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COMMENTARY

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The development of a staphylococcus aureus four antigen vaccine for use prior to elective orthopedic surgery

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ABSTRACT

Staphylococcus aureus (*S. aureus*) is a challenging bacterial pathogen which can cause a range of diseases, from mild skin infections, to more serious and invasive disease including deep or organ space surgical site infections, life-threatening bacteremia, and sepsis. *S. aureus* rapidly develops resistance to antibiotic treatments. Despite current infection control measures, the burden of disease remains high. The most advanced vaccine in clinical development is a 4 antigen *S. aureus* vaccine (SA4Ag) candidate that is being evaluated in a phase 2b/3 efficacy study in patients undergoing elective spinal fusion surgery (S*Taphylococcus aureus* suRgical Inpatient Vaccine Efficacy [STRIVE]). SA4Ag has been shown in early phase clinical trials to be generally safe and well tolerated, and to induce high levels of bactericidal antibodies in healthy adults. In this review we discuss the design of SA4Ag, as well as the proposed clinical development plan supporting licensure of SA4Ag for the prevention of invasive disease caused by *S. aureus* in elective orthopedic surgical populations. We also explore the rationale for the generalizability of the results of the STRIVE efficacy study (patients undergoing elective open posterior multilevel instrumented spinal fusion surgery) to a broad elective orthopedic surgery population due to the common pathophysiology of invasive *S. aureus* disease and commonalties of patient and procedural risk factors for developing postoperative *S. aureus* surgical site infections.

Staphylococcus aureus disease-an unmet medical need

S. aureus disease

S. aureus is a commensal Gram-positive coccus that colonizes the nares, axillae, pharynx, and other mucosal and skin surfaces of approximately 30% of humans at any given time.[1–3] While *S. aureus* colonisation in healthy individuals generally does not lead to disease, the association between *S. aureus* nasal carriage and *S. aureus* infection risk at surgical sites is well established for cardiothoracic and orthopedic surgeries.[4] Breaches in the skin or mucosa which allow bacteria to enter a normally sterile site can result in a wide range of infections, including invasive surgical site infections (SSIs).[5] SSIs are the most common cause of healthcare-associated infections (HAI) in low-income settings and the second most common cause of HAI in high-income countries. *S. aureus* including both methicillin-resistant (MRSA) and methicillin-sensitive *S. aureus* (MSSA) is responsible for approximately 20% of all HAI in hospitalized patients and 30% of SSIs in the United States.[6–10] *S. aureus* SSIs are associated with increased morbidity and mortality; sequelae include revision surgeries, poor quality of life, prolonged antibiotic treatment and rehabilitation, and associated lost work and productivity.[3,11–15] Moreover, SSIs are associated with a substantial economic burden to the healthcare system as a result of increased length of hospital stay and increased risk of readmission.[16,17]

Current strategies aimed to prevent *S. aureus* SSIs include improved hygiene, aseptic surgical techniques, carrier screening, skin and nares decolonization, application of antibiotics to the surgical site prior to wound closure, and intravenous antibiotic prophylaxis.[4,18–22]

Some of these targeted preventative strategies have been shown to reduce SSIs in randomized controlled clinical trials and are often delivered as bundles. Strategies to prevent SSIs such as the Surgical Care Improvement Project (SCIP) initiative[23-25], Epic Guidelines 1, 2, and 387[26,27] and National Institute for Health and Clinical Excellence (NICE) SSI quality standards[28] have been widely adopted. However, no consensus exists on the key components of a successful preventative bundle. Adherence to bundles is also resource intensive for clinical staff, and poor patient compliance has been implicated in lower than expected effectiveness.[29] In addition, routine use of antibiotic prophylaxis and nasal decolonization agents such as mupirocin, have resulted in selection pressure on colonizing strains.[30,31] Reports of increasing mupirocin resistance are of serious concern[32,33] and the promotion of mupirocin resistance may also aid in the spread of multidrug resistance through co-selection with other resistance genes[34] (e.g. high rates of clindamycin resistance in

mupirocin resistant *S. aureus* isolates). Perioperative systemic antibiotic prophylaxis is a key preventative intervention shown to result in up to an 81% reduction in SSI incidence in orthopedic surgery.[35] To be effective, systemic antibiotic prophylaxis has to achieve therapeutic tissue concentrations at the time of incision and while the wound is open.[36,37] The effectiveness of intravenous antibiotics demonstrates that infections can be prevented at the time of surgery by systemic intervention strategies, which also supports a vaccine-based prevention strategy for *S. aureus* disease.[38–41]

Despite advancements in preventative strategies and improved adherence to infection control practices, *S. aureus* SSIs continue to occur, placing a substantial burden to the healthcare system. Thus, despite currently recommended prophylactic practices, there is a high unmet medical need for new strategies to prevent postoperative *S. aureus* infections including a safe and efficacious prophylactic vaccine.

The quest to develop a prophylactic vaccine to prevent *S. aureus* infections has been fraught with difficulties. Most notably two different monovalent vaccines were evaluated in phase 3 efficacy studies and failed. One contained two capsular polysaccharide (CP) conjugates serotypes (CP5 and CP8 linked to recombinant *Pseudomonas aeruginosa* exoprotein A; StaphVax [Nabi])[42,43], an approach that has been highly successful for other pathogens.[44] The second vaccine contained a single protein antigen (iron surface determinant B; IsdB) associated with iron acquisition.[45] The potential reasons of the vaccine failures have been extensively reviewed.[46] In addition to the IsdB vaccine not being efficacious, it also was associated with a safety signal of increased incidence of death and multiple organ failure in those who received vaccine and developed *S. aureus* infections.[45] There are different theories as to what caused the safety signal for the IsdB-based vaccine.[45,47] Of note though is that the design of the vaccine (single antigen without strong evidence of inducing a bacterial killing response and bacterial redundancy of iron acquisition mechanisms[48]) was different from other vaccines in clinical development. In addition, there is no established mechanism for the safety signal, and no such signal was observed with capsular polysaccharide-based StaphVax. Thus, there is no evidence to substantiate that the safety event is a class effect associated with all *S. aureus* vaccines.

SA4AG vaccine design and preclinical assessment

Learnings from previously unsuccessful vaccine development and pre-clinical research programs suggest that an effective vaccine against *S. aureus* should contain multiple antigens targeting different virulence mechanisms.[49–51] An investigational four antigen vaccine (SA4Ag) targeting multiple virulence mechanisms is currently undergoing clinical development by Pfizer. SA4Ag contains four surface-expressed *S. aureus* antigens that target three virulence mechanisms deployed early in the infection process and are highly conserved, expressed in-vivo by the vast majority of global clinical isolates, and required by *S. aureus* to initiate and maintain infection.[52–57] These antigens include CP5 and CP8, each conjugated to the nontoxic mutant form of diphtheria toxin (cross-reactive material 197 [CRM$_{197}$]), (CP5-CRM$_{197}$ and CP8-CRM$_{197}$).[58] The third antigen is a

recombinant form of clumping factor A (ClfA) with a single amino acid substitution (Y338A) that prevents it from binding to its natural ligand fibrinogen.[59] The fourth antigen is a recombinant non-lipidated form of the *S. aureus* manganese transporter C (MntC) protein called rP305A.[60]

Capsular polysaccharides (CP)

Expression of CP is a common mechanism by which pathogenic bacteria, including *S. aureus*, evade opsonophagocytosis (ie, complement-mediated uptake by neutrophils and macrophages).[58] CP provide an effective immune evasion strategy by cloaking the bacteria and rendering them invisible to innate immune responses. Studies have shown that encapsulated *S. aureus* strains are more virulent in bacteremia models compared with capsule-defective isogenic mutants.[52,53] Although 13 putative CPs have been described in *S. aureus*, all isolates have the genetic pathway for expression of CP5 or CP8.[58,61] Preclinical animal studies using CP5 and CP8 antibodies or vaccinating with CP conjugates have shown evidence of protection against *S. aureus* infection in challenge studies.[60,62–64] Moreover, vaccine induced anti-CP5 and anti-CP8 antibodies mediate opsonophagocytic killing activity as shown in preclinical and human clinical studies with the CP5-CRM$_{197}$ and CP8-CRM$_{197}$ conjugates or SA3Ag and SA4Ag vaccines.[65–68] It is interesting to note that while StaphVAX (by Nabi Biopharmaceuticals), a bivalent vaccine containing capsular polysaccharide conjugates was found to be safe; it did not meet its efficacy endpoints in two studies to prevent *S. aureus* bacteraemia.[43] Amongst possible explanations for the lack of efficacy were quoted manufacturing issues[43], failure of consistently assessing vaccine immunogenicity with functional, bacterial killing responses and the challenge of protecting an immunocompromised end-stage renal disease population for a prolonged period of time. Furthermore, Scully et al. (2018) demonstrated that O-acetylation of the *S. aureus* capsular polysaccharide has to be maintained in the CP 5 and 8 conjugates for them to induce bacterial killing antibodies.[69]

Clumping factor a (CLFA)

ClfA is a surface adhesin that binds to the C-terminus of the plasma fibrinogen γ chain,[70,71] and is present in 99% of *S. aureus* isolates including MRSA and MSSA.[59] ClfA promotes fibrin cross-linking and mediates the binding of *S. aureus* to platelets, resulting in thrombus (blood clot) formation.[72,73] It has also been shown to play a key role in the agglutination of staphylococci in the blood during infection, which leads to thromboembolic lesions in heart tissue and sepsis.[54] The fibrinogen-binding activity of ClfA is linked to the ability of *S. aureus* to cause disease, as *S. aureus* strains with ClfA point mutations that prevent fibrinogen binding showed reduced virulence.[74] This has also been shown in a *Lactococcus lactis* model that specifically demonstrated ClfA-attributed virulence, which was reversed by mutating the fibrinogen-binding domain of the protein (rClfAm). Virulence attributed to the native ClfA protein could only be prevented with antibodies that prevented ClfA from binding to fibrinogen.[75] Preclinical studies evaluating ClfA as a vaccine antigen showed antibody-mediated protection in several animal models including osteomyelitis and septic arthritis.[74] Furthermore, vaccination of

mice with SA4Ag resulted in anti-ClfA antibodies that prevent *S. aureus* from binding to fibrinogen, which was in contrast to immunization with a vaccine comprised of ClfA expressing dead *S. aureus* cells.[59,70] A fibrinogen binding inhibition (FBI) assay[59] measuring anti-ClfA antibody-mediated inhibition of binding to fibrinogen of live *S. aureus* clinical isolates that express diverse ClfA variants as well as a competitive Luminex immunoassay (cLIA) were subsequently developed for clinical use.[76] Humans naturally have ClfA binding antibodies through natural exposure; however, these antibodies are not potent enough to block the ability of ClfA to bind to fibrinogen and thus are not considered "functional". It's noteworthy that antibody infusions that were enriched for ClfA binding antibodies were not successful in phase 3 trial aimed at preventing *S. aureus* bacteremia among neonates[77]; the lack of potency and functionality of antibodies found naturally in unvaccinated humans may have contributed to this outcome. A ClfA monoclonal antibody (mAb) (tefibazumab, Aurexis; Inhibitex)[78] was evaluated in phase 2 trial as an adjunct to standard therapy for adult patients with *S. aureus* bacteraemia also failed to demonstrate any significant differences in time to recovery with the mAb and antibiotic treatment compared to antibiotic treatment alone. It is noteworthy that tefibazumab was a humanized antibody derived from Ab12-9. The body of the preclinical data was demonstrated with Ab12-9 and so it cannot be conclusively assumed that the biological properties for Ab12-9 are the same as tefibaxumab. MAbs in general have the limitation that they only recognize a single epitope. The difference between a polyclonal antibody preparation and a monoclonal one was exemplified by Hawkins et al[59] who demonstrated that polyclonal antibodies generated by an early formulation of SA4Ag in humans, were more potent than Ab12-9 at preventing *S. aureus* cells from binding to fibrinogen thus the lack of efficacy of the MAbs together with a lack of demonstrating bacterial killing in clinical studies may not be surprising retrospectively.

Manganese transporter c (MNTC)

A primary host defense mechanism against bacterial invasion is the sequestration of metal ions that are essential for bacterial survival. Like other bacteria, *S. aureus* has developed approaches to rapidly scavenge divalent cations like manganese and iron from the host when the bacterium establishes an infection. MntC is a highly conserved (>98% sequence identity) lipoprotein that is the surface-exposed metal binding subunit of MntABC, a heterotrimeric membrane transporter responsible for the acquisition of manganese.[55–57] As a cofactor for a number of diverse enzymes, manganese plays important roles in bacterial metabolism, cell wall synthesis, and virulence. Most notably, it is the sole cofactor for superoxide dismutase enzymes, which inactivate reactive oxygen species generated during the oxidative burst in the phagosome of activated macrophages and neutrophils.[79–81] Therefore, antibodies that target MntC have the potential to interfere with two critical *S. aureus* virulence mechanisms: nutrient acquisition and phagosome survival. MntC has been proposed as a potential vaccine candidate due to early expression in infection and its ability to provide protection in preclinical models of staphylococcal infection.[55,82] In a study evaluating *S. aureus*

antigens, IgG levels against 27 *S. aureus* antigens, including MntC (SA0688), were significantly elevated in bacteremia patients compared to controls indicating that MntC is an immunogenic and ubiquitously expressed antigen. The *in vivo* expression and antibody characterization data generated by our group and others provide a plausible mechanism of protection afforded by MntC antigen where anti-MntC antibodies deprive *S. aureus* of the ability to sequester manganese and thus make the bacteria more vulnerable to oxidative stress and killing by neutrophils (neutrophil respiratory burst) and macrophages.[55–57,76]

SA4AG clinical development

Phase 1/2a studies

The first clinical study in the SA4Ag program was initiated in January 2010, and demonstrated the safety and immunogenicity of a first-generation 3-antigen vaccine (SA3Ag) containing CP5 and CP8 conjugates and ClfA.[83,84] Clinical development of SA4Ag including rP305A (MntC) began in August 2011 following preclinical studies demonstrating that the vaccine was efficacious in sepsis, bloodstream infection and implanted device animal models.[55,69,75,85] A listing of completed and planned clinical studies is shown in Table 1. In February 2014, the FDA granted Fast Track designation for SA4Ag. Results from the completed Phase 1/Phase 2a clinical trials conducted in healthy volunteers in the United States confirmed that a single dose of SA4Ag elicited rapid and robust production of functional antibodies against the 4 vaccine antigens (CP5-CRM$_{197}$, CP8-CRM$_{197}$, ClfA, and MntC) and had an acceptable safety profile in healthy subjects 18 through 85 years of age.[65,66,86] Both younger and older adults responded to the vaccine with an anamnestic-like response, which was anticipated given that humans are being exposed to *S. aureus* antigens since birth. Persistent immune responses were observed through 36 months after a single vaccination (data pending publication).[87]

Selection of the population for initial efficacy evaluation

A population of patients undergoing elective open posterior multilevel instrumented spinal fusion was chosen for the clinical efficacy and safety evaluation of SA4Ag in the prevention of invasive *S. aureus* disease. This population was chosen as it is a stringent and well-defined orthopedic surgery subpopulation. Patients undergoing these procedures typically have a competent immune system (including those with comorbidities such as diabetes, obesity, vascular disease, and other non-immunocompromising conditions) who can be vaccinated prior to surgery with a known and defined time period of infection risk. Similar to patients undergoing other elective orthopedic surgeries, the period of risk for *S. aureus* infection is initiated by the surgical site incision and maintained while the wound is open. In addition, this population has a relatively high (~ 1.5%) and predictable incidence of invasive *S. aureus* disease, with the majority of SSIs occurring within 180 days of surgery, and 75–90% of infections occurring within 90 days of surgery.[88–90] This allows for observation of invasive *S. aureus* clinical endpoints within a defined period of time.

Table 1. SA4Ag clinical development plan.

Study Number/Subject Age	Study Description	Study Design and Type of Control	Healthy Subjects Receiving SA4Ag Final Formulation	SA4Ag-Vaccinated Subjects Undergoing Surgery	Placebo	Study Status
B3451001 Healthy nonsurgical adults 18–< 65 years of age	Dose escalation; safety and immunogenicity	Phase 1/2a, multicenter, randomized, placebo-controlled, double-blind, sponsor-unblinded	112	0	112	Completed
B3451011 Healthy nonsurgical adults 65–< 86 years of age	Dose escalation; safety and immunogenicity	Phase 1/2a, multicenter, randomized, placebo-controlled, double-blind, sponsor-unblinded	57	0	60	Completed
B3451014 Healthy nonsurgical adults 18–< 86 years of age	Antibody persistence up to 36 months after vaccination	Phase 2a, multicenter, open-label	Subjects from 1001/1011	0	Subjects from 1001/1011	Completed
B3451015 (CTM Resupply) Healthy nonsurgical adults 18–< 65 years of age	Safety and immunogenicity of investigational CTM for STRIVE	Phase 1, single-arm, open-label	100	0	0	Completed
B3451003 (FIH in Japan); Clinicaltrials.gov: NCT02492958 Healthy nonsurgical adults 20–< 86 years of age	Safety and immunogenicity in Japanese subjects	Phase 1/2a, placebo-controlled, randomized, double-blind, sponsor-unblinded	68	0	68	Completed
B3451002 (STRIVE)/ Adults 18–< 86 years of age scheduled to undergo elective, open posterior, spinal fusion procedures with multilevel instrumentation	Efficacy and safety	Phase 2b/3[a], randomized, placebo-controlled, double-blind	0	3000	3000	Ongoing
B3451006 Healthy nonsurgical adults 18–< 50 years of age	Clinical lot consistency	Phase 3	2061	0	687	Planned
Total Number			2398	3000	3927	

Abbreviations: CTM = clinical trial material (ie, investigational SA4Ag); FIH = first in human.
[a]Pfizer plans to convert STRIVE to a pivotal Phase 3 study.

Figure 1 illustrates that the optimal timing for vaccination with SA4Ag is 10 to 60 days before surgery based on the immune response profile elicited. The vaccination time window ensures the induction of robust functional antibodies to high levels at the time of incision and at the surgical site (ie, tissue, fascia, and joints). In healthy non-surgical subjects, antibody levels were shown to persist beyond the 180-day period of infection risk and remain elevated above baseline or placebo responses for up to 3 years after initial vaccination.

Sa4ag phase 2b/3 study design

Pfizer identified an elective orthopedic surgical subpopulation (patients undergoing elective open multilevel instrumented spinal fusion) that, while representative of other orthopedic surgical populations, has *S. aureus* infection rates at the higher end of the spectrum for orthopedic surgery populations.

The STaphylococcus aureus suRgical Inpatient Vaccine Efficacy (STRIVE) study (NCT 02388165) is a double-blind, placebo-controlled study evaluating the safety and efficacy of SA4Ag administered to adults 18 through 85 years of age undergoing elective open posterior multi-level instrumented spinal fusion surgery (index surgical procedure). Subjects are randomized in a 1:1 ratio to receive a single dose of SA4Ag or placebo 10 to 60 days prior to undergoing the index surgical procedure. From the time of consent, subjects are monitored for vaccine reactogenicity for 10 days after vaccination, all adverse events (AEs) through 6 weeks after the index surgery, and serious adverse events (SAEs) and newly diagnosed chronic medical disorders through Day 180 after the index surgery at 6 scheduled study visits. In addition, STRIVE includes pre-defined criteria to prospectively monitor and independently evaluate multiple organ failure and deaths following surgery. These comprehensive safety assessments have been included as a precaution due to the safety signal observed in the phase 3 study of the IsdB-based vaccine.[45]

STRIVE was initiated in July 2015, and enrollment and vaccination is ongoing at ~ 100 sites in the United States, United Kingdom, France, Spain, Germany, Hungary, Austria, Sweden, Canada, and Japan. The timing of the final efficacy assessment is based on case-accrual in STRIVE. It is estimated that approximately 6000 subjects will be needed to reach the number of cases required to evaluate vaccine efficacy.

To evaluate vaccine efficacy, subjects are monitored for occurrence of protocol-defined infections, including blood-stream infections (BSI), SSIs, and other invasive *S. aureus* infections, for 180 days after surgery, at each visit after the index surgical procedure. All protocol-defined infections undergo adjudication by an independent external event adjudication committee (EAC) that includes infectious disease physicians and surgeons with specialized expertise in SSIs. Protocol-defined infections caused by other organisms are also referred to the EAC and adjudicated. Subjects with EAC-confirmed postoperative *S. aureus* BSI and/or deep incisional or organ/space SSIs occurring within 90 days after the index surgical procedure contribute to the primary efficacy endpoint analysis. The STRIVE study design is outlined in Figure 2.
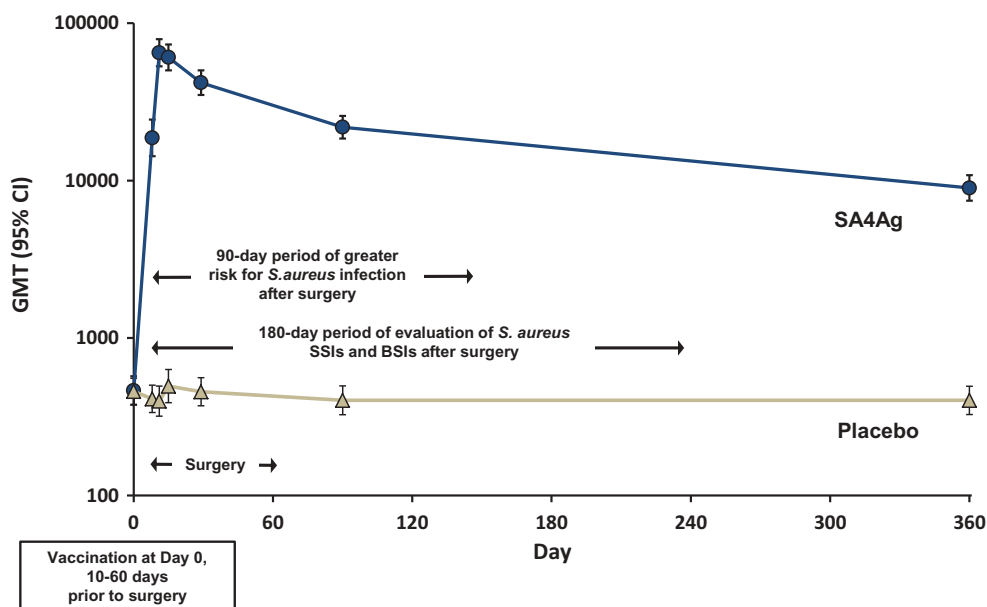
Figure 1. CP5 antibody levels measured by opsonophagocytic assay after SA4Ag vaccination and the risk period for *S. aureus* infection after surgery.

Abbreviations: BSIs = bloodstream infections; CP5 = *S. aureus* capsular polysaccharide serotype 5; GMT = geometric mean titer; SA4Ag = *S. aureus* 4-antigen vaccine; SSIs = surgical-site infections.Note: Graph represents GMTs (95% CI) for CP5 in healthy adult subjects 18 through 64 years of age. Arrows illustrate the window of time for vaccination, surgery, maximum risk of infection, and efficacy endpoint evaluation in patients included in STRIVE.Reprinted from "Safety, tolerability, and immunogenicity of a 4-antigen Staphylococcus aureus vaccine (SA4Ag): Results from a first-in-human randomised, placebo-controlled phase 1/2 study", Frenck RW, Creech CB, Sheldon EA, et al. Vaccine; 2017:375–384, with permission from Elsevier.
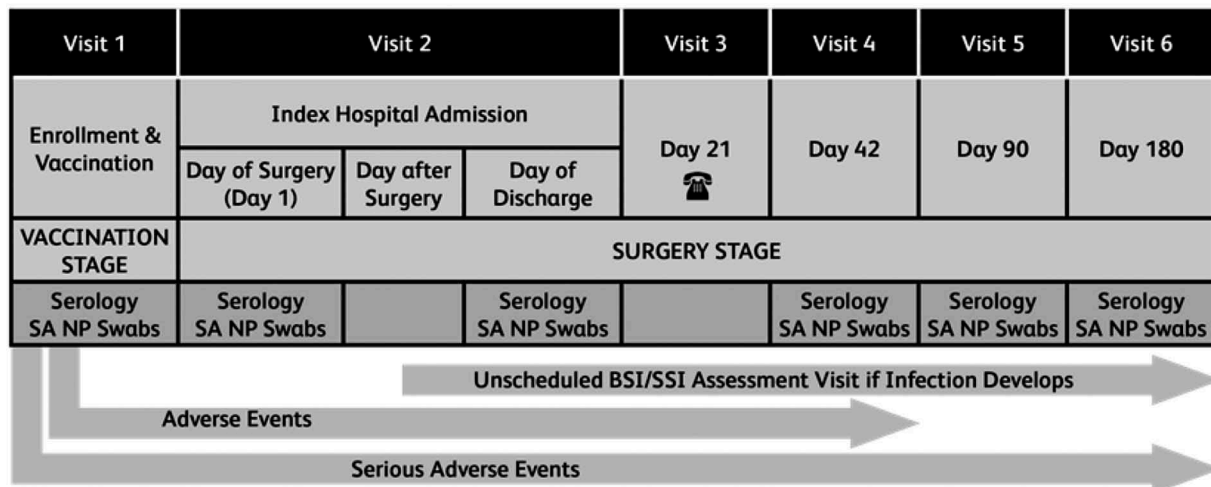

Figure 2. Summary of STRIVE study design.

Abbreviations: SA NP = *Staphylococcus aureus* Nasal and Pharyngeal

Generalizability of strive study results to all elective orthopedic surgical populations

The STRIVE study population is representative of other elective orthopedic surgical populations, with multiple commonalities in pathophysiology of infection, patient demographics, and surgical procedures. The risk factors for developing an infection are similar across elective orthopedic surgeries and include patient-related factors (eg, smoking, health status, and comorbidities) and procedure-related factors (eg, duration of surgery, involvement of similar anatomical structures, use of implanted instrumentation, and perioperative care).[23,91–102] The advantage of evaluating vaccine efficacy in the STRIVE

population is that the infection rates are at the higher end of the spectrum for elective orthopedic surgeries. This is primarily due to these surgeries being of longer duration[93,97] with longer incisions compared to other elective orthopedic procedures.[100,101]

Similar pathophysiology of S. aureus ssis in elective orthopedic surgeries

For most elective orthopedic surgeries, the primary risk for establishing infection is during the surgical procedure itself (from the time of incision to wound closure), when bacteria

can enter an otherwise normally sterile site.[103,104] This is supported by data on the timely perioperative administration of prophylactic antibiotics that can significantly reduce SSIs across the surgical spectrum, whereas postoperative prophylactic antibiotic use has limited utility.[105–107] The risk of wound inoculation is higher in patients colonized with *S. aureus*, yet the likelihood of colonization is independent of surgical procedure.

Additionally, the early pathophysiology of *S. aureus* SSI is similar across elective orthopedic surgical procedures, and specific strains are not linked to specific surgery types.[4,108,109] Across all elective procedure types, early virulence factors, such as those targeted in SA4Ag, are required for *S. aureus* to initiate and maintain infection.[60] Immediately upon entering the surgical site, *S. aureus* upregulate expression of genes to adapt to the wound microenvironment and avoid immune-mediated killing.[110–112] Upregulation of capsular polysaccharides that help the bacteria to evade neutrophil-mediated killing (such as CP5 and CP8),[52,53,58,111] tissue adhesion factors (such as ClfA), or bacterial proteins to obtain essential nutrients limited in the host microenvironment (such as MntC) are observed early in the infection process.[76,111,112] Blocking these early virulence mechanisms should preclude the establishment of a productive infection and bacterial adhesion to host proteins on implant surface, subsequent biofilm formation and dissemination.

The association between *S. aureus* nasal carriage and *S. aureus* infection risk at surgical sites is well established.[108,113–115] However, no evidence exists linking specific *S. aureus* strains to specific surgical procedures that would suggest a strain- or surgery-associated pathogenesis. Various *S. aureus* clonal types have been isolated from SSIs irrespective of surgery type. In situations where hospitals periodically have disease outbreaks caused by specific *S. aureus* isolates, these infections are not limited to particular surgical procedures.[116,117]

Rather, disease outbreaks are linked to a patient coming into contact with the outbreak strain either through carriage or from an exogenous source.[4,108,109] Thus, both the accessibility to a previously sterile site during surgery and the presence of *S. aureus* during the surgery are prerequisites of SSIs, but not the type of elective surgery or the *S. aureus* strain.

Similar immune responses across elective orthopedic surgeries

The efficacy to be demonstrated in STRIVE is expected to be translatable to other elective orthopedic surgical sites including other anatomical joints and bone spaces, since these sites are accessible to immune responses elicited by SA4Ag. The various orthopedic surgical sites (eg, spine, knee, hip,) are sterile under normal circumstances (no exposure to pathogens) but have full access to the human immune repertoire. Vasculature is found in all bones throughout the body, and joints are drained by lymphatics. Both vasculature and lymph ensure that bones and joints are connected to and protected by the immune system. Therefore, the components required for the proposed mechanism of action of SA4Ag (induction of functional antibodies and host phagocytes that kill the bacteria) are available at these different anatomical sites.[118]

Similar risk factors across elective orthopedic surgeries

While the risk of postoperative invasive *S. aureus* disease is directly attributable to the surgical incision and duration of surgery, numerous preoperative, intraoperative, and postoperative patient and procedural risk factors influence risk of developing SSIs. The risk factors for SSI are common among elective open posterior multilevel instrumented spinal fusion surgical and other orthopedic surgical populations.[88,92,119–121]

Patient demographics for the spinal fusion population are broadly representative of other elective orthopedic surgical populations (Table 2).[93,102] Patient risk factors are largely driven by the health status of the patient. The important patient-related risk factors for SSI are similar in patients undergoing open posterior multilevel instrumented spinal fusion surgery and other elective orthopedic surgeries and include age (>60 yrs), high BMI, diabetes, and smoking status.[122] The percentage of patients with these risk factors and other comorbidities (ie, chronic obstructive pulmonary disease, congestive heart failure) are also similar across elective orthopedic surgical populations.[93,100–102] Patients undergoing spinal surgery and other elective orthopedic surgeries have a similar Charlson Comorbidity Index (a validated prognostic indicator for factors that increase the risk of short-term mortality) affirming the similarity of the prevalence of comorbidities and the overall general health status among these populations.[93,100–102] Additionally, rates of *S. aureus* nasal carriage, which has a well-established association with postoperative SSIs, are similar in patients undergoing spinal procedures and other orthopedic surgeries.[22,52,123]

Procedural risk factors for postoperative infection include duration of surgery, wound characteristics, involvement of similar anatomical structures (eg, bone, cartilage, and joint spaces with synovial fluid), use of implanted devices and blood transfusions, and perioperative care (Table 3).[91–98] Surgical techniques and procedural characteristics for elective open posterior multilevel instrumented spinal fusion surgeries have numerous commonalities shared with other elective orthopedic surgeries. Each of these surgical procedures involves disruption of the dermis, soft tissue, fascial and muscle layers, and bone, allowing possible introduction of infection through the wound. The recommended perioperative care is the same for patients undergoing spinal surgery and other orthopedic surgeries.[124] The wounds of >93% of these surgeries are classified as clean or clean/contaminated.[125,126] Many of these surgeries have similar median durations, with spinal surgery having the longest median duration, which corresponds to infection rates at the higher end of the range for elective orthopedic surgeries.[93,100,101] Many spinal surgeries and other major elective orthopedic procedures such as hip and knee arthroplasties commonly use implanted materials composed of titanium or cobalt chromium alloys, plastics, and stainless steel. In addition, the rate of postsurgical complications and mortality after these procedures is low (0.18 to 0.35%). Complications such as pulmonary embolism and myocardial infarction are comparable between hip and knee replacements and spinal surgery (Table 4).[93,100,127]

Table 2. Patient demographics and risk factors are similar across elective orthopedic surgical populations.

	Primary Total Knee Arthroplasty N = 15,157[a]	Primary Total Hip Arthroplasty N = 7791[a]	Spinal Fusion N = 9719[b]
Age (mean, years)	67.3	65.4	56.7
Male (%)	35.5	44.3	46.2
White (%)	79.3	80.5	82.7
Diabetes (%)	18.2	11.6	15.1
Smoking (%)	8.6	13.8	26.4
COPD (%)	3.7	4.5	NR
Congestive heart failure (%)	0.2	0.5	NR
Peripheral vascular disease (%)	0.6[e]	0.5[f]	NR
BMI (kg/m^2) [SD]	32.8 [7.3][e]	29.8 [6.5][f]	NR
BMI >30 (%)	NR	NR	42.9
ASA: 1–2 (%)	51.0[e,g]	56.8[f]	56.4[h]
ASA: 3–4 (%)	48.9[e,g]	43.2[f]	43.6[h]

Abbreviations: ACS NSQIP = The American College of Surgeons National Surgical Quality Improvement Program; ASA = American Society of Anesthesiologists (adopted a 5-category physical score); BMI = body mass index; COPD = chronic obstructive pulmonary disease; NR = not reported; SD = standard deviation.
[a]ACS NSQIP: 2005–2010[102]
[b]70% lumbar spine; 66% posterior/posteriorlateral approach; 90% single level[93]
[e]The total population was N = 27,745.[128]
[f]The total population varied: BMI N = 17,514; peripheral vascular disease/ASA N = 17,628.[100]
[g]Percentages were derived by adding individual ASA scores from Table 1 of Duchman et al, 2014.[128]
[h]Percentages were derived by adding individual ASA scores from Table 1 of McCutcheon et al, 2015.[93]

Table 3. Procedural characteristics of spinal and other elective orthopedic surgeries.

	Total Knee Arthroplasty	Total Hip Arthroplasty	Instrumented Spinal Surgery
OR time (mean minutes [SD])	96.9 (37.9)[a]	97.6 (42.9)[b]	196.6 (SD not provided)[c]
Incision length (mean [in])	~ 8–10	~ 8–12	~ 10–12 inches (larger incision if more vertebrae fused)[d]
Most common approaches	medial parapatella	anterior (lateral); posterior	PLIF, TLIF
Procedural overview	dermis → dissects between the muscles, tendons, and nerves to reach the joint	dermis → dissects between the muscles, tendons, and nerves to reach the joint	dermis → dissects between the muscles, tendons, and nerves to reach the vertebrae
Implant material	metal alloys (titanium or cobalt-chromium); plastics (ultra-high molecular weight polyethylene); ceramic; bone cement	plastic (polyethylene liner); metals (cobalt/chromium); ceramic; bone cement	plastics (PEEK), metals (titanium, stainless steel, cobalt); bone graft (autograft/allograft/BMP); bone cement

Abbreviations: ACS NSQIP = The American College of Surgeons National Surgical Quality Improvement Program; BMP = bone morphogenetic protein; in = inches; OR = operating room; PEEK = polyetheretherketone; PLIF = posterior lumbar interbody fusion; SD = standard deviation; TLIF = transforaminal lumbar interbody fusion.
Source: http://orthoinfo.aaos.org/topic.cfm?topic=a00405/a00406.
[a]ACS NSQIP: 2005–2011[128]
[b]ACS NSQIP: 2006–2011[100]
[c]ACS NSQIP: 2005–2011[93]
[d]Incision length calculated based on data available on the AAOS website regarding spinal surgery (http://orthoinfo.aaos.org/topic.cfm?topic=A00543) and adjusted for the mean vertebrae fused in STRIVE to date (5.1 vertebrae).

Table 4. Similar incidence of 30-day postoperative complications across elective orthopedic surgeries.

	Primary Total Knee Arthroplasty N = 15,321[a]	Primary Total Hip Arthroplasty N = 17,640[b]	Spinal Fusion N = 9719[c]
Total events (n)	1058	1074	NR
Mortality (%)	0.18	0.35	0.35
UTI (%)	1.49	1.45	1.96
Superficial wound infection (%)	0.79	0.83	1.24
Deep venous thrombosis (%)	1.34	0.51	0.90
Postoperative sepsis (%)	0.44	0.47	1.08
Pneumonia (%)	0.37	0.42	0.84
Pulmonary embolism (%)	0.78	0.31	NR
Myocardial infarction (%)	NR	0.24	0.20
Septic shock (%)	0.13	0.12	0.30
Wound dehiscence (%)	0.27	0.14	0.35
Cardiac arrest requiring CPR (%)	0.09	0.12	0.20
Peripheral nerve injury (%)	0.10	0.11	0.23
Acute renal failure (%)	0.12	0.07	0.5

Abbreviations: ACS NSQIP = The American College of Surgeons National Surgical Quality Improvement Program; CPR = cardiac pulmonary resuscitation; NR = not reported; SSIs = surgical-site infections; UTI = urinary tract infection.
[a]ACS NSQIP: 2006–2010[127]
[b]ACS NSQIP: 2006–2011[100]
[c]70% lumbar spine; 66% posterior; posteriorlateral approach; 90% single level[93,100]

Table 5. Projected US annual procedure volume for major elective orthopedic surgeries (2021–2030).

	2021	2022	2023	2024	2025	2026	2027	2028	2029	2030	Total
Spinal fusion	549,625	561,807	574,260	586,989	599,999	613,299	626,893	640,788	654,991	669,509	6,078,160
Spinal decompression	329,702	337,010	344,480	352,115	359,920	367,898	376,052	384,387	392,907	401,616	3,646,087
Inpatient[a]	96,370	98,506	100,689	102,921	105,202	107,534	109,918	112,354	114,845	117,390	1,065,730
Outpatient[a]	233,332	238,504	243,790	249,194	254,717	260,363	266,134	272,033	278,063	284,226	2,580,357
Hip arthroplasty	534,674	546,525	558,639	571,021	583,678	596,615	609,839	623,357	637,173	651,297	5,912,817
Knee arthroplasty	1,008,230	1,030,578	1,053,421	1,076,770	1,100,637	1,125,033	1,149,970	1,175,459	1,201,514	1,228,145	11,149,757
Other arthroplasty	67,154	68,643	70,164	71,719	73,309	74,934	76,595	78,293	80,028	81,802	742,642

[a]Spinal decompressions are often conducted at the inpatient and outpatient settings, which could have an implication on the infection rate; therefore, they were also analyzed separately.

Source: Projected from Life Science Intelligence Report 2015, with adjustment based upon HCUP (2014) data analysis to eliminate overlapping multiple surgeries and emergent surgeries.

Table 6. Potential US public health impact from a *S. aureus* vaccine assuming 70% efficacy on prevention of *S. aureus* infections following major elective orthopedic surgeries (2021–2030).

	Spinal Surgeries			Arthroplasty				
Estimated 10-Year Vaccine Impact	Spinal Fusion	Spinal Decompression	Total	Hip Arthroplasty	Knee Arthroplasty	Other Arthroplasty	Total	Spinal Surgery/ Arthroplasty Total
Surgical procedure volume	6,078,160	3,646,087	9,724,247	5,912,817	11,149,757	742,642	17,805,216	27,529,463
Total number of *S. aureus* infections averted	39,569	17,214	56,783	31,870	37,463	1,248	70,581	127,364
Total number of MRSA infections averted	15,377	5764	21,141	12,659	13,771	459	26,889	48,030
Total number of ISA infections averted	19,146	8065	27,211	15,728	18,732	624	35,084	62,295
Total number of deaths averted	938	156	1094	845	300	5	1149	2243
Total number of hospitalizations averted	19,146	8065	27,211	31,456	37,464	1248	70,168	97,379
Total number of disability-adjusted life years averted	29,257	5889	35,146	21,000	12,277	319	33,596	68,742

Abbreviations: ISA = invasive *S. aureus*; MRSA = methicillin-resistant *S. aureus*.

Note: Formulas and data for these calculations are shown in Appendix 3.

Conclusions/future directions

As no immune correlate or threshold of protection has been established for *S. aureus*, a clinical endpoint efficacy study is required for *S. aureus* vaccine licensure. The ongoing STRIVE study is being conducted in a specific elective orthopedic surgical subpopulation of spinal fusion surgery recipients. Safety and efficacy of SA4Ag demonstrated in the STRIVE population is expected to be representative of the vaccine's safety and efficacy in other elective orthopedic surgical populations because of the common pathophysiology of invasive *S. aureus* disease, similar immune function at the surgical incision, wound, and in synovial fluid across orthopedic surgical sites, and similar patient and procedural risk factors for developing postoperative SSIs across these elective surgical populations. Therefore, assuming STRIVE is successful at achieving its pre-specified safety and efficacy endpoints, the data should be representative of safety and efficacy in other orthopedic populations and support the licensure of SA4Ag for use in adults aged 18 years and older who are undergoing elective orthopedic surgery.

Following licensure, as with other vaccines, it is expected that national Vaccine Technical Committees will make recommendations for the use of SA4Ag to maximize the public health benefit of vaccine implementation. To provide an estimate of the potential public health impact of an effective *S. aureus* vaccine on the prevention of *S. aureus* infections after elective orthopedic surgeries, Pfizer conducted an analysis that incorporated epidemiological and clinical data to predict outcomes over a 10-year time horizon from 2021 to 2030. For this analysis, only major elective orthopedic surgeries were considered (projected US annual procedure volumes for major elective orthopedic surgeries are listed in Table 5). Pfizer estimates that if all eligible patients undergoing major elective orthopedic surgery in the 10 year time period received a 70% effective vaccine, vaccination could prevent 127,364 postoperative *S. aureus* infections, including 48,030 MRSA infections and 62,295 invasive infections (Table 6). Such a reduction in postoperative infections would also avert 2,243 deaths, 97,379 hospitalizations, and 68,742 disability-adjusted life years.

Disclosure of potential conflicts of interest

The authors are employees of Pfizer, the company developing SA4Ag for commercial use.

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