

Persistent Colonization of Ciprofloxacin-Resistant and Extended-Spectrum β -Lactamase (ESBL)-Producing *Salmonella enterica* Serovar Kentucky ST198 in a Patient with Inflammatory Bowel Disease

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Objective: *Salmonella enterica* serovar Kentucky ST198 has emerged as a global threat to humans. In this study, we aimed to characterize the prolonged carriage of ciprofloxacin-resistant and extended-spectrum β -lactamase (ESBL)-producing *S. Kentucky* ST198 in a single patient with inflammatory bowel disease (IBD).

Methods: Three *S. Kentucky* strains were collected from a single patient with IBD on 11th January, 23rd January, and 8th February, 2022, respectively. Antimicrobial susceptibility testing, whole-genome sequencing, and phylogenetic analysis with 38 previously described Chinese *S. Kentucky* ST198 strains from patients and food were performed.

Results: All three *S. Kentucky* isolates belonged to ST198. They carried identical 16 resistance genes, such as *bla*_{CTX-M-55}, *tet*(A), and *qnrS1*, and had identical mutations within *gyrA* (S83F and D87N) and *parC* (S80I). Therefore, they exhibited identical multidrug-resistant profiles, including the clinically important antibiotics cephalosporins (ceftazidime and cefepime), fluoroquinolones (ciprofloxacin and levofloxacin), and third-generation tetracycline (tigecycline). Our three *S. Kentucky* strains were classified into the subclade ST198.2–2, and were genetically identical (2–6 SNPs) to each other. They exhibited a close genetic similarity (15–20 SNPs) to the isolate NT-h3189 from a patient and AH19MCS1 from chicken meat in China, indicating a possible epidemiological link between these *S. Kentucky* ST198 isolates from the patients and chicken meat.

Conclusion: Long-term colonization of ciprofloxacin-resistant and ESBL-producing *S. Kentucky* ST198 in a single patient is a matter of concern. Due to the potential transfer of *S. Kentucky* ST198 from food sources to humans, ongoing surveillance of this particular clone in animals, animal-derived food products, and humans should be strengthened.

Keywords: *Salmonella*, MDR, Kentucky, persistent colonization

Introduction

Salmonella is an important cause of food-borne disease in humans. In Europe, a total of 65,208 cases of salmonellosis in 2022, making it the second most common zoonotic pathogen in the European Union.¹ Different types of animals, particularly poultry, pigs, and cattle, can serve as reservoirs for *Salmonella*.¹ The consumption of contaminated food is a common route of infection for humans.¹ Salmonellosis outbreaks linked to food have been

previously reported in multiple countries with a variety of *Salmonella* serotypes. For example, multistate outbreak of *Salmonella enterica* serovar Thompson linked to the consumption of seafood was reported in the United States.² Multiple countries have been affected by an outbreak of *S. Typhimurium* linked to chocolate products from Belgium in 2022.³ The rapid emergence and dissemination of antimicrobial resistance in *Salmonella* spp. from human cases pose a significant threat to clinical therapy. According to the World Health Organization (WHO), third-generation cephalosporin-resistant *Enterobacteriaceae* and fluoroquinolone-resistant *Salmonella* are classified as critical and high-priority pathogens, respectively. There is an urgent need for research and development of new antibiotics.⁴

Salmonella enterica serovar Kentucky is a common nontyphoid *Salmonella* serotype that could infect a variety of hosts, including humans.¹ *S. Kentucky* has multiple sequence types (STs), such as ST198, ST314, and ST521.³ Among them, *S. Kentucky* ST198 is becoming a globally prevalent clone that caused human clinical infections and also frequently detected in various sources (eg, livestock, animal-derived food products, vegetable, the environment).^{5–10} Recently, there has been a growing prevalence of ciprofloxacin- and third-generation cephalosporin-resistant *S. Kentucky* ST198 strains worldwide.^{6,7,10–12}

Inflammatory bowel diseases (IBDs) are chronic inflammatory diseases of the gastrointestinal tract characterized by a relapsing and remitting course, with Crohn's disease and ulcerative colitis being the most common clinical manifestations.^{13,14} Although the etiology of IBD is not well defined, environmental, genetic, and dietary risk factors influence or contribute to the development and severity of this disease.^{15,16} Enteric infections with pathogens such as *Salmonella* or *Campylobacter* have been suggested to promote the onset of IBD.^{15,16}

In this study, we characterized three ciprofloxacin-resistant and extended-spectrum β -lactamase (ESBL)-producing *S. Kentucky* ST198 strains from a single patient with IBD, to highlight the prolonged carriage of *S. Kentucky* ST198 in a single patient, and their potential epidemiological link to such organisms from chicken meat.

Materials and Methods

Patient and Bacterial Isolates

A 28-year-old female patient was diagnosed with IBD in February 2019 at a tertiary hospital in Shenzhen, China, and experienced symptoms including diarrhea and rectal bleeding. The symptoms were alleviated by the administration of prednisone and mesalazine. In July 2021, the patient was hospitalized because of diarrhea, rectal bleeding, vomiting, and low-grade fever. *Salmonella* infection was detected and the symptoms improved following treatment with antibiotics and prednisone. The patient was discharged in September 2021 and prescribed a regimen of mesalazine (3 g/d) and azathioprine (50 mg/d) for ongoing treatment. Subsequent follow-up visits were conducted in October and November 2021, as well as in January and February 2022.

Three *S. Kentucky* strains (designated as SZ22HS1 to SZ22HS3) were isolated from three fecal samples collected from this patient on 11th January, 23rd January, and 8th February, 2022, respectively. Stool samples were cultured on *Salmonella* Shigella agar and then identified using matrix-assisted laser desorption/ionization time-of-flight mass spectrometry. The serotype was determined through the conventional slide agglutination assay with the somatic (O) and flagellar (H) antigens according to the White-Kauffmann scheme.¹⁷

Antimicrobial Susceptibility Testing

Three *Salmonella* isolates were tested for their susceptibility to 14 antimicrobial agents by the broth microdilution method using BD PhoenixTM susceptibility panels, including ceftazidime, cefepime, aztreonam, ticarcillin/clavulanic acid, piperacillin/tazobactam, imipenem, meropenem, ciprofloxacin, levofloxacin, doxycycline, minocycline, tigecycline, colistin, and sulfamethoxazole/trimethoprim. The results were interpreted according to the standards provided by the Clinical and Laboratory Standards Institute (CLSI) M100, 32nd edition.¹⁸ The interpretation of tigecycline (>0.5 mg/L) was based on the clinical breakpoints for *Enterobacterales* established by the European Committee on Antimicrobial Susceptibility Testing (EUCAST) (<https://www.eucast.org/>).

Whole-Genome Sequencing and Analysis

The genomic DNA of three *S. Kentucky* isolates was extracted using the TIANamp Bacterial DNA kit (Tiangen Biotech, Beijing, China), following the manufacturer's instructions. Sequence libraries were prepared using the NEB Next[®] UltraTM DNA Library Prep Kit for Illumina (NEB, USA), and subsequently subjected to genome sequencing on the Illumina HiSeq 2500 platform. The resulting raw reads with less than 90% Q30 bases were trimmed and filtered using the NGSQC Toolkit (v2.3.3), and *de novo* genome assembly of 150-bp paired-end reads was performed using SPAdes v.3.8.2. The draft genomes have been deposited in GenBank under accession numbers JAVCBR000000000, JAVCBS000000000, and JAVCBT000000000. The genomic sequences were analyzed using MLST 2.0 (<https://cge.food.dtu.dk/services/MLST/>) to identify the sequence types. Additionally, the identification of resistance genes and chromosomal point mutations was performed using ResFinder and PointFinder, respectively (<http://genepi.food.dtu.dk/resfinder>). Plasmid replicons with >95% sequence identity and >60% coverage were identified using PlasmidFinder (<https://cge.food.dtu.dk/services/PlasmidFinder/>).

Phylogenetic Analysis

The genome sequences of 38 *S. Kentucky* ST198 strains from China were downloaded from the NCBI database (Table S1). This dataset consists of 27 strains collected from patients and food products in China from 2013 to 2017,⁷ one isolate from a patient in 2022,¹⁹ and our previously described ten strains from chicken meat in 2019.¹¹ To analyze their genetic relatedness, a phylogenetic tree was constructed using Parsnp (<https://harvest.readthedocs.io/en/latest/content/parsnp.html>), based on core genome single-nucleotide polymorphisms (cgSNPs). The genome of *S. Kentucky* strain AH19MCS1 (accession number CP102719.1) was used as a reference for comparison. The bacterial source tracking analysis of *S. Kentucky* strains in this study was performed using BacWGSTdb webserver.²⁰ The resulting tree and heatmap of the SNP count matrix were visualized and edited using Chiplot (<https://www.chiplot.online/>).

Results

Analysis of Antimicrobial Susceptibility and Resistance Determinants

The results of antimicrobial susceptibility testing showed that three *S. Kentucky* isolates were resistant to ceftazidime, cefepime, aztreonam, ciprofloxacin, levofloxacin, doxycycline, minocycline, tigecycline, and sulfamethoxazole/trimethoprim, and intermediate to ticarcillin/clavulanic acid, but susceptible to piperacillin/tazobactam, imipenem, meropenem, and colistin (Tables 1 and S2). In accordance with their multidrug-resistant (MDR) profiles, three *S. Kentucky* strains possessed 16 resistance genes. These genes confer resistance to various antibiotics, including β -lactams (*bla*_{CTX-M-55} and *bla*_{TEM-1b}), aminoglycosides [*aadA7*, *aadA17*, *aph(3')-Ia*, *aac(3)-Id*, *aac(3)-IId*, and *aac(6')-Iaa*], tetracyclines [*tet(A)*], phenicols (*floR*), quinolones (*qnrS1*), sulfonamide/trimethoprim (*sulI* and *dfrA14*), lincosamide [*lnu(F)*], macrolides [*mph(A)*], and rifampicin (*arr-2*) (Table 1). The presence of the PMQR gene *qnrS1* and mutations within *gyrA* (S83F and D87N) and *parC* (S80I) could explain their resistance to fluoroquinolone (ciprofloxacin and levofloxacin) (Table 1).

Intriguingly, all three *S. Kentucky* strains in this study exhibited resistance to tigecycline, with a minimum inhibitory concentration (MIC) of 8 mg/L. However, no tigecycline resistance genes [*tet(X)* and *tmexCD-toprJ*] or any alterations in

Table 1 Characterizations of *Salmonella Kentucky* Isolates from a Patient in This Study

Strain	Sampling Date	MLST	Resistance Patterns	Resistance Genes	Mutation	
					<i>gyrA</i>	<i>parC</i>
SZ22HS1	2022.01.11	ST198	CAZ/CPE/ATM/CIP/LVX/DOX/MIN/TIL/SXT	<i>bla</i> _{CTX-M-55} / <i>bla</i> _{TEM-1b} / <i>aadA7/aadA17/aph(3')-Ia/aac(3)-Id/aac(3)-IId/aac(6')-Iaa/tet(A)/sulI/dfrA14/floR/lnu(F)/mph(A)/arr-2/qnrS1</i>	S83F, D87N	S80I
SZ22HS2	2022.01.23	ST198	CAZ/CPE/ATM/CIP/LVX/DOX/MIN/TIL/SXT	<i>bla</i> _{CTX-M-55} / <i>bla</i> _{TEM-1b} / <i>aadA7/aadA17/aph(3')-Ia/aac(3)-Id/aac(3)-IId/aac(6')-Iaa/tet(A)/sulI/dfrA14/floR/lnu(F)/mph(A)/arr-2/qnrS1</i>	S83F, D87N	S80I
SZ22HS3	2022.02.08	ST198	CAZ/CPE/ATM/CIP/LVX/DOX/MIN/TIL/SXT	<i>bla</i> _{CTX-M-55} / <i>bla</i> _{TEM-1b} / <i>aadA7/aadA17/aph(3')-Ia/aac(3)-Id/aac(3)-IId/aac(6')-Iaa/tet(A)/sulI/dfrA14/floR/lnu(F)/mph(A)/arr-2/qnrS1</i>	S83F, D87N	S80I

Abbreviations: CAZ, ceftazidime; CPE, cefepime; ATM, aztreonam; CIP, ciprofloxacin; LVX, levofloxacin; DOX, doxycycline; MIN, Minocycline; TIL, tigecycline; SXT, sulfamethoxazole/trimethoprim.

the amino acid sequences of AcrAB-TolC, RamA, RamR, MarA, and MarR were identified in these strains. Nevertheless, these *S. Kentucky* isolates harbored the tetracycline resistance gene *tet(A)* variant, which was possibly linked to their tigecycline resistance.

Phylogenomic Analysis of *S. Kentucky* ST198 Strains

Genome sequencing analysis revealed that all three *S. Kentucky* isolates (SZ22HS1, SZ22HS2, and SZ22HS3) belonged to sequence type 198 (ST198). The genome sizes of SZ22HS1, SZ22HS2, and SZ22HS3 were 4,806,845 bp with a GC content of 52.21%, 4,804,955 bp with a GC content of 52.21%, and 4,841,148 bp with a GC content of 52.14%, respectively (Figure S1). Furthermore, no known plasmid replicons were identified in these three *S. Kentucky* strains. In order to assess the genetic variations among three *S. Kentucky* ST198 isolates in this study and additional 38 Chinese *S. Kentucky* ST198 strains, we constructed a phylogenetic tree using cgSNPs analysis (Figure 1). The findings demonstrated a relatively close genetic relationship (2–6 SNPs) among three *S. Kentucky* strains (SZ22HS1, SZ22HS2, and SZ22HS3) derived from a single patient in this study (Figure 2). Additionally, the bacterial source tracking analysis based on cgMLST showed that three *S. Kentucky* strains in this study were close to multiple *S. Kentucky* strains from humans, water, poultry tissue, and chicken carcass from the United Kingdom, USA, Nigeria, and Egypt.

As shown in Figure 1, 41 *S. Kentucky* ST198 strains were divided into two clades, namely ST198.1 and ST198.2. With the exception of two isolates (sc-h42 and sc-h43) collected from patients in Sichuan Province, China, in 2013, which lacked any resistance genes and were assigned to the clade ST198.1, the remaining 39 isolates were grouped into ST198.2. The clade ST198.2 was further divided into two subclades, namely ST198.2–1 and ST198.2–2. Within the subclade ST198.2–1, a total of 19 isolates were identified with 18 of them carrying the same resistance genes. The subclade 198.2–2 consisted of six isolates from humans and 14 isolates from animal-derived food products with close genetic relatedness (Figure 2). Our three *S. Kentucky* ST198 strains (SZ22HS1, SZ22HS2, and SZ22HS3) in the subclade ST198.2–2 exhibited a close genetic similarity to the isolates NT-h3189 from a patient in Nantong, Jiangsu

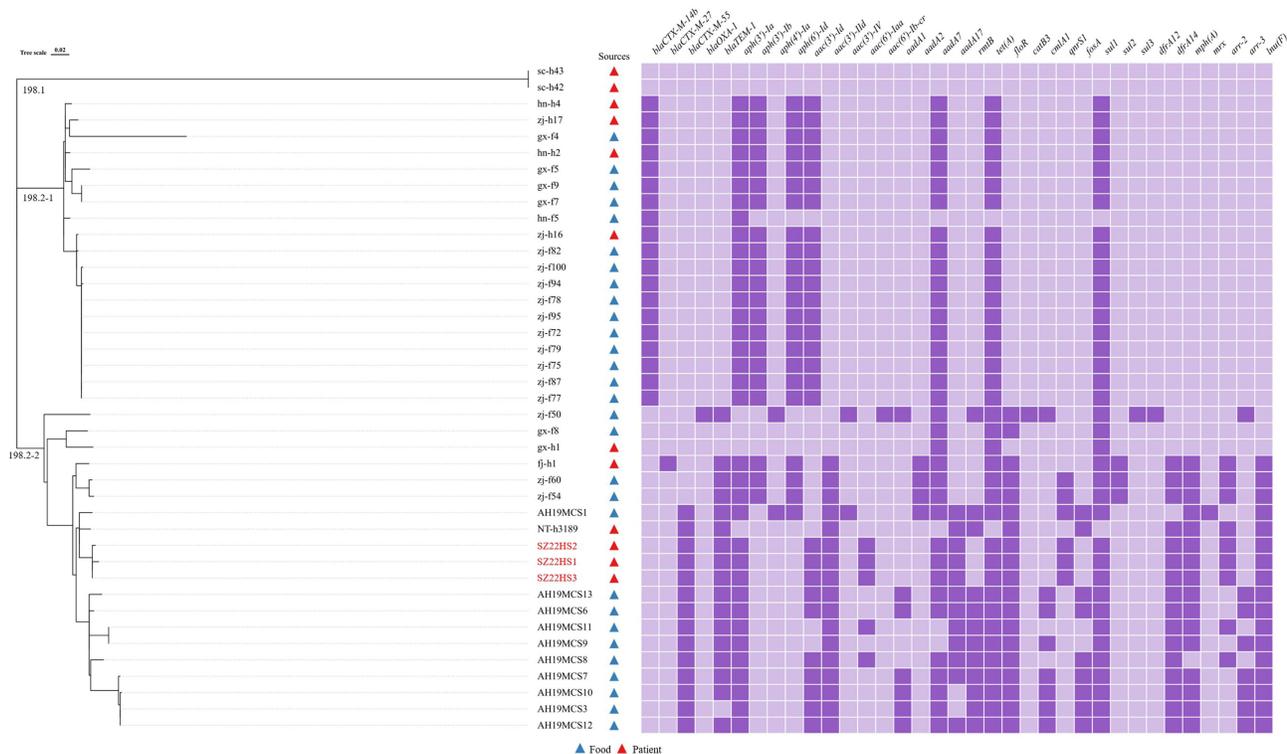


Figure 1 Maximum likelihood tree of *S. Kentucky* ST198 isolates in this study compared with 38 *S. Kentucky* ST198 isolates from China based on cgSNP analysis. The dark purple rectangle indicates the presence of this gene in the corresponding isolate, while the light purple rectangle represents its absence in the corresponding isolate. Antibiotic resistance genes with >95% sequence identity and >60% coverage are shown. The isolates obtained in this study were indicated in red.

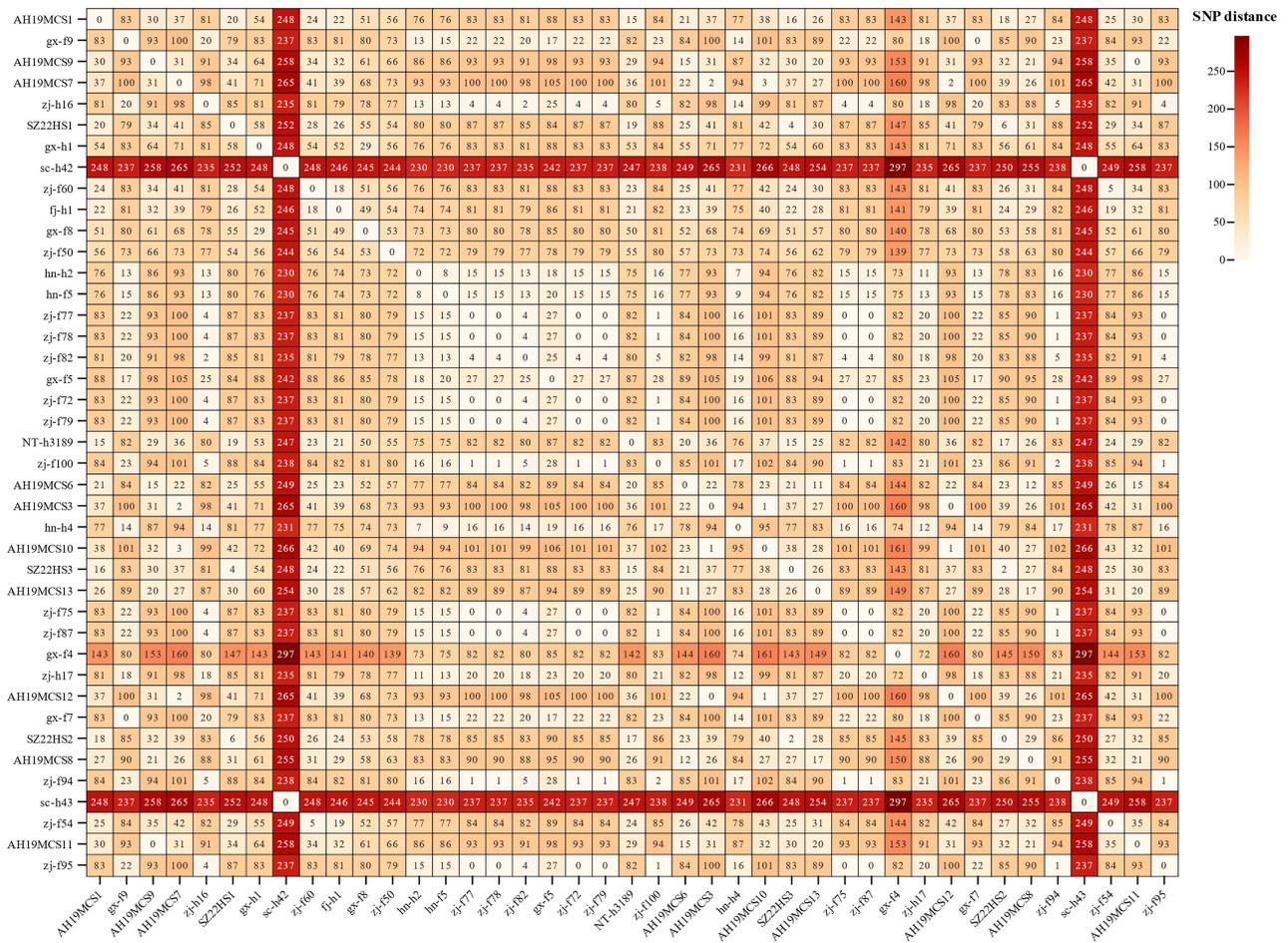


Figure 2 Pairwise SNP matrix of *S. Kentucky* ST198 isolates in this study compared with 38 *S. Kentucky* ST198 isolates from China.

Province, and AH19MCS1 from chicken meat in Anhui Province, differing by 15 to 20 SNPs (Figure 2). It indicates a possible epidemiological link between these *S. Kentucky* ST198 isolates from the patients and chicken meat.

Discussion

Many bacteria have the ability to establish long-term infections within their hosts despite antibiotic treatment, which can be attributed to several factors, including compromised immune system of the host, immune escape of pathogens, and/or inadequate eradication of pathogens by antibiotics.²¹ Although rare, previous studies have reported cases of long-term persistence of *S. Kentucky* in patients. Hawkey et al collected three *S. Kentucky* ST198 strains from a single patient who was infected in Egypt over a span of three consecutive years (2009–2011). These strains shared a most recent common ancestor that can be traced back to around 2005, indicating a prolonged colonization period of approximately six years.⁶ In a study conducted in Switzerland, it was observed that out of 156 patients infected with *S. Kentucky* between 2010 and 2020, 16 patients (10.3%) exhibited persistent carriage of the bacteria for more than three weeks, and four of them were identified as chronic carriers, with the bacteria persisting for over 12 months.¹² Three *S. Kentucky* strains collected from a single patient in this study share identical resistance genes and display a high degree of similarity with only minor cgSNP differences. It suggests that these strains are not only genetically identical but are likely to be duplicates. According to the available medical records, the patient experienced a *Salmonella* infection in July 2021. Unfortunately, due to the patient being transferred from a different medical facility, we did not obtain the *Salmonella* strain and are unsure of the specific serotype. At least, this particular clone successfully colonized in the patient’s intestinal tract for a duration exceeding four weeks.

These *S. Kentucky* strains detected in this patient contained numerous resistance genes and exhibited MDR phenotype, which may be one of the reasons for the failure of antimicrobial therapy. For instance, they carried resistance genes *aadA7*, *sull*, *tet(A)*, and *bla*_{TEM-1}, which were known to be associated with *Salmonella* genomic island 1 (SGI-1) in *S. Kentucky* ST198 strains.^{10,11} Multiple resistance genes such as *bla*_{TEM-1b}, *aph(3')-Ia*, *aadA17*, *aac(3)-IId*, *floR*, *qnrS1*, *dfrA14*, *lnu(F)*, *mph(A)*, and *arr-2* were previously detected within the multiresistance region on the chromosomes in *S. Kentucky* ST198 strains.^{10,11} Additionally, increasing dynamics were observed in several resistance genes including *bla*_{TEM-1b}, *aph(3')-Ia*, *floR*, and *dfrA14* in *Salmonella* from China.²²

Cephalosporins and fluoroquinolones are the first-line antimicrobials for the treatment of nontyphoidal *Salmonella* infections.²³ However, our three *S. Kentucky* ST198 strains exhibited resistance to cephalosporins (ceftazidime and cefepime) and fluoroquinolones (ciprofloxacin and levofloxacin). This resistance significantly restricts the available treatment options, thereby impacting the effectiveness of treatment outcomes. In recent years, extended-spectrum β -lactamases (ESBLs)-producing *S. Kentucky* ST198 encoding by CTX-M-14b has been increasingly reported in Europe and China.^{7,9,10,24,25} Interestingly, the *bla*_{CTX-M-14b} gene located within the chromosome was exclusively found in Chinese and European genomes within clade 198.2–1.²⁵ However, the *bla*_{CTX-M-14b} gene carried by an IncHI2 plasmid was previously described in *S. Kentucky* in Zimbabwe.²⁶ Our three *S. Kentucky* strains contained the *bla*_{CTX-M-55} gene, which is frequently reported in both animals and humans in China²⁷ and has been sporadically reported in subclade ST198.2–2 from China.^{10,11} Mutations in *gyrA* and *parC* genes and the presence of PMQR genes (eg, *qnrS1*) have been the primary causes of fluoroquinolone resistance in *Salmonella*, including *S. Kentucky* ST198 clone.^{7,10}

Tigecycline is listed as a critically important antimicrobial for human medicine by the World Health Organization due to its effectiveness in treating MDR Gram-negative bacteria.²³ Thus, resistance to tigecycline has become a global concern. Previous studies have identified the *tet(A)* variant as the reason for tigecycline resistance in *Salmonella*, *Klebsiella pneumoniae*, and *Enterobacter hormaechei*.^{24,28,29} A previous study found that most of the *S. Kentucky* ST198.2 isolates carried the *tet(A)* variant and exhibited resistance to tigecycline.¹⁰ Similarly, our three *S. Kentucky* ST198.2 isolates also displayed tigecycline resistance, potentially due to the presence of the *tet(A)* variant. Evidently, the *tet(A)* variant is prevalent among *S. Kentucky* ST198.2 strains and plays a significant role in the emergence and spread of tigecycline resistance in this particular subclade.

Rifampicin is an important first-line antibiotic for the treatment of tuberculosis.³⁰ It also has clinical efficacy against *Staphylococcus aureus*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Neisseria*, and some other bacteria.³¹ According to CLSI M100, 32th edition, Enterobacteriaceae are intrinsically resistant to rifampicin.¹⁸ However, Mumbo et al reported that rifampicin resistance was observed in 11.1% of *Salmonella* isolates, and clinical efficacy was also observed in *Salmonella* Typhi and *E. coli*.^{31,32} Furthermore, *Salmonella* was previously used as a model organism to investigate rifampicin resistance.^{33–35} The wild-type *Salmonella enterica* exhibited MIC against rifampicin was 12 mg/L, whereas its rifampicin-resistant mutants showed high rifampicin resistance with MICs of 1500 to >3000 mg/L.³³ In this study, three *S. Kentucky* strains carried rifampicin resistance gene *arr-2*, which was previously found in 51.85% (56/108) of *S. Kentucky* ST198 isolates.¹⁰ Although the proportion of rifampicin resistance gene *arr-3* has an increased trend over time in both human and non-human origins in 1713 *Salmonella* isolates from China between 2006 and 2019,²² it was only detected in one *S. Kentucky* ST198 strains.¹⁰

In recent years, *S. Kentucky* has become a common serotype causing human nontyphoidal salmonellosis.¹ Significantly, MDR *S. Kentucky* ST198 strains have been increasingly reported in poultry, poultry products, and humans worldwide, including China.^{6–12,19,24,25} It has become a global epidemic clone, and poses a potential threat to both human and animal well-being. Furthermore, *S. Kentucky* ST198 has recently differentiated into two distinct clades, namely ST198.1 and ST198.2, with the latter being more prevalent on a global scale.^{10,25} Consistent with prior research,^{6,7,10,25} the ST198.2 clade analyzed in this study was further classified into two subclades ST198.2–1 and ST198.2–2. The close genetic relationship observed among isolates from patients and animal-derived food products within subclade ST198.2–2, particularly a strong correlation between our three patient-source isolates and an isolate originating from chicken meat, indicates the potential transfer of *S. Kentucky* ST198 from food sources to humans. Poultry and poultry productions are recognized to be the main reservoir of MDR *S. Kentucky* ST198 causing human infections.¹⁰ It should be a matter of concern in the monitoring and prevention of human salmonellosis in China.

However, our study has several limitations. As an important foodborne pathogen, humans generally become infected with *Salmonella* by eating poorly cooked, contaminated food.¹ Our study provides a few information and insights into Salmonellosis surveillance since we only collected three *S. Kentucky* isolates from one patient with IBD within four

weeks. Although poultry production was the main reservoir of ciprofloxacin- and tigecycline-resistant extended-spectrum β -lactamase-producing *S. Kentucky* ST198.2–2 causing human infections in China,¹⁰ and a possible epidemiological link between *S. Kentucky* strains from the patient and chicken meat was observed in the current study, the precise source of *S. Kentucky* strains colonized this patient is unclear. Broader and detailed studies involving more patients and strains are needed to surveillance the colonization of *S. Kentucky* ST198 in patients and to elucidate the transmission mechanism of this organism from animals to patients via the food chain. Additionally, it is crucial to perform long-term monitoring and evaluate the efficacy of current therapy for the eradication of this MDR *S. Kentucky* clone in this patient with IBD.

In conclusion, the prolonged colonization of ciprofloxacin-resistant and ESBL-producing *S. Kentucky* ST198 in a single patient is of concern. It is recommended to conduct ongoing surveillance of this particular clone in humans, as well as poultry and poultry products in China. More importantly, exploring effective strategies such as phage therapy for bacterial decolonization in humans is urgently needed to prevent hosts from developing infections and reduce the spread of MDR organisms.³⁶

Ethics Statement

This research was reviewed and approved by Yangzhou University. The patient was informed and consented to participate in this study, and the patient gave informed consent to publish the case details. This study complies with the Declaration of Helsinki.

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Disclosure

The authors report no conflicts of interest in this work.

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