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Cost-Effectiveness Analysis of Ceftazidime/Avibactam Versus Polymyxin E in The Treatment of Carbapenem-Resistant Enterobacteriaceae Infections: Literature Review

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ABSTRACT

Background: Antibiotic resistance is a global issue that is rapidly spreading. The emergence of multi-drug resistant strains has been attributed to the overuse or misuse of antibiotics. Despite the lack of national data, the prevalence of multidrug resistant (MDR) bacteria in Egypt is comparable to or even higher than the global average. The US CDC defines carbapenem-resistant Enterobacteriaceae (CRE) as enterobacteria non-susceptible to any carbapenem or documented to produce a carbapenemase. Ceftazidime/Avibactam (CAZ/AVI) is a novel β-lactam and non-β-lactamase inhibitor with a distinct mechanism of action. The use of CAZ/AVI, compared with other sequential antibiotics including Colistin results in reduced mortality and less hospitalization time.

Objective: The study aimed to compare the cost-effectiveness of Ceftazidime/Avibactam (CAZ/AVI) to Polymyxin E in treating carbapenem-resistant Enterobacteriaceae (CRE) infections in hospitalized adult patients in Egypt from the public payer perspective.

Method: We used PubMed database for the search and only English-language papers were considered, with no restriction on publication date. Two independent reviewers performed the title and abstract screening, and a third principal reviewer resolved conflicts. All article titles and abstracts were initially screened using predefined exclusion criteria, such as no English abstract, no economic evaluation of an antibacterial agent, prevention strategies and non-transparent reporting of methodology. Based on the findings of the literature review, a decision tree model linked to a survival Markov model was developed to compare CAZ/AVI and Polymyxin E in hospitalized adult patients. The effectiveness measures were quality-adjusted life years (QALYs) and life years (Lys). From the public payer's perspective, costs in Egyptian health care settings were estimated. Deterministic and probabilistic sensitivity analyses were used to evaluate the model's robustness.

Results: The discounted incremental QALYs associated with CAZ/AVI versus Colistin were 0.30, the life-years gained were 0.42 years, and the discounted incremental costs were EGP 51,528 over a five-year time horizon. These resulted in EGP 170,832 per QALY and EGP 121,473 per life-year gained.

Conclusion: CAZ/AVI provides a breakthrough in the health benefit for CRE intensive care unit patients; however, it is not cost-effective against Colistin in the Egyptian health care settings at the current price level. Using a managed entry agreement could improve CAZ/AVI's cost-effectiveness and accessibility.

Keywords: Ceftazidime/Avibactam, Polymyxin E, carbapenem-resistant Enterobacteriaceae, Multidrug resistance.

INTRODUCTION

Antibiotic resistance is a global issue that is rapidly spreading. Antibiotic use in recent decades has been linked to a worldwide increase in antibiotic-resistant strains of bacteria known as superbugs or multi-drug resistant (MDR) bacteria [1]. The emergence of multi-drug resistant strains has been attributed to the overuse or misuse of antibiotics. Multiple drug resistance mechanisms have been discovered, but the development of novel antibiotics to overcome these mechanisms has lagged behind the emergence rate of those new multi-drug resistant strains [2]. Despite the lack of national data, the prevalence of MDR bacteria in Egypt is comparable to or even higher than the global average [3, 4].

Carbapenem resistance is defined as the ability of bacteria to survive in the presence of adequate carbapenem concentrations. The US CDC defines carbapenem-resistant Enterobacteriaceae (CRE) as enterobacteria non-susceptible to any carbapenem (i.e. showing a MIC of ≥4 mg/L for doripenem, meropenem or imipenem or ≥2 mg/L for ertapenem) or documented to produce a carbapenemase [5]. The three main mechanisms in carbapenem resistance are (1) carbapenemase production, which inactivates carbapenems by hydrolysis, (2) increase in the production of efflux pumps, which can actively extrude carbapenems from the bacterial cell and (3) porin mutation or loss, which leads to decreased carbapenem entry through the bacterial cell wall [5]. CRE is a serious threat because it has a high mortality rate even when treated early [6].

CAZ/AVI is a novel β-lactam and non-β-lactamase inhibitor with a distinct mechanism of action. It is a predetermined drug combination: (a) Avibactam is a novel non-β-lactam β-lactamase inhibitor. Its spectrum includes β-lactamases from classes A and C, as well as ESBLs and serine-based carbapenems (KPCs). It also works on class D β-lactamases (e.g. OXA-48 type carbapenems). (b) Ceftazidime is a cephalosporin approved for the treatment of complicated intra-abdominal infection (cIAI),

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complicated urinary tract infection (UTI), nosocomial pneumonia (NP) and other infections in Egypt. Except for cases of streptococci and anaerobes, it has no notable antibacterial activity against Gram-positive pathogens [7]. Furthermore, in the cost-effectiveness study, CAZ/AVI was compared with other sequential antibiotics, including Colistin [8] and it was found that the group with CAZ/AVI had reduced mortality by around two days (10.65 days for the CAZ/AVI group to 12.5 days for the Imipenem and Colistin group).

One of the CAZ/AVI efficacy factors for lifetime care is the difference in hospitalization time between CAZ/AVI and Colistin. According to ***Van Duin et al.*** [9], patients are either discharged to home or released but not to home.

Around 19% of patients are discharged home, whereas 73% are not released home, meaning they must stay in an inpatient facility for a week after being discharged from the intensive care unit (ICU). This study aimed to compare the cost-effectiveness of CAZ/AVI with Polymyxin-E (Colistin) in treating complicated CRE infections in hospitalized adult patients in Egypt from the public payer perspective.

MATERIALS AND METHODS

An in-depth literature review was conducted to identify different economic models that addressed antibacterial agents specifically for antimicrobial resistance and to highlight the cost drivers, outcomes and methodologies used in these models. The review also aimed to validate how these models managed specific observations, such as treatment switching, mortality and hospital stay reduction. We used PubMed database for the search, which was conducted in August 2020. Domains related to antimicrobial resistance, various infections and economic evaluation were included in the search term (Appendix presents the syntax of the search term).

Only English-language papers were considered, with no restriction on publication date. Two independent reviewers performed the title and abstract screening, and a third principal reviewer resolved conflicts. All article titles and abstracts were initially screened using predefined exclusion criteria, such as no English abstract, no economic evaluation of an antibacterial agent, prevention strategies and non-transparent reporting of methodology. Subsequently, all identified articles were subjected to full-text screening using the same criteria. Finally, two independent researchers extracted data twice; the principal researcher analyzed the data. Different modelling techniques for various infections with resistant bacteria were identified in the data analysis.

Model design:

A cost-effectiveness model was developed comparing CAZ/AVI with Polymyxin E (Colistin) in Egyptian healthcare settings to estimate costs, quality-adjusted life-years (QALYs) and life-years gained (LYs). The model considered the major medical occurrences that affected patients, including discharge to home, discharge to home with long-term care and death. The clinical experts' panel discussion determined that nephrotoxicity was not a significant reported adverse event. The justification for this strategy was twofold: i) to maintain a conservative outlook regarding the anticipated healthcare gains of CAZ/AVI; and (ii) to account for the 1% of cases receiving Colistin who will require long-term renal replacement therapy,[10] a marginal proportion that was expected to have little impact on the model's outcomes. After consulting with clinical experts and reviewing the literature review findings, we expected reduced mortality and reduced length of stay in the hospital for patients on CAZ/AVI to be the model's main value drivers.

The model was created in Microsoft Excel 365©, Visual basic enabled that consists of a decision tree linked to a simple survival Markov model to capture the drug's short- and long-term effects (Figure 1). Because the model was designed from the public payer perspective, only direct medical costs were considered.

The model had a time horizon of 61 months. The decision tree spans one month, representing the initial hospitalization period. Moreover, the mortality rates were based on ***Van Duin et al.***[9] following the decision tree model, a Markov survival model lasts five years to evaluate the long-term survival benefit and extra costs. The model uses an annual 3.5% discount rate for costs and QALYs, as recommended by the Egyptian Pharmacoeconomics guidelines [11].

In this model, the patient population was defined as CRE patients in the ICU with hospital-acquired pneumonia, including ventilator-associated pneumonia, complicated intra-abdominal infections, complicated urinary tract infections, including kidney infection and Gram-negative bacteria infections, when other treatments might not work. It is reasonable not to differentiate between different initial sites of infections because the patient has already received empirical treatment, which is usually followed by carbapenems and then CAZ/AVI or Colistin at this stage. According to expert interviews, that was caused by majority of the patients who would have progressed to septicemia by that time, and the prognosis is more or less the same.

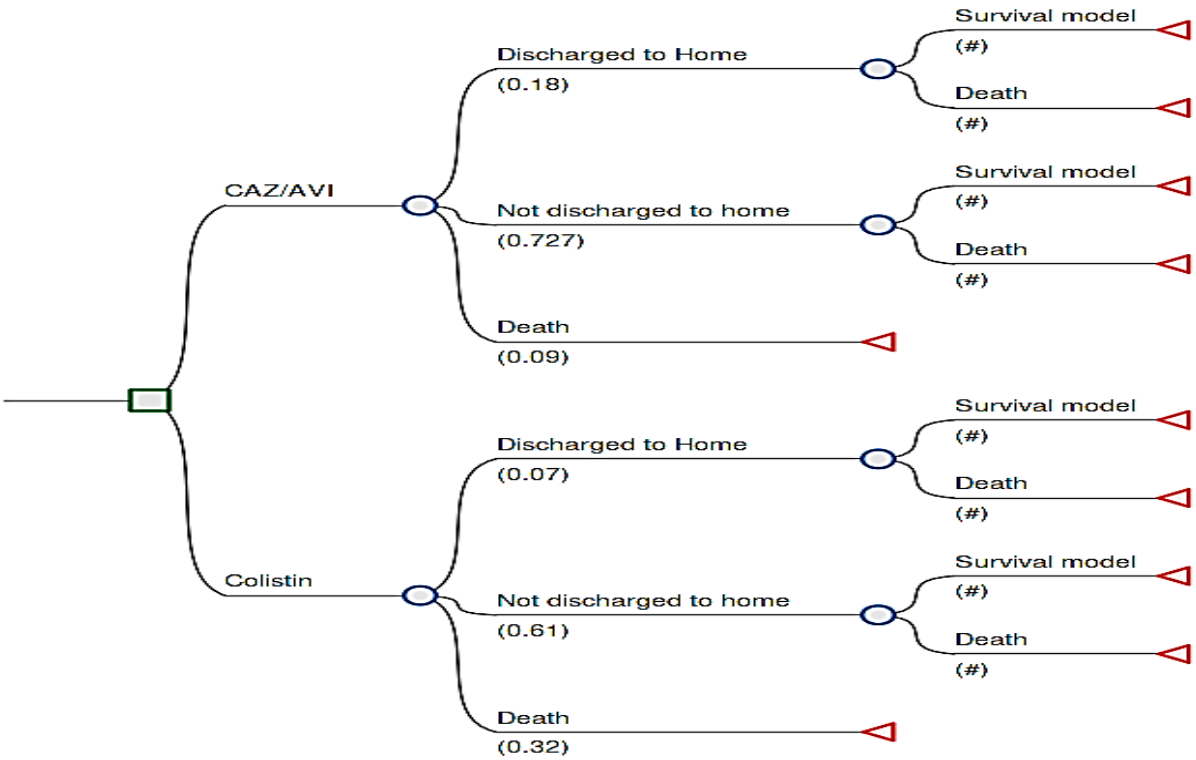

Figure (1): Model design.

Treatment Efficacy parameters

The primary efficacy parameters between CAZ/AVI and Colistin were hospitalization, survival and long-term care admission. However, adverse events were negligible compared to the primary efficacy parameters. ***Kongnakorn et al.***[8] and ***Van Duin et al.***[9] have only studied and compared Colistin versus CAZ/AVI study for 30 days. The results of a Medicare claims-based retrospective cohort study of survivors of severe sepsis were used to model all-cause mortality at one year and the annual mortality risk after that. They included a 5-year mortality risk stratified by whether the patient was discharged home or to a skilled nursing facility. We assumed that long-term survival and discharge disposition probabilities did not vary as a function of treatment arm.[12]

Resource utilization, costs and utility parameters

Secondary sources were used to collect data on health care resource utilization and costs, which were then validated by a panel of ICU specialists (Table 1). Due to the lack of published Egyptian guidelines for the compared drugs, four experts were interviewed for dosage data. Only one of the experts used a 9-million-unit dose per day, whereas the other three used 6 million units per day administered every 8 hours due to toxicity. This equates to 3.375 2 million international unit vials per day on average. Because CAZ/AVI was not widely used in Egypt, the label dose of three vials per day was used to calculate the recommended dose for all types of infection [7]. For drug prices, out-of-pocket pharmacy dispensing prices were utilized due to the lack of reimbursement price. Expert opinion suggested that the average treatment duration for Colistin was 17 days. In comparison, the CAZ/AVI treatment duration was 14 days based on the most conservative approach represented by the upper limit of days [7]. Noteworthy, the treatment duration has been reported to be shorter in several publications (e.g. 10 days [9], 11 days [22], 9.5 days [8] and 10.7 [23]).

The costs of hospitalization were calculated as a weighted average for each drug, considering the number of inpatients, ICU without ventilators and ICU with ventilators. The expert panel assumed that ICUs with ventilators accounted for approximately 70% of the total. It also accounted for the time difference between CAZ/AVI and Colistin [8] in the hospital.

Lifetime care is divided into two groups: those who were discharged directly to home with minimal treatment costs following hospitalization (EGP 1,000) and those who were not discharged home. The latter group is usually discharged to an inpatient ward after ICU. Consequently, according to the expert panels, the costs equal seven inpatient hospitalization days. Furthermore, the costs in discharge to home and not discharged to home after the second cycle are assumed to be equal. Prices were in Egyptian pounds based on 2021 prices. The panel of experts commented that the initial ICU costs, which were adopted from the HIO 2018 price list [14] at 820 EGP per day, were unrealistic, especially given that those patients typically receive a number of other services and medications during their stay in addition to utilizing ICU beds. Instead, the Ministry of Health and Population (MoHP) price

regulation for ICU costs during the COVID-19 pandemic was used as a reference [24].

The MoHP established an initial range of EGP 5k–7k for ICU patients who do not need ventilators and EGP 7.5k–10k for those who do [25]. MoHP has agreed to raise its prices by 20%, following the mandatory pricing scheme it had released for private hospitals treating COVID-19 patients [26].

This was after the private sector objected to the current scheme being unreasonable.

Furthermore, patients usually do not pay for the hospital bed only. Several other accompanying services and medications incur costs, depending on the case severity and the disease. However, our model does not use a bottom-up costing or a top-down approach due to lack of records, so we used COVID-19 ICU data as a proxy, which is especially appropriate given that it is also a serious infection.

We used the lower limit of the publicly disclosed prices for the current model. Based on the number of days for each of CAZ/AVI and Colistin, respectively, weighted to the percentage of the cure for each drug, the average number of days spent in the hospital or receiving treatment for CAZ/AVI and Colistin was calculated.

When there is a clinical response, the average length of hospitalization is 11.71 days; when there is not, it is 24.13 days. For CAZ/AVI and Colistin, the cure rates were 91.7% and 75%, respectively.

Health utilities were extracted from the literature [13] or estimated based on expert assumptions (Table 1).

Table (1): Model Parameters

Drug costs	**Value**	**Source**
Cost of CAZ/AVI per vial	1,842	Public Price
Cost of Colistin per vial	220	Public Price
Vials per day CAZ/AVI	3	[7]
Vials per day colistin 2 million unit	3.38	Expert opinion
Average treatment course duration CAZ/AVI	14	[7]
Average treatment course duration Colistin	17	Assumption
CAZ/AVI discount rate	0	user input
Hospital stays costs	**Value**	**Source**
Regular ward cost per day	1,275	[14]
ICU cost per day with ventilator	9,000	[24,25,26]
ICU cost per day without a ventilator	6,000	[24,25,26]
% of ICU admission per stay	0.80	Expert opinion
The average number of days on Hospitalization/treatment on CAZ/AVI	12.74	[8]
The average number of days on Hospitalization/treatment on Colistin	14.82	[8]
Number of inpatients days after the ventilator	7	Expert opinion
Lifetime care	**Value**	**Source**
One year of discharge to home	1,000	Expert opinion
Population	**Value**	**Source**
The proportion of patients who need a ventilator	0.70	Expert opinion
User-defined utilities	***Value***	***Source***
Hospitalization	*0.730*	[13]
Discharged to home	*0.840*	[13]
Not discharged to home	*0.640*	[13]

The deterministic sensitivity analyses were programmed and run through the model to find the most sensitive parameters by systematically changing the base-case estimates by ±10%. Probabilistic sensitivity analysis (PSA) was also used to account for the concurrent effect of uncertainty in model parameter values. A PSA run contained 5,000 model iterations. Uncertainty about critical model parameters was described by probability distributions, which were then propagated through the model using Monte Carlo sampling techniques to produce distributions of expected costs and QALYs for each arm.

Threshold:

According to ***Fasseeh et al.*** [15] the Egyptian willingness-to-pay (WTP) threshold is set at 2.5 times the GDP per capita. This threshold is based on the Palbociclib's Incremental Relative QALY Gain (IRQG), which is calculated as:

$$IRQG = \frac{QALY_{new\ technology} - QALY_{comparator}}{QALY_{new\ technology}}$$

For the base-case results, the numerator equals 0.3. Hence, the World Bank reports that the most recent GDP per capita figure is from 2021, at 3,876.4 USD/capita [16]. Using a conversion rate of 15.6971 EGP/USD from July 1, 2021, Exchangerates.org.uk[17] translates to 60,848 EGP. This value would result in a threshold of 152,120 EGP/QALY.

RESULTS

The literature review: During the preliminary search, 444 papers were discovered. We found 34 eligible papers for full-text screening after the title-abstract screening. Data were extracted from 25 papers. However, the final data analysis only included 18 articles (Figure 2).

PRISMA diagram for the systematic review

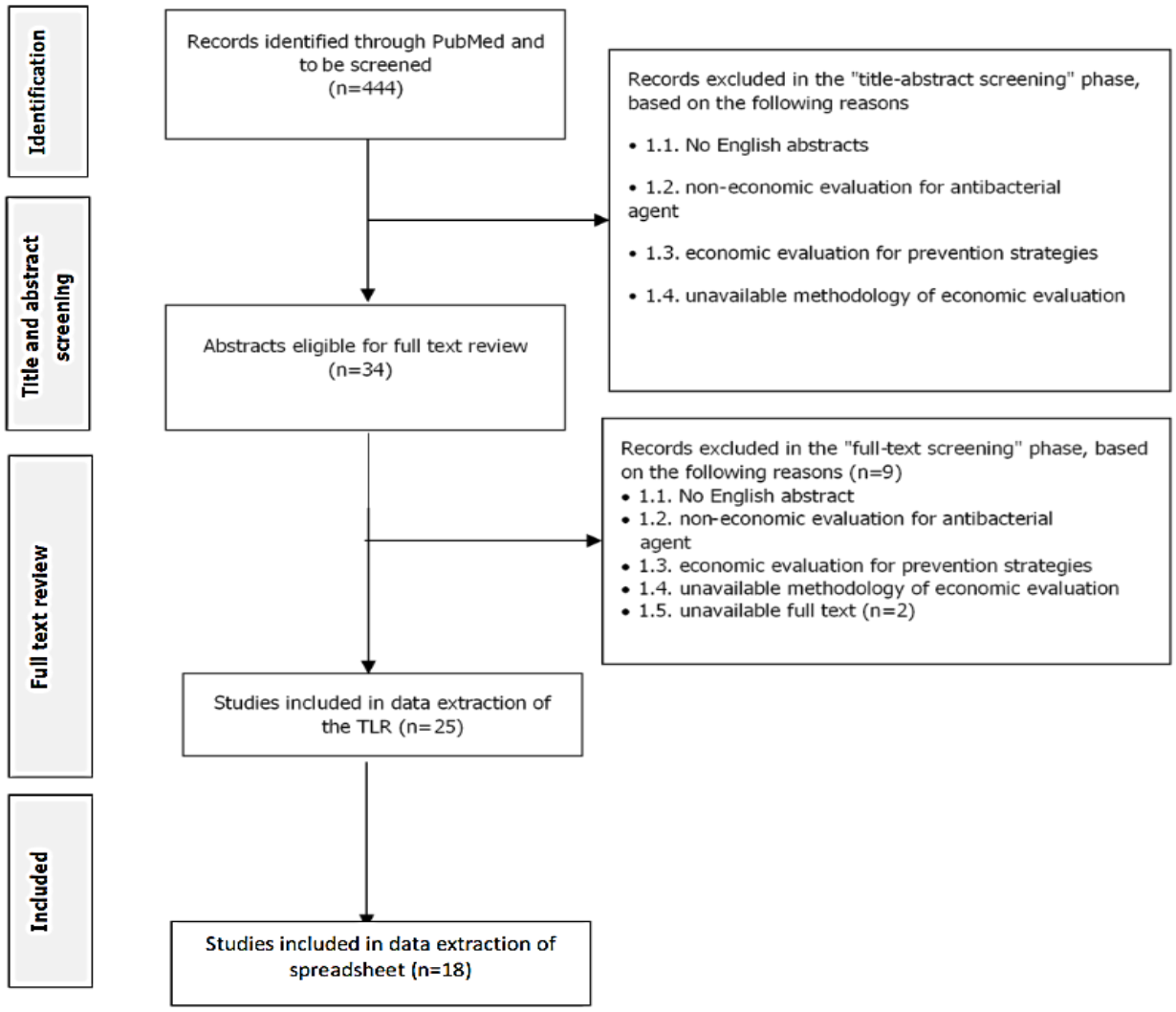

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Figure (1): PRISMA diagram for the literature review

Among the 18 papers, 9 (50%) used the decision tree model, 4 (22%) used a simulation model and the remaining 4 (22%) used a discrete event simulation model. A statistical model was used in one of the papers. In terms of analysis type, 12 (67%) were cost-utility analysis (CUA), 4 (22%) were cost-effectiveness analysis (CEA) and 2 (11%) papers were cost-minimization analysis (CMA). The health outcome measures were utility in 12 (67%) papers, and only 6 (33%) reported using clinical endpoints as a health outcome.

Concerning perspective, the healthcare provider, payer and societal perspectives were used in 10 papers (56%), 8 papers (44%) and 1 paper (6%), respectively. The cost drivers were as follows: medication costs in 10 papers (56%), hospitalization stays in 8 papers (44%), adverse events in 5 papers (28%) and recurrence costs in 3 papers (17%). Each paper mentioned post-discharge costs and lifetime expenditure (6%). A decrease in mortality and in hospitalization was observed in 12 papers (67%) and 17 papers (97%), respectively.

COST-EFFECTIVENESS ANALYSIS RESULTS

Base-case analysis results

Table (2) displayed the base case deterministic pairwise cost-effectiveness results (CAZ/AVI vs. Colistin).

The discounted incremental QALYs associated with CAZ/AVI veus Colistin over a 5-year time horizon are 0.30, whereas the life-years gained are 0.42. This led to an ICER of EGP 170,832, 121,473 for CAZ/AVI versus Colistin per QALYs and Life years, respectively, from the discounted total costs of EGP 51,528.

Table (2): Model results

	QALY (per patient)	Life Years (Lys)	Cost (per patient in EGP)
CAZ/AVI	0.99	1.511	166,960
Colistin	0.69	1.086	115,432
Incremental	0.30	0.42	51,528
Incremental cost-effectiveness ratio	170,832 EGP/QALY	121,473 EGP/LY	

SCENARIOS ANALYSES

Using arbitrary price reduction rates on drug prices, we ran various scenario analyses (Table 3).

The scenario with 15%, 25% and 35% discounts showed cost-effective according to the Egyptian threshold providing EGP 132,414, EGP 106,802 and EGP 81,190 per QALY, respectively.

Table (3): Scenario analysis

	CAZ/AVI		**Colistin**		**Incremental**		
Scenario	**Cost in EGP (per patient)**	**QALY (per patient)**	**Cost in EGP (per patient)**	**QALY (per patient)**	**Cost (per patient)**	**QALY (per patient)**	**ICER (EGP)**
Base case	166,960	0.992	53,902	0.691	51,528	0.302	170,832
35% discount	139,921				24,489		81,190
25% discount	147,647				32,215		106,802
15% discount	155,372				42,769		132,414

Sensitivity analyses results

The Tornado diagram depicts the deterministic sensitivity analysis (Figure 3), highlighting the most sensitive variables on the ICER when base case estimates were changed by ±10%. It demonstrated that the model is most sensitive to the average number of CAZ/AVI and Colistin hospitalizations/treatments, the cost of vials and the number of CAZ/AVI vials.

A scatter plot and a cost-effectiveness acceptability curves were used to display the PSA results (Figures 4 and 5). According to ***Fasseeh et al.*** [15], using the WTP threshold revealed a 40% likelihood of cost-effectiveness. According to the World Bank, Egypt's WTP in 2021, it was EGP 152,120 based on GDP per capita.

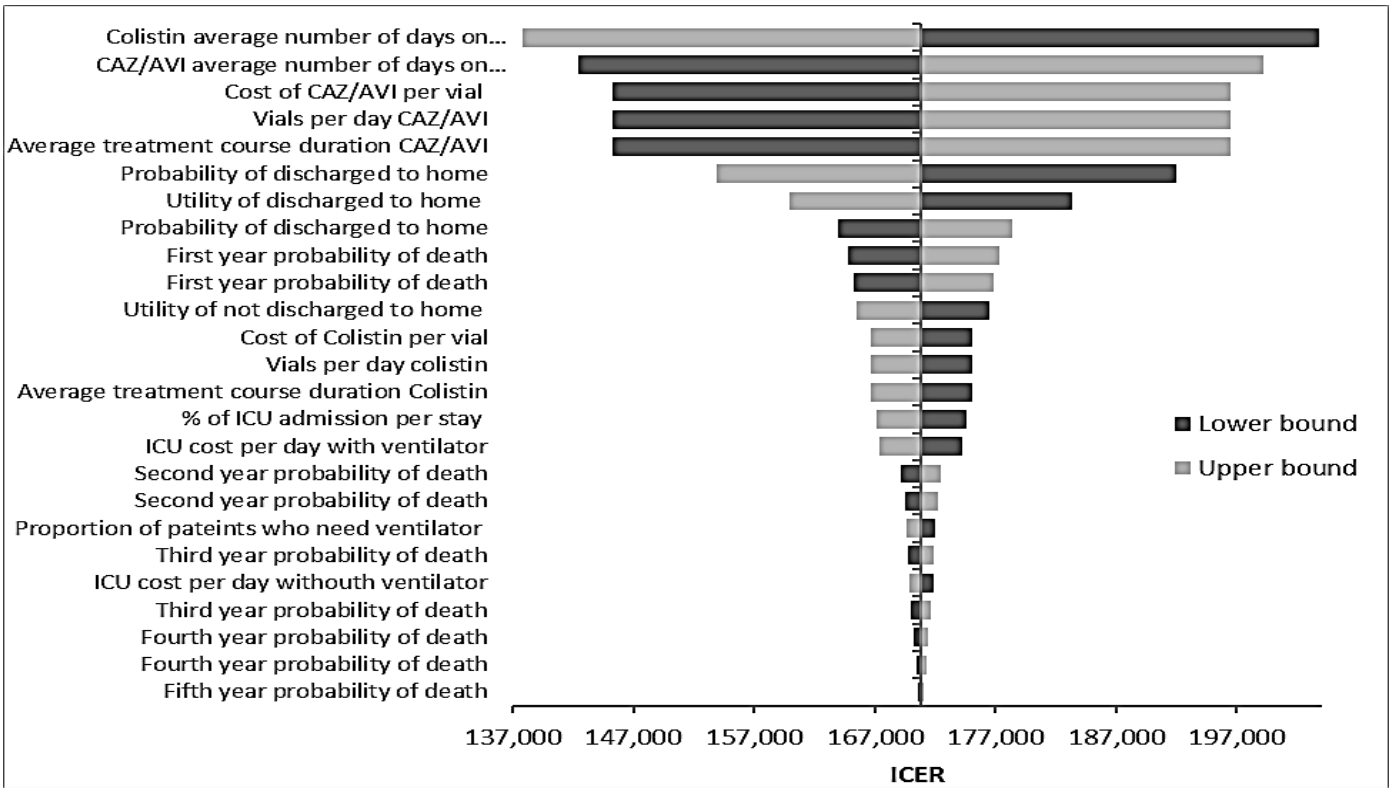

Figure (3): Deterministic sensitivity analyses Tornado diagram for CEA.

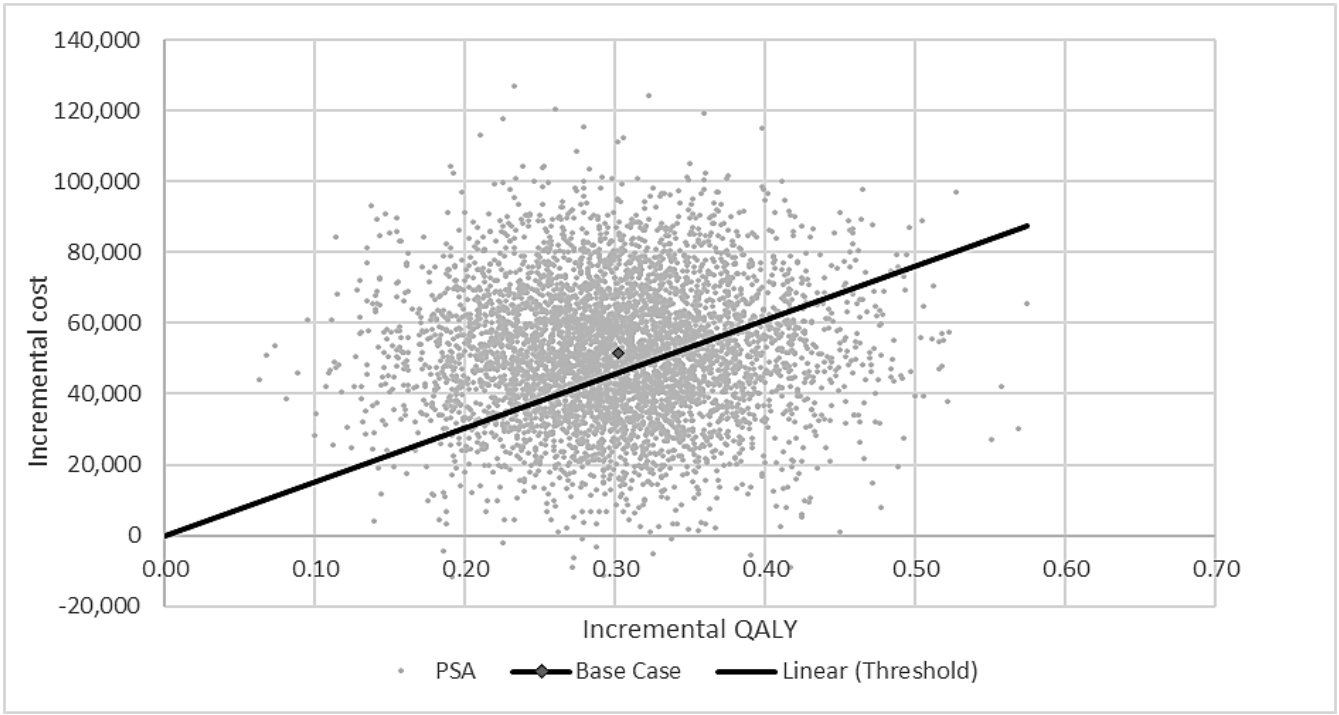

Figure (4): PSA Scatter plot diagram for CEA.

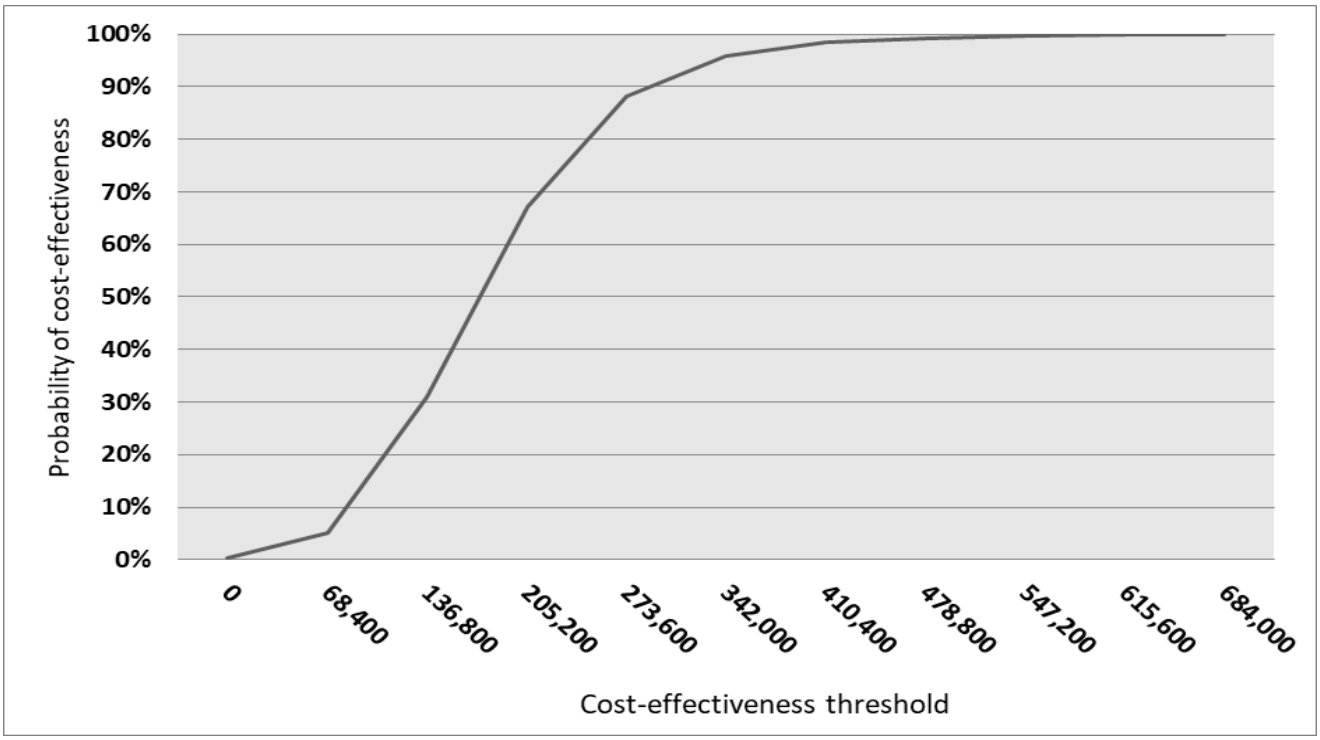

Figure (5): Cost-effectiveness acceptability curve.

DISCUSSION

A prior in-depth literature review based on the Model design was conducted to evaluate the cost-effectiveness of CAZ/AVI compared to Polymyxin E. According to the base-case results, CAZ/AVI is not cost-effective when compared to Colistin in Egyptian settings. This resulted from a discounted total cost of EGP 51,528 and an ICER of EGP 170,832 for CAZ/AVI versus Colistin per QALY, which is higher than Egypt's WTP threshold.

Despite the fact that our model's input values are based on expert opinion or international data, model results are robust in the face of input uncertainty. Furthermore, deterministic and probabilistic sensitivity analyses were performed, and the model results were consistent despite not being cost-effective. Similarly, in a specific scenario analysis with the drug price reduction, namely, the 25% and 35% reduction, the CAZ/AVI was cost-effective.

Most studies did not address the comparators used for this evaluation, except for one using identical comparators: CAZ/AVI & Colistin [13]. Only 4 of the 18 studies compared CAZ/AVI. Some models that have been researched have considered CAZ/AVI side effects, such as kidney affection, but our expert panel determined that this actor be excluded from our model. Some literature contends hospitalization times vary [13], even though the difference in hospitalization time between the two drugs is a crucial element in the drug efficacy.

Due to limited documentation of CRE cases and information on antimicrobial resistance in Egypt generally, clinical expert opinions were used as inputs for this model, which had some limitations.

Furthermore, there are no published guidelines in Egypt for CRE or hospital-acquired infection, which led to more dependence on clinical expert opinions.

This economic evaluation study did not find CAZ/AVI to be cost-effective at the current Egyptian threshold. Simultaneously, it may be more cost-effective than Polymyxin E (Colistin) in CRE infection, with better health outcomes (QALYs and LYs) at specific price discounts.

CAZ/AVI was found cost-effective earlier against Colistin based therapy in the USA [13] and China with limited treatment options.[18] Notably, CAZ/AVI was considered cost-effective in middle-income countries, such as Colombia [19], where it was cost-effective against Colistin plus Meropenem [20] and Peru using Colistin as a comparator.[21]

CONCLUSIONS

Although CAZ/AVI provides a breakthrough in the health benefit for CRE ICU patients, it is not cost-effective when compared to Colistin in Egyptian settings at the current price. However, in the case of CAZ/AVI, using managed entry agreements could be a cost-effective option.

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Author Contributions: AF, AS, BN and AR contributed to the study design. AF and AS built the model. AR, TB and MR provided input data. AS and AR managed the data collection phase. LS, HG and BN validated the model. All authors participated in proposing specific actions and recommendations. AF and AS wrote the draft manuscript. All authors revised the manuscript, provided comments, and approved its final version.

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