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Reverse MIC drift of nemonoxacin and its advantages against Gram-positive bacteria: A 10-year multicenter surveillance study

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ABSTRACT

Background: Antimicrobial resistance (AMR) threatens global health. Conventional fluoroquinolones have experienced accelerated resistance due to target-enzyme mutations and are further constrained by safety concerns. Nemonoxacin, as the first non-fluorinated quinolone, overcomes the aforementioned drawbacks by removing the fluorine atom at C-6 and introducing a methoxy substitution at C-8, but the trends in its antibacterial activity and the evolution of its antimicrobial spectrum remain unclear.

Objective: To assess the long-term evolution of the antibacterial activity of the novel non-fluorinated quinolone nemonoxacin against clinical isolates, evaluate its resistance risk, and compare it with conventional quinolones.

Methods: Clinical Gram-positive and Gram-negative isolates were collected from a multicenter network of 22 hospitals nationwide between 2015 and 2024. Minimum inhibitory concentrations (MICs) of nemonoxacin and comparator drugs were determined by agar dilution according to the Clinical and Laboratory Standards Institute (CLSI) standards; MIC trends were analyzed using Spearman's rank correlation coefficient and the Cochran–Armitage trend chi-square test.

Results: Nemonoxacin exhibited markedly superior antibacterial activity against Gram-positive bacteria compared with conventional quinolones. During the 10-year surveillance period, the isolation rate of methicillin-resistant *Staphylococcus aureus* (MRSA) was 34.95% and that of methicillin-resistant *Staphylococcus epidermidis* (MRSE) was 82.08%. The susceptibility rate of MRSA to nemonoxacin was 78.5%, and susceptibility rates among other *staphylococci* were all ≥ 80%, which is 19.4%–27.7% higher than that of conventional quinolones; for *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae*, and the viridans group *streptococci*, the MIC_{50} and MIC_{90} values were 1/2–1/64 those of fluoroquinolones, with a susceptibility rate of 99.4%. Among Gram-negative bacteria, *Escherichia coli* (extended-spectrum β-lactamase [ESBL]-positive rate 53.3%) and *Klebsiella pneumoniae* (ESBL-positive rate 23.5%) showed susceptibility rates to nemonoxacin of 41.0% and 60.9%, respectively, outperforming ciprofloxacin and levofloxacin; carbapenem-susceptible, ESBL-negative *K. pneumoniae* had a susceptibility rate up to 90.2%. For *Haemophilus influenzae*, nemonoxacin MICs ranged from 0.004 to 8 mg/L, which are 1/2–1/4 those of other quinolones; for *Moraxella catarrhalis*, the MICs were similar to those of fluoroquinolones. The resistance of *Staphylococcus aureus* and *Escherichia coli* to nemonoxacin showed a declining trend compared with the start year, manifesting as a "reverse MIC drift," and the decrease in *S. aureus* resistance was not significantly correlated with the decline in MRSA isolation rate. Among Gram-positive bacteria, isolates from intensive care unit (ICU) patients and elderly patients, as well as *S. aureus* recovered from sputum and urine specimens, exhibited higher rates of resistance to nemonoxacin than isolates from other sources; among Gram-negative bacteria, ICU-isolated *Klebsiella pneumoniae*, *Haemophilus influenzae* isolated from adult patients, and *Escherichia coli* and *K. pneumoniae* isolated from urine specimens showed higher nemonoxacin resistance rates than isolates from other sources.

Conclusion: By virtue of its non-fluorinated structure and dual-target mechanism, nemonoxacin effectively curtailed the development of resistance over the 10-year period, demonstrating a sustained advantage particularly in infections caused by *S. aureus*, *Streptococcus pneumoniae*, and *H. influenzae*. The maintained or improved trend in its antibacterial activity suggests that, through the synergy of structural innovation and precision use, reversal of resistance evolution may be achievable, providing a new direction for optimizing anti-infective therapy.

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Antimicrobial resistance (AMR) has become a major global public health challenge and poses a serious threat to human health.[1] A thorough understanding of trends in the antimicrobial activity of existing drugs and the evolution of their antimicrobial spectra is critically important for guiding rational clinical use and delaying the emergence of resistance.

Nemonoxacin is the world's first non-fluorinated quinolone and has demonstrated broad-spectrum activity against a range of clinically relevant pathogens, particularly Gram-positive bacteria.[2] By virtue of its distinctive C-8 methoxy structural modification, it not only enhances antibacterial potency but also avoids the resistance mechanisms associated with conventional fluoroquinolones.[3] As the clinical use of nemonoxacin has been extended over time, it is necessary to systematically assess the long-term evolution of its antibacterial activity and spectrum. MIC is an important indicator for assessing the *in vitro* antibacterial activity of antimicrobial drugs; long-term dynamic monitoring can reveal subtle "drift" (MIC creep) in bacterial susceptibility to a specific drug, foreshadow potential resistance trends, and provide early warning for adjustments to clinical treatment strategies.[4]

This study, based on ten years (2015–2024) of nationwide multicenter MIC monitoring data from clinical isolates, systematically analyzes the changes in nemonoxacin's antibacterial activity against Gram-positive and Gram-negative bacteria, compares resistance spectrum differences with related drugs and commonly used clinical drugs, and aims to elucidate nemonoxacin's spectrum advantages and resistance risks across different infection scenarios to provide evidence for optimizing its clinical application strategies and guiding anti-infective therapy.

Materials and methods

Test strains

Clinical bacterial isolates were collected from 22 designated hospitals nationwide; for the same patient, only the first isolate of the same strain was selected. According to CLSI standards, the standard quality control strains used were *Staphylococcus aureus* (American Type Culture Collection [ATCC] 29213), *Streptococcus pneumoniae* ATCC 49619, *Escherichia coli* ATCC 25922, *Escherichia coli* ATCC 35218, *Haemophilus influenzae* ATCC 49247, and *Haemophilus influenzae* ATCC 49766, provided by the Institute of Clinical Pharmacology, Peking University. All strains were stored at −80℃ and were revived prior to testing.

Test drugs

Nemonoxacin, produced by Xinchang Pharmaceutical Factory, Zhejiang Medicine Co., Ltd.; ciprofloxacin, produced by Shangyu Jingxin Pharmaceutical Co., Ltd.; moxifloxacin, produced by Hangzhou Yangyangkang Biotechnology Co., Ltd.; levofloxacin, produced by Daiichi Sankyo Pharmaceutical (Shanghai) Co., Ltd. or by the China Institute for the Control of Pharmaceutical and Biological Products; penicillin, amoxicillin, cefuroxime, ceftriaxone, tazobactam, clavulanic acid, and sulbactam, purchased from the China Institute for the Control of Pharmaceutical and Biological Products; ceftazidime, products of the China Institute for the Control of Pharmaceutical and Biological Products or Qilu Antibiotics Pharmaceutical Co., Ltd.; ampicillin, product of INALCO; vancomycin, purchased from the China Institute for the Control of Pharmaceutical and Biological Products or Eli Lilly and Company; linezolid, products of Pfizer or Bayer HealthCare Pharmaceuticals; imipenem, products of Merck & Co., Inc. or AstaTech; meropenem, products of the China Institute for the Control of Pharmaceutical and Biological Products or Sumitomo Pharma (Suzhou) Co., Ltd.; piperacillin, product of TargetMol. For the combination formulations, the ampicillin/sulbactam ratio was 2:1; in piperacillin/tazobactam the tazobactam concentration was fixed at 4 mg/L; and in amoxicillin/clavulanic acid the clavulanic acid concentration was fixed at 4 mg/L.

Test methods

The standard agar two-fold dilution method recommended by the CLSI was used: test bacterial suspensions were inoculated with a multipoint inoculator, with an inoculum of 1×10^4 CFU per spot. In each experiment a standard strain was used as the quality control strain for susceptibility testing; drug-free plates were used as growth controls for the test strains. Phenotypic detection of ESBL was performed according to the CLSI-recommended method, using cefotaxime with 4 mg/L clavulanic acid for determination. Carbapenem-susceptible was defined as susceptibility to imipenem or meropenem, while carbapenem-non-susceptible defined as non-susceptibility to imipenem or meropenem.

Statistical analysis

MIC data were analyzed using SPSS 27.0 to calculate MIC_{50} and MIC_{90}. According to the antimicrobial breakpoints issued by CLSI 2025, bacterial susceptibility and resistance rates were calculated.[5] For drugs without interpretive criteria, calculations were referenced to EUCAST 2025 standards; see the notes following the tables for details.[6] The susceptibility to nemonoxacin was interpreted using the breakpoints provided in the package insert for nemonoxacin maleate sodium chloride injection. Spearman rank correlation coefficient analysis was performed using SPSS 27.0 to assess changes in nemonoxacin geometric mean MIC (GM MIC) over the 10-year period, in order to evaluate the overall resistance level of each species to nemonoxacin during the decade; $P < 0.05$ was considered statistically significant. The Cochran-Armitage trend chi-square test was performed in R 4.2.2 to evaluate, for each species, the annual trend in the proportion of isolates with nemonoxacin MICs greater than the nemonoxacin MIC_{50} of the surveillance start year (2015 or 2017), thereby assessing changes in the share of high-MIC isolates over the ten years; $P < 0.05$ was considered statistically significant.

Results

In vitro activity of nemonoxacin and comparator drugs against Gram-positive bacteria

Changes in MIC values and resistance rates of nemonoxacin and comparator drugs against Gram-positive bacteria are shown in Table 1. During the 10-year study period, the detection rates of MRSA and MRSE were 34.95% and 82.08%, respectively. Nemonoxacin MICs for *Staphylococcus aureus*, *S. epidermidis*, *Staphylococcus haemolyticus* and other staphylococci were 1/8 those of moxifloxacin and 1/16–1/64 those of ciprofloxacin and levofloxacin. Except that MRSA had a susceptibility rate of 78.5% to nemonoxacin, susceptibility rates for the remaining bacteria were all > 80%, markedly higher than those of other quinolones and also superior to azithromycin, oxacillin and gentamicin.

Nemonoxacin exhibited good activity against streptococcal species, with MICs ranging from 0.008 to 16 mg/L. For *Streptococcus pneumoniae*, *Streptococcus pyogenes*, *Streptococcus agalactiae* and the viridans group streptococci, MICs were 1/2–1/4 those of moxifloxacin and 1/4–1/64 those of ciprofloxacin and levofloxacin. During the 10-year study period, the susceptibility rate of *Streptococcus pneumoniae* to nemonoxacin was 99.4%, outperforming macrolides, β-lactams, and others.

In vitro activity of nemonoxacin and comparator drugs against Gram-negative bacteria

In this surveillance, the ESBL phenotype detection rates for *Escherichia coli* and *Klebsiella pneumoniae* were 53.3% and 23.5%, respectively. The susceptibility rates to nemonoxacin for *Escherichia coli*

Table 1
Antibacterial activity of nemonoxacin and comparator drugs against Gram-positive (G+) bacteria.

Species	Antibacterials	MIC_{50}	MIC_{90}	S	R
Staphylococcus aureus (*n* = 3505)	Nemonoxacin	0.062	1	92.2	7.8
	Ciprofloxacin	0.5	64	68.7	24.1
	Levofloxacin	0.25	32	78.2	21.0
	Moxifloxacin	0.062	8	78.8	20.4
	Oxacillin	0.5	256	67.4	32.6
	Gentamicin	0.25	32	79.0	19.3
	Azithromycin	512	512	38.1	61.5
	Minocycline	0.125	2	94.1	2.8
	Linezolid	1	2	100.0	0
	Vancomycin	1	2	100.0	0
MSSA (*n* = 2280)	Nemonoxacin	0.062	0.5	99.6	0.4
	Ciprofloxacin	0.5	8	78.3	13.2
	Levofloxacin	0.25	4	89.1	10.4
	Moxifloxacin	0.062	2	89.4	10.1
	Oxacillin	0.5	1	100.0	0
	Gentamicin	0.25	16	86.3	12.4
	Azithromycin	64	512	47.7	51.9
	Minocycline	0.125	0.125	99.5	0
	Linezolid	1	2	100.0	0
	Vancomycin	1	1	100.0	0
MRSA (*n* = 1225)	Nemonoxacin	0.062	2	78.5	21.5
	Ciprofloxacin	1	128	50.8	44.2
	Levofloxacin	0.5	64	57.8	40.9
	Moxifloxacin	0.125	16	59.1	39.4
	Oxacillin	64	512	6.9	93.1
	Gentamicin	0.5	128	65.6	32.1
	Azithromycin	512	512	20.2	79.3
	Minocycline	0.125	8	84.2	7.8
	Linezolid	1	2	100.0	0
	Vancomycin	1	2	100.0	0
Staphylococcus epidermidis (*n* = 798)	Nemonoxacin	0.125	0.5	93.2	6.8
	Ciprofloxacin	4	32	41.4	54.3
	Levofloxacin	2	16	43.5	49.5
	Moxifloxacin	1	4	49.9	27.2
	Oxacillin	2	128	18.8	81.2
	Gentamicin	0.25	64	57.8	37.0
	Azithromycin	128	512	23.2	76.4
	Minocycline	0.25	0.5	99.1	0.6
	Linezolid	0.5	1	99.2	0.8
	Vancomycin	1	2	100.0	0
MSSE (*n* = 143)	Nemonoxacin	0.031	0.25	98.6	1.4
	Ciprofloxacin	0.25	8	69.2	25.9
	Levofloxacin	0.25	4	71.3	23.8
	Moxifloxacin	0.062	1	76.9	9.8
	Oxacillin	0.125	0.25	100.0	0
	Gentamicin	0.125	16	79.0	15.4
	Azithromycin	128	512	34.3	65.0
	Minocycline	0.125	0.5	99.3	0.7
	Linezolid	0.5	1	100.0	0
	Vancomycin	1	2	100.0	0
MRSE (*n* = 655)	Nemonoxacin	0.25	1	92.1	7.9
	Ciprofloxacin	4	32	35.3	60.5
	Levofloxacin	4	16	37.4	55.1
	Moxifloxacin	1	4	44.0	31.0
	Oxacillin	4	256	1.1	98.9
	Gentamicin	0.5	128	53.1	41.7
	Azithromycin	128	512	20.8	78.9
	Minocycline	0.25	0.5	99.1	0.6
	Linezolid	0.5	1	99.1	0.9
	Vancomycin	1	2	100.0	0
Staphylococcus haemolyticus (*n* = 261)	Nemonoxacin	0.5	1	92.7	7.3
	Ciprofloxacin	32	64	17.2	80.8
	Levofloxacin	16	32	19.9	79.3
	Moxifloxacin	2	8	20.3	70.9
	Oxacillin	512	512	10.0	90.0
	Gentamicin	32	128	25.7	70.5
	Azithromycin	128	512	5.7	94.3
	Minocycline	0.25	0.5	98.1	1.5
	Linezolid	1	2	99.6	0.4
	Vancomycin	1	2	100.0	0
Other staphylococci (*n* = 684)	Nemonoxacin	0.25	2	81.3	18.7
	Ciprofloxacin	4	64	47.5	50.7
	Levofloxacin	2	128	48.1	49.1
	Moxifloxacin	0.5	16	50.9	44.0

(*continued on next page*)

Table 1 (*continued*)

Species	Antibacterials	MIC_{50}	MIC_{90}	S	R
	Oxacillin	16	256	26.9	73.1
	Gentamicin	4	32	62.1	22.4
	Azithromycin	128	512	23.4	75.4
	Minocycline	0.125	0.25	99.0	0.7
	Linezolid	1	2	95.5	4.5
	Vancomycin	0.5	1	100.0	0
Streptococcus pneumoniae (n = 1366)	Nemonoxacin	0.062	0.125	99.4	0.6
	Ciprofloxacin	1	2	-	-
	Levofloxacin	1	2	97.7	1.3
	Moxifloxacin	0.125	0.25	98.8	0.8
	Penicillin	1	4	88.9	1.3
	Ceftriaxone	0.5	2	78.2	6.7
	Azithromycin	256	512	2.3	96.7
	Linezolid	0.5	1	100.0	-
Viridans group streptococci (n = 600)	Nemonoxacin	0.062	0.5	-	-
	Ciprofloxacin	1	32	-	-
	Levofloxacin	0.5	16	82.2	16.5
	Moxifloxacin	0.125	2	-	-
	Penicillin	0.062	2	71.2	4.8
	Ceftriaxone	0.125	1	90.0	8.2
	Azithromycin	2	256	39.3	55.5
	Linezolid	0.5	1	100.0	-
Streptococcus pyogenes (n = 207)	Nemonoxacin	0.062	0.125	-	-
	Ciprofloxacin	0.25	1	-	-
	Levofloxacin	0.5	1	96.6	3.4
	Moxifloxacin	0.125	0.25	96.6	3.4
	Penicillin	0.016	0.062	99	-
	Ceftriaxone	0.016	0.031	98.1	-
	Azithromycin	256	512	6.3	93.7
	Linezolid	0.5	1	100	-
Streptococcus agalactiae (n = 581)	Nemonoxacin	1	1	-	-
	Ciprofloxacin	16	32	-	-
	Levofloxacin	16	32	42.3	57.5
	Moxifloxacin	2	4	42.3	57.7
	Penicillin	0.031	0.062	98.1	-
	Ceftriaxone	0.062	0.062	98.5	-
	Azithromycin	256	512	15.7	84.3
	Linezolid	1	1	99.8	-

Note: For staphylococci, the susceptibility to nemonoxacin is interpreted using the breakpoints provided in the package insert of nemonoxacin malate sodium chloride injection (susceptible: ≤ 1 mg/L; resistant ≥ 2 mg/L); for *Streptococcus pneumoniae*: the susceptibility to penicillin and ceftriaxone are interpreted using the CLSI non-meningitis intravenous breakpoints; the susceptibility to nemonoxacin is interpreted using the breakpoints provided in the package insert of nemonoxacin malate sodium chloride injection (susceptible: ≤ 0.5 mg/L; resistant ≥ 1 mg/L). For *Streptococcus pyogenes* and *Streptococcus agalactiae*: the susceptibility to moxifloxacin is interpreted using EUCAST standards (susceptible: ≤ 0.5 mg/L; resistant > 0.5 mg/L). -: No interpretive criteria

and *Klebsiella pneumoniae* during the 10-year study were 41.0% and 60.9%, respectively, both superior to those of ciprofloxacin and levofloxacin (Table 2). Quinolones retained good activity against carbapenem-susceptible, ESBL-negative *Klebsiella pneumoniae*, with susceptibility rates ≥ 80%; nemonoxacin showed the highest susceptibility at 90.2%. For ESBL-positive *Escherichia coli* and *Klebsiella pneumoniae*, carbapenem antibacterial drugs still demonstrate very good activity, bacterial susceptibility rates were above 87%.

Nemonoxacin exhibited good activity against *Haemophilus influenzae*, with MICs of 0.004–8 mg/L, equivalent to 1/4 that of moxifloxacin, and a susceptibility rate of 97.1%. Nemonoxacin MICs for *Moraxella catarrhalis* were 0.004–8 mg/L, similar to those of moxifloxacin and levofloxacin.

Trends in resistance of nemonoxacin across different strains

The Spearman rank correlation coefficients ρ for *Staphylococcus aureus* and *Escherichia coli* were −0.711 and −0.833, respectively, with P values of 0.021 and 0.01, indicating that over time the GM MIC decreased significantly and that the overall 10-year resistance levels of both species showed a declining trend. In the Cochran-Armitage trend chi-square test, the P values for both species were < 0.05; for *Staphylococcus aureus* and *Escherichia coli*, the annual proportion of isolates with MICs greater than the baseline MIC_{50} decreased over time, indicating a significant reduction in the proportion of high-MIC isolates. The Cochran-Armitage trend test found that for MRSE, viridans group streptococci, and *Klebsiella pneumoniae*, the proportion of isolates with nemonoxacin MICs above the baseline MIC_{50} showed an increasing trend over time ($P < 0.05$); conversely, for MRSA, ESBL-positive *Escherichia coli*, carbapenem-susceptible and ESBL-negative *Klebsiella pneumoniae*, and *Moraxella catarrhalis*, the proportion showed a decreasing trend ($P < 0.05$). However, Spearman rank correlation analysis did not show a significant monotonic change in the GM MICs of the species mentioned above. This suggests that the composition proportion of highly resistant strains within the population structure may be changing, but the change has not yet been strong enough to drive a statistically significant shift in the overall MIC level — it is only statistically significant in the Cochran-Armitage trend chi-square test.

Joint evaluation by Spearman rank correlation coefficients and the Cochran-Armitage trend chi-square test indicates that *Staphylococcus aureus* and *Escherichia coli* demonstrate a reduction in resistance to nemonoxacin both at the overall level and in population structure (Table 3).

Because the observed MRSA isolation rate was broadly consistent with the overall trend in *Staphylococcus aureus* GM MIC (Fig. 1), this

Table 2
Antibacterial activity of nemonoxacin and comparator drugs against Gram-negative bacteria.

Species	Antibacterials	MIC_{50}	MIC_{90}	S	R
Escherichia coli (*n* = 2899)	Nemonoxacin	8	64	41.0	59.0
	Ciprofloxacin	8	128	31.0	63.0
	Levofloxacin	8	32	31.3	61.3
	Piperacillin/Tazobactam	2	16	87.9	9.8
	Ceftriaxone	64	512	41.0	58.5
	Ceftazidime	2	64	60.6	31.5
	Imipenem	0.125	0.25	97.0	2.8
	Meropenem	0.016	0.031	97.2	2.4
	Amikacin	4	8	75.8	6.7
	Minocycline	4	32	67.5	19.6
Carbapenem-susceptible, ESBL-negative *Escherichia coli* (*n* = 1279)	Nemonoxacin	1	32	61.1	38.9
	Ciprofloxacin	0.5	64	48.7	43.8
	Levofloxacin	1	16	48.2	42.2
	Piperacillin/Tazobactam	2	8	93.4	5.3
	Ceftriaxone	0.062	0.5	92.2	7.0
	Ceftazidime	0.25	1	93.4	5.3
	Imipenem	0.125	0.25	99.8	0.2
	Meropenem	0.016	0.031	99.9	0.1
	Amikacin	4	8	80.1	2.7
	Minocycline	2	16	74.5	15.3
Carbapenem-nonsusceptible, ESBL-negative *Escherichia coli* (*n* = 76)	Nemonoxacin	32	256	14.5	85.5
	Ciprofloxacin	64	256	5.3	93.4
	Levofloxacin	32	128	5.3	89.5
	Piperacillin/Tazobactam	512	512	1.3	96.1
	Ceftriaxone	512	512	0	100.0
	Ceftazidime	512	512	0	100.0
	Imipenem	16	64	0.0	98.7
	Meropenem	16	64	0.0	88.2
	Amikacin	4	512	53.9	39.5
	Minocycline	8	128	34.2	47.4
ESBL-positive *Escherichia coli* (*n* = 1544)	Nemonoxacin	16	64	25.6	74.4
	Ciprofloxacin	16	128	17.6	77.4
	Levofloxacin	8	32	18.7	75.8
	Piperacillin/Tazobactam	2	32	87.6	9.2
	Ceftriaxone	256	512	0.6	99.2
	Ceftazidime	8	128	36.3	49.9
	Imipenem	0.125	0.25	99.5	0.3
	Meropenem	0.016	0.062	99.7	0.2
	Amikacin	4	8	73.2	8.4
	Minocycline	4	32	63.3	21.8
Klebsiella pneumoniae (*n* = 2297)	Nemonoxacin	1	128	60.9	39.1
	Ciprofloxacin	0.5	256	48.1	45.3
	Levofloxacin	0.5	128	52.2	38.2
	Piperacillin/Tazobactam	4	512	64.6	30.7
	Ceftriaxone	0.25	512	52.8	46.8
	Ceftazidime	0.5	512	58.6	38.3
	Imipenem	0.25	64	75.8	23.6
	Meropenem	0.031	128	75.8	23.7
	Amikacin	2	512	78.8	18.9
	Minocycline	4	32	61.4	24.9
Carbapenem-susceptible, ESBL-negative *Klebsiella pneumoniae* (*n* = 1271)	Nemonoxacin	0.25	2	90.2	9.8
	Ciprofloxacin	0.062	1	80.0	13.3
	Levofloxacin	0.062	1	82.6	9.1
	Piperacillin/Tazobactam	4	8	91.7	4.2
	Ceftriaxone	0.062	0.25	94.8	4.5
	Ceftazidime	0.25	1	94.6	4.2
	Imipenem	0.125	0.25	99.6	0.2
	Meropenem	0.031	0.062	99.7	0.2
	Amikacin	2	4	97.1	1.5
	Minocycline	4	8	82.3	9.0
Carbapenem non-susceptible, ESBL-negative *Klebsiella pneumoniae* (*n* = 487)	Nemonoxacin	128	256	4.7	95.3
	Ciprofloxacin	128	512	2.3	96.9
	Levofloxacin	64	256	3.9	94.9
	Piperacillin/Tazobactam	512	512	0.4	99.2
	Ceftriaxone	512	512	0.0	100.0
	Ceftazidime	512	512	0.4	99.2
	Imipenem	64	128	0.0	98.6
	Meropenem	128	256	0.0	98.8
	Amikacin	512	512	25.7	71.7
	Minocycline	16	128	30.0	53.0
ESBL-positive *Klebsiella pneumoniae* (*n* = 539)	Nemonoxacin	8	128	42.3	57.7
	Ciprofloxacin	4	256	14.5	74.2
	Levofloxacin	2	128	24.1	55.7
	Piperacillin/Tazobactam	8	512	58.6	31.4

(*continued on next page*)

Table 2 (*continued*)

Species	Antibacterials	MIC_{50}	MIC_{90}	S	R
	Ceftriaxone	256	512	1.3	98.5
	Ceftazidime	32	256	26.0	63.8
	Imipenem	0.125	8	88.3	11.1
	Meropenem	0.031	8	87.9	11.5
	Amikacin	2	512	83.5	12.2
	Minocycline	8	64	40.6	36.9
Haemophilus influenzae (n = 1314)	Nemonoxacin	0.031	0.25	97.1	2.9
	Ciprofloxacin	0.016	0.5	97.9	-
	Levofloxacin	0.016	0.5	99.3	-
	Moxifloxacin	0.031	1	96.3	-
	Ampicillin/Sulbactam	4	16	39.1	60.9
	Ceftriaxone	0.062	0.5	99.8	-
	Azithromycin	2	128	64.6	-
	Minocycline	0.25	1	96.9	3.1
Moraxella catarrhalis (n = 501)	Nemonoxacin	0.062	0.125	-	-
	Ciprofloxacin	0.031	0.062	99.6	-
	Levofloxacin	0.031	0.125	99.8	-
	Moxifloxacin	0.062	0.125	96.8	3.2
	Amoxicillin/Clavulanate	0.004	0.125	100.0	0
	Ceftriaxone	0.5	1	98.8	-
	Azithromycin	0.125	256	63.7	-
	Minocycline	0.062	0.25	98.8	1.2

Note: The susceptibility of *Escherichia coli* and *Klebsiella pneumoniae* to monoxacin was interpreted using the breakpoints provided in the package insert of nemonoxacin malate sodium chloride injection (susceptible: ≤ 2 mg/L; resistant: ≥ 4 mg/L); for *Haemophilus influenzae*, the susceptibility to minocycline was interpreted by EUCAST criteria (susceptible: ≤ 1 mg/L; resistant: > 1 mg/L); the susceptibility to monoxacin was interpreted using the breakpoints provided in the package insert of nemonoxacin malate sodium chloride injection (susceptible: ≤ 0.5 mg/L; resistant: ≥ 1 mg/L); for *Moraxella catarrhalis*, the susceptibility to minocycline was interpreted by EUCAST criteria (susceptible: ≤ 1 mg/L; resistant: ≥ 2 mg/L); the susceptibility to moxifloxacin was interpreted by EUCAST criteria (susceptible: ≤ 0.25 mg/L; resistant: ≥ 0.5 mg/L). -: No interpretive criteria.

Table 3
Statistical validation results of the MIC creep trend for nemonoxacin.

Species	Spearman's ρ (P value)	Cochran-Armitage X^2 (P value)
Staphylococcus aureus	-0.711($P < 0.05$)	4.891($P < 0.05$)
MRSA	-0.624	8.860($P < 0.05$)
MRSE	0.455	4.321($P < 0.05$)
Staphylococcus epidermidis	0.073	0.126
Staphylococcus haemolyticus	0.248	3.029
Other staphylococci	0.37	0.315
Viridans group streptococci	0.31	5.044($P < 0.05$)
Streptococcus pneumoniae	-0.164	1.12E-05
Streptococcus pyogenes	0.146	0.592
Streptococcus agalactiae	-0.467	1.136
Escherichia coli	-0.833($P < 0.05$)	14.986($P < 0.05$)
Carbapenem-susceptible, ESBL-negative *Escherichia coli*	0	3.38
ESBL-positive *Escherichia coli*	-0.667	22.207($P < 0.05$)
Klebsiella pneumoniae	0.619	6.437($P < 0.05$)
Carbapenem-susceptible, ESBL-negative *Klebsiella pneumoniae*	-0.548	27.127($P < 0.05$)
ESBL-positive *Klebsiella pneumoniae*	0.452	1.074
Haemophilus influenzae	-0.43	3.448
Moraxella catarrhalis	0.043	4.964($P < 0.05$)

Note: A negative Spearman's ρ indicates a declining trend in MIC values over time (reverse MIC drift), while a positive ρ indicates an increasing trend. $P < 0.05$ was considered statistically significant. MIC, minimum inhibitory concentration; MRSA, methicillin-resistant Staphylococcus aureus; MRSE, methicillin-resistant Staphylococcus epidermidis; ESBL, extended-spectrum β-lactamase.

study further investigated whether the decline in MRSA isolation rate could explain the improvement in *S. aureus* resistance to nemonoxacin. A Spearman rank correlation analysis was performed between the annual MRSA isolation rates and the annual overall *S. aureus* nemonoxacin resistance rates for 2015–2024 and found no statistical significance between MRSA isolation rate and overall *S. aureus* nemonoxacin resistance rate (Spearman's $\rho = 0.407$, $P = 0.243 > 0.05$). This indicates that the annual variation in MRSA isolation rate is not synchronously associated with changes in *S. aureus* resistance to nemonoxacin, suggesting that the decline in MRSA isolation rate is not the main driver of the observed improvement in *S. aureus* nemonoxacin susceptibility.

Nemonoxacin resistance characteristics in different patient populations and infection sites

Nemonoxacin resistance across different subgroups is shown in Fig. 2A–H. In *Staphylococcus aureus*, resistance rates were higher in ICU patients than in non-ICU patients. Across patient groups, elderly patients had the highest resistance rate (10.4%), while pediatric patients had the highest susceptibility rate (98.4%). There were differences by infection site: isolates from sputum exhibited a markedly higher resistance rate (13.7%) compared with isolates from secretions and blood. Overall resistance in *Streptococcus pneumoniae* was well controlled; susceptibility rates reached 99.8% in pediatric patients, and 99.6% and 98.8% in adult and elderly patients, respectively.

For *Klebsiella pneumoniae*, ICU patients had higher resistance rates than non-ICU patients, whereas *Escherichia coli* showed no significant difference. For different patient populations, resistance among Gram-negative bacteria was mainly concentrated in adult and elderly patients and was relatively uncommon in pediatric patients. *Klebsiella pneumoniae* showed similar resistance rates across infection sites, whereas *Escherichia coli* differed; isolates from urine had a resistance rate (66.8%) that was significantly higher than those from blood and secretions. Resistance in *Haemophilus influenzae* and *Moraxella catarrhalis* remained relatively stable across subgroups, with both retaining good susceptibility to quinolones.

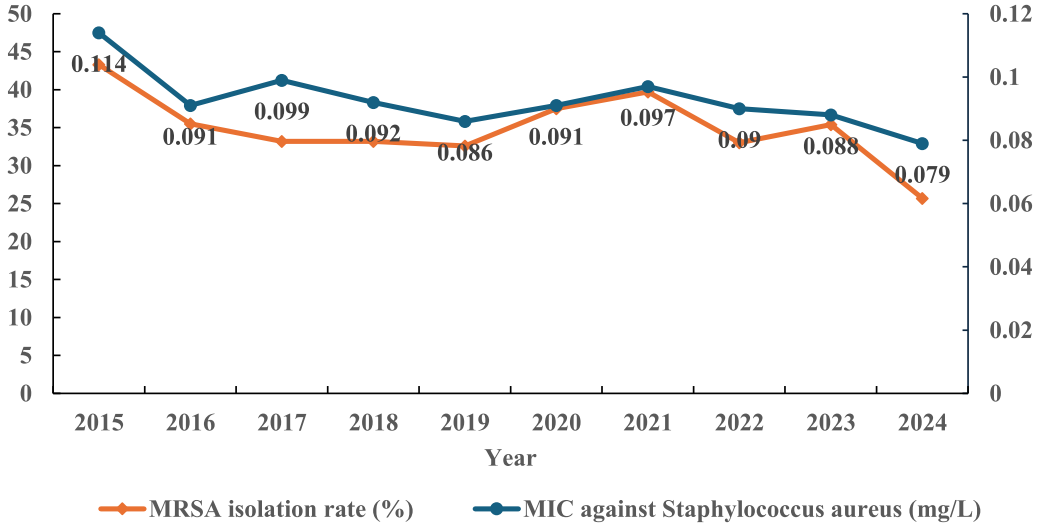

Fig. 1. Time trends of nemonoxacin GM MIC against *Staphylococcus aureus* and the MRSA isolation rate.

Discussion

Nemonoxacin, as a new-generation non-fluorinated quinolone antibacterial drug, lacks the fluorine atom at C-6, introduces an aminomethyl piperidine ring at C-7, and retains a cyclopropyl group at N-1 and a methoxy group at C-8.[3] This unique molecular structure not only broadens the antibacterial spectrum but also reduces the risk of resistance induced by the widespread use of traditional fluoroquinolones.[7] This study, based on ten years of dynamic surveillance data (2015–2024) of clinical isolates from 22 multicenter sites nationwide, systematically elucidates the long-term evolution of nemonoxacin's antibacterial activity and the potential risk factors influencing its resistance. The results show that nemonoxacin's *in vitro* antibacterial activity against multiple Gram-positive bacteria is significantly superior to traditional quinolones such as ciprofloxacin and levofloxacin, and it exhibited a "reverse MIC drift" phenomenon over the ten-year period, providing important evidence for optimizing clinical anti-infective strategies.

In this ten-year surveillance, the susceptibility rates of *Staphylococcus aureus* and *Staphylococcus epidermidis* to nemonoxacin were 93.2% and 92.2%, respectively, significantly better than those of other quinolones tested and consistent with previous *in vitro* studies.[3,8,9] *Streptococcus pneumoniae* showed a susceptibility rate to nemonoxacin of 99.4%; nemonoxacin is widely distributed in lung tissue and bronchial mucosa, achieving concentrations in alveolar epithelial lining fluid more than four times those in plasma, suggesting potential advantages in treating community-acquired pneumonia.[10,11] For Gram-negative bacteria, nemonoxacin retains good activity against carbapenem-susceptible, ESBL-negative *Klebsiella pneumoniae*, approaching that of carbapenems; future research could explore sequential therapy with the two drugs to reduce carbapenem overuse. Resistance rates in ICU patients were generally higher than in non-ICU populations, highlighting the need for enhanced individualized dosing in critically ill patients. Elderly patients often show lower susceptibility to nemonoxacin, which may be related to pharmacokinetic changes due to physiological decline. In urinary tract infections, attention should be paid to carbapenem-susceptible, ESBL-negative *Escherichia coli* (resistance rate 47.8%); combination therapy with other drugs be needed to enhance efficacy.

This study found that nemonoxacin is not prone to marked MIC drift and may, with rational use, maintain or even improve susceptibility over time. Because the structure of nemonoxacin is fundamentally different from that of traditional quinolones. Nemonoxacin has an extra methoxy group at the C-8 position compared with traditional quinolones, allowing it to bind to both topoisomerase IV and II.[12] This dual-target action can simultaneously inhibit DNA gyrase (GyrA/B) and topoisomerase IV (ParC/E), thereby significantly reducing the risk of resistance caused by single-point mutations in these genes.[3,13] Mutations in any subunit of GyrA, GyrB, ParE, or ParC can lead to bacterial resistance to fluoroquinolones. According to Chen *et al.*, when MRSA strains have two amino acid mutation sites in the quinolone resistance-determining regions, nemonoxacin remains effective; only when the number of mutation sites is ≥ 3 does the non-susceptibility rate increase markedly.[13] For *Streptococcus pneumoniae*, the mutated genes in nemonoxacin strains are confined to GyrA, GyrB and ParE, with no ParC gene mutations observed[12]; ParC is typically the primary target site of quinolones in Gram-positive bacteria and a common mutation locus conferring resistance to other quinolones, and the lack of ParC-region mutations induced by nemonoxacin is one reason it is less prone to resistance development and less likely to exhibit cross-resistance with other quinolones.[14] Third, nemonoxacin has high bioavailability and a half-life exceeding 10 h, supporting once-daily dosing; consequently, the selective pressure for resistance from frequent dosing is low.[15] Reverse MIC creep suggests that nemonoxacin has avoided the pressure-driven resistance caused by misuse of traditional quinolones, and its low propensity for resistance makes it a preferred option in clinical practice. Furthermore, the rational use of nemonoxacin can reduce excessive exposure to carbapenems and vancomycin, thereby decreasing the emergence of multidrug-resistant organisms. The study by Huang *et al.* also showed that combining nemonoxacin with vancomycin can synergistically enhance bactericidal activity against MRSA (fractional inhibitory concentration index [FICI] ≤ 0.5), reducing the selection pressure for resistant mutants.[16] Notably, carbapenem-non-susceptible, ESBL-negative *Klebsiella pneumoniae* shows a marked increase in resistance to nemonoxacin, indicating vigilance is needed for the emergence of novel resistance phenotypes.

Ten years of surveillance data indicate that nemonoxacin's antimicrobial-spectrum advantage is especially pronounced in the field of Gram-positive infections. Future research could focus on precision-dosing models targeting resistance mutation sites to further unlock nemonoxacin's clinical potential. These results provide a new perspective for antimicrobial stewardship; through synergy between molecular-structure innovation and rational drug use, it may be possible to control or even reverse the evolution of resistance.

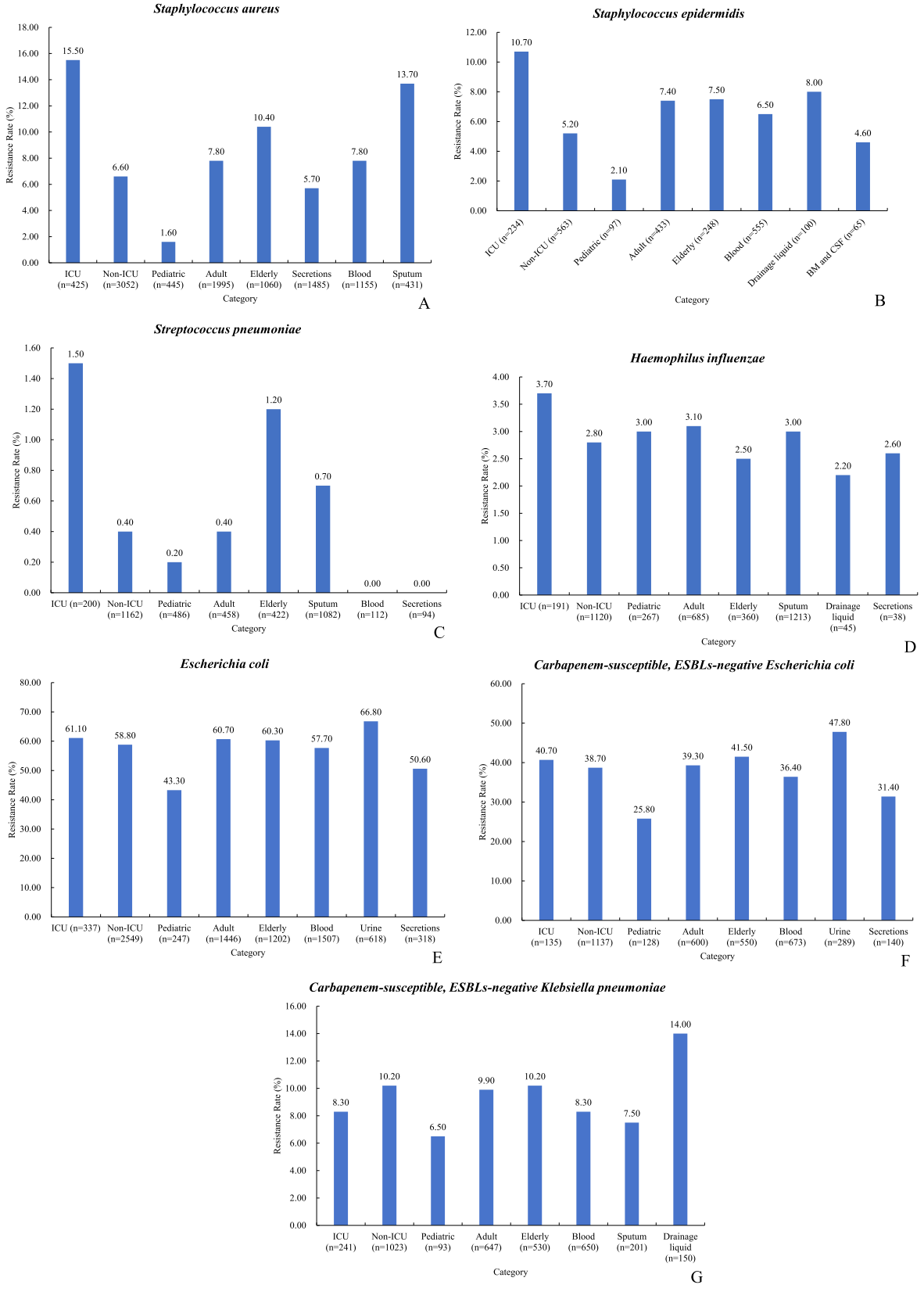

Fig. 2. Analysis of nemonoxacin resistance characteristics across different patient populations and infection sites.

Declarations

Not applicable.

CRediT authorship contribution statement

Jie Wu: Conceptualization, Data curation, Writing - original draft. Yun Li: Methodology, Software, Writing - review & editing. Bo Zheng: Supervision; Validation.

Ethics approval and consent to participate

This study was approved by the Ethics Committee of Peking University First Hospital (Approval No. 2024-RD-394-001). All study participants have signed informed consent forms.

Consent for publication

All authors have read and agreed to the published version of the manuscript and give their consent for publication in this journal.

Availability of data and materials

Not applicable.

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Declaration of Competing Interest

The authors declare no competing interests.

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Authors' other information

Not applicable.

References

1. Adhikary K, Ganguly K, Chakrabarty S, et al. Understanding antimicrobial resistance: from mechanisms to public health implications. *Curr Pharm Biotechnol.* 2025;26.
2. Chung DT, Tsai CY, Chen SJ, et al. Multiple-dose safety, tolerability, and pharmacokinetics of oral nemonoxacin (TG-873870) in healthy volunteers. *Antimicrob Agents Chemother.* 2010;54(1):411–417.
3. Yin H, Shao Y, Sun F. The latest research progress on the clinical application of nemonoxacin. *Front Med.* 2025;12:1671640.
4. Mondal S, Mandal A, Saha S, Partha Sarathi Chakrabarty u, Das D. Minimum inhibitory concentration creep in Enterobacterales – A rising concern. *Asian J Med Sci.* 2024;15(6):81–85.
5. CLSI. Performance standards for antimicrobial susceptibility testing. 35th ed., M100-Ed35. Wayne, PA: Clinical and Laboratory Standards Institute. 2025.
6. EUCAST. Breakpoint tables for interpretation of MICs and zone diameters. *Version.* 2025;15(0).
7. Yuan J, Zhang X, Chen J, Zhang Y, Zhu F, Huang H. Safety of oral nemonoxacin: a systematic review of clinical trials and postmarketing surveillance. *Front Pharmacol.* 2022;13:1067686.
8. Li CR, Li Y, Li GQ, et al. vivo antibacterial activity of nemonoxacin, a novel nonfluorinated quinolone. *J Antimicrob Chemother.* 2010;65(11):2411–2415.
9. Adam HJ, Laing NM, King CR, Lulashnyk B, Hoban DJ, Zhanel GG. Vitro activity of nemonoxacin, a novel nonfluorinated Quinolone, against 2,440 Clinical Isolates. *Antimicrob Agents Chemother.* 2009;53(11):4915–4920.
10. Cheng SL, Wu RG, Chuang YC, et al. Integrated safety summary of phase II and III studies comparing oral nemonoxacin and levofloxacin in community-acquired pneumonia. *J Microbiol Immunol Infect = Wei mian yu gan ran za zhi.* 2019;52(5):743–751.
11. Li X, Chen Y, Xu X, et al. Pharmacokinetics and pharmacodynamics of nemonoxacin in a neutropenic murine lung infection model against streptococcus pneumoniae. *Front Pharmacol.* 2021;12:658558.
12. Yang JJ, Cheng A, Tai HM, Chang LW, Hsu MC, Sheng WH. Selected mutations by nemonoxacin and fluoroquinolone exposure among relevant gram-positive bacterial strains in Taiwan. *Microb Drug Resist (Larchmt NY).* 2020;26(2):110–117.
13. Chen P, Ho MW, Lu PL, Tang HJ, Sy CL, Wang JT. Comparative In vitro antibacterial activity of nemonoxacin and other fluoroquinolones in correlation with resistant mechanisms in contemporary methicillin-resistant Staphylococcus aureus blood isolates in Taiwan. *Ann Clin Microbiol Antimicrob.* 2025;24(1):5.
14. Roychoudhury S, Makin K, Twinem T, Leunk R, Hsu MC. Vitro resistance development to nemonoxacin in streptococcus pneumoniae: a unique profile for a novel nonfluorinated quinolone. *Microb Drug Resist.* 2016;22(7):578–584.
15. Kocsis B, Domokos J, Szabo D. Chemical structure and pharmacokinetics of novel quinolone agents represented by avarofloxacin, delafloxacin, finafloxacin, zabofloxacin and nemonoxacin. *Ann Clin Microbiol Antimicrob.* 2016;15(1):34.
16. Huang J, Guo S, Li X, et al. Nemonoxacin enhances antibacterial activity and antiresistance mutation ability of vancomycin against methicillin-resistant staphylococcus aureus in an in vitro dynamic pharmacokinetic/pharmacodynamic model. *Antimicrob Agents Chemother.* 2022;66(2):e01800–01821.