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**Budget Impact Analysis of Aztreonam-Avibactam (ATM-AVI)** for the Treatment of Infections Caused by Confirmed and Suspected Metallo-β-Lactamase (MBL)-producing Enterobacterales in Italy

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## Background

- Antimicrobial resistance is one of the major threats to human health around the world, with a substantial public health burden and global economic damage.<sup>1</sup> MBLs are a type of carbapenemase produced by bacteria that confer resistance to a wide range of antibiotics.<sup>2-4</sup>
- ATM-AVI (EMBLAVEO<sup>®</sup>) is approved in Europe in adult patients for the treatment of complicated intra-abdominal infection (cIAI); hospital-acquired pneumonia (HAP), including ventilator-associated pneumonia (VAP); complicated urinary tract infection (cUTI), including pyelonephritis and for infections due to aerobic Gram-negative organisms with limited treatment options (LTO).

# Objective

- This analysis evaluates the budget impact of introducing ATM-AVI ± metronidazole (MTZ) for the treatment of infections caused by confirmed and suspected MBL-producing Enterobacterales (MBL-CREs) including cIAI, HAP/VAP, cUTI and those with LTO in the Italian setting.
- Data from REVISIT were used to cover the indications cIAI and HAP/VAP and the combined results for cIAI

	Cost per vial	Vial size	Info on dosing	Average Daily Dose	Daily cost
ATM-AVI	€200.41	1.5 g ATM 0.5 g AVI	<ul> <li>Doses are infused over 3 hours, q6h, requiring loading on Day 1 of the treatment cycle.</li> <li>Total dose on Day 1 is 6.5 g of ATM and 2.17 g of AVI. On subsequent days the total dose is 6.0 g of ATM and 2.0 mg of AVI.<sup>5</sup></li> </ul>	6 g ATM 0.5 g AVI	€801.64
MTZ	€0.13	500 mg	500 mg MTZ IV infusion q8h <sup>5, 10</sup>	1,500 mg	€0.39
Meropenem	€18.44	1,000 mg	1,000 mg meropenem by 180 min IV infusion q8h <sup>5, 11</sup>	3,000 mg	€55.32
Colistin	€11.65	1 million IU	18 million IU on Day 1; 9 million IU daily on subsequent days <sup>5, 12</sup>	9million IU	€104.85
Cefiderocol	€135.38	1,000 mg	2 g q8h <sup>13</sup>	6,000 mg	€812.28

and HAP/VAP from the REVISIT trial were extrapolated for the indications cUTI and infections with LTO to cover all the label indications.<sup>5,6</sup>

# Methods

- The model compared two scenarios (world "with" and world "without" ATM-AVI ± MTZ) to assess the budget impact of introducing ATM-AVI ± MTZ for the treatment of confirmed and suspected MBL-CRE infections over a 3-year time horizon.
- A Phase 3 randomised clinical trial (REVISIT) investigated ATM-AVI ± MTZ for the treatment of cIAI and HAP/VAP.<sup>5, 6</sup>
- The number of patients receiving each treatment is based on the estimated market share of each treatment and total eligible patients.<sup>7, 8</sup>
- The model accounts for the burden of antimicrobial resistance to the treated individual. Compared to susceptible infections, resistant infections were associated with higher length of stay (LoS) and treatment costs, higher probability of death and higher probability of infection recurrence.<sup>9</sup>
- Subsequent treatments are not modelled explicitly but are assumed to be captured in the extended hospital days. The net budget impact is calculated as the difference in total cost between the worlds "with" and "without" ATM-AVI ± MTZ.

### Results

- In the world "with ATM-AVI", there were:
- 780 additional cures
- 281 fewer deaths
- 4,056 fewer bed days.
- Overall, the budget impact of infections suspected or documented to be caused by MBL-CRE including cIAI, HAP/VAP, cUTI and infections with LTO is €6,837,527 over 3 years, equivalent to €356 per patient.
- Deterministic sensitivity analysis indicates that results are sensitive to probability of cure, proportion of MBL-CRE, incidence of nephrotoxicity (NTX), hospitalisation cost, and LoS in intensive care unit (ICU).

Table 4: Treatment duration (days)							
Treatment	cIAI	cUTI	HAP/VAP	With LTO	Source		
ATM-AVI	7.80	7.80	10.40	10.40			
MTZ	7.50	7.50	-	-	EMBLAVEO <sup>®</sup> SmPC <sup>14</sup>		
COL + MER	8.50	8.50	10.30	10.30			
Cefiderocol	7.50	7.50	10.50	10.50	FETCROJA <sup>®</sup> SmPC <sup>13</sup>		

Abbreviations: ATM-AVI, aztreonam-avibactam; cIAI, complicated intra-abdominal infections; COL + MER, colistin + meropenem; CSR, clinical study report; cUTI, complicated urinary tract infections; HAP, hospitalacquired pneumonia; MTZ, metronidazole; SmPC, summary of product characteristics; VAP, ventilator-associated pneumonia

Table 5: Resource use inputs			
	Value	Source	
ICU cost per day	€1,590.17	Tan et al. 2012 <sup>15</sup>	
General ward cost per day	€867.83	Ministero dell'Economia e delle Finanze 2007 <sup>16</sup>	
Non-RRT additional LoS (days)	2.3	Simon et al. 2019 <sup>17</sup>	
RRT additional LoS (days)	5.2		
Number of in-hospital dialysis sessions	2.6	Assumes dialysis every other day per duration of additional Los	
Cost per instance of in-hospital dialysis	€147.25	Tariffe assistenza specialistica ambulatoriale <sup>18</sup>	
Annual cost of long-term dialysis	€26,518	Roggeri et al. 2017 <sup>19</sup>	
Length of receiving EoL care (weeks)	1	Assumption	
% time in ICU	50%	Assumption	

Abbreviations: AKI, acute kidney injury; BSC, best supportive care; EoL, end of life; ICU intensive care unit; LoS, length of stay; RRT, renal replacement therapy.

Table 6: Results

#### Figure 1: BIA model structure



#### Table 1: Number of patients with MBL-CREs

Indication	Year 1	Year 2	Year 3
cIAI	88	91	94
cUTI	1,430	1,480	1,531
HAP/VAP	825	854	884
LTO	443	458	474
Total targeted	2,786	2 <i>,</i> 883	2,984
Total number of patients targeted & suspected (1 targeted + 1.2 suspected)	6,191	6,407	6,632

Abbreviations: cIAI, complicated intra-abdominal infections; CRE, carbapenem-resistant Enterobacterales; cUTI, complicated urinary tract infections; HAP, hospital-acquired pneumonia; LTO, limited or no treatment options; MBL, metallo-β-lactamase; VAP, ventilator-associated pneumonia.

Treatment	World with- out ATM-AVI ± MTZ	World with ATM-AVI ± MTZ Year 1	World with ATM-AVI ± MTZ Year 2	World with ATM-AVI ± MTZ Year 3
ATM-AVI ± MTZ	0.00%	6.27	10.98%	15.09%
COL + MER	70.00%	66.73%	64.02%	62.91%
Cefiderocol	30.00%	27.00%	25.00%	22.00%

	World without		Difference	% change
Number of cured nationts				
	330	364	35	1በ
		<u></u>	<u></u>	10.5%
μαρ/ι/αρ	1 826	1 97/	1/17	8 1%
	1 357	1 /198	1/1	10.4%
Across all indications	7 891	8 671	780	9.9%
Number of deaths	7,051	0,071	780	5.570
	68	61	-7	-10.4%
	1 479	1 345	, _13 <u>/</u>	
ΗΔΡ/\/ΔΡ	1 157	1 054	-98	-8 5%
With ITO	458	417	-42	-9.1%
Across all indications	3.158	2.876	-281	-8.9%
Number of hospital bed days	0,200	2,070	201	0.070
cIAI	6.935	6.799	-136	-2.0%
cUTI	140.844	138.977	-1.867	-1.3%
HAP/VAP	133,861	132,386	-1,474	-1.1%
, With LTO	43,639	43,061	-578	-1.3%
Across all indications	325,279	321,223	-4,056	-1.2%
Total budget impact				
cIAI	€10,056,211	€10,170,563	€114,352	1.1%
cUTI	€196,062,828	€198,689,933	€2,627,105	1.3%
HAP/VAP	€201,354,091	€203,817,344	€2,463,253	1.2%
With LTO	€62,629,650	€64,262,466	€1,632,816	2.6%
Across all indications	€470,102,779	€476,940,307	€6,837,527	1.5%
Budget impact per patient				
cIAI	€16,544	€16,732	€188	1.1%
cUTI	€19,868	€20,135	€266	1.3%
HAP/VAP	€35,347	€35,779	€432	1.2%
With LTO	€20,484	€21,018	€534	2.6%
Across all indications	€24,446	€24,802	€356	1.5%

### Conclusion

- This study is **the first budget impact analysis** of ATM-AVI ± MTZ.
- The probability of cure, proportion of MBL-CRE, incidence of NTX, hospitalisation cost, and LoS in ICU are key drivers of model outcomes.
- A key strength of this analysis is that it gives an estimate of the impact of introducing ATM-AVI ± MTZ on the hospital formulary, using inputs and assumptions that have been validated with leading clinicians.
- A key limitation of the study is that results in the model are driven by resistance, however resistance rates are constantly evolving.
- This analysis includes the value of ATM-AVI considering the impact of resistant infections on the broader population value or the value from a public health perspective were included in the model. For example, adding a novel Gram-negative antibacterial agent such as ATM-AVI to the treatment diversity and may reduce the transmission of resistant pathogens and prevent infections in the wider population.
- These results show that, in the Italian setting, while the introduction of ATM-AVI ± MTZ is associated with higher drug acquisition costs, there is also an increase in the number of cured patients and a decrease in mortality and hospital LoS. This leads to cost savings, which largely offset the increased drug costs.

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