COST-EFFECTIVENESS OF CEFTAZIDIME-AVIBACTAM IN PATIENTS WITH COMPLICATED INTRA-ABDOMINAL INFECTIONS OR HOSPITAL-ACQUIRED PNEUMONIA CAUSED BY CARBAPENEM-RESISTANT ENTEROBACTERIACEAE IN CHINA

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Baiyi C[1], Furnback W[2], Chen Y[3], Dong P[3], Wang B[4], Ansari W[5], Charbonneau C[6]

[1]The First Hospital of China Medical University, Shenyang, NY, China, [2]Elysia Group Ltd, NY, USA, [3]Pfizer Investment Co., Ltd., Beijing, China, [4]Elysia Group Ltd, Taipei, Taiwan, [5]Pfizer Inc., New York, NY, USA, [6]Pfizer Inc., Paris, France

OBJECTIVE

- This study evaluates the cost-effectiveness of ceftazidime-avibactam (CAZ-AVI) a novel combination antibiotic in China for cIAI or HAP/VAP infections caused by carbapenem-resistant enterobacteriaceae (CRE).

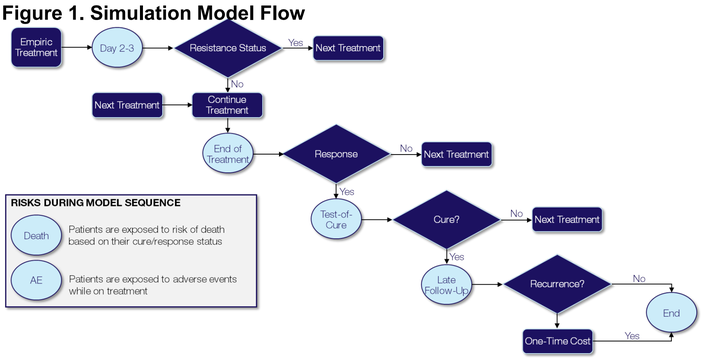
CONCLUSION

- CAZ-AVI is a cost-effective alternative to the standard of care as a first-line antibiotic for patients with CRE cIAI and HAP/VAP in China.

METHODS

- A previously developed patient-level simulation model was localized to China. The simulation model creates a unique cohort of patients based on pathogen prevalence and resistance characteristics. The cohort is then replicated and used in the comparator arm as well. The model includes different events, for which patients are assigned different times to the events based on the patient characteristics or treatment. The flow of the model is shown in Figure 1.
- To highlight the economic consequences of antibiotic resistance, the model allows resistance to have an impact in the following ways:
  - Switch treatment (i.e., start a new antibiotic course) at the time of microbiological results (24-72 hours), thus extended treatment & hospitalization duration
  - Have extended hospital length of hospital, following similar to that of patients with clinical failure
- The model took on a 5-year time horizon, the perspective of the China Ministry of Health and Welfares, and a 3% discount rate for both the cIAI and HAP/VAP indications.

Figure 1. Simulation Model Flow



- CAZ-AVI was evaluated as a first-line antibiotic and compared against meropenem for both the cIAI and HAP/VAP scenarios. CAZ-AVI was paired with metronidazole in patients with CRE cIAI. The second-line treatments for both comparator arms were colistin + tigecycline + high dose meropenem and colistin + high dose carbapenem (CBP) for cIAI and HAP/VAP, respectively.
- Utility values were not specific to indication and were 0.61 (0.31) for no response (Delate and Coons 2011) and 0.92 (0.09) for response / cured (Song et al. 2012).
- The base case effectiveness data (general trial populations) from the global model for *K. pneumonia*, *E. coli*, and *E. cloacae* was weighted in accordance with the pathogen prevalence to derive the effectiveness within the modeled CRE population. The effectiveness data was not adjusted beyond weighting for the pathogens prevalent in China from the Wang et al. paper (Table 1). Mortality inputs for each indication are shown in Table 2.

Table 1. Effectiveness, AEs, and Recurrence

	EFFECTIVENESS		PROBABILITY OF AE	PROBABILITY OF RECURRENCE
	TEST OF CURE	END OF TREATMENT		
cIAI				
First-Line Regimens				
CAZ-AVI + Metronidazole	99.7%[1]	94.0%[1]	4.90%[1]	0.00%[1]
Meropenem	97.1%[1]	94.8%[1]	3.80%[1]	0.57%[1]
Second-Line Regimens				
Colistin + Tigecycline + HD Meropenem	100.0%[2]	75.0%[2]	14.77%[5]	0.00%[4]
HAP / VAP				
First-Line Regimens				
CAZ-AVI	88.5%[3]	88.2%[3]	8.64%[3]	0.00%[4]
Meropenem	88.6%[3]	88.5%[3]	6.45%[3]	0.00%[4]
Second-Line Regimens				
Colistin + HD CBP	100.0%[4]	58.0%[2]	6.50%[6]	0.00%[4]

[1]RECLAIM CSR; [2]KOL Opinion; [3]REPROVE CSR; [4]Assumption; [5]Pooled Data (Chen et al. 2010; Fomin et al. 2005; Oliva et al. 2005; Qvist et al. 2012; Towfigh et al. 2010); [6]Assumed Same as Meropenem

and failure, respectively. Hospitalization rates were taken from the global model.

Hospital-Acquired Pneumonia (Including VAP)

- The resistance rate for CAZ-AVI was 2.5% (Sader et al. 2018). Resistance to meropenem was 81.83% (Wang et al. 2018). Second-line resistance was 2.00% for colistin (Wang et al. 2018)
- Drug costs per day were ¥4,188 for CAZ-AVI, ¥405 for meropenem, and ¥895 for colistin + high dose CBP. The cost per adverse event was ¥16,692 (Global Model; Adjusted Using PPP)
- The cost per day in the general ward of the hospital was ¥234 (WHO 2005), and ¥4,820 (Ye et al. 2017) in the ICU for both indications.

Complicated Intra-Abdominal Infections

- Resistance rates to CRE were 2.5% for CAZ+AVI + metronidazole, 84.9% of meropenem, and 1.89% for colistin + tigecycline + high dose meropenem (Sader et al. 2018; Wang et al. 2018). The resistance to the second-line antibiotic regimen for both indications was assumed to be equal to the resistance rate for colistin (1.89%), as it was lower than the rates for tigecycline and carbapenem.
- Drug costs per day were ¥4,417 for CAZ-AVI + metronidazole, ¥405 for meropenem, and ¥1,473 for colistin + tigecycline + HD meropenem. The cost per adverse event was ¥14,760 (Global Model; Adjusted Using PPP), and ¥15,645 per recurrence (Ouyang et al. 2016).
- The average number of days in the hospital were 11.71 for patients with a cure and 24.13 for patients with treatment failure. The proportion of hospitalized days in the ICU were 26.92%, 11.45% for patients with a cure.

Table 2. Mortality

	MORTALITY	
	RELATIVE RISK	DEATH (PROBABILITY)
cIAI		
Appropriate ET		4.80%[1]
Inappropriate ET w/o Resistant Pathogen	2.23[1]	
Inappropriate ET w/ Resistant Pathogen	2.68[2]	
HAP / VAP		
Appropriate ET		14.02%[3]
Inappropriate ET w/o Resistant Pathogen	1.88[3]	
Inappropriate ET w/ Resistant Pathogen	2.26[2]	

Note: ET = Empiric Therapy
[1]Sturkenboom et al. 2005; [2]Assumption; [3]Wilke et al. 2011

RESULTS

- CAZ-AVI was cost-effective (<3x GDP Per Capita) as a first-line treatment compared to meropenem in both cIAIs and HAP/VAP.

Complicated Intra-Abdominal Infections (cIAIs)

- CAZ-AVI + metronidazole had higher costs (¥18,823), and higher QALYs (1.11) compared to meropenem resulting in an ICER of ¥17,004 per QALY.
- The additional incremental costs for CAZ-AVI were driven by higher treatment costs of ¥28,639, which was partially offset by lower incremental hospitalization costs (-¥8,919), adverse event costs (-¥891), and recurrence costs (¥-6).
- The percentage of patients resistant to empiric therapy was reduced by 81.88% (2.82% vs. 84.70%) with CAZ-AVI + metronidazole. The percentage of patients with overall clinical cure during the 5-year time horizon was 86.72% for CAZ-AVI + metronidazole and 15.16% for meropenem. Mortality was decreased by 6.44%, and adverse events were reduced by 6.04% with CAZ-AVI + metronidazole compared to meropenem.

Table 3. Cost-Effectiveness Results

	COMPLICATED INTRA-ABDOMINAL INFECTION			HOSPITAL-ACQUIRED PNEUMONIA		
OUTCOME	CAZ-AVI + MDZ	MEROPENEM	INCREMENTAL	CAZ-AVI	MEROPENEM	INCREMENTAL
Costs						
Treatment Costs	¥41,211	¥12,572	¥28,639	43,934	13,630	30,304
Hospitalization Costs	¥17,955	¥26,874	-¥8,919	48,696	70,932	-22,236
Adverse Event Costs	¥897	¥1,788	-¥891	1,458	954	504
Recurrence Costs	¥0	¥6	-¥6	0	0	0
Total Costs	¥60,063	¥41,240	¥18,823	94,089	85,517	8,572
Health Outcomes						
LYs	4.40	4.11	0.30	3.93	3.35	0.58
QALYs	3.94	2.83	1.11	3.38	2..31	1.08
		ICER (QALYs)	¥17,004		ICER (QALYs)	¥7,953

Notes: MDZ = Metronidazole

Hospital-Acquired Pneumonia (Including VAP)

- Compared to meropenem total costs were ¥8,572 higher for CAZ-AVI. Incremental QALYs were 1.08 higher for CAZ-AVI, which resulted in an ICER of ¥7,953 per QALY gained for CAZ-AVI compared to meropenem.
- Incremental total costs were driven by an increase of ¥30,304 in treatment costs, and ¥504 in additional costs for adverse events. However, there was a reduction of ¥22,236 in hospitalization costs that were observed for CAZ-AVI compared to meropenem.
- Patients resistant to first-line therapy was 80.18% better for CAZ-AVI (2.25%) compared to meropenem (82.43%). The percentage of patients with an overall clinical cure during the 5-year time horizon was 66.80% for CAZ-AVI compared to 13.73% for the meropenem arm. Mortality was improved by 12.58% for CAZ-AVI (15.37%) compared to meropenem (27.95%).

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