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Cost-Effectiveness Analysis of Aztreonam-Avibactam (ATM-AVI) Versus Meropenem ± Colistin for the Treatment of Serious Infections Due to Gram-Negative Bacteria for Which There Are Limited Treatment Options (LTO) in Italy

EE34

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Background

Antimicrobial resistance (AMR) is one of the major threats to human health around the world with substantial public health burden and global economic damage.[1] Globally, it is estimated that 1.27 million deaths were attributable to AMR in 2019.[1] Furthermore, the World Bank estimates that, by 2050, the economic impact of AMR could be similar to that of the 2008 financial crisis, with potential annual losses to global gross domestic product (GDP) of 3.8%.[2]

A recent study looking at a platform of hospitals in Italy found that carbapenem-resistant (CR) gram-negative bacteria are associated with an excess of mortality, with metallo-β-lactamases (MBL) producing CR Enterobacterales (CRE) carrying the highest risk of death (30 day mortality 36.4%).[3]

MBLs are a type of carbapenemase produced by bacteria that confer resistance to a wide range of antibiotics making them a considerable hazard.[4–6] It is very concerning that MBL-producing gram-negative bacteria are on the rise globally, with remarkably increased dissemination in 2015–2020.[4–6] MBL producing CRE **have increased 8-fold since 2014.**[7] **Due to their rapid spread and high mortality, MBL-producing pathogens are prioritised by the World Health Organization (WHO) as critical.**[5] Therefore, there is a high unmet need for treatments that address pathogens with resistant organisms such as CRE, including MBL-producing CRE infections.

Aztreonam-avibactam (ATM-AVI) is a combination therapy, including the monobactam aztreonam (ATM) and the non-β- lactam β-lactamase inhibitor avibactam (AVI) active against carbapenem resistant Enterobacterales including MBL-producing multidrug-resistant bacteria.

A Phase 3 randomised clinical trial (REVISIT) investigated ATM-AVI for the treatment of serious gram-negative infections (GNI) including suspected or documented MBL-producing pathogens for which there are limited treatment options (LTO).

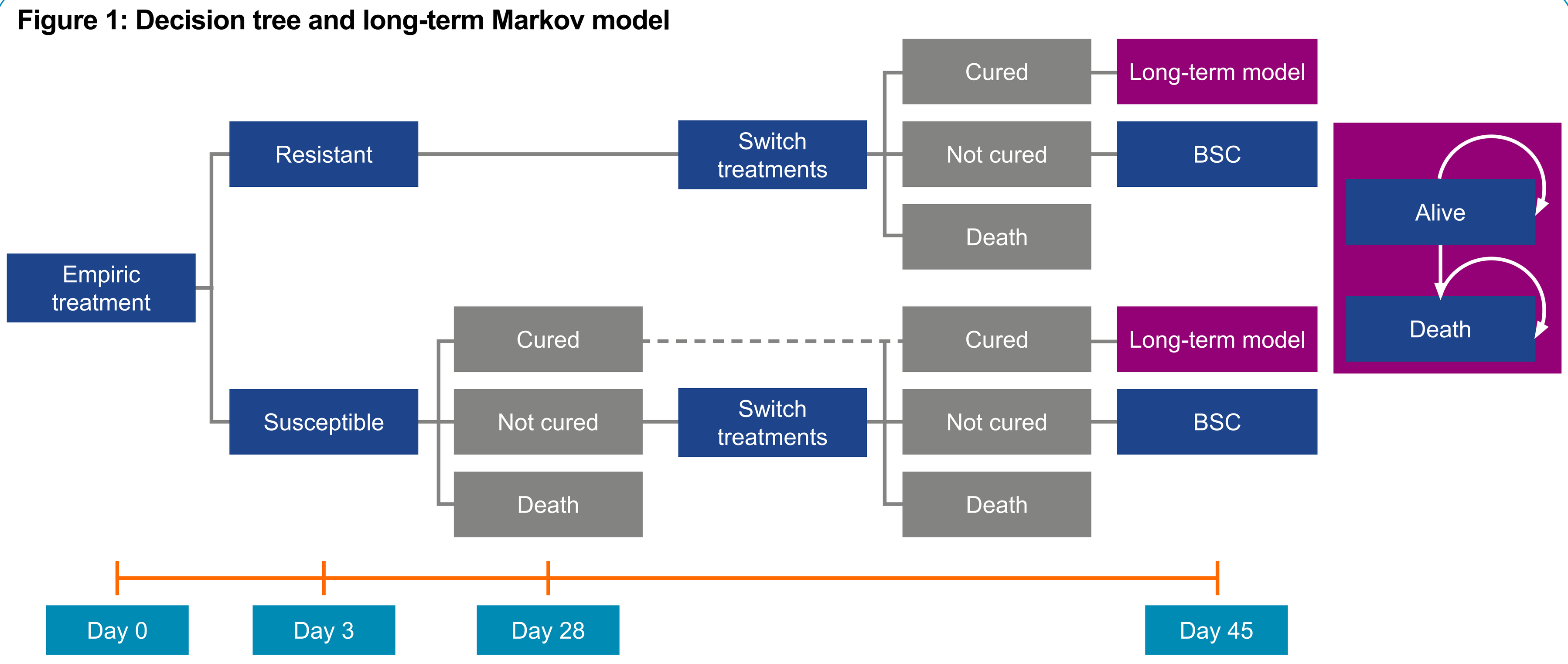
Objective

This analysis evaluates the cost-effectiveness of ATM-AVI + metronidazole versus meropenem ± colistin for the treatment of complicated intra-abdominal infections (cIAI) and ATM-AVI vs meropenem ± colistin for the treatment of hospital-acquired pneumonia/ventilator-associated pneumonia (HAP/VAP) in the Italian setting. Uncertainty in the model was assessed using probabilistic sensitivity analysis, one-way deterministic sensitivity analysis, and scenario analyses.

Methods

- A cost-effectiveness analysis used a decision tree model for the first 45 days that aligns with the trial design for REVISIT, with three health states: Cured, Not Cured, and Death. Cured patients would enter a long-term Markov model with two states, Alive and Death, used to capture longer term outcomes.
- To reflect the clinical pathway, patients enter the decision tree model and begin empiric treatment until Day 3 when depending on antimicrobial susceptibility testing (AST) results they either continue with the empirical treatment (if susceptible) until test of cure (TOC) or switch to a susceptible treatment (if resistant).
- As per the REVISIT trial design, TOC is at Day 28. At TOC, cured patients move to the long-term survival model and uncured patients would switch to the next line of therapy.
- The model accounts for the burden of antimicrobial resistance assuming that patients with resistant infections have worse outcomes than those with susceptible infection. To reflect this, the model uses recent data on the impact of AMR burden on mortality and length of stay: an increase of 80% in the odds of mortality at second line and a corresponding 80% reduction in the odds of a cure, as well as a 40% increase in length of hospital stay for patients with resistant infections was applied.[8]
- Patients that failed their first-line treatment went on to receive colistin and high-dose carbapenem. Uncured patients after two lines of treatment would then receive best supportive care (BSC) until they die.
- Mortality in the long-term was derived from Italian lifetables,[9] adjusted according the Charlson Comorbidity Index scores of patients.[10] Utility values were modelled using general population utilities.[11]
- The model adopted Italian National Health System perspective with a 3% discount rate and a lifetime time horizon.

Figure 1: Decision tree and long-term Markov model



Abbreviations: BSC, best supportive care.

Table 1: Model inputs

Parameter	ATM-AVI (+metronidazole in cIAI only)		Meropenem ± colistin		Source
	cIAI	HAP/VAP	cIAI	HAP/VAP	
Drug, dose	**Starting dose:** 2,000 mg aztreonam + 667 mg avibactam **Maintenance dose:** 1,500 mg aztreonam + 500 mg avibactam, every 6 hours. 500 mg/100 mL metronidazole IV every 8 hours	**Starting dose:** 2,000 mg aztreonam + 667 mg avibactam **Maintenance dose:** 1,500 mg aztreonam + 500 mg avibactam, every 6 hours.	**Meropenem:** 1,000 mg q8h **Collistin:** Loading dose, 9 million IU Maintenance dose, 9 million IU 8 patients receive colistin	**Meropenem:** 1,000 mg q8h **Collistin:** Loading dose, 9 million IU Maintenance dose, 9 million IU 7 patients receive colistin	REVISIT[12]
Cure at TOC (micro-ITT population)	79.86%	47.37%	77.33%	52.63%	
Death at TOC (micro-ITT population)	1.44%	7.89%	2.67%	21.05%	
Duration of hospitalisation	**ICU:** 5.44 days **General ward:** 5.53 days	**ICU:** 19.89 days **General ward:** 6.27 days	**ICU:** 5.44 days **General ward:** 5.53 days	**ICU:** 19.89 days **General ward:** 6.27 days	
Treatment duration (days)	7.8 days	10.4 days	8.5 days	10.3 days	
Price per day of treatment	Expected list price per day 760$		€125.76	€142.68	Pfizer Archivio Farmadati
Treatment cost per day (second line)	€215.49				
Resistance rates					
Klebsiella pneumoniae	0.0%	0.0%	24.2%	24.2%	Sader et al.[7] Stracquadanio et al.[13]
Escherichia coli	0.0%	0.0%	0.3%	0.3%	
Enterobacter cloacae	0.0%	0.0%	6.2%	6.2%	
Utility value – cured	0.92				Song et al.[14]
Utility value – uncured	0.61				Delate et al.[15]
Cost per day – ICU	€1,383.00				Tan et al.[16]
Cost per day – general ward	€674.00				Ministero dell'Economia e delle Finanze.[17]
Cost per day - BSC	€202.00				Mennini et al.[18]

Abbreviations: ATM-AVI, aztreonam-avibactam; BSC; best supportive care; cIAI, complicated intra-abdominal infections; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; ICU, intensive care unit; ITT, intent-to-treat; IU, international unit; IV, intravenous; mg, milligram; mL, millilitre; q8h, every eight hours; TOC, test of cure.

Results

- For cIAI, treatment with ATM-AVI + metronidazole versus meropenem ± colistin leads to a gain of 0.23 life years (LYs), 0.21 quality-adjusted life years (QALYs), and incremental costs of €3,970, generating an incremental cost-effectiveness ratio (ICER) of €18,997/QALY.
- For the HAP/VAP, there was a gain of 0.46 LYs, 0.42 QALYs, and incremental costs of €4,480, generating an ICER of €10,725/QALY.
- For both cIAI and HAP/VAP indications, the ICER is well below the willingness-to-pay threshold of €30,000/QALY accepted in Italy. The probabilistic sensitivity analysis shows that in both indication ATM-AVI was cost-effective in more than 90% of simulations.
- Deterministic sensitivity analysis indicates that results are sensitive to the proportion of patients with resistant infections.

Table 2: Results - cIAI

	ATM-AVI + metronidazole	Meropenem ± colistin	Incremental vs. meropenem ± colistin
Total costs	€ 20,215	€ 16,246	€ 3,969
Total QALYs	7.37	7.16	0.21
ICER	-	-	€ 18,997

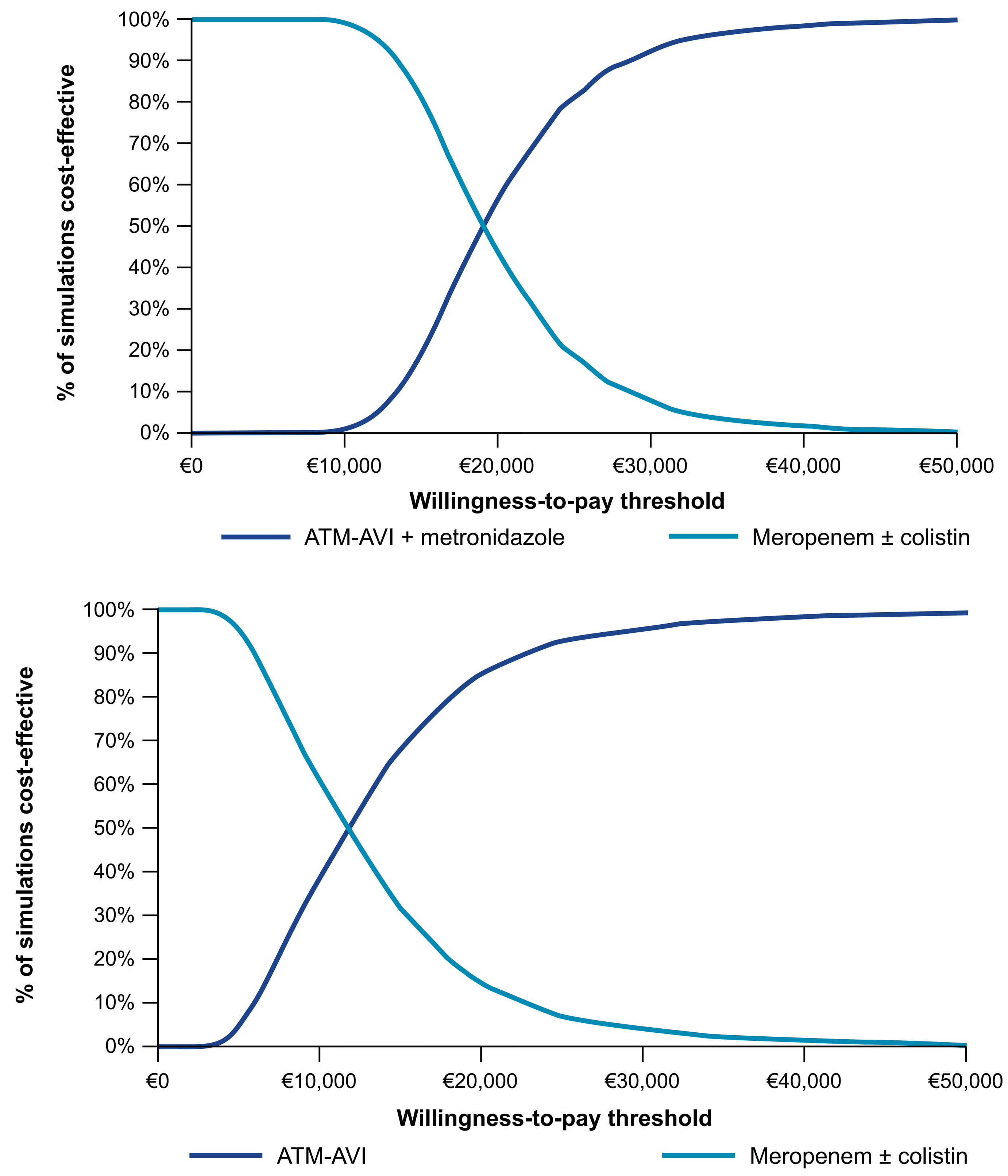
Abbreviations: ATM-AVI, aztreonam-avibactam; cIAI, complicated intra-abdominal infections; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.

Table 3: Results – HAP/VAP

	ATM-AVI	Meropenem ± colistin	Incremental vs. meropenem ± colistin
Total costs	€ 44,036	€ 39,556	€ 4,480
Total QALYs	2.9936	2.5759	0.4177
ICER	-	-	€ 10,725

Abbreviations: ATM-AVI, aztreonam-avibactam; HAP/VAP, hospital-acquired pneumonia/ventilator-associated pneumonia; ICER, incremental cost effectiveness ratio; QALYs, quality-adjusted life years.

Figure 2: CEACs, top panel cIAI, bottom panel HAP/VAP



Abbreviations: ATM-AVI, aztreonam-avibactam; CEAC, cost-effectiveness acceptability curve; cIAI, complicated intra-abdominal infections; HAP/VAP, hospital-acquired pneumonia/ventilator assisted pneumonia.

Discussions

- This study is the first cost-effectiveness analysis of ATM-AVI.
- The impact of resistant pathogens is a key driver of model outcomes, influencing mortality, costs and QALY gains in the long-term model.
- A key strength of this analysis is that efficacy parameters have been derived from a Phase 3 RCT, REVISIT, directly comparing the two treatment options. The model structure builds upon previous modelling GNIs[18–20] and can capture multiple facets of the clinical pathway, including antibiotic resistance and the impact of reduced mortality on long-term outcomes.
- A key limitation of the study is the assumption that patients that are uncured after two lines of treatment would receive 1 month of BSC, followed by death. However, scenario analyses varying the duration of BSC between 1 month and 1 year had minimal impact on the results.

Conclusions

These results show that, in the Italian setting, the introduction of ATM-AVI will lead to improved outcomes for patients with cIAI and HAP/VAP, with a minimal cost impact, meaning that ATM-AVI is a cost-effective strategy compared to meropenem ± colisitin for patients with serious GNI including suspected or documented MBL producing multi drug resistant bacteria.

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