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Study on the drug resistance in *Salmonella* and counter measure for it
(サルモネラ菌の薬剤耐性とその対策に関する研究)

Nontyphoidal *Salmonella* is a leading cause of acute gastroenteritis globally, with Southeast Asia having the highest incidence. Fluoroquinolones are a preferred treatment for *Salmonella* infection, but their overuse leads to resistance. Moreover, their stable residues in wastewater may contribute to antimicrobial resistance in aquatic environments involving canals. Canals are vital in Thailand, especially in Bangkok, serving as crucial agricultural and daily water sources while also acting as environmental pathways connecting humans and animals. This study consists of three chapters aimed to explore the drug resistance in *Salmonella* and counter measures for it.

CHAPTER I examined *Salmonella* spp. isolated from 6 canals in Bangkok during 2016 and 2020. Out of 333 water samples, a high prevalence (92.2%) of *Salmonella* spp. was detected in canal water. Among 399 isolates, a significant proportion of isolates (35.8%) carried plasmid-mediated quinolone resistance (PMQR) genes with *qnrS* being the most prevalent. Notably, six isolates harbored multiple PMQR genes and *qnrD* was first detected in *Salmonella* spp. isolated from environmental water in Thailand. Moreover, 9.3% and 3.8% of the isolates were resistant to nalidixic acid and ciprofloxacin, respectively.

CHAPTER II employed whole genome sequencing to characterize 30 selected *Salmonella* genomes from CHAPTER I. The predominant serotype identified was *S. Agona*. The analysis revealed the presence of 35 antimicrobial resistance genes and 30 chromosomal-mediated gene mutations, with 21 strains harboring both acquired genes and mutations associated with fluoroquinolone resistance. Notably, 75.9% of the strains exhibited multidrug resistance, and all strains carried essential virulence factors for the pathogenesis of salmonellosis. The identification of various plasmid types suggests the potential for horizontal transfer of antimicrobial resistance genes among the strains. Furthermore, the phylogenetic analysis revealed the potential circulation of *S. Agona* between canal water and food sources in Thailand and the possible introduction of drug-resistant *Salmonella* to Thailand from foreign countries or vice versa via international transportation.

Quinolone-resistant nontyphoidal *Salmonella* has become a public health concern globally. The World Health Organization has ranked fluoroquinolone-resistant *Salmonella* as a high-priority pathogen for researching and developing new antibiotics. CHAPTER III examined the inhibitory effects of novel fluoroquinolones, WQ-3034 and WQ-3154, against wild-type and mutant *Salmonella* Typhimurium DNA gyrases. The results from this study showed that WQ-3034 demonstrated the highest inhibitory effect against both wild-type and mutant *Salmonella* Typhimurium DNA gyrases and WQ-3034 and WQ-3154 exhibited a significantly higher inhibitory effect than ciprofloxacin against *Salmonella* Typhimurium DNA gyrase with double amino acid substitution, Ser83Phe-Asp87Asn. Thus, WQ-3034 and WQ-3154 could potentially be effective therapeutic agents against quinolone-resistant nontyphoidal *Salmonella*.

This study emphasizes the importance of urban environmental water as a reservoir for antimicrobial-resistant *Salmonella*. It underscores the necessity for stringent regulations on antimicrobial usage, enhancements in wastewater treatment systems, and comprehensive surveillance, all within the framework of the One Health approach that includes environmental sampling to address antimicrobial resistance issues in Thailand. Additionally, this study paves the way for antimicrobial drug development and potential *in vivo* studies to assess their efficacy in real-world scenarios, ultimately striving to create effective countermeasures against drug-resistant *Salmonella*.