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Title: Mechanisms of adaptation of the zoonotic *Staphylococcus aureus* ST398 as a human pathogen

Aims: In the past decade there has been a dramatic increase in infections due to *S. aureus* acquired from the community. We recently observed the emergence of the originally zoonotic *S. aureus* strain ST398 in Northern Manhattan. This is the most prevalent methicillin-resistant *S. aureus* (MRSA) in parts of Europe. However, the genetic basis for its change in host adaptation and rapid dissemination remains unclear. We hypothesize that these changes are likely to involve altered pathogen-host receptor interactions, rapid genome diversification and adaptive metabolic changes that can lead to enhanced survival on inert surfaces. This hypothesis will be pursued using a combined approach, where epidemiological studies are informed by detailed genetic analyses to examine mechanisms of ST398 transmission and fitness. We posit that a deeper understanding of the epidemiological, genetic and functional mechanisms of this strain's adaptation will enable us to develop integrated and novel strategies to optimize interventions to reduce epidemic *S. aureus* transmission and infections in the community.

Aim 1: To define the reservoirs and modes of transmission of ST398 in Northern Manhattan. We propose a cluster-based study design to define the basis of ST398 transmission in Northern Manhattan. Subjects infected with ST398, and their cluster of contacts will be examined for nasal or environmental colonization and transmission and recruited into a network referral chain of six waves. Each cluster will be reexamined after four and eight months to estimate the spread of the strain. This will allow the first definition of niches and modes of transmission of the ST398 strain present in the community.

Aim 2: To determine how the pig strain ST398 has evolved as a human pathogen. We aim to identify the genetic changes that have led to inter-species transmission and animal-independent spread of ST398 by *de novo* sequencing of ST398, combined with whole-genome comparative sequencing of zoonotic, persisting or particularly transmissible ST398 isolates. Sequence differences will subsequently be studied in recombinant strains and will be tested *in vitro* for adherence to different tissues, survival on environmental surfaces, as well as *in vivo* in *S. aureus* animal models of local and invasive disease.