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Status of vaccine research and development of vaccines for *Staphylococcus aureus*☆

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ABSTRACT

Staphylococcus aureus is a highly versatile gram positive bacterium that is resident as an asymptomatic colonizer on the skin and in the nasopharynx of approximately 30% of individuals. Nasopharyngeal colonization is a risk for acquiring *S. aureus* infections, which can cause a range of clinical symptoms that are commonly associated with skin and soft-tissue infections. The emergence of *S. aureus* strains that are highly resistant to antimicrobials has recently become a major public health concern. In low-income countries the incidence of *S. aureus* disease is highest in neonates and children up to one year of age and mortality rates are estimated to be up to 50%. In the United States, *S. aureus* infection accounts for approximately 300,000 hospitalizations per year. A vaccine against multi-drug resistant *S. aureus*, therefore, is urgently needed. Two vaccine candidates have previously been evaluated in late-stage clinical trials but have not demonstrated efficacy. At present, one vaccine candidate and two monoclonal antibody are undergoing clinical evaluation in target groups at high risk for *S. aureus* infection. This review provides an overview of current vaccine development efforts and presents the major technical and regulatory challenges to developing a licensed *S. aureus* vaccine.

1. About the disease and pathogen

Staphylococcus aureus is a bacterium that is both an asymptomatic colonizer and frequent cause of disease in humans [1]. It is a highly versatile pathogen that causes a range of clinical manifestations of varying severity, and is the most commonly isolated pathogen in the setting of skin and soft-tissue infections, septic arthritis, pneumonia, endovascular infections, osteomyelitis, foreign-body associated infections, septicemia and toxic shock syndrome [2]. *S. aureus* infections strike people of all ages and backgrounds, but are most severe in young children, the elderly, the immunosuppressed and other individuals with major co-morbidities [3,4]. The incidence of *S. aureus* infection in low income countries is highest in neonates and children up to one year of age with mortality rates of up to 50% [5], in contrast to high income countries where the disease appears to increase with age, or is most prevalent at the extremes of the age spectrum. However, there have been very few epidemiological studies in low and middle income countries, and it is likely that there is an under-reporting of *S. aureus*-associated disease generally, and particularly in the elderly in these settings [6,7].

S. aureus is known to be highly adaptable, and in recent history has shown a remarkable epidemiologic transition. Since 1959, when methicillin was first introduced, strains of methicillin-resistant *S. aureus* (MRSA) have been documented at a rapid and increasing rate. Hospital-associated MRSA (HA-MRSA) clones are now recognized to be the leading cause of nosocomial infections in low-, middle-, and high-income countries [5,8,9]. The emergence of community-associated MRSA (CA-MRSA) in the past several decades has also become a point of concern, as virulent strains of CA-MRSA are fast-spreading and can affect seemingly healthy individuals [10]. Vancomycin is currently the first-line treatment for severe CA-MRSA and HA-MRSA infections, however strains with reduced susceptibility to this antimicrobial (vancomycin-intermediate *S. aureus* (VISA) and vancomycin resistant *S. aureus* (VRSA)) have been reported with increasing frequency [11]. Since

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nasal carriage is a well-defined risk factor for infection, decolonisation protocols have had some moderate success in reducing the incidence of infection in specific hospitalized groups. However, clearance is not consistent or long-lived, and this strategy is not applicable to community settings. Efforts to prevent MRSA infection in high-income countries are well-resourced, but risk factors and infection are poorly monitored in low- and middle-income settings, where in some cases over-the-counter antibiotics are available and frequently self-administered [12]. MRSA's status as a global public health threat will only be exacerbated by inappropriate anti-microbial use and will further accelerate the spread of CA-MRSA and other resistant microorganisms.

S. aureus, which is constitutes the normal flora in up to 30% of individuals (either persistently or intermittently), is typically spread *via* close contact from carriers to non-carriers. Transmission has been found to be most efficient within healthcare and athletic facilities [2,13]. In high income countries, target groups for potential *S. aureus* vaccination would be at-risk healthcare workers, the elderly ≥65 years, and the immunocompromised, as well as patients with recurrent invasive staphylococcal infection [3,14]. The global burden and spread of *S. aureus* infection is currently unknown and more data from low- and middle-income countries are needed, but in the US alone, *S. aureus* infection is reported as a discharge diagnosis for around 300,000 hospital stays per year. *S. aureus* infection is also associated with a five-fold increased risk of in-hospital death and three-fold higher cost of hospital stay compared to inpatients without infection [15]. A US study in 2003 estimated that *S. aureus* infections accounted for $14.5 billion in all inpatient hospital stays and $12.3 billion for surgical stays [16].

2. Overview of current efforts

A. Either vaccines currently available and their limitations or biological feasibility for vaccine development

Prior *S. aureus* infection does not provide protection against subsequent infection, but infections among carriers are less severe, suggesting that some form of immunity does develop during prolonged colonization. Although all adults have pre-existing binding antibodies to *S. aureus* antigens, including capsule and clumping factor A (ClfA), these do not typically include functional antibodies that have opsonophagocytic or neutralizing properties, and therefore do not provide protection against infection.

There is precedence for the development of safe and effective bacterial vaccines that target single antigens or toxins, particularly capsular polysaccharides. The most prominent examples are the tetanus toxoid and pneumococcal conjugate vaccines. Application of these technologies to *S. aureus* is complicated by the bacterium's complex mechanisms of pathogenesis. *S. aureus* can comprise the normal human flora and, as such, has evolved a number of strategies to colonize and evade the host immunity, including polymorphic expression of surface antigens and release of multiple redundant virulence factors [17,18]. These include iron acquisition factors such as IsdB, manganese uptake receptors such as MntABC, fibronectin binding proteins (ClfA, ClfB), polysaccharide capsule molecules (CP5 and CP8) and toxic shock syndrome toxin (TSST). To date, vaccine candidates have targeted individual cell surface components, such as the polysaccharide capsule, extracellular polysaccharides or cell wall associated proteins that aid attachment, invasion or act as a receptor (*e.g.*, hemoglobin for iron utilization). Although multiple vaccine candidates have shown promise through preclinical development in a range of animal models, those that have reached late stage clinical testing have failed to demonstrate efficacy in human trials [19,29].

B. General approaches to vaccine development for this disease for low and middle income country markets

S. aureus has not been viewed as a high-priority pathogen in low-income countries. However, based on the limited data available, the incidence and mortality from multidrug-resistant *S. aureus* in these regions is likely significant, To date, only two vaccines have completed human efficacy, and neither have contemplated target populations or indications that are prevalent in low- and middle-income countries [20]. StaphVAX is a bivalent polysaccharide- and protein-conjugated vaccine, directed against *S. aureus* capsular polysaccharide types 5 and 8 (CP5 and CP8), which are associated with approximately 80% of *S. aureus* clinical infections. The candidate was evaluated in two phase III studies to prevent bacteremia in end-stage renal dialysis patients in the 3–54 weeks following immunization. In the first 40 weeks, bacteremia was reduced by 57% but efficacy dropped to 26% by week 54 [21]. A confirmatory Phase III study involving 3600 heamodialysis patients who were evaluated for bacteremia showed no difference between vaccinated individuals and the placebo controls. The functional antibody titers induced by the vaccine in this second follow-up phase III study have not yet been made publicly available. Currently, then, the main reason for the second trial's failure is being attributed to manufacturing inconsistencies between different vaccine lots used for the two studies [22]. Development of the candidate has been discontinued.

Another candidate, V710, elicits immunity against the cell-wall anchored iron scavenger protein IsdB, and was evaluated in a Phase III randomized controlled trial in approximately 8000 adults scheduled for cardiac surgery. This trial was terminated when an interim analysis showed a statistically significant increase in mortality rate due to *S. aureus* infection and a significantly higher rate of other adverse events [23].

Passive immunization strategies utilizing both polyclonal and monoclonal antibodies (mAbs) have been targeted for those who are immunocompromised and cannot mount an independent, robust immune response and for those at immediate risk of infection and do not have time to for an active immunization to take effect. Five antibody candidates have been developed and evaluated in late stage clinical studies; none have demonstrated efficacy [24].

The focus has been on development of a prophylactic product that will protect against life-threatening *S. aureus* infections, but it is hoped that such a vaccine would also protect against all *S. aureus* infections including more commonly encountered skin and soft tissue infections. To date, however, no product has been shown to protect against any tested outcome.

3. Technical and regulatory assessment

Active and passive immunization approaches have been based on increasing the concentration of opsonic antibodies to single surface antigens, and all have failed to demonstrate protection. Antigenic variation and the multiple invasion and colonization mechanisms of *S. aureus*, absence of representative preclinical models and lack of immune correlates or surrogates of protection all present significant obstacles to the rational design, development and evaluation of potentially successful vaccine candidates.

Leaders in the field have been speculating about the future directions for *S. aureus* vaccine development, particularly in the aftermath of the failed efficacy trials [25–28]. First and foremost, a multi-antigen approach that targets both cell surface components and secreted virulence factors, and potentially responses against the disease causing toxins, have been hypothesized as essential to the success of a vaccine. Because *S. aureus* causes

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