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ORIGINAL RESEARCH

Clinical and Economic Value of Reducing Antimicrobial Resistance in the Management of Hospital-Acquired Infections with Limited Treatment Options in Greece

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ABSTRACT

Introduction: Antimicrobial resistance (AMR) is a major public health threat worldwide. Greece has the highest burden of infections due to antibiotic-resistant bacteria among European Union/European Economic Area (EU/EEA) countries. One of the most serious AMR threats in Greece is hospital-acquired infections (HAIs) with limited treatment options (LTO) caused by resistant gram-negative pathogens. Thus, this study sought to estimate the current AMR burden in Greece and the value of reducing AMR to gram-negative pathogens for the Greek healthcare system.

Methods: The current model was adapted from a previously published and validated model of AMR to investigate the overall and AMR-specific burden of treating the most common HAIs with LTO in Greece and scenarios to demonstrate the benefits associated with reducing AMR levels from a third-party payer perspective. Clinical and economic outcomes were estimated over a 10-year time horizon; life years (LYs) and quality-adjusted life years (QALYs) were calculated over a lifetime (based on the annual number of infections over 10 years) at a willingness-to-pay of €30,000 per QALY gained and a 3.5% discount rate.

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Results: In Greece, the current AMR levels in HAIs with LTO caused by four gram-negative pathogens account for > 316,000 hospital bed days, €73 million in hospitalisation costs, and > 580,000 LYs and 450,000 QALYs lost over 10 years. The monetary burden is estimated at €13.9 billion. A reduction in current AMR levels by 10–50% results in clinical and economic benefit; 29,264–151,699 bed days may be saved, leading to decreased hospitalisation costs (€6.8 million–€35.3 million) and a gain in LYs (85,328–366,162) and QALYs (67,421–289,331), associated with a monetary benefit of between €2.0 billion and €8.7 billion.
Conclusion: This study shows the substantial clinical and economic burden AMR represents to the Greek healthcare system and the value that can be achieved by effectively reducing AMR levels.

Keywords: Antimicrobial resistance; Economic evaluation; Greece; Hospital-acquired infections; Infectious disease; Limited treatment options; National action plan

Key Summary Points

Why carry out this study?

Greece has the highest burden of infections due to antibiotic resistant bacteria among EU/EEA countries. This burden has a significant clinical and economic impact on the Greek healthcare system.

Despite these known concerns and attempts by policy makers to implement AMR control, a Greek AMR national action plan is yet to be fully implemented.

This study aims to estimate the current AMR burden in Greece and the clinical and economic value of reducing AMR levels to highlight the need to address AMR as an imminent threat to public health in Greece.

What was learned from the study?

This study quantifies the considerable burden of resistant HAIs with LTO and the clinical and economic value of reducing current AMR in Greece; a 50% reduction of current AMR levels can result in a gain of > 360,000 LYs and 280,000 QALYs equating to a lifetime monetary benefit of up to €8.7 billion considering a 10-year transmission period.

These analyses highlight the need to address the AMR crisis in Greece and supports policy makers striving to fully implement a national action plan.

INTRODUCTION

Antimicrobial resistance (AMR) is considered a significant global health crisis; the World Health Organisation (WHO) has reported AMR as one of the top ten global public health threats facing humanity [1]. As more pathogens develop multi-drug resistance mechanisms, infections become more challenging to treat and in some cases no active treatments are available [2]. The Organisation for Economic Co-operation and Development (OECD) predicts a 72% increase in AMR levels against second-line treatment options and a greater than double increase against third-line treatments by 2030 compared to 2005 in the European Union (EU) [3]. Whilst resistance develops naturally, overutilisation and misuse of antimicrobials in both health and agriculture sectors are key contributors to increasing resistance levels [4, 5]. Moreover, the inability to effectively treat resistant bacterial infections is linked to substantial social and economic burdens [6]. Based on predictive statistical models, around 4.95 million deaths were associated with bacterial AMR and 1.27 million deaths were estimated to be attributable to bacterial AMR in 2019 globally, with the highest burdens in low-resource settings [7]. If the rate at which resistance is rising globally is not effectively managed, it is estimated that by 2050, 10 million lives per year

and a cumulative $100 trillion in economic output are at risk [8]. In Europe, according to published epidemiological reports, AMR results in > 35,000 deaths and > 1 million disability-adjusted life years (DALYs) annually and is predicted to cause greater mortality than cancer by 2050 if no action is taken [6, 9]. In addition to increased morbidity and mortality, the impact of AMR on the economy is significant, with resistant infections associated with longer hospital length of stay and the need for additional antibiotic treatments as well as the individual and societal financial implications [1]. Approximately €1.5 billion in healthcare expenditure is attributed to increased AMR levels and related productivity losses each year, as reported by the European Commission [6].

Greece has the highest overall burden of infections caused by antimicrobial-resistant bacteria among EU/European Economic Area (EEA) countries when adjusted for population size, consistently reporting higher than EU average rates of AMR in hospital-acquired infections (HAIs), and has the highest prevalence of HAIs [10, 11]. Infections caused by antimicrobial-resistant bacteria in Greece have increased by 76% from 23,199 to 40,891 between 2016 and 2020. One of the most serious threats are HAIs caused by antimicrobial-resistant pathogens, with the highest burden in 2020; 69% (28,184) of the 40,891 HAIs were caused by gram-negative pathogens with limited treatment options (LTO) [12]. In particular, such infections are estimated to result in > 580 DALYs per 100,000 population and 2100 deaths annually in Greece [10, 12].

Despite a small decline in antimicrobial consumption over recent years, Greece had the highest antimicrobial utilisation rate across the last decade in the EU/EEA [13]. In 2021, Greece had the fourth highest utilisation rate of antimicrobials for systemic use in community and hospital settings combined, with 23.5 defined daily doses per 1000 residents per day [13]. Overuse and misuse of antimicrobials continue to fuel high antibiotic-resistant rates, despite interventions targeted at introducing stricter guidelines and prescription-only dispensing [14]. Greece remains the highest consumer of carbapenems and second in consumption of polymyxins in the EU/EEA, in notable parallel to the observed increased resistance rates [15].

In recognition of the global AMR threat, in 2015, the WHO issued the Global Action Plan on Antimicrobial Resistance, which adopts a multisectoral 'one health' approach to tackling AMR through country-specific national action plans. Each national action plan aims to achieve the goals set out in the Global Action Plan on Antimicrobial Resistance: AMR awareness, surveillance, infection control, effective stewardship, and economic investment in AMR interventions [16]. In response, the European Commission published the EU One Health Action Plan against AMR in 2017, building on the 2001 community strategy against AMR [6], its aim being to serve as a 'best practice' example to aid the development of nation action plans through the preservation of effective treatment and expanding the antimicrobial pipeline [6]. In 2020, a series of updated initiatives were introduced by the European Commission, including [17]: the Farm to Fork Strategy to promote responsible antimicrobial use in agriculture [18], the Pharmaceutical Strategy for Europe with a focus on the appropriate use, under investment in antimicrobials and AMR awareness [19], and the Commission Implementing Decision (EU) 0220/1729 improving monitoring and reporting of AMR [20].

To address the clinical and economic burden of this phenomenon in Greece, AMR was incorporated as an actionable public health issue in the Strengthening Capacity for Universal Coverage (SCUC) incentive plan 2017–2021, which seeks to improve the overall health of the Greek population [21]. The Greek Ministry of Health has implemented measures that prohibit the distribution of antibiotics without a prescription to combat inappropriate use [21]. This objective has also been supported in the hospital setting through hospital-specific stewardship groups that monitor the implementation of prescribing guidelines and evaluate the consumption of antibiotics and AMR levels; however, the implementation of this initiative across all Greek hospitals is still in progress [21, 22]. Additionally, stewardship

awareness and education around infection prevention and control has been instigated through the Agency for Quality Assurance in Health S.A. [23]. However, whilst these attempts have been made by policy makers to implement AMR control, a Greek AMR national action plan in line with the objectives of the WHO's Global Action Plan on Antimicrobial Resistance is yet to be fully implemented [24]. The economic and clinical value of introducing a new antimicrobial in Greece has previously been investigated and supports the implementation of an action plan which incentivises and improves access to new antibacterial treatments [25]. This study aims to supplement the previous modelling work by adopting a broader view to understand the current AMR burden in Greece and the value of reducing current AMR levels to four major gram-negative pathogens to highlight the clinical and economic benefits that may be achieved and the need to address AMR as imminent threat to public health in Greece.

METHODS

Overview

A previously published and validated model of AMR was used to develop the deterministic AMR Value Model [26]. The model investigates the total burden of HAIs with LTO based on current resistance levels and scenarios to demonstrate the AMR burden associated with HAIs with LTO and to explore with scenarios how alternative AMR levels impact total burden in Greece from a third-party payer perspective. HAIs with LTO represent a substantial burden of HAIs in Greece; therefore, the model aimed to consider outcomes associated with treating HAIs with LTO. The analysis included HAIs with LTO categorised by four groups: complicated urinary tract infections (cUTI), complicated intra-abdominal infections (cIAI), hospital-associated pneumonia including ventilator-associated pneumonia (HAP/VAP), and other HAIs with LTO (including bloodstream infections, digestive tract infections, skin and soft tissue infections, and other less frequent infections) caused by the resistant gram-negative pathogens: *Escherichia coli*, *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Acinetobacter* spp. Inputs were informed by literature and validated by local expert clinical opinion, where required, to best represent current clinical practice in Greece (Tables 1 and 2).

Model Structure

The economic and clinical impact of a specified treatment sequence, at a given resistance level, was estimated through a deterministic treatment pathway (Fig. 1). A simplified two-line treatment pathway comprised of meropenem and colistin was assumed to best represent the standard of care in Greece for the pathogens of interest. Infected patients are first treated with meropenem; once treated, infected patients are either cured (successful treatment or natural resolution of the infection), remain infected, or die as a result of the infection. Colistin is initiated as second-line treatment for patients who are unsuccessfully treated after first-line treatment with meropenem. If treatment remains unsuccessful or the infection does not naturally resolve after utilising all available treatment strategies, it is assumed that death from infection occurs 4 days after receiving the last treatment.

Model Inputs

A total of 15,946 annual HAIs represent the modelled patient population of HAIs with LTO in Greece as reported in Cassini et al. [27] (calculation based on European Antimicrobial Resistance Surveillance Network [EARS-Net] data collected during 2015) (Table 1). Treatment-specific resistance levels for each pathogen were informed by WHONET data [28], published literature [29, 30], and expert opinion (Table 1), with additional key model inputs presented in Table 2. Indication-specific inputs are detailed in Table S1 in the supplementary material.

Table 1 Annual number of LTO infections and AMR levels for meropenem and colistin in Greece

	Pathogen				Total
	E. coli	*K. pneumoniae*	*P. aeruginosa*	*Acinetobacter spp.*	
No. infections[a]	3066	4772	3454	4654	15,946
% Infections[b]	19.23%	29.93%	21.66%	29.19%	100.00%
Meropenem resistance[c]	3.00%	75.00%	46.00%	98.00%	NA
Colistin resistance[c]	2.00%	40.00%	3.70%	47.00%	NA

[a]This included antibiotic-resistant bacteria of colistin-resistant, carbapenem-resistant, or multidrug-resistant *Acinetobacter* spp; colistin-resistant, carbapenem-resistant, or third-generation cephalosporin-resistant *E. coli*; colistin-resistant, carbapenem-resistant, or third-generation cephalosporin-resistant *K. pneumoniae*; colistin-resistant, carbapenem-resistant, or multidrug-resistant *P. aeruginosa*
[b]Cassini et al. [27]
[c]WHONET [28], published literature [29, 30], and expert opinion

Table 2 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 [31, 32]
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. [33]
Mortality rate (given successful treatment)	Daily rate of mortality associated with successful treatment	0.000032[a]	Hellenic statistical authority [31]
Treatment efficacy (given no resistance)	Probability of treatment success in patients with no resistance to treatment	87%	Expert opinion
Probability of infection resolving naturally	Probability of treatment success in patients with resistance to treatment	6.0%	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

Analysis

The total clinical and economic burden of the modelled HAIs with LTO was assessed over a 10-year horizon, based on the current AMR levels in Greece. The specific burden associated with AMR in the modelled indications was derived from the incremental difference

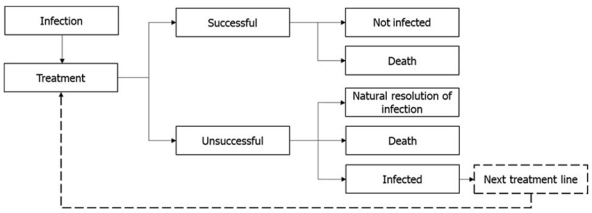

Fig. 1 Deterministic treatment pathway. Source: Gordon et al. (2020) [26]

between the total burden of HAIs (current AMR levels) and the total burden of AMR HAIs (current AMR levels reduced by 100%). Additional scenarios were explored considering reductions in current AMR levels by 10%, 25%, and 50% to illustrate the potential clinical and economic value of decreasing AMR in the Greek population. Resistance inputs for each scenario are presented in Table S2 in the supplementary material.

The clinical and economic burden was estimated through the following 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. TDT is defined as the total number of days patients are on treatment. These outcomes were considered from a third-party payer perspective in Greece. Whilst the model utilises a 10-year time horizon, QALYs and LYs were calculated over a patient's lifetime considering the number of infections over the 10-year time horizon. The life expectancy of a successfully treated patients was estimated as 20.12 years, based on the average age of patients with HAIs (65 years) informed by expert clinical opinion and general population life tables in Greece [31, 32]. Monetary benefit associated with reducing current AMR levels in Greece was estimated according to the equation:

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

There are no standard willingness-to-pay (WTP) threshold or discount rate recommendations in Greece; thus, a WTP threshold of €30,000 per QALY gained and a 3.5% discount rate were applied in line with European health technology appraisal guidance and WHO recommendation [34, 35].

One-way Sensitivity Analysis

A one-way sensitivity analyses (OWSA) determined the impact of model inputs on estimates for hospitalisation costs saved and QALYs gained under the scenario where AMR is reduced by 50%. The key model inputs listed in Table 2 were adjusted by ± 20%; an additional scenario was explored where no discount rate was included.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Clinical and economic outcomes for the total burden of HAIs with LTO and the burden of AMR in HAIs with LTO as well as scenarios where current AMR levels are reduced by 10%, 25%, 50%, and 100% for the pathogens of interest over a 10-year time horizon are presented in Table 3 and Fig. 2. The burden of AMR in HAIs with LTO is derived from the incremental difference between the total burden of HAIs and a 100% reduction in AMR. Pathogen-specific clinical and economic outcomes for each scenario are presented in Table S3 in the supplementary material.

Over a 10-year period, HAIs caused by the four major gram-negative pathogens in Greece account for a total burden of > 630,000 LYs lost (over 500,000 QALYs), > 2,000,000 hospital bed days, and approximately €466 million in hospitalisation costs. The burden of AMR in HAIs with LTO is associated with > 580,000 LYs lost (> 450,000 QALYs), approximately 316,000 hospital bed days, and > €73 million in hospitalisation costs. The monetary burden of AMR in HAIs with LTO over 10 years was calculated

Table 3 Clinical and economic outcomes based on current AMR levels and the AMR burden of HAIs with LTO in Greece over 10 years

Outcomes	Current AMR levels[a]	10% reduction in AMR[b]		25% reduction in AMR[b]		50% reduction in AMR[b]		100% reduction in AMR[b]	
	Total burden of HAIs	Total burden	Incremental change	Total burden	Incremental change	Total burden	Incremental change	Total burden	Incremental change (Burden of AMR in HAIs with LTO)
Hospital length of stay (days)	2,002,715	1,973,451	29,264	1,928,546	74,168	1,851,015	151,699	1,685,867	316,848
Total days on treatment	1,827,003	1,821,181	5822	1,808,323	18,680	1,775,897	51,106	1,669,804	157,199
Hospitalisation costs	€466,139,265	€459,325,071	€6,814,194	€448,868,905	€17,270,359	€430,815,633	€35,323,632	€392,360,347	€73,778,917
Life years lost[c]	639,597	544,269	85,328	437,616	201,981	273,435	366,162	58,471	581,126
QALYs lost[d]	506,116	438,695	67,421	346,520	159,596	216,785	289,331	46,895	459,221

AMR antimicrobial resistance, *HAI* hospital-acquired infections, *LTO* limited treatment options, *QALYs* quality-adjusted life years

[a]Current AMR levels for meropenem and colistin in Greece are presented in Table 1

[b]Current AMR levels for meropenem and colistin in Greece when reduced by 10%, 25%, 50%, and 100% are presented in Table S2 in the supplementary material

[c]Life years lost based on a life expectancy of 20.1 years after treatment prior to discounting

[d]QALYs lost based on a quality-adjusted life expectancy of 15.9 years after treatment prior to discounting

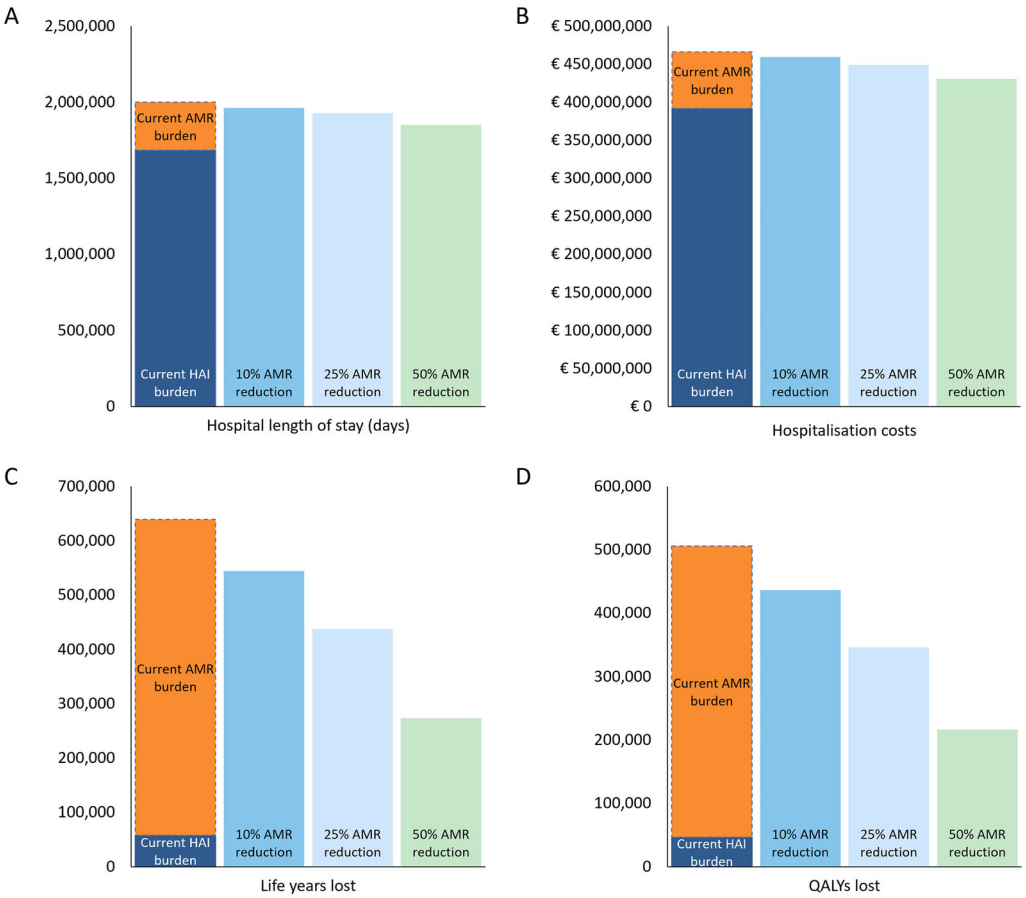

Fig. 2 Clinical and economic outcomes associated with reducing AMR levels based on current AMR levels and the AMR burden of HAIs with LTO in Greece over 10 years. **A** Hospital length of stay, **B** hospitalisation costs, **C** life years lost, and **D** QALYs lost. *AMR* antimicrobial resistance, *QALYs* quality-adjusted life years

as €13.9 billion using a WTP threshold of €30,000 per QALY (Fig. 3).

A 10% reduction in current AMR levels, over a 10-year time horizon is associated with 29,264 bed days saved, €6,814,194 saved in hospitalisation costs, 5822 fewer TDT, and a gain of 85,328 LYs (67,421 QALYs gained). In addition, a reduction in current AMR levels by 25% could result in 74,168 bed days saved, a saving of €17,270,359 in hospitalisation costs, an estimated 18,680 fewer TDT, and a gain of 201,981 LYs corresponding to 159,596 QALYs. Furthermore, an AMR reduction of 50% was estimated to result in greater economic and clinical benefit. This reduction was associated with 151,699 bed days saved, a saving of €35,323,632 in hospitalisation costs, 51,106 fewer TDT, and 366,162 LYs gained (289,331 QALYs gained). Reducing AMR by 10%, 25%, and 50% in Greece was estimated to provide a monetary benefit of €2.0 billion, €4.8 billion, and €8.7 billion, respectively, to the third party-payer in Greece over a lifetime considering a 10-year transmission period (Fig. 3).

Sensitivity Analysis

An OWSA of hospitalisation costs saved and QALYs gained, in a scenario where AMR levels are reduced by 50%, showed that LOS when patients are unsuccessfully and successfully treated (± 20%) had the largest impact on hospitalisation costs. This ranged from €21.2 million to €49.2 million and €47.6 million to €23.0

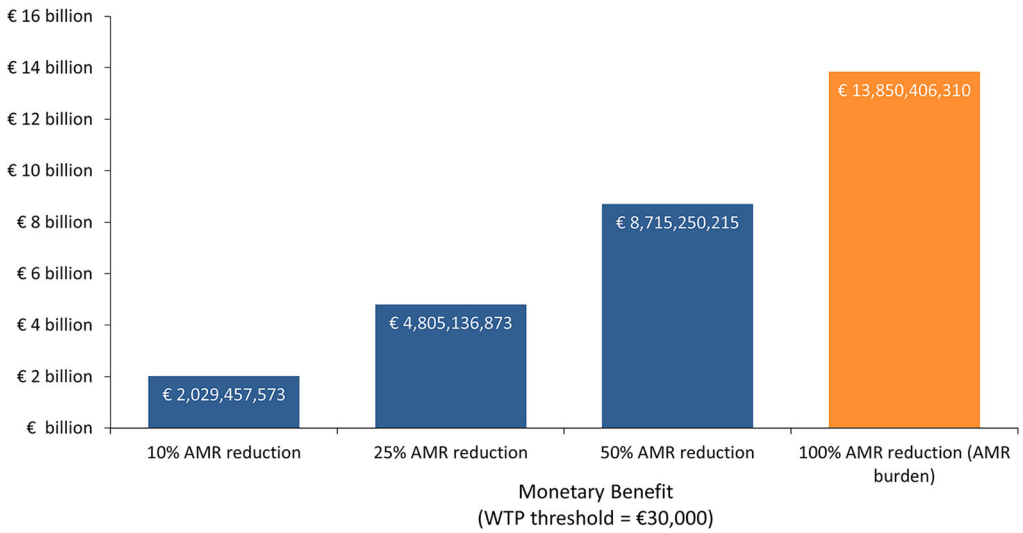

Fig. 3 Monetary benefit associated with reducing current AMR levels in Greece. *AMR* antimicrobial resistance, *WTP* willingness-to-pay

million, respectively. Treatment efficacy (± 20%) was also influential of hospitalisation costs with a range of €26.5 million to €42.4 million. Additionally, excluding discounting and utility (not infected) had the greatest impact on QALYs gained. Excluding discounting resulted in a QALY gain of 397,416 and varying utility (not infected) by ± 20% achieved a gain of 347,241 QALYs, as presented in Fig. 4.

DISCUSSION

Although AMR is recognised as a serious public health threat in Greece, insufficient data and a lack of economic analyses have contributed to ineffective implementation of policy decisions. This study helps to fill the evidence gap quantifying the clinical and economic burden of AMR in HAIs with LTO caused by resistant gram-negative pathogens and the value of reducing AMR in Greece. The current monetary burden of AMR in HAIs with LTO in Greece was estimated at up to €13.9 billion at a WTP threshold of €30,000 per QALY over a lifetime horizon based on 15,946 annual HAIs with LTO caused by four major gram-negative pathogens over 10 years. The clinical value of eliminating AMR in Greece can offer a gain of up to 459,221 QALYs and an additional 581,126 LYs over a lifetime (based on the annual number of infections over a 10-year period). Whilst eradicating AMR completely may be unrealistic, by reducing current AMR levels by 10–50%, considerable clinical and economic value can be realised. Over 10 years, between 29,264 and 151,699 bed days may be saved, leading to decreased hospitalisation costs (€6.8 million to €35.3 million) and a gain in LYs (85,328 to 366,162) and QALYs (67,421 to 289,331), equating to a monetary benefit of between €2.0 billion and €8.7 billion.

Greece suffers from a disproportionately high number of AMR deaths compared with other European countries with similar population sizes [3, 27]. High antibiotic consumption in both the community and hospitals is a driver of AMR in Greece. National education campaigns to improve awareness of AMR risks to both patients and physicians and the availability and use of rapid diagnostic testing have been shown to reduce the antibiotic consumption [14]. In 2020, a new law was implemented, where antibiotics can be dispensed from pharmacies only with electronic prescription, which potentiates the previous poorly executed law of 1973 (GG 172 8.8.1973) [36, 37]. This simple legislative change has had a significant impact

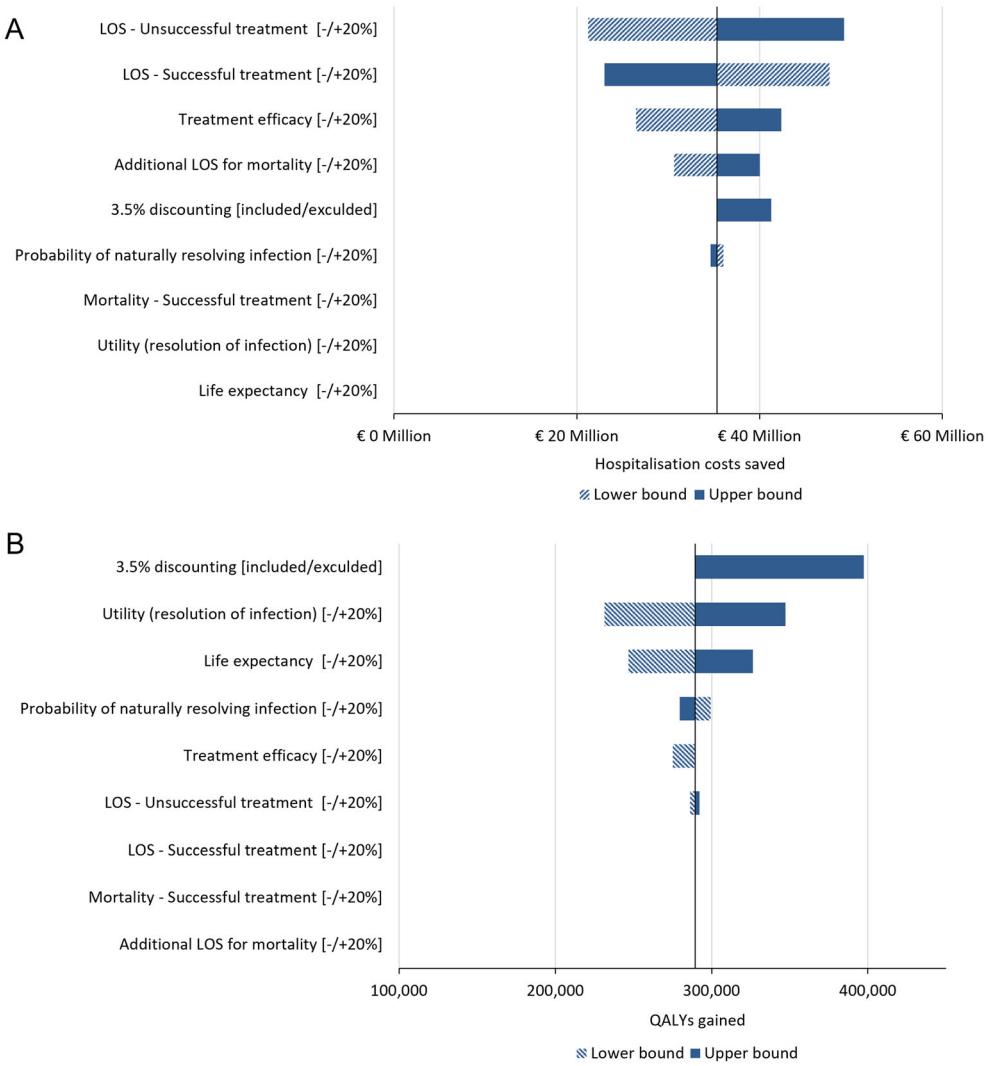

Fig. 4 One-way sensitivity analysis varying key inputs by ± 20% for **A** hospitalisation costs saved and **B** QALYs gained when current AMR levels are reduced by 50%. *LOS* length of stay, *QALYs* quality-adjusted life years

on the availability of antibiotics without prescriptions in pharmacies in Athens compared to a study in 2008; however, the impact in rural areas, where patient relationships with dispensing pharmacists may be stronger or the pharmacist knows it may be difficult for the patient to obtain a prescription, has yet to be demonstrated [38]. Antimicrobial resistance in the community is linked to resistance in hospitals, and visa-versa; community-strains may be responsible for some HAIs and therefore, interventions to reduce AMR in the community can be effective in reducing resistance in the hospital setting. Other initiatives enforced in 2014–2015 were the mandatory formation of Antibiotic Stewardship Committees in every hospital. However, the periodic report of specific antibiotic consumption indicators has been jeopardized by the COVID-19 pandemic (GG τ. 388 B'/2014). AMR and antimicrobial stewardship programmes including educational activities have also stepped back for the same reason worldwide [39, 40].

Public health actions to reduce AMR in Greece should include national public awareness campaigns on proper use of antimicrobials,

vaccination, and diagnostic tests. Every hospital should operationalise specialist hospital infectious diseases and antimicrobial stewardship teams who can enforce infection prevention and stewardship protocols. Improved hygiene in healthcare is estimated by the OECD to reduce the health burden (in DALYs) by 40% and a combined approach by up to 85% [41]. Furthermore, surveillance and reporting of key outcome indicators such as the prevalence of infections, resistance, and infection prevention could be monitored. The use of pull incentives should be implemented to ensure the development and accelerated access of new antimicrobials; incentives could also be extended to aid the introduction and availability of affordable rapid diagnostic tests. Such multifaceted interventions to reduce AMR require nationwide coordination and continued political support. In this context, University of Peloponnese developed a governance framework that could be set as a basis of a National Action Plan that could combat AMR in Greece [42]. The proposed framework defines specific actions, introduces the accountable entities for coordination and implementation, and suggests tools and metrics to track progress for each action. In line with the goals of the WHO's Global Action Plan on AMR [16], the key domains included were public awareness and education, infection prevention and control, stewardship, surveillance and reporting, and access to treatment, to be implemented over a 3-year period. A wide range of AMR experts in Greece validated the framework and highlighted, among others, the importance of increasing public awareness and education, the implementation of stewardship and surveillance programmes, an expedited assessment for novel antibiotics, and including AMR value elements to ensure the right argumentation to reward the underestimated value of antimicrobials.

Despite these interventions, limitations in data availability have contributed to the absence of a fully implemented AMR national action plan in Greece [24]. Urgent investment in AMR action is needed across the EU to alleviate the burden [43]; this is in line with our findings that clinical and economic value can be sought through reducing AMR in Greece. Thus, a fully funded and supported AMR national action plan which encompasses the objectives of the WHO Global Action Plan on Antimicrobial Resistance and the key issues driving infection resistance in Greece, including overuse, misuse, and an insufficient antimicrobial pipeline, should be imminent. The benefits of introducing new antimicrobial treatment in Greece has previously been quantified and supports the implementation of an action plan that also aims to incentivise research and development and timely access to new antimicrobials [25].

As with all economic analyses the outcomes presented should be interpreted within the context of the limitations. In line with other economic analyses, there is uncertainty related to outcome extrapolation outside of the available data and the lack of consideration of underlying transmission components and simplification of the treatment response. Modelling infectious diseases is complex involving dynamic parameters for transmission; the current model is a simple deterministic model and therefore does not consider changes in transmission dynamics such as resistance or incidence rates during the model time horizon. Therefore, the current burden may be underestimated as current resistance trends are increasing. Other model simplifying assumptions do not consider indication- or treatment-specific LOS or efficacy inputs. In addition, this analysis only considered outcomes associated with a limited number of pathogens and indications included in the context of a hospital setting. The true burden of AMR in Greece and the benefit of reducing AMR likely extend beyond those presented in this analysis.

CONCLUSION

This study provides valuable insights into the clinical and economic burden of AMR in Greece and the substantial benefit of addressing AMR. These analyses highlight the critical need to address the AMR problem in Greece and the extent of potential real-world benefits which could be achieved. This can be used to inform

policy makers striving to fully implement a national action plan in Greece.

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Author contributors. Jason P. Gordon conceptualised and designed the study. Ryan L. Miller was responsible for data analysis. All authors (Myrto Barmpouni, Jason P. Gordon, Ryan L. Miller, James W. Dennis, Vassilis Grammelis, Aris Rousakis, Kyriakos Souliotis, Garyphallia Poulakou, George L. Daikos, Amer Al-Taie) contributed to interpretation of the results, preparation and review of the manuscript, and approval of the final manuscript for publication.

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Compliance with Ethics Guidance. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

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

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