIs with LTO in Greece. This analysis shows the additional benefit when a new antibacterial is introduced to treatment sequences. These findings can be used to inform decision makers to implement policies to ensure timely access to new antibacterial treatments in Greece.

PLAIN LANGUAGE SUMMARY

Antimicrobial resistance is a major issue for the Greek healthcare system. The overuse of antibacterial agents contributes to the growing resistance levels, making currently available treatment options less effective. As a result, there is an imperative need to address antimicrobial resistance in Greece. This study developed a mathematical model to investigate the clinical and economic benefits of introducing a new antibacterial to current treatment practice. The model uses regression equations to describe the relationships between inputs and outputs from a published and validated model, which describes the transmission and treatment of infections. The model is used to estimate the impact of a new treatment in Greece, considering differing treatment sequence scenarios. The largest health and financial benefits were seen when a new antibacterial was introduced at first line prior to currently used treatments. Over 10 years, savings of up to 93,000 hospital bed days and €21 million in hospitalisation costs could be achieved, as well as a gain of 286,000 patient life years and 226,000 patient quality-adjusted life years (QALYs), a measure of a patient's quality and length of life, over their remaining lifetime. The introduction of a new antibacterial into the current treatment pathway resulted in an overall monetary benefit of €6.8 billion over 10 years, when additional QALYs are valued at €30,000. This study demonstrates considerable health economic benefits of introducing a new antibacterial in Greece and can help inform decision makers when developing a national action plan to combat resistance and improve access to treatments.

Keywords: Infectious diseases; Antimicrobial resistance; Hospital-acquired infections; Gram-negative bacteria; Economic evaluation

Key Summary Points

Why carry out the study?

Increasing antimicrobial resistance (AMR) in hospital-acquired infections (HAIs) with limited treatment options (LTO) represents an important challenge for the healthcare system in Greece; rates of HAIs are 50% higher in Greece, with a significantly higher burden of multidrug-resistant infections than the rest of Europe.

To combat HAIs with LTO there is a need to both preserve the effectiveness of current treatments by decreasing AMR emergence and spread, and to improve access to new effective treatments.

This study aimed to assess the current burden of HAIs with LTO and to estimate the clinical and economic value of introducing a new antibacterial agent in Greece.

What was learned from the study?

The analysis showed that introduction of a new antibacterial agent in the management of HAIs with LTO in Greece could generate considerable clinical and economic benefits, representing a monetary benefit to healthcare providers of up to €6.8 billion, over 10 years; the greatest benefits were recognised when the new antibacterial agent was introduced to the treatment sequence as the first line.

This analysis can support decision makers on implementing an effective AMR national action plan to alleviate AMR burden and encourage access to new treatments in Greece.

INTRODUCTION

Hospital-acquired infections (HAIs) are a major public health concern, representing a threat to patient safety and a substantial economic burden globally [1]. Patients with HAIs have an 80% increased 90-day risk of death after admission to the hospital compared to those without (HR 1.8%; 95% CI 1.3–2.6) [2]. Greece is amongst the European countries worst affected by HAIs [2–9]. According to a study from the European Center for Disease Prevention and Control (ECDC) in which 33 European countries participated, it was estimated that the rate of HAIs in public hospitals in Greece is 50% higher than the European average (9.1% vs 6%) [2, 3, 5, 10]. Further compounding this issue, Greece, alongside Italy, has a significantly higher burden of infections caused by multidrug-resistant (MDR) bacteria than the rest of Europe. In Greece, a high proportion of this infection burden is caused by gram-negative pathogens resistant to carbapenems or colistin [5].

In Greece, gram-negative MDR pathogens present a major threat for both clinical medicine and public health by causing infections for which few effective antimicrobials are available [2–15]. In addition, the SARS-CoV-2 pandemic has further complicated the epidemiological situation, as it is associated with increased morbidity and mortality of patients with COVID-19 due to secondary bacterial infections [15].

Some of the most frequently isolated pathogens in hospitals in Greece, with particularly high rates of resistance, are *Klebsiella* spp., *E. coli*, *Acinetobacter* and *Pseudomonas aeruginosa* [8]. Resistance developed amongst these pathogens against established antibiotics (cephalosporins, carbapenems, colistin, tigecycline, fosfomycin, aminoglycosides) is highly concerning to the medical community. Especially against carbapenems, which are considered the last treatment option for many infections, the resistance of these pathogens (*with the exception of E. coli*) in Greece in 2020 ranged between 36% and 95% [16]. Meanwhile, the limited available treatment options are associated with increased adverse effects, off-label administration and use as salvage therapies that have limited effectiveness and increased treatment costs [6–9, 11–15, 17, 18]. Thus, these pathogens are considered by the World Health Organization (WHO) as the most dangerous resistant bacteria and are ranked as top priority for research and development of new antimicrobials [19].

Therefore, a multilevel strategy is important to curb the entry and spread of these highly resistant bacteria in hospitals. This is outlined in the European Union (EU) Council Recommendation on patient safety, including the prevention and control of HAIs [20]. Furthermore, in order to tackle increasing AMR, the WHO published the Global Action Plan on Antimicrobial Resistance in 2015, calling for an integrated "one health" response, involving international organisations, with the aim of optimising the health of people, animals and the environment by coordinated actions [21]. The Global Action Plan called on supporting countries to implement national action plans to achieve the objectives of increased awareness, generating evidence, infection control, stewardship and developing an economic case for investment [21]. In 2017, the EU devised a European One Health Action Plan against AMR,

centred around the one health approach [1]. Its aim was to preserve the effectiveness of current treatments for infections in both humans and animals by decreasing AMR emergence and spread, and to increase new effective antimicrobial deployment and availability [1].

In that context, the Ministry of Health in Greece has developed a series of actions and policies that show advancements in the prioritisation of AMR and recognition by policy makers of the crucial nature of AMR reduction. The establishment of a stewardship group per hospital that monitors the implementation of prescribing guidelines and evaluates the consumption of antibiotics in comparison with the relevant AMR levels has been a critical step in the AMR battle [22]. Moreover, in 2020, the Ministry of Health created the Agency for Quality Assurance in Health S.A. (AQAH SA), which is responsible, among others, for the implementation of educational programmes on (nosocomial) infection prevention and control [23]. However, Greece is yet to fully implement a country-specific AMR national action plan that ensures a homogenous uptake of these measures [24]. Limited availability of local data makes it difficult to conduct robust estimations of the economic burden of HAIs and of AMR in general in Greece and may have contributed to the delays and the hesitancy in policy-making.

To provide valuable insights to decision makers on the benefits of addressing AMR and highlight the imperative need and value of new antibacterial agents, the present study sought to assess the current burden of HAIs with LTO and estimate the clinical and economic value of introducing a new antibacterial agent in Greece.

METHODS

Overview

On the basis of a previously published and validated dynamic model of AMR [25], we developed a simplified model that aims to demonstrate the value of a new antibacterial. Regression equations were used to describe the relationships between key inputs and outputs that characterise the transmission dynamics of HAIs, described in the original model, and allowed the estimation of outcomes, in the Greek setting, whilst reducing the complexity and data requirements of the analysis [25]. The regression equations were derived by running over 1 million simulations of the original dynamic transmission model [25], including varying key model inputs (population, baseline resistance, treatment strategy, treatment duration and treatment efficacy) to generate a data set of input–output relationships. Outputs captured included time on treatment and mortality. Input values used to run the simulations in the original model to generate the regression equations are provided in Supplementary Table 1. In the current model, inputs were sourced from the literature and were validated from two local infectious diseases experts to ensure that they fully reflect the current clinical Greek practice (Tables 3 and 4). These local inputs were used in the regression equations to estimate the clinical and economic impact of introducing a new antibacterial as compared to the current treatment strategy in Greece. The underlying transmission dynamics and prevalence of infection in the original model were calibrated to UK data and were assumed to be applicable to Greece for the generation of regression equations. The model considered outcomes associated with treating HAIs with LTO, responsible for a considerable burden in Greece; the HAIs with LTO and responsible pathogens considered in the model are summarised in Table 1. Since it is less likely for a new treatment to be effective against all pathogens, the analysis followed a more realistic and moderate approach and, therefore, excludes infections caused by *Acinetobacter* from the model.

Model Structure

Infected patients are assigned to either current treatment pathway or to an alternative treatment pathway which includes the introduction of a new antibacterial. The current treatment pathway includes meropenem as the first-line treatment and colistin as the second-line treatment; this was assumed to be a best

Table 1 Hospital-acquired infections and antibiotic resistance-causing pathogens included in the analysis

Hospital-acquired infections (HAI)	Antibiotic-resistance causing pathogens
Complicated urinary tract infections (cUTIs)	*E. coli*
Complicated intra-abdominal infections (cIAIs)	*Klebsiella* spp.
Hospital-acquired pneumonia including ventilator-associated pneumonia (HAP/VAP)	*P. aeruginosa*
Other HAI: bloodstream infections, digestive tract infections, skin and soft tissue infections and other less frequent infections	

representation of current clinical practice in Greece when considering a simplified two-line treatment strategy and was informed by local expert clinical opinion.

Patients receiving first-line treatment are either cured (via successful treatment or natural resolution of the infection), remain infected or die. If treatment fails to resolve the infection, patients move to the next line of treatment (Fig. 1). It was assumed that patients who have exhausted all available treatment lines without achieving a successful resolution of the infection die from infection 3 days after receiving their last treatment. The model accounts for the development of resistance to all modelled treatments over time as a consequence of increased treatment exposure. Changes to resistance rates are captured implicitly within the regression equations based on the dynamic AMR model.

As a result of differences in treatment characteristics (efficacy and resistance levels), treatment sequence may impact patients' clinical course and population-level AMR levels. Thus, we explored three alternative strategies, where the new antibacterial's use is varied, i.e. it is introduced either as a third-, second- or first-line treatment (Table 2). Additionally, the impact of treatment diversification was also explored to demonstrate the impact of stewardship practices, yielding in total six alternative treatment scenarios. In treatment diversification, the patient population was split evenly between all three treatments, as their first-line treatment (i.e. 33% patients received meropenem, 33% received colistin and 33% received the new antibacterial as their first-line treatment). Following unsuccessful treatment patients move to the next available treatment in the defined treatment sequence, regardless of

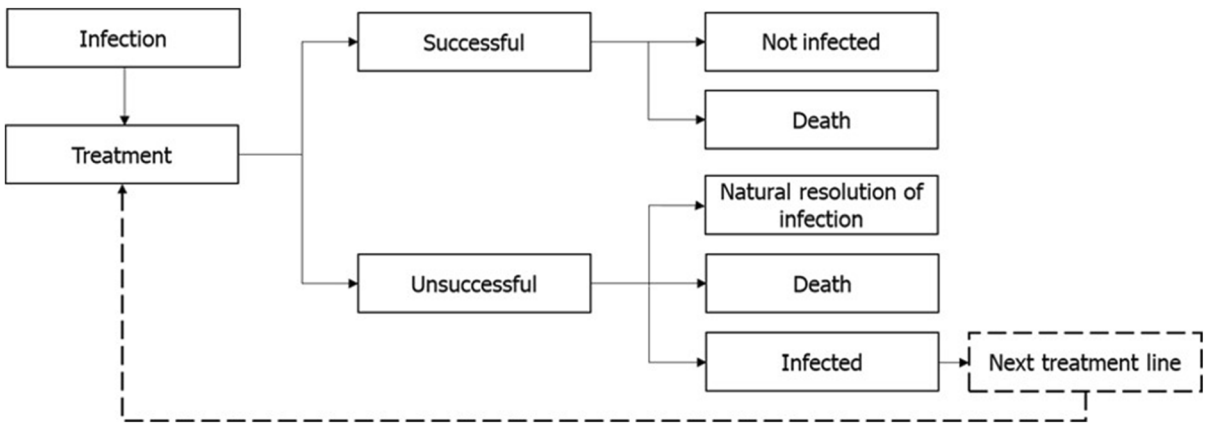

Fig. 1 Deterministic treatment pathway. Source: Gordon et al. (2020) [25]

Table 2 Value of new antibacterial model—modelled treatment strategies

Strategy	Treatment pathway
Current	No diversification
	Meropenem → *Colistin*
New antibacterial in third line	
Alternative 1	No diversification *Meropenem* → *Colistin* → *New antibacterial*
Alternative 2	Diversification
	33% of patients receive: *Meropenem* → *Colistin* → *New antibacterial*
	33% of patients receive *Colistin* → *Meropenem* → *New antibacterial*
	33% of patients receive *New antibacterial* → *Meropenem* → *Colistin*
New antibacterial in second line	
Alternative 3	No diversification *Meropenem* → *New antibacterial* → *Colistin*
Alternative 4	Diversification
	33% of patients receive: *Meropenem* → *New antibacterial* → *Colistin*
	33% of patients receive: *New antibacterial* → *Meropenem* → *Colistin*
	33% of patients receive: *Colistin* → *Meropenem* → *New antibacterial*
New antibacterial in first line	
Alternative 5	No diversification
	New antibacterial → *Meropenem* → *Colistin*
Alternative 6	Diversification
	33% of patients receive: *New antibacterial* → *Meropenem* → *Colistin*
	33% of patients receive: *Meropenem* → *New antibacterial* → *Colistin*
	33% of patients receive: *Colistin* → *New antibacterial* → *Meropenem*

which treatment they started with, until all available treatments are exhausted.

Model Inputs

The incidence rates of HAIs with LTO due to antibiotic-resistant bacteria in Greece were extracted from Cassini et al. 2019 [5] (calculation was based on EARS-Net data collected during 2015). Overall, the number of annual HAIs with LTO due to *E. coli*, *Klebsiella* spp. and *P. aeruginosa* in Greece was estimated to be 11,292. The number and relative proportion of infections according to causing pathogen are shown in Table 3. Pathogen-specific resistance levels for each treatment were informed by WHONET data [26], published literature [14, 15] and expert opinion (Table 3). It was assumed that the new antibacterial would have a resistance level of 0%. Additional key model inputs are described in Table 4. Indication-specific inputs and inputs weighted by indication are presented in Supplementary Table 2.

Table 3 Annual number of LTO infections and AMR levels for meropenem and colistin in Greece

	Pathogen			Total
	E. coli	*Klebsiella* spp.	*P. aeruginosa*	
Infections (*n*)[a]	3066	4772	3454	11,292
Infections (%)[b]	27.15%	42.26%	30.59%	100.00%
Baseline resistance				
Meropenem[c]	3.00%	75.00%	46.00%	NA
Colistin[c]	2.00%	40.00%	3.700%	NA
New antimicrobial	0.00%	0.00%	0.00%	NA

[a]This included antibiotic-resistant bacteria of colistin-resistant, carbapenem-resistant or third-generation cephalosporin-resistant *Escherichia coli*; colistin-resistant, carbapenem-resistant or third-generation cephalosporin-resistant *Klebsiella pneumoniae*; colistin-resistant, carbapenem-resistant or multidrug-resistant *Pseudomonas aeruginosa*
[b]Cassini et al.[5]
[c]WHONET [26], published literature [14, 15] and expert opinion

Analysis

A 10-year time horizon was utilised, to capture the value provided by a new antibacterial over time but to limit the uncertainty associated with modelling over long time horizons [25]. The model estimates clinical and economic outcomes (hospital length of stay [LOS], total days on treatment [TDT], quality-adjusted life years [QALYs] and life years [LY], hospitalisation costs and monetary benefit [MB]). For the purpose of this analysis, TDT is defined as the total number of days patients are on treatment. QALYs and LYs were considered over the lifetime of the patient, based on the number of infections modelled over the 10-year time horizon. Therefore, a lifetime horizon considers the number of infections over the next 10 years. A lifetime is based on the life expectancy of a successfully treated member of the general population in Greece (20.12 years). Outcomes were considered from the perspective of a third-party payer in Greece.

Monetary benefit was estimated according to the following equation:

$$\begin{aligned}&\text{Monetary Benefit}\\&= (\text{QALY gain} \times \text{willingness} - \text{to} - \text{pay threshold})\\&+ \text{hospitalisation costs saved}\end{aligned}$$

In Greece, no standard willingness-to-pay (WTP) threshold or discount rate is applied; therefore, a WTP threshold of €30,000 per QALY gained and a 3.5% discount rate were utilised to align with health technology assessment guidance in Europe and with WHO recommendation [30, 31].

Sensitivity Analyses

One-way sensitivity analyses were performed to assess the impact of uncertainty around key model input parameters. Key model inputs, outlined in Table 4, were varied by ± 20%. An additional scenario excluded the 3.5% discount rate for costs and benefits, in this scenario the discount rate was set at 0%. The impact was assessed on model estimates of hospitalisation costs and QALYs gained, of introducing the new antibacterial as a first-line treatment and diversifying all treatment lines equally between patients.

Table 4 Key model inputs

Model input	Description	Value	Source
Life expectancy post treatment success	Life expectancy of a successfully treated patient	20.12 years[a]	Hellenic statistical authority [27, 28]
Treatment duration with a successful treatment	Length of stay (per therapy line) of a patient when a line of treatment is successful (days)	10 days	Expert opinion
Treatment duration with an unsuccessful treatment	Length of stay (per therapy line) of a patient when a line of treatment is unsuccessful (days)	5 days	Expert opinion
Length of stay accounting for mortality	Additional length of stay associated with patients who die in hospital (days)	4 days	Expert opinion
Utility (resolution of infection)	Health state utility for patients whose infection has been resolved	0.79	Szende et al. [29]
Utility (infected)	Health state utility of an infected patient	0.62[b]	See Supplementary Table 3
Daily hospitalisation cost	Cost associated with each day a patient spends in the general ward	€267.25	See Supplementary Table 3
Treatment efficacy of meropenem (when no resistance)	Probability of treatment success in patients with no resistance to treatment	85.00%	Expert opinion
Treatment efficacy of colistin (when no resistance)		90.00%	Expert opinion
Treatment efficacy of the new antibacterial (when no resistance)		92.00%	Expert opinion

[a]Based on an average 65-year-old in Greece, assumed to be the average age of the infected population as validated by expert opinion

[b]Value weighted on the basis of infection distribution and associated input value across appropriate indication and pathogen

Ethics Approval

Ethics approval was not required for this study; the analysis in this article is based on previously publicly available data and does not involve any new studies of human or animal subjects performed by any of the authors.

RESULTS

Absolute health economic outcomes are estimated over the 10-year time horizon. These are based on treating the modelled HAIs using the current treatment strategy in Greece, and in the alternative scenarios, treatment with a new antibacterial. These are presented in Fig. 2 and Table 5. The burden of treating the infected population with the current treatment strategy was estimated at 1.4 million hospital bed days resulting in an expenditure of €320.4 million in hospitalisation costs, as well as substantial LYs and QALYs lost (403,489 and 318,873, respectively; Table 5).

Over a 10-year time horizon, introducing a new antibacterial resulted in substantial savings, reducing both bed days, and hospitalisation costs. The introduction of a new antibacterial also yielded considerable LYs and QALYs gains (Fig. 2 and Table 5). The

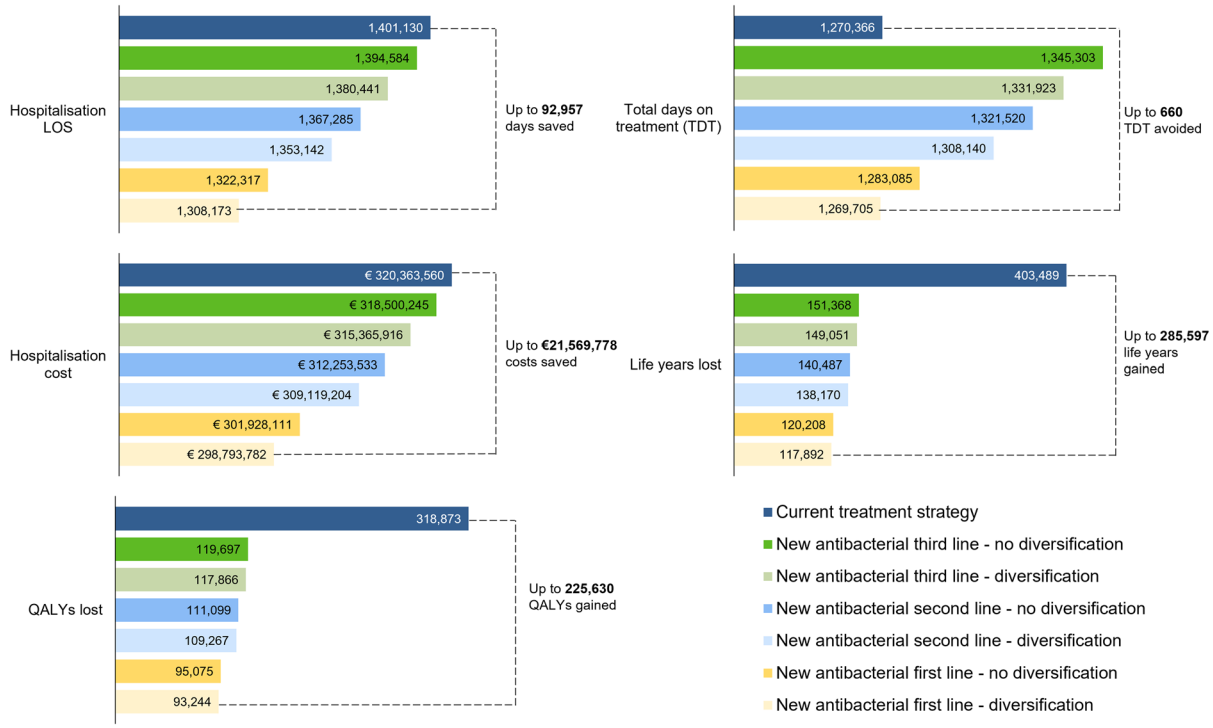

Fig. 2 Absolute outcomes based on current and alternative treatment strategies, over 10 years, for the treatment of infections with LTO caused by *E. coli*, *Klebsiella* spp. and *P. aeruginosa* pathogens. *LOS* length of stay, *QALYs* quality-adjusted life years, *TDT* total days on treatment

introduction of a new antibacterial as a first-line treatment with diversification was associated with the greatest economic and clinical benefit. Compared to the current treatment strategy, this alternative strategy was associated with 92,957 bed day saved, hospitalisation cost savings of €21.6 million, 661 fewer TDT and 285,597 LYs gained (corresponding to 225,630 QALYs), over 10 years (Fig. 2).

Based on a WTP threshold of €30,000 per QALY gained, the monetary benefit associated with introducing a new antibacterial to the current treatment strategy was estimated to be up to €6.8 billion (when the antibacterial was introduced as a first-line treatment with diversification), over the 10-year time horizon (Fig. 3).

Whilst the overall health economic benefits of introducing a new antibacterial are apparent, when considering individual pathogens, we observed an increase in bed days and up to €1.8 million and €4.5 million in additional hospitalisation costs associated with *E. coli* and *P. aeruginosa* infections, respectively, as compared to the current treatment pathway. This is due to the relatively low baseline resistance levels of these pathogens and the dynamics of resistance gain. Nevertheless, the use of the new antibacterial for the treatment of *E. coli* and *P. aeruginosa* infections was still associated with substantial LY and QALY gains, regardless of the position of the new antibacterial treatment in the treatment pathway. In addition, the savings obtained when introducing a new antibacterial treatment for *Klebsiella* spp. infections largely offset hospitalisation costs accrued for the treatment of *E. coli* and *P. aeruginosa* infections, resulting in net overall savings (Table 5). Importantly, across all pathogens, introducing a new antibacterial resulted in gains in LYs and QALYs. In *Klebsiella* spp. infections, over 230,000 and 180,000 additional LYs and QALYs, respectively, over a lifetime (Table 5). The key driver of monetary benefit was the increase in QALY gains in all pathogens considered.

Table 5 Pathogen-specific outcomes

Pathogen	Current treatment strategy	Alternative treatment strategies					
		New antibacterial third line		New antibacterial second line		New antibacterial first line	
		No diversification (Alternative 1)	Diversification (Alternative 2)	No diversification (Alternative 3)	Diversification (Alternative 4)	No diversification (Alternative 5)	Diversification (Alternative 6)
Hospitalisation LOS							
E. coli	336,738	345,077 (− 8339 bed days saved)	341,021 (− 4283 bed days saved)	344,899 (− 8162 bed days saved)	340,843 (− 4105 bed days saved)	342,605 (− 5867 bed days saved)	338,549 (− 1811 bed days saved)
Klebsiella spp.	672,680	637,340 (35,340 bed days saved)	630,426 (42,254 bed days saved)	613,279 (59,400 bed days saved)	606,365 (66,314 bed days saved)	582,220 (90,459 bed days saved)	575,306 (97,373 bed days saved)
P. aeruginosa	391,713	412,168 (− 20,455 bed days saved)	408,994 (− 17,282 bed days saved)	409,107 (− 17,394 bed days saved)	405,933 (− 14,221 bed days saved)	397,492 (− 5779 bed days saved)	394,318 (− 2606 bed days saved)
Total	1,401,130	1,394,584 (6545 bed days saved)	1,380,441 (20,689 bed days saved)	1,367,285 (33,844 bed days saved)	1,353,142 (47,988 bed days saved)	1,322,317 (78,813 bed days saved)	1,308,173 (92,957 bed days saved)
Hospitalisation cost							
E. coli	€77,008,674	€78,817,424 (− €1,808,750 costs saved)	€77,918,481 (− €909,807 costs saved)	€78,778,192 (− €1,769,517 costs saved)	€77,879,249 (− €870,574 costs saved)	€78,252,124 (− €1,243,449 costs saved)	€77,353,181 (− €344,506 costs saved)
Klebsiella spp.	€153,662,094	€145,486,952 (€8,175,141 costs saved)	€143,964,798 (€9,697,296 costs saved)	€139,984,611 (€13,677,482 costs saved)	€138,462,457 (€15,199,637 costs saved)	€132,851,043 (€20,811,050 costs saved)	€131,328,889 (€22,333,205 costs saved)
P. aeruginosa	€89,692,792	€94,195,868 (− €4,503,076 costs saved)	€93,482,637 (− €3,789,845 costs saved)	€93,490,730 (− €3,797,938 costs saved)	€92,777,499 (− €3,084,707 costs saved)	€90,824,944 (− €1,132,151 costs saved)	€90,111,713 (− €418,920 costs saved)
Total	€320,363,560	€318,500,245 (€1,863,315 costs saved)	€315,365,916 (€4,997,644 costs saved)	€312,253,533 (€8,110,027 costs saved)	€309,119,204 (€11,244,356 costs saved)	€301,928,111 (€18,435,450 costs saved)	€298,793,782 (€21,569,778 costs saved)
Total days on treatment							
E. coli	327,943	339,533 (11,590 TDT gained)	335,781 (7839 TDT gained)	339,370 (11,427 TDT gained)	335,618 (7675 TDT gained)	337,374 (9431 TDT gained)	333,622 (5680 TDT gained)
Klebsiella spp.	571,991	604,553 (32,562 TDT gained)	597,976 (25,985 TDT gained)	583,564 (11,573 TDT gained)	576,987 (4996 TDT gained)	556,915 (− 15,076 TDT gained)	550,338 (− 21,654 TDT gained)

Table 5 continued

Pathogen	Current treatment strategy	Alternative treatment strategies					
		New antibacterial third line		New antibacterial second line		New antibacterial first line	
		No diversification (Alternative 1)	Diversification (Alternative 2)	No diversification (Alternative 3)	Diversification (Alternative 4)	No diversification (Alternative 5)	Diversification (Alternative 6)
P. aeruginosa	370,432	401,217 (30,785 TDT gained)	398,165 (27,734 TDT gained)	398,586 (28,154 TDT gained)	395,535 (25,103 TDT gained)	388,797 (18,365 TDT gained)	385,745 (15,314 TDT gained)
Total	1,270,366	1,345,303 (74,937 TDT gained)	1,331,923 (61,557 TDT gained)	1,321,520 (51,154 TDT gained)	1,308,140 (37,774 TDT gained)	1,283,085 (12,720 TDT gained)	1,269,705 (− 660 TDT gained)
LYs lost							
E. coli	26,954	17,034 (9920 LYs gained)	16,113 (10,841 LYs gained)	16,992 (9962 LYs gained)	16,071 (10,883 LYs gained)	16,065 (10,888 LYs gained)	15,144 (11,809 LYs gained)
Klebsiella spp.	310,264	100,363 (209,901 LYs gained)	99,344 (210,920 LYs gained)	90,862 (219,402 LYs gained)	89,843 (220,421 LYs gained)	77,188 (233,076 LYs gained)	76,169 (234,095 LYs gained)
P. aeruginosa	66,271	33,972 (32,300 LYs gained)	33,595 (32,676 LYs gained)	32,633 (33,638 LYs gained)	32,257 (34,015 LYs gained)	26,955 (39,316 LYs gained)	26,579 (39,693 LYs gained)
Total	403,489	151,368 (252,121 LYs gained)	149,051 (254,438 LYs gained)	140,487 (263,002 LYs gained)	138,170 (265,319 LYs gained)	120,208 (283,281 LYs gained)	117,892 (285,597 LYs gained)
QALYs lost							
E. coli	21,321	13,485 (7836 QALYs gained)	12,757 (8564 QALYs gained)	13,452 (7869 QALYs gained)	12,724 (8597 QALYs gained)	12,720 (8601 QALYs gained)	11,992 (9329 QALYs gained)
Klebsiella spp.	245,165	79,340 (165,825 QALYs gained)	78,534 (166,631 QALYs gained)	71,832 (173,332 QALYs gained)	71,027 (174,138 QALYs gained)	61,027 (184,138 QALYs gained)	60,221 (184,943 QALYs gained)
P. aeruginosa	52,387	26,872 (25,515 QALYs gained)	26,574 (25,813 QALYs gained)	25,814 (26,573 QALYs gained)	25,517 (26,871 QALYs gained)	21,328 (31,060 QALYs gained)	21,030 (31,357 QALYs gained)
Total	318,873	119,697 (199,176 QALYs gained)	117,866 (201,007 QALYs gained)	111,099 (207,775 QALYs gained)	109,267 (209,606 QALYs gained)	95,075 (223,798 QALYs gained)	93,244 (225,630 QALYs gained)
Monetary benefit (WTP = €30,000)							

Table 5 continued

Pathogen	Current treatment strategy	Alternative treatment strategies					
		New antibacterial third line		New antibacterial second line		New antibacterial first line	
		No diversification (Alternative 1)	Diversification (Alternative 2)	No diversification (Alternative 3)	Diversification (Alternative 4)	No diversification (Alternative 5)	Diversification (Alternative 6)
E. coli	NA	€233,271,729	€256,010,681	€234,306,965	€257,045,917	€256,791,837	€279,530,789
Klebsiella spp.		€4,982,922,672	€5,008,613,653	€5,213,652,078	€5,239,343,059	€5,544,941,960	€5,570,632,941
P. aeruginosa		€760,954,563	€770,597,028	€793,388,986	€803,031,451	€930,653,045	€940,295,510
Total		€5,977,148,964	€6,035,221,362	€6,241,348,029	€6,299,420,427	€6,732,386,842	€6,790,459,240

LOS length of stay, *LYs* life years, *QALYs* quality-adjusted life years, *TDT* total days on treatment, *WTP* willingness-to-pay

Sensitivity Analysis

Varying LOS, treatment efficacy and utility (resolution of infection) by ± 20%, and excluding discounting were shown to have the greatest impact on hospitalisation costs and QALYs, in all scenarios explored (Fig. 4). Treatment efficacy had the greatest influence on hospitalisation cost savings (from €11.2 million to €26.1 million). Excluding discounting impacted on QALYs estimates, resulting in QALY gains of 364,613.

DISCUSSION

The findings of the present analysis highlight the urgent need and the potential benefits of introducing new effective antibacterial agents to existing treatment pathways for HAIs, as a tool to counteract the continuously evolving AMR threat in Greece. Consistent with previous analyses [5, 32], this study confirms that HAIs with LTO are responsible for a significant clinical and economic burden to the Greek healthcare system. The addition of a new antibacterial for the treatment of HAIs with LTO would provide considerable benefit to healthcare providers in Greece when compared with currently available antibacterial treatment strategies.

With the rise of LTO infections [33], Greece is heading towards an era of pan-drug resistance [34]. Since the mid-1980s, no new classes of antimicrobial treatments have been approved for use [35]. The limited diversity of antimicrobial classes has resulted in increased exposure to treatments with shared mechanisms of action, increasing selection pressure and AMR levels in the population [19]. With an inadequate clinical pipeline and many pharmaceutical companies withdrawing investment [36, 37], push and pull incentives have been proposed, to reduce the economic risk, to incentivise research and development of new antibacterial agents [38]. Push incentives aim to reduce preclinical research costs while pull incentives are intended to reward pharmaceutical companies' efforts for antibiotic development, following the introduction of new antibacterial agents [38, 39]. Pull incentives include novel reimbursement

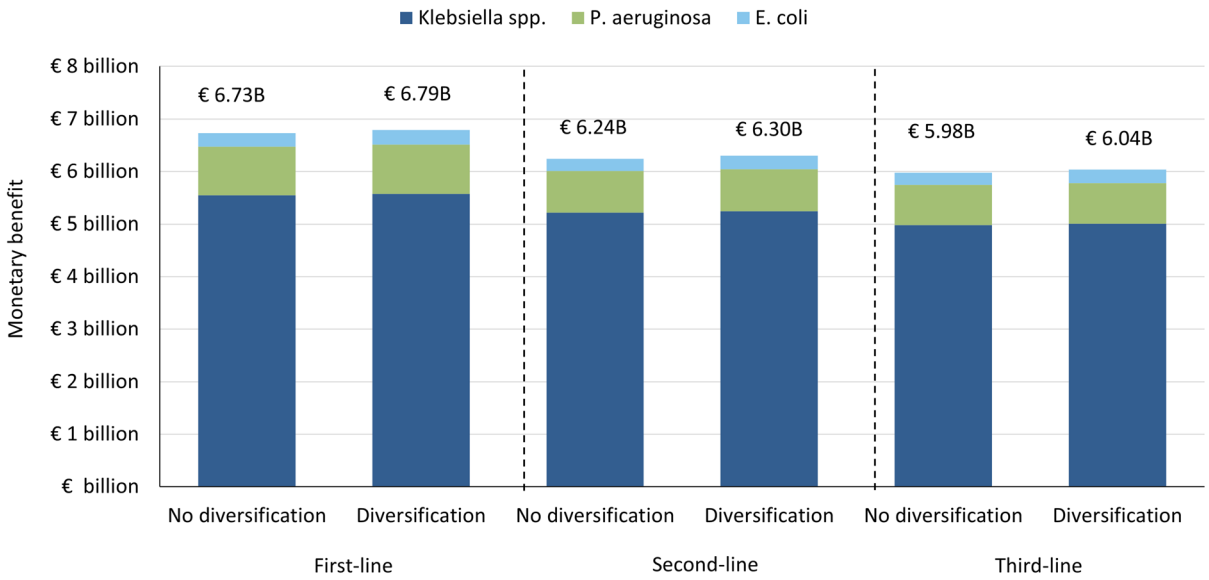

Fig. 3 Monetary benefit when introducing a new antibacterial at first, second or third line with or without diversification compared to current treatment strategy. *WTP* willingness-to-pay

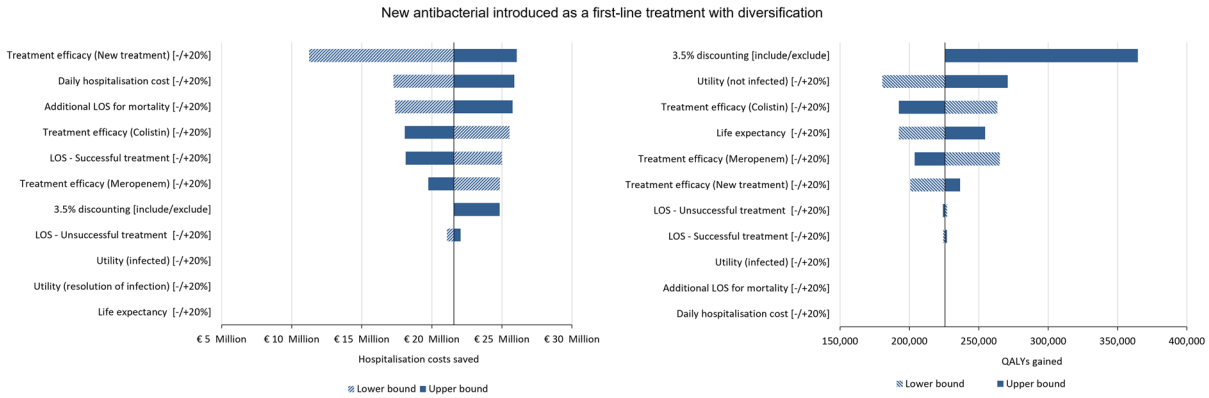

Fig. 4 One-way sensitivity analysis varying key inputs by ± 20% exploring hospitalisation costs saved and QALYs gained when a new antibacterial is introduced as a first-line treatment with diversification: *LOS* length of stay, *QALYs* quality-adjusted life years

models that de-link revenue from volume of sales and provide financial assurance to companies that bring new treatments to market, such as the PASTEUR act in the USA (introduced to Congress 2021) [40, 41], and the first 'subscription-style' model launched by the National Institute for Health and Care Excellence (NICE) and National Health Service (NHS) England [42, 43]. These mechanisms aim to stimulate antimicrobial research and development whilst enabling the appropriate use of antimicrobials. For such initiatives to be effective in providing an economic incentive capable of reinvigorating research and development efforts globally, a proportional worldwide response is required [42]. In order to develop adequate reimbursement mechanisms that promote patient access to new treatments, there is a need to assess the societal value of antimicrobials specific to individual countries.

Development of new antimicrobials needs to be accompanied by optimal use of existing

ones, to slow and reduce AMR, through the enforcement of stewardship programmes. This is still a significant issue in Greece, where consumption in both community and hospital settings ranks amongst the highest in Europe [10, 44], contributing to the increasing burden of MDR infections. In order to reduce the significant burden of AMR in Greece, a series of measures have been implemented based on the WHO Global Action Plan on Antimicrobial Resistance 2015 [21] and the European One Health Action Plan against AMR 2017[1]. These include the introduction of prescribing guidelines and antibiotic consumption monitoring by hospital stewardship groups [22], and infection prevention and control education programmes [23]. Despite these attempts, Greece is yet to fully implement a national AMR action plan [24]. The lack of local data practicality and actionability issues have likely contributed to policy-making delays and uneven uptake of these measures in the country. A strong political commitment and unified efforts are needed to implement the multifaceted interventions required to both reduce the burden of AMR in Greece and enable prompt access to new treatments.

The analysis presented in this study is associated with a number of limitations as with any study of its kind. Firstly, the model only considered the impact of resistance in the hospital environment and not in the community within a select number of pathogens and indications; therefore, our analysis may under-represent the actual burden in Greece. Additionally, it must also be noted that the assumptions for Greek transmission dynamics and prevalence of infection were based on UK data, which may not be fully reflective of the Greek context. Furthermore, as with all economic models, the model presented is subject to the uncertainty associated with two key factors: (1) extrapolation of outcomes beyond the available data and (2) necessary simplification of the underlying disease pathology and interpatient variability in natural disease course, response to treatment, mechanisms of treatment failure, and other relevant phenomena. Variation in resistance levels between sources may also be considered a limitation. Additionally, while this analysis is specific to the Greek setting and may not be generalisable between countries, the findings from this study may also be informative to other countries with a high AMR burden.

CONCLUSION

This study provides a quantitative estimation of the potential clinical and economic benefits that may be realised through the introduction of a new antibacterial in Greece, as well as highlighting the significant burden of HAIs with LTOs. There is a significant and urgent need for a coordinated response from both healthcare and political leaders to tackle the antibiotic crisis. The findings presented in this study can be used to inform decision makers in Greece about the potential benefits of implementing a national action plan that incentivises and improves access to new antibacterial agents, alongside improving education, preventing infection and enhancing stewardship measures.

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Compliance with Ethics Guidelines. The analysis in this article is based on previously publicly available data and does not involve any new studies of human or animal subjects performed by any of the authors.

Data Availability. The data sets generated during and/or analysed during the current study are available from the corresponding author on reasonable request.

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