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Human origin for avian pathogenic *Staphylococcus aureus*

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Staphylococcus aureus is a major human pathogen associated with nosocomial and community-acquired infections, and is also responsible for several economically important infections of livestock. However, the evolutionary origin of animal strains and the potential for cross-species transmission has not been well examined. We recently traced the origin of a common *S. aureus* clone which is a significant cause of morbidity in the global broiler poultry industry. We provided evidence that it evolved from a single human to poultry host jump which was followed by extensive genetic diversification including acquisition of novel mobile genetic elements and loss of virulence gene function. The clone has since been disseminated widely to several different continents presumably through globalization of the poultry industry. In the current article, we summarise the findings of the paper, discuss their implications and speculate on the potential for other *S. aureus* cross-species transfer events.

In recent years considerable attention has been paid to the potential for the zoonotic transfer of pathogens from animals to humans resulting in disease epidemics. For example, a global health alert has been triggered by the recent swine flu pandemic, and livestock-borne pathogens such as *Campylobacter* and *E. coli* 0157:H7 continue to cause significant levels of morbidity among humans.¹⁻³ The potential for *Staphylococcus aureus* colonizing animals to cause infections of humans is unclear. However, the recent identification of strains of livestock-associated MRSA, such as the CC398 clone found in pigs, cows, poultry and horses, which

have also been associated with disease of humans, is worrisome.⁴ Furthermore, the recent emergence of community-acquired MRSA as a major cause of disease in the USA and other countries, has led to speculation regarding the possible existence of an animal reservoir for newly emergent strains which are pathogenic for humans.^{4,5} In addition, the potential impact of industrialization and globalization of agriculture on the emergence and spread of new pathogens from livestock animals is an issue of public health concern. However, little attention has been paid to the possibility that humans could represent a source of new pathogens for animals which could have economic and food security implications. For example, infectious diseases are a major economic burden on the global poultry industry and *S. aureus* is a common cause of broiler poultry infections such as dermatitis, subdermal abscesses (colloquially known as 'bumble foot'), and bacterial chondronecrosis with osteomyelitis (BCO). In a recent paper, we used a combination of population genetics and comparative genome sequencing to investigate the evolutionary origin of *S. aureus* strains from poultry.⁶ Unexpectedly, we discovered that the majority of isolates examined belonged to a single clonal complex (CC5) defined by multilocus sequence typing which was widespread among both healthy and diseased birds.⁶ A recent study by Smyth et al. (2009) was the first report in the literature which identified CC5 isolates among poultry (on a farm in northern Ireland⁷) which led the authors to speculate about the possibility of a cross-species transfer event.⁸ We demonstrated that the CC5 poultry isolates were widespread in countries in several different continents, but

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that all isolates can be traced back to a single likely human to poultry host-jump which happened about 40 years ago and which originated in or near to Poland.⁶ This situation contrasts strongly with human strains of CC5 which demonstrated strong phylogeographic clustering, indicating that the intercontinental spread of human CC5 strains and subsequent fixation in local populations is rare.⁹ We propose that the subsequent spread of the poultry ST5 clade has been facilitated by the globalized nature of the poultry industry whereby a small number of broiler breeding lines (and their resident normal flora) are distributed widely around the world.

Comparative genome sequencing of a representative poultry CC5 strain ED98 and the closely-related basal human strain MR1 allowed us to examine the genetic basis for the adaptation of *S. aureus* to an avian niche.⁶ A number of mutations leading to loss of gene function have occurred in the poultry strain ED98 since divergence from a common ancestor with the human strain MR1. For example, a nonsense mutation has occurred in the gene *spA* which encodes a major surface protein SpA involved in several aspects of human disease pathogenesis including the inhibition of phagocytosis by human neutrophils via the non-specific binding of IgG at the Fc fragment.¹⁰ Importantly, the Fc region of IgY which is the avian equivalent of IgG does not bind to SpA suggesting that SpA would not inhibit phagocytosis during infection of chickens.¹¹ Of note, a poultry biotype of *S. aureus* was described previously which had a combination of unique phenotypic characteristics, including lack of expression of SpA, which differentiated it from human and other animal strains.¹² In the genome of poultry *S. aureus* strain ED98 we discovered several novel mobile genetic elements which were not found in human or ruminant strains but were widely distributed among poultry *S. aureus* strains of distinct clonal origin, suggesting a fundamental role in avian host adaptation.⁶ A central role for horizontal gene transfer in bacterial adaptation to different host species has long been postulated but clear evidence for this is lacking. Taken together, these data represent the first clear evidence of

a human to animal bacterial host jump leading to the emergence of a strain which is endemic in livestock. In addition to the common CC5 poultry subtype, we identified less common genotypes of poultry *S. aureus* which are identical or closely-related to extant human genotypes and which contain MGE unique for poultry strains. These data suggest that the ST5 human to poultry host jump may not have been a unique event and that other host switches followed by host adaptation may have occurred on numerous occasions.⁶ The wide association of the common CC5 poultry clade of *S. aureus* with the normal flora of broiler chickens in different countries has led to concerns of a potential public health issue. Although very difficult to predict, the genetic diversification leading to avian adaptation including the loss of function of genes involved in human disease suggests that the clone may now be attenuated for virulence in humans and may have become avian host-restricted. Nonetheless, in the future it will be important to monitor poultry-related food poisoning episodes for a possible *S. aureus* CC5 etiology, particularly as the symptoms are mediated by enterotoxins and would not require *S. aureus* with the capacity to infect humans.

The extent to which the human to animal host switch phenomenon may be occurring in other livestock is unknown at this stage. Evidence to date suggests that ruminant *S. aureus* strains also have an ancestor which resembled human strains but it may have existed much longer ago than the most recent common ancestor of the common poultry clade.¹³ Increased sampling of pathogenic bacteria from animal infections and high resolution population genomic analysis of both human and animal strains will allow us to trace their evolutionary origins and to predict how often *S. aureus* host switches have occurred. These studies will be important to predict if animals represent a reservoir for the emergence of new virulent strains affecting humans, and conversely if human to animal host switches may represent a significant threat to food security and animal health. Furthermore, the molecular characterization of the host-pathogen interactions which are central to host adaptation could lead to the

identification of novel therapeutic targets for the control of bacterial infections.¹⁴

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