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Investigation of the Emergence of Livestock-Associated
Methicillin-Resistant *Staphylococcus aureus* Clonal Complex 398 in
Thailand's Swine Industry using Whole-Genome Sequencing
(全ゲノム解析によるタイの養豚業における家畜関連メチシリン耐性
黄色ブドウ球菌クローナルコンプレックス 398 の出現に係る研究)

Livestock-associated methicillin-resistant *Staphylococcus aureus* (LA-MRSA) is commonly identified in pigs. It can therefore be transmitted from pigs to individuals through direct contact, especially those working on farms. In Thailand, LA-MRSA clonal complex (CC) 9 has been the predominant LA-MRSA lineage among pigs since 2011. However, in 2019, LA-MRSA CC398 was first reported in both swine and swine workers in Thailand. The CC398 lineage is mainly associated with European pig populations, whereas the CC9 is more commonly found among pig herds in Asia. This dissertation aimed to apply whole-genome sequencing (WGS) technologies to investigate zoonotic transmission of LA-MRSA CC398 between farm Thai pigs and swine workers, and to identify the potential original source of LA-MRSA CC398 detected in Thailand.

In Chapter I, WGS data of LA-MRSA CC398 isolates obtained from pigs ($n = 13$) and swine workers ($n = 3$) were generated using short-read sequencing for maximum-likelihood phylogenetic analysis. Human and porcine isolates sourced from the same farms were found to be phylogenetically related. The porcine isolates differed from the human isolates by only three to 11 single-nucleotide polymorphisms (SNPs). Furthermore, their antimicrobial resistance and virulence gene profiles were highly similar, corroborating the phylogenetic analysis. This chapter provides empirical evidence supporting the utility and effectiveness of WGS in investigating zoonotic transmission of LA-MRSA CC398.

Chapter II aimed to trace the potential original source of LA-MRSA CC398 in Thai swine and to determine the factors associated with the emergence of LA-MRSA

CC398 in the Thai swine industry. Complete genome sequences of the 13 LA-MRSA CC398 isolates were obtained from short-read sequencing data, previously generated in the first chapter, and long-read sequencing data. Five additional genomes of Thai LA-MRSA CC398 were included. For comparative genomic analysis, a total of 1,197 genomes of *S. aureus* CC398 were retrieved from Pathogenwatch database. Subsequently, two SNP-based phylogenetic trees were inferred using maximum-likelihood method ($n = 1,215$) and Bayesian inference ($n = 168$). Both phylogenetic trees revealed that the CC398-staphylococcal cassette chromosome (SCC) *mec* Vc (5C2&5)-t034 genotype among Thai pigs may have originated from porcine CC398 isolates in Denmark, while the composite CC398-SCC*mec*-t034 genotype was found to have evolved separately from the CC398-SCC *mec* Vc (5C2&5)-t034 genotype and exhibited no association with CC398 isolates from Denmark. This chapter emphasizes the significant impact of international livestock movement, possibly facilitating the spread of LA-MRSA CC398 from Denmark to Thailand. It also highlights the genetic complexity within the CC398 lineage in Thailand, underscoring the need of increased genomic surveillance.

In conclusion, this dissertation has identified two genotypes of LA-MRSA CC398 colonizing Thai pigs: the CC398-SCC *mec* Vc (5C2&5)-t034 genotype and the CC398-composite SCC*mec*-t034 genotype. Zoonotic transmission involving both genotypes is elucidated using the WGS approach. In Chapter II, comprehensive genomic analysis employing two different sequencing technologies has revealed that both genotypes evolve independently. The CC398-SCC *mec* Vc (5C2&5)-t034 genotype is closely related to porcine *S. aureus* CC398 isolates in Denmark, possibly reflecting the impact of international animal trade. In contrast, the origin of the composite CC398-SCC*mec*-t034 genotype remains unclear.