Human Origin for Livestock-Associated Methicillin-Resistant Staphylococcus aureus

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ABSTRACT **Methicillin-resistant *Staphylococcus aureus* (MRSA) is a major cause of human morbidity and mortality worldwide. The emergence in the last decade of a livestock-associated MRSA (LA-MRSA) clone which also has the capacity to cause zoonotic infections in humans has raised important questions regarding its origin and its potential to cause human epidemics. An important study by L. B. Price et al. [mBio 3(1):e00305-11, 2012] provides evidence for a human ancestral origin for LA-MRSA, raising concerns about agricultural practices that may have contributed to its emergence and expansion. The study highlights the potential for comparative whole-genome sequencing of closely related strains to provide valuable insights into the evolutionary history of bacterial pathogens.**

The emergence in the last decade of a livestock-associated methicillin-resistant clone of *Staphylococcus aureus* (LA-MRSA) that can cause zoonotic disease in humans has been a major public health concern. A paper published by Price et al. addresses the evolutionary origin of the LA-MRSA multilocus sequence type 398 (ST398) strains (1). ST398 strains were first identified in France in 2005 but subsequently came to prominence in the Netherlands as a common component of the skin microbiome of pigs and pig farmers (2, 3). ST398 MRSA has since been isolated from numerous countries in Europe, North America, and Asia from pigs, veal calves, turkeys, and chickens (4). Importantly, reports of ST398 infections, including severe infections in pig farmers and their family members, are increasing (5, 6). However, studies have demonstrated that ST398 MRSA strains do not readily transmit between humans, and carriage rates diminish rapidly in livestock farmers once the infection reservoir is removed (7, 8). These data imply that LA-MRSA ST398 is largely pig (or veal calf) adapted and has a low level of epidemicity for humans. However, worrisomely, several recent publications have reported the occurrence of methicillin-sensitive ST398 infections in humans without recent exposure to pig farms (9, 10), implying that subtypes of ST398 exist which are circulating among human populations.

The relatedness of these human strains of ST398 to LA-MRSA was unclear until the Price et al. study. CC398 is defined by multilocus sequence typing (MLST), a method which has proven extremely useful for defining the population structure of many bacterial pathogens, including *S. aureus*, and has resulted in a population framework which facilitates studies into bacterial evolution, pathogenesis, and antibiotic resistance (11). However, MLST involves the indexing of populations based on sequences at 7 gene loci only, and the lack of variation found at those loci among closely related strains limits its utility for examining the recent evolution of bacterial clones. In contrast, the use of whole-genome sequencing (WGS) for the identification of genetic variation provides the ultimate level of detail for discriminating between closely related strains and facilitates a high-resolution phylogenetic reconstruction.

Price et al. employed a WGS approach in their study of 89 isolates of ST398 from different host species from four continents, in order to examine the relatedness of strains within the clonal lineage and to understand their recent evolution (1). The authors reconstructed the phylogeny of the ST398 strains and demonstrated that strains of ST398 associated with livestock (or humans with recent contact with livestock) belong to several closely related subclades. Importantly, human-associated ST398 strains all belong to distinct clades within the CC398 tree that are basal to the livestock strains, which implies that the ancestral host state for the ST398 strains included in the study was most likely human (Fig. 1). Moreover, these data indirectly imply that the recently reported ST398 strains circulating in human populations may have had a long-term human host association and that the strains do not represent an emergent human clone which originated in livestock. The study provides important information regarding the emergence of ST398 LA-MRSA, which was previously speculated to have had a long-term association with livestock such as pigs. Although the study did not examine the time frame for the human-to-livestock host jump event and its subsequent expansion in livestock, it would appear that it was a relatively recent event. This discovery is analogous to that described previously by Lowder et al., who found that the major pathogenic clone of *S. aureus* that affects poultry likely originated in humans before switching hosts and adapting to colonize and cause disease in broiler chickens (12). This emphasizes an emerging theme, namely, that humans represent an important source of new bacterial strains which cause disease in livestock animals, and accordingly represent a potential threat to food security. The recent industrialization and globalization of food animal production may well provide increased opportunities for the anthroponotic transmission of bacteria, selection of adapted strains, and their international dissemination.

Related to the poultry *S. aureus* study by Lowder et al., Price et al. included several ST398 isolates from turkeys in the United States and discovered the existence of a member of the β-converting bacteriophage family found only in poultry strains

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FIG 1 A livestock market in Saqisili, Ecuador, in August 2010. Printed with permission by Pierre Jean Durieu.

of *S. aureus*, providing further evidence for an important role for this phage in avian host adaptation. In contrast, almost all human-associated strains of ST398 contained a ΦSa3 β-converting phage containing the immune evasion cluster known to encode factors involved in evasion of the human innate immune response (13). The vast majority of livestock-associated ST398 strains did not contain a bacteriophage inserted in the β-toxin gene. Overall, these findings highlight the central role for mobile genetic elements (MGEs) in *S. aureus* adaptation to different host species and imply that some MGEs may represent markers for the host origin of *S. aureus* strains.

The ubiquity of a tetracycline resistance determinant (*tetM*) and the large number of identified independent acquisitions of methicillin resistance by livestock-associated ST398 suggest that an antibiotic selective pressure exists within the livestock industry which has promoted the development of resistance since the host switch from humans to livestock animals. Of note, the authors state that expanded-spectrum cephalosporins are widely used in food animal production and could select for the evolution of MRSA. These findings highlight the critical importance of bodies such as the World Health Organization and the U.S. Food and Drug Administration in providing robust advice and regulations to limit the use in food animal production of antibiotic classes which are useful in human medicine. Furthermore, the increasing demand for meat and the associated threats to global food security mean that the development of novel alternative antimicrobial or vaccine-based approaches for the control of infections of food production animals is an urgent public health issue (14).

The ST398 genome sequence-based analysis has provided a remarkable insight into the likely ancestral host state of the ST398 clone. It will now be exciting to mine the data for additional insights relating to the evolutionary history of CC398. In particular, Bayesian evolutionary analyses could be used to identify the time frame of the host switching event and subsequent clonal expansion in livestock. In addition, it will be important to identify the genetic events which have contributed to its host adaptation in livestock and its apparent reduced epidemicity among humans. This may lead to the identification of determinants of host specificity which could be targeted for alternative therapeutic approaches. Furthermore, phylogeographic analysis of the data set may allow the identification of transmission routes for LA-MRSA ST398 strains. In particular, it will be important to know if livestock trade routes have contributed to the spread of ST398 on a regional basis between farms and on an international level. Finally, it is worth commenting that the large number of countries represented by the authors of the paper highlights the critical importance of international cooperation in examining infectious disease issues of global importance.

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