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VIEWPOINT

A path forward for *Staphylococcus aureus* vaccine development

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The pursuit of a vaccine to quell *Staphylococcus aureus* disease has been unfruitful. In this Viewpoint, we explore the biological linkage between microbial niche acquisition and host immunity as a basis to guide future vaccine efforts.

At the start of this decade, the world again witnessed the remarkable ability of vaccination to mitigate an infectious disease threat. SARS-CoV-2 spread rapidly within the human population wherein pre-existing immunity was negligible. On this backdrop, targeting a single viral antigen through mRNA-based vaccine technology engendered population-level immunity at an unprecedented speed. In stark contrast, more than 20 years have elapsed since the initial Phase III clinical trial of a vaccine to prevent *Staphylococcus aureus* infection (Shinefield et al., 2002). Since that time, our understanding of the molecular pathogenesis of *S. aureus* disease has become more sophisticated, kindling additional vaccine trials. These efforts, however, have not yet culminated in the development of a successful vaccine (Miller et al., 2020), compelling a much-needed focus on investigation of the human immune response to *S. aureus*.

Observations on *S. aureus* disease readily illustrate the complexity of the interaction between this microbe and its human host. In 1928, 21 children in Australia that received von Behring's diphtheria toxin-antitoxin serum were unknowingly injected with the so-called "Bundaberg staphylococcus" as a contaminant of the vaccine lot. Among these, twelve died from fulminant infection, six became ill but recovered, and three did not experience systemic disease but developed local abscess lesions at the immunization site. In the official report on this incident, it was noted that "a very large number of organisms was directly introduced into the subcutaneous tissues of extremely susceptible, partially susceptible, and almost insusceptible children" (Kellaway et al., 1928), highlighting variation in clinical outcome despite identical inoculation. Nearly a century later, our understanding of human anti-staphylococcal immunity is insufficient to predict susceptibility to infection or to provide prognostic insight on clinical outcomes. This fact underscores the fundamental gap in knowledge that hinders vaccine development.

Humans serve as the primary ecologic niche for *S. aureus*. While the precise definition of a "niche" has been the subject of debate in ecology, it is reasonable to consider the *S. aureus* niche as that environment within its human host that provides both the physical and biological context necessary for survival. Niche acquisition depends upon competitive fitness within the human microbiome, but also requires protection from sterilizing host immunity. Initial population of the *S. aureus* niche occurs in the first weeks to months of human life, documented both by assessment of colonization frequency and detection of host immune responses specific to this microbe (Lebon et al., 2010; Li et al., 2021; Tomaszewski et al., 2024). While persistent colonization with *S. aureus* is limited to ∼20–30% of the adult population, carriage in infancy can approach 70% (reviewed in Piewngam and Otto, 2024). Infants and children under the age of 4 exhibit an increased burden of *S. aureus* disease (GBD 2019 Antimicrobial Resistance Collaborators, 2022), likely reflecting the fact that colonization is a risk factor for infection (Wertheim et al., 2004). Together, these observations highlight early life as a unique developmental period in which adaptation of *S. aureus* to its human niche occurs.

The importance of canonical microbial "virulence" factors in bacterial niche establishment has only recently been recognized (Hill et al., 2024; Rivera-Chavez and Mekalanos, 2019; Sun et al., 2018). Two broad classes of well-studied *S. aureus* virulence factors include surface-exposed proteins and secreted molecules. While surface proteins are instrumental for *S. aureus* to interact with host tissue and acquire nutrients, many secreted exoproteins and toxins facilitate evasion of innate and adaptive immunity. Through an ecological lens, these two classes of virulence factors may cooperate in homeostatic niche acquisition and maintenance. Caldera et al. (2014) recently revealed that discrete, non-protective immune responses are raised against an array of *S. aureus* surface proteins in response to natural infection. In contrast, the elicited immune response to several toxins exhibits neutralizing capacity, consistent with prior observations in the field (Lee et al., 2020; Wu et al., 2018). It is interesting to speculate that perturbation of the adaptive immune response by *S. aureus* may specifically bias

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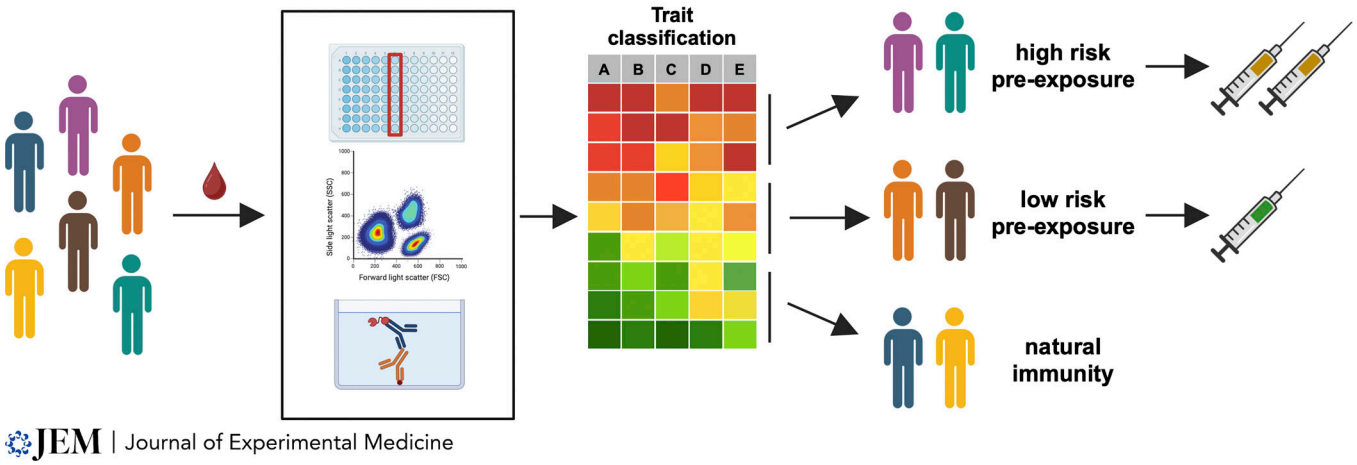

Figure 1. **Conceptual framework for use of an immunoscore to inform *S. aureus* vaccine development.** Humans exhibit heterogeneity of the host immune response to *S. aureus*. Positioning the field to develop and implement a functional assessment of the protective immune response (displayed as quantifiable traits A–E) will enable risk stratification of the population that has been exposed to *S. aureus*. The application of this PISA can be utilized to guide targeted vaccine-based interventions. Illustration created with https://BioRender.com.

the host toward the generation of non-productive responses to staphylococcal surface proteins, thereby safeguarding the molecular interactions vital to niche maintenance. Multiple human-adapted bacterial species including *Mycobacterium tuberculosis*, *Klebsiella pneumoniae*, *Escherichia coli*, *Chlamydia trachomatis*, *Clostridioides difficile*, and *Pseudomonas aeruginosa* exhibit a dynamic interface between niche ecology and host immunity. Like *S. aureus*, these are the very pathogens for which vaccine development has proven most challenging.

For each of these microbes, immunologic adaptations that favor niche acquisition must be durable in order to ensure resilience of the niche. By virtue of antigen specificity and memory, the T and B cell compartments underlie durability of the immune response. Whether in the setting of microbial exposure or vaccination, the initial elicited T and B cell response will be amplified upon re-encounter of the stimulating antigen(s). This knowledge has led to an application of the doctrine of "original antigenic sin" (also referred to as antigenic or immunologic imprinting) to explain the failures of vaccine-elicited immunity against *S. aureus* (Creech, 2022). In the case of *S. aureus*, however, it may be more instructive to consider perturbation of the adaptive immune response as a microbe-induced immunologic adaptation that ensures potential for long-term maintenance of the ecologic niche. As proposed by Graham and Xavier (2023), this type of adaptation is a "conditioning" response predicated on the existence of specific molecular interactions between a microbe and its host that preserve niche homeostasis.

Analysis of the *S. aureus* pan-genome reveals the preservation of multiple conserved core genome-encoded immunomodulatory proteins across human host-adapted *S. aureus* isolates (Howden et al., 2023). Specifically relevant to the adaptive immune response, a growing body of data points to a critical role for α-toxin and staphylococcal protein A in modulation of the T and B cell response to *S. aureus*, respectively (Kim et al., 2015; Lee et al., 2020). While the difference between "imprinting" and microbe-driven conditioning may appear little more than semantics, considering modification of the adaptive immune response as a product of co-evolution of *S. aureus* and its human host has important implications for vaccine development.

Recognition of the intrinsic link between niche acquisition and staphylococcal antigen exposure compels the development of a pre-exposure vaccine specifically designed to protect against *S. aureus*–induced immunologic adaptation early in life. Neonates and infants likely represent the only population in which a truly preventive *S. aureus* vaccine may be implemented. Beyond the expected regulatory challenges that must be embraced in vaccine development for this population, several important biologic considerations must also be acknowledged. Targeting staphylococcal factors that modulate immunity to facilitate niche homeostasis may engender changes in *S. aureus* ecology. Moreover, development and implementation of a *S. aureus* vaccine for infants cannot be expected to confer immediate widespread protection against disease. The field must commit to the "long game," recognizing that vaccine-elicited immunity in this population has the unique potential to confer lifetime protection for each population-based vaccine cohort.

Development of a *S. aureus* vaccine for pre-exposed populations of children and adults has proven to be a formidable task. Among individuals who have already been exposed to *S. aureus*, two broad populations are likely to exist: (1) those who exhibit a favorable immune profile sufficient to confer protection against disease, i.e., a population that has developed some degree of natural immunity, and (2) those whose functional immunologic profile suggests a non-protective response. In the former group, vaccine delivery may not confer benefit, and harbors risk of degrading the native immune response. In the latter group, vaccine design will need to either augment specific antigenic responses that are partially protective or elicit a novel response, avoiding amplification of non-protective responses. Rather than focus on development of a single vaccine expected to elicit protective immunity across all populations (the so-called

"universal vaccine"), it will be prudent to stratify the pre-exposed population into biologically distinct groups based on immunologic profiling. The oncology field has pioneered use of tumor-associated immune signatures to discriminate heterogeneous responses among individuals (Bruni et al., 2020). Leveraging quantifiable, individual-specific traits through predictive algorithms, cancer "immunoscoring" guides personalized clinical care and prognostication. Adaptation of this concept within the *S. aureus* field through the development of a Precision Immunoscore for *S. aureus* (PISA) may enable stratification of immunologic risk in the setting of heterogeneous pre-existing anti-staphylococcal immune responses to inform vaccine design, delivery, and outcomes prediction (Fig. 1). As experience in oncology illustrates, the foundation for such an immunoscore must rely on functional analysis of human immunity to *S. aureus*.

To this end, and moreover the greater goal of vaccine development, the field will need to seek a detailed understanding of the humoral and cellular responses present in humans that exhibit protection against infection while being absent or diminished in susceptible individuals. Candidate vaccine targets must be defined based on quantifiable immunologic outcomes, distinguishing immunogenicity of a vaccine antigen(s) from its ability to elicit protective immunity. Rigorous mechanistic evaluation of both the targeted antigen(s) and vaccine formulation will be essential, necessitating complementary studies in human populations and reductionist model systems to support vaccine design and clinical trials.

These considerations do not offer assurance that a *S. aureus* vaccine for pre-exposed individuals is close at hand. Now is the time to accelerate translational research within the field through the development of diverse teams of investigators whose expertise spans microbiology, immunology, and investigation of human clinical disease. Much as the mounting morbidity and mortality attributable to SARS-CoV-2 drove innovation in vaccine development and implementation, so must the *S. aureus* field be driven by the recognition that nearly 400,000 newborns worldwide are beginning to "adapt" to this microbe each day.

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