DOI: 10.7860/JCDR/2026/82000.22707

Original Article

Microbiology Section

In-vitro Activity of Ceftazidime-avibactam Against Multidrug-resistant Pseudomonas Aeruginosa: Cross-sectional Study from a Tertiary Care Hospital

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ABSTRACT

Introduction: Multidrug-resistant (MDR) *Pseudomonas aeruginosa* poses a major therapeutic challenge in tertiary-care settings, necessitating local, Clinical and Laboratory Standards Institute (CLSI) -anchored susceptibility data for empiric therapy and stewardship. This study characterises Ceftazidime–Avibactam (CZA) activity and Minimum Inhibitory Concentration (MIC) distribution to support stewardship and local guideline updates

Aim: To evaluate the in-vitro activity of CZA against MDR *Pseudomonas aeruginosa* clinical isolates from a tertiary care hospital in North India.

Materials and Methods: This was a hospital-based, cross-sectional study conducted in the Bacteriology Division, Postgraduate Department of Microbiology, Government Medical College, Srinagar, Jammu and Kashmir, India, from January 2022 to December 2022 and included 108 non duplicate MDR *Pseudomonas aeruginosa* clinical isolates. Standardised workflows encompassed specimen culture and identification, Kirby-Bauer disc diffusion, and ceftazidime-avibactam MIC determination by E-test interpreted per CLSI M100 (2022), while demographic parameters recorded for context included age group and gender. Susceptibility was reported as proportions, and predictors of CZA non susceptibility were estimated using multivariable logistic regression. A p-value of <0.05 was considered statistically significant.

Results: Ceftazidime-Avibactam susceptibility was 63/108 (58.38%) and exceeded most β-lactam comparators, while *aztreonam* showed the highest susceptibility at 98/108 (90.74%). The MIC distribution clustered at 2-8 µg/mL with a peak at 8 µg/mL. In multivariable modelling, burn diagnosis {adjusted Odds Ratio (aOR)=2.15; 95% Confidence Interval (CI) 1.05-4.41}, carbapenem non susceptibility (aOR=2.72; 95% CI 1.34-5.51), and ceftazidime non susceptibility (aOR=2.08; 95% CI 1.01-4.29) independently predicted CZA non susceptibility.

Conclusion: Ceftazidime-avibactam was the most active among core antipseudomonal β-lactams, while *aztreonam* showed the highest overall susceptibility. The MIC histogram peaked at 8 µg/mL, with most isolates clustering between 2-8 µg/mL. Burn diagnosis, carbapenem non susceptibility, and ceftazidime non susceptibility independently predicted CZA non susceptibility.

Keywords: Beta-lactamase inhibitors, Cross resistance, Drug resistance, Microbial sensitivity tests

INTRODUCTION

An alarming rise in the prevalence of Multidrug-Resistant (MDR) gram-negative bacteria is a global public health issue [1]. Antimicrobial drug resistance among gram-negative pathogens (especially to β-lactam antibiotics) is typically caused by the production of β-lactamase enzymes, thereby limiting the treatment options available [2]. A class of β-lactamases that hydrolyses penicillins, first, second, and third generation cephalosporins and monobactams is referred to as extended spectrum β-lactamases or ESBLs. A substantial increase in the prevalence of ESBLs has led to unrestricted use of carbapenems [3]. Now, with the emergence of carbapenemase-producing bacteria (such as *Enterobacteriaceae*, *Pseudomonas aeruginosa*, and *Acinetobacter baumannii*) and their subsequent spread, there's an urgent need for coordinated action to reduce antimicrobial resistance [4,5].

A potent way to combat these β-lactamase-producing bacteria has been to combine a β-lactam antimicrobial agent with a β-lactamase inhibitor. However, classical β-lactamase inhibitors (i.e. Clavulanic acid, Tazobactam and Sulbactam) lack activity against many important groups or classes of β-lactamases and, thus, first-generation β-lactam/β-lactamase inhibitor combinations are frequently ineffective against MDR pathogens [6]. Ceftazidime is a proven, broad-spectrum, third-generation cephalosporin that binds to the bacterial cell wall Penicillin-binding Proteins (PBPs) and inhibits peptidoglycan cross-linking during its cell wall synthesis, thereby leading to bacterial cell lysis and death [7]. Avibactam is a novel, non β-lactam, β-lactamase inhibitor with no significant intrinsic antimicrobial activity but a comparatively broader spectrum of activity than classical β-lactamase inhibitors. Avibactam protects third-generation cephalosporins like ceftazidime from degradation by serine β-lactamases; Ambler class A (e.g. TEM-1, CTX-M-15, KPC-2, KPC-3), class C (e.g. AmpC) and some class D enzymes (e.g. OXA-10, OXA-48). It has no activity against class B enzymes (metallo- β-lactamases) [8].

Ceftazidime-avibactam is a combination of a third-generation cephalosporin, ceftazidime, and the novel, non β-lactam β-lactamzase inhibitor avibactam. It's available as an intravenous preparation and is administered in a fixed ratio of 4:1. CZA has excellent in-vitro activity against many gram-negative pathogens, including extended-spectrum β-lactamase, AmpC, *Klebsiella pneumoniae* carbapenemase and OXA-48-producing *Enterobacteriaceae* and drug-resistant *Pseudomonas aeruginosa* isolates; it is not active against metallo- β-lactamase-producing strains [9]. CZA is approved in adults (aged ≥18 years) for the treatment of complicated intra-abdominal infections in combination with metronidazole (cIAIs), complicated Urinary Tract Infections, including pyelonephritis (cUTIs) and hospital-acquired and ventilator-associated bacterial pneumonia Hospital-acquired Bacterial Pneumonia (HABP)/

Ventilator-associated Bacterial Pneumonia (VABP) HABP/VABP caused by susceptible gram-negative microorganisms: *E.coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterobacter cloacae*, *Klebsiella oxytoca*, *Citrobacter freundii* complex, and *Pseudomonas aeruginosa* [9-10]. CZA is also approved for the treatment of adults with complicated UTI, including pyelonephritis, as well as for the treatment of other infections due to aerobic gram-negative organisms in adult patients with limited treatment options [11]. In India, CZA is approved for the management of infections caused by carbapenem-resistant strains of *Enterobacteriaceae* alone if in-vitro susceptibility has been demonstrated or in combination with *aztreonam* if a synergy test demonstrates a zone of inhibition [12].

The primary objective of the study was to determine the susceptibility pattern and Minimum Inhibitory Concentrations (MICs) of CZA against MDR *Pseudomonas aeruginosa* isolates, and the secondary objectives were to compare the in-vitro susceptibility of CZA with other routinely used antipseudomonal agents and to analyse the distribution of MDR *Pseudomonas aeruginosa* across different clinical specimens and patient demographics. Hence, the study aimed to evaluate the in-vitro activity of CZA against MDR *Pseudomonas aeruginosa* clinical isolates from a tertiary care hospital in North India.

MATERIAL AND METHODS

This was a hospital-based, cross-sectional study conducted in the Bacteriology Division, Postgraduate Department of Microbiology, Government Medical College, Srinagar, Jammu and Kashmir, India, from January 2022 to December 2022, encompassing specimen receipt, organism identification, and antimicrobial susceptibility testing workflows as per departmental Standard Operating Procedures (SOPs). Ethical clearance for the study was obtained from the Institutional Ethics Committee of Government Medical College, Srinagar (IEC No: IEC-GMC-SGR/35/2021). As only de-identified, leftover clinical specimens submitted for routine diagnostics were included, informed consent was waived in accordance with institutional policy.

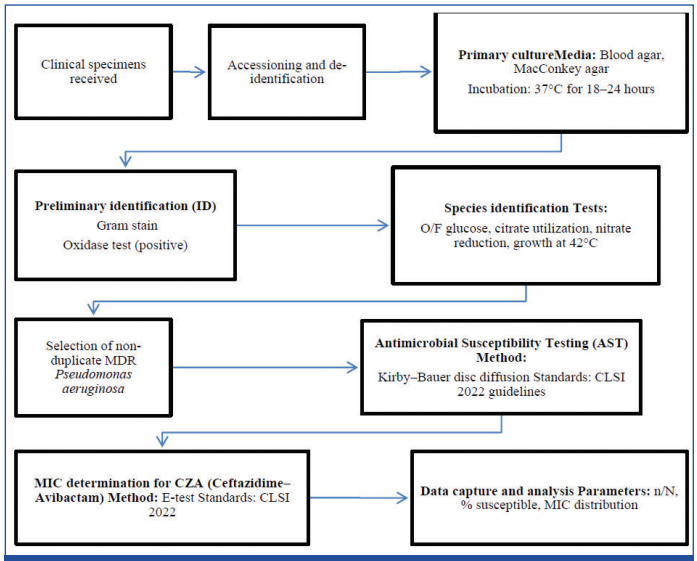
This was a time-bound study, and all subjects available during the study duration (January 2022- December 2022) were included in the study. The final sample comprised 108 non duplicate MDR isolates meeting the inclusion criteria.

Inclusion criteria: The inclusion criteria were clinical specimens from inpatients across all ages with culture-confirmed *Pseudomonas aeruginosa* that met MDR screening criteria during the study window Specimens of the patients admitted to the burn unit were included and clinically documented. All other cases were categorised according to the primary clinical diagnosis recorded in the case file (e.g. infected wound, Chronic obstructive pulmonary disease (COPD), Chronic suppurative otitis media (CSOM), sepsis/ community-acquired pneumonia, CSOM, gas gangrene).

Exclusion criteria: Duplicate isolates from the same patient episode, mixed cultures without resolvable pure growth, and isolates lacking complete susceptibility or MIC data required for analysis.

Study Procedure

Clinical samples, including pus, swabs, aspirates, and sputum, were collected according to the standard protocol and subjected to aerobic bacterial cultures in the laboratory as per the standard microbiological procedures [13]. The clinical specimens were processed and analysed following the workflow illustrated in [Table/Fig-1]. Once received, the clinical specimens were subjected to gram staining and subsequently inoculated on sheep blood agar, MacConkey agar plates, and incubated at 37°C for 18-24 hours for identification of the infectious agent. *Pseudomonas aeruginosa* was identified using routine spot tests (oxidase, catalase, pigment production) and a conventional biochemical panel per laboratory SOPs to species level. Further, Antimicrobial Susceptibility Testing (AST) was done on Mueller-Hinton Agar (MHA) by Kirby-Bauer disc diffusion method, and individual zone diameters were interpreted according to CLSI guidelines, 2022 [14] [Table/Fig-2].



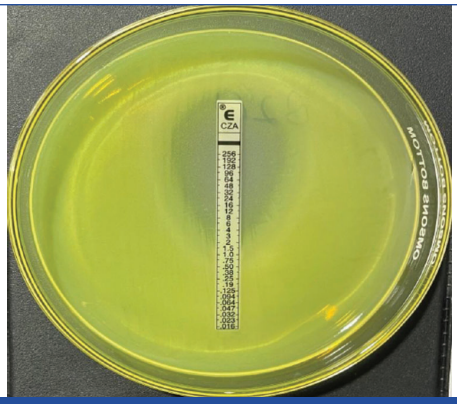
[Table/Fig-1]: Flowchart depicting sample processing and analysis.

[Table/Fig-2]: Antibiotic susceptibility testing of a clinical isolate on Mueller-Hinton agar using the Kirby-Bauer disc diffusion method.

Antibiotic discs considered for the routine primary testing panel were chosen according to the latest CLSI 2022 guidelines [14]. For cultures that were identified as *Pseudomonas aeruginosa*, following antibiotic discs were used: Tobramycin (TOB), Piperacillin/ Tazobactam (PIT), Ceftazidime (CAZ), Ceftazidime/Avibactam (CZA), Cefepime (CPM), Imipenem (IMP), Meropenem (MRP), Amikacin (AK), Gentamicin (GEN), Ciprofloxacin (CIP), Levofloxacin (LEV), Minocycline (MIN), Colistin (CS), Co-trimoxazole (COT). *Pseudomonas aeruginosa* American Type Culture Collection (ATCC) 27853 was used as a control.

All the *Pseudomonas aeruginosa* isolates were further classified as sensitive or resistant based on the interpretative zone sizes of Ceftazidime (3rd generation Cephalosporins), and Imipenem, Meropenem (Carbapenems). Those resistant to 3rd generation cephalosporins were noted as possible ESBL producers, and isolates showing resistance to Carbapenems were noted as possible Carbapenemase producers. CZA disc (30/20 µg) zone inhibition diameter was measured and interpreted as susceptible (≥21 mm) and resistant (≤20 mm) according to the latest CLSI guidelines [15].

Ceftazidime-avibactam MIC were detected for all the recovered *Pseudomonas aeruginosa* isolates by using the E-strips of CZA (Biomerieux) [Table/Fig-3].



[Table/Fig-3]: E-strip test for ceftazidime-avibactam.

Antimicrobial susceptibility testing was interpreted according to CLSI M100 performance standards for *Pseudomonas aeruginosa*; for ceftazidime-avibactam, MIC susceptible was (avibactam fixed at 4 mg/L) and resistant, consistent with Food and Drug Administration (FDA) interpretive criteria [14].

STATISTICAL ANALYSIS

Data were entered in Microsoft Excel and analysed using IBM SPSS Statistics for Windows, software version 26.0 (IBM Corp., Armonk, NY, USA). Categorical variables, including susceptibility profiles, were summarised as counts and percentages and compared using the Chi-square test or Fisher's exact test when any expected cell count was <5. Predictors of CZA non susceptibility were evaluated using multivariable logistic regression, and results were presented as adjusted odds ratios with 95% confidence intervals. All tests were two-sided, and a p-value<0.05 was considered statistically significant.

RESULTS

A total of 108 MDR *Pseudomonas aeruginosa* isolates were analysed, with 62 (57.41%) from female subjects and 46 (42.59%) from male subjects. Most isolates originated from swabs 87 (80.56%), followed by aspirates 17 (15.74%) and pus 4 (3.70%). Clinical categories contributing isolates included burns 41 (37.96%), infected wounds 27 (25.00%), sepsis/CAP 9 (8.33%), COPD 9 (8.33%), CSOM 7 (6.48%), with the remaining 15 samples comprised of gas gangrene, sub-phrenic abscess and surgical site. Ceftazidime-avibactam (CZA) showed higher activity among the tested, with 63/108 (58.38%) susceptible [Table/Fig-4].

Parameters	Category	n (%)
Gender	Males	46 (42.59 %)
	Females	62 (57.41%)
Age of patient	≤ 40 years	24 (22.22%)
	41-59 years	45 (41.67%)
	≥ 60 years	39 (36.11%)
Sample type	Swabs	87 (80.56%)
	Aspirates	17 (15.74%)
	Pus	4 (3.7%)
Clinical diagnosis	Burn	41 (37.96%)
	Infected wound	27 (25%)
	Sepsis/CAP	9 (8.33%)
	COPD	9 (8.33%)
	CSOM	7 (6.48%)
	Gas gangrene	6 (5.56%)
	Sub-phrenic abscess	6 (5.56%)
	Surgical site	3 (2.78%)

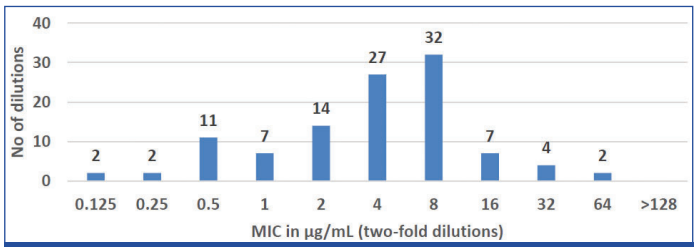
[Table/Fig-4]: Clinical and demographic profile for subjects (N=108)
CAP: Community-acquired pneumonia, COPD: Chronic obstructive pulmonary disease, CSOM: Chronic suppurative otitis media.

Among the tested antimicrobial agents, *aztreonam* exhibited the highest susceptibility rate, with 98 out of 108 isolates (91.59%) demonstrating sensitivity. Piperacillin-tazobactam showed moderate activity, with 54 isolates (49.75%) susceptible, followed by meropenem 48/108 (44.59%) and imipenem 46/108 (42.24%). Lower susceptibility rates were observed for ticarcillin 36/108 (33.11%), levofloxacin 27/108 (24.82%), and ceftazidime 27/108 (24.82%). Aminoglycosides such as amikacin and tobramycin exhibited limited efficacy [Table/Fig-5].

Antimicrobial category	Antimicrobial agent	Sensitive, n (%)
Aminoglycosides	Tobramycin	17 (15.66%)
	Amikacin	18 (16.55%)
Anti-pseudomonal Carbapenems	Imipenem	46 (42.24%)
	Meropenem	48 (44.59%)
Anti-pseudomonal Penicillin's	Ticarcillin	36 (33.11%)
Anti-pseudomonal Cephalosporins	Ceftazidime	27 (24.82%)
	Cefepime	9 (8.26%)
Anti-pseudomonal β-lactam + β-lactamase inhibitor	Piperacillin/Tazobactam	54 (49.75%)
	Ceftazidime/Avibactam	63 (58.38%)
Anti-pseudomonal Fluoroquinolones	Levofloxacin	27 (24.82%)
Monobactams	*Aztreonam*	98 (90.74%)

[Table/Fig-5]: Antimicrobial categories and their susceptibility pattern, *Pseudomonas aeruginosa* (N=108).

The MIC distribution for CZA spanned 0.125-64 µg/mL, with most of the isolates clustering between 2 and 8 µg/mL and a peak at 8 µg/mL. Very few isolates exhibited higher MICs at 16-64 µg/mL. No isolates were observed at >128 µg/mL, indicating that most isolates were within the susceptible or intermediate range [Table/Fig-6].



[Table/Fig-6]: Minimum inhibitory concentration (MIC) distribution of ceftazidime-avibactam against multidrug-resistant *Pseudomonas aeruginosa* isolates (N=108).

Burn diagnosis and carbapenem non susceptibility had an independent association with CAZ-AVI non susceptibility, consistent with shared resistance mechanisms and high antimicrobial exposure in burn units. Prior ceftazidime non susceptibility was a significant predictor after adjustment, suggesting overlapping β-lactamase or porin/efflux contributions. Demographics and specimen type were not independently associated with resistance [Table/Fig-7].

Predictor	aOR	95% CI	p-value
Age ≥60 years	1.42	0.70-2.87	0.33
Females	0.91	0.47-1.76	0.78
Swab specimen	1.68	0.70-4.03	0.24
Burn diagnosis	2.15	1.05-4.41	0.036
Carbapenem NS (MEM or IMP)	2.72	1.34-5.51	0.006
Ceftazidime NS	2.08	1.01-4.29	0.048

[Table/Fig-7]: Predictors of CZA non susceptibility (N=108).
NS=Non Susceptible (Intermediate and resistant on MIC); Nonsusceptible is defined per CLSI 2022 M100 as I+R; *Multivariable logistic regression; The swab included wound/pus swab; carbapenem NS was positive if either imipenem or meropenem is NS.

DISCUSSION

The present study evaluated the in-vitro activities of CZA against 108 non duplicate MDR *Pseudomonas aeruginosa*. In the current study,

CZA demonstrated meaningful in-vitro activity with 63/108 (58.4%) isolates classified as susceptible, outperforming several routinely used antipseudomonal β-lactams. This finding supports the role of CZA as an important therapeutic option for difficult-to-treat *P. aeruginosa* in settings with high β-lactam resistance. The results are consistent with multiple previous studies that also demonstrated *Pseudomonas* to be most susceptible to CZA [16,17]. *Aztreonam* showed the highest activity at 98/108 (91.6%). High susceptibility of *Pseudomonas* to *Aztreonam* has been reported by multiple previous studies [18,19]. However, its use is often limited by co-resistance patterns and the need for combination therapies in severe infections. As noted by Taha R et al., *aztreonam's* role is increasingly confined to specific cases involving Metallo-β-lactamase (MBL) producers when combined with avibactam [18]. The relatively lower cefepime and ceftazidime susceptibilities are coherent with β-lactam resistance driven by AmpC β-lactamase /*Pseudomonas*-derived cephalosporinase, (AmpC/PDC), efflux, and porin alterations, whereas CZA's inhibitor component mitigates some enzyme effects, explaining its intermediate position between *aztreonam* and other β-lactams [19,20]. Tobramycin and amikacin, representing the aminoglycoside class, showed limited efficacy, with susceptibility rates of 15.66% and 16.55%, respectively. These findings align with global trends, where aminoglycosides face declining efficacy due to enzymatic modification by aminoglycoside-modifying enzymes [21,22]. Comparable resistance levels were noted by Aliakbarzade K et al., highlighting the global nature of aminoglycoside resistance [23]. Imipenem and meropenem, cornerstone therapies for gram-negative infections, demonstrated susceptibility rates of 42.24% and 44.59%, respectively. The emergence of carbapenemase-producing strains significantly compromises their effectiveness, as seen in the present study. Similar concerns were raised in a review by Cantón R et al., which emphasised the need for alternative therapies [4]. Ceftazidime and cefepime showed lower susceptibility rates (24.82% and 8.26%, respectively), reflecting the widespread prevalence of β-lactamase-mediated resistance. The addition of avibactam to ceftazidime significantly enhances its efficacy, as evidenced by the improved susceptibility profile of CZA. Findings from Kempf M et al., further corroborate these observations, showing the enhanced activity of CZA against resistant strains [24]. Levofloxacin's susceptibility rate of 24.82% highlights the diminished role of fluoroquinolones in treating MDR *P. aeruginosa*. This trend is consistent with the work of multiple previous studies, which documented widespread fluoroquinolone resistance [25,26].

The MIC distribution was unimodal with a prominent peak at 8 µg/mL and most isolates clustering in the 2-8 µg/mL range. Observing the bulk of MICs in this intermediate-to-low range indicates that many isolates lie close to susceptibility breakpoints and that small shifts in resistance mechanisms could materially affect categorical interpretations. The present MIC histogram therefore aligns with previous reports where CZA exhibited strong in-vitro activity against resistant *P. aeruginosa* strains, particularly those producing class A and class C β-lactamases [27]. Ongoing surveillance is essential, as recent reports indicate that resistance to CZA is increasing in certain geographic regions, particularly in isolates co-harbouring MBLs and other resistance determinants [28].

In multivariable analysis, burn diagnosis, carbapenem non susceptibility, and ceftazidime non susceptibility independently predicted CZA non susceptibility in the current study cohort. The higher likelihood of CZA non susceptibility among burn isolates likely reflects both heavy prior antimicrobial exposure and transmission dynamics in burn units; this mirrors older and contemporary reports documenting increased resistance in thermally injured patients. Similarly, the strong association between carbapenem non susceptibility and reduced CZA susceptibility supports the concept of overlapping resistance determinants (e.g., co-occurrence of carbapenemases, porin/efflux changes) that can compromise multiple β-lactam agents [26].

The current study's findings reinforce that CZA remains a key option against MDR *Pseudomonas aeruginosa*, though its efficacy is context-dependent. When MICs approach breakpoints or in settings with burn unit exposure and carbapenem resistance, monotherapy may be inadequate; combination strategies such as *aztreonam* for MBL producers and stewardship-driven use are recommended.

Limitation(s)

Notably, the study's limitations, including single-centre design, lack of molecular data, and modest sample size, restrict generalisability but underscore practical priorities. Ongoing MIC surveillance, targeted molecular testing, and judicious formulary policies to sustain CZA's clinical utility.

CONCLUSION(S)

Ceftazidime-avibactam exhibited notable in-vitro activity against MDR *Pseudomonas aeruginosa*, surpassing several conventional antipseudomonal agents. Most isolates had MICs within the susceptible range, supporting its role as an effective therapeutic option in this setting. These findings highlight the need to integrate CZA into local antibiograms and treatment protocols for difficult-to-treat gram-negative infections. Continued surveillance and molecular characterisation are essential to detect emerging resistance, alongside robust antimicrobial stewardship to optimise use and preserve efficacy.

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PLAGIARISM CHECKING METHODS: [Jain H et al.]
- Plagiarism X-checker: Aug 02, 2025
- Manual Googling: Dec 25, 2025
- iThenticate Software: Dec 27, 2025 (8%)

ETYMOLOGY: Author Origin

EMENDATIONS: 7

AUTHOR DECLARATION:
- Financial or Other Competing Interests: None
- Was Ethics Committee Approval obtained for this study? Yes
- Was informed consent obtained from the subjects involved in the study? No
- For any images presented appropriate consent has been obtained from the subjects. No

Date of Submission: **Jul 13, 2025**
Date of Peer Review: **Sep 18, 2025**
Date of Acceptance: **Dec 29, 2025**
Date of Publishing: **Apr 01, 2026**