Clinical Infectious Diseases

MAJOR ARTICLE

Efficacy of a 4-Antigen *Staphylococcus aureus* Vaccine in Spinal Surgery: The *STaphylococcus aureus* suRgical Inpatient Vaccine Efficacy (STRIVE) Randomized Clinical Trial

Hamid Hassanzadeh,[1] James Baber,[2] Elizabeth Begier,[3] David C. Noriega,[4] Hiroaki Konishi,[5] Yoshiyuki Yato,[6] Michael Y. Wang,[7] Jean Charles Le Huec,[8] Vikas Patel,[9] Peter Varga,[10] Ulf Liljenqvist,[11] John Conly,[12] Charu Sabharwal,[3] Iona Munjal,[3] David Cooper,[3] David Radley,[3] Anna Jaques,[2] Michael Patton,[13] William C. Gruber,[3] Kathrin U. Jansen,[3] Annaliesa S. Anderson,[3] and Alejandra Gurtman[3]; for the *STaphylococcus aureus* suRgical Inpatient Vaccine Efficacy Investigator Team[a]

[1]Department of Orthopaedic Surgery, Johns Hopkins University, Baltimore, Maryland, USA; [2]Pfizer Inc, Vaccine Clinical Research, Sydney, New South Wales, Australia; [3]Pfizer Inc, Vaccine Research, Pearl River, New York, USA; [4]Department of Orthopaedics, Hospital Universitario de Valladolid, Valladolid, Spain; [5]Department of Orthopaedic Surgery, Nagasaki Rosai Hospital, Nagasaki, Japan; [6]National Hospital Organization Murayama Medical Center, Orthopedics and Sports Medicine Neurosciences & Neurology Surgery, Tokyo, Japan; [7]Neurological Surgery, University of Miami, Miami, Florida, USA; [8]Department of Orthopaedic and Traumatology, Polyclinique Bordeaux Nord Aquitaine, Bordeaux University, Bordeaux, France; [9]Department of Orthopaedic Surgery, University of Colorado School of Medicine, Denver, Colorado, USA; [10]National Center for Spinal Disorders, Buda Health Center, Spine Center, Budapest, Hungary; [11]Department of Orthopaedic Surgery, St. Franziskus-Hospital Munster Orthopaedie II, Muenster, Germany; [12]Department of Medicine, Foothills Medical Centre, Alberta Health Services and University of Calgary, Calgary, Alberta, Canada; and [13]Pfizer Ltd, Vaccine Clinical Research, Hurley, United Kingdom

(See the Editorial Commentary by Proctor on pages 321–2.)

Background. *Staphylococcus aureus* is a global pathogen that is frequently responsible for healthcare-associated infections, including surgical site infections (SSIs). Current infection prevention and control approaches may be limited, with *S. aureus* antibiotic resistance remaining problematic. Thus, a vaccine to prevent or reduce *S. aureus* infection is critically needed. We evaluated the efficacy and safety of an investigational 4-antigen *S. aureus* vaccine (SA4Ag) in adults undergoing elective open posterior spinal fusion procedures with multilevel instrumentation.

Methods. In this multicenter, site-level, randomized, double-blind trial, patients aged 18–85 years received a single dose of SA4Ag or placebo 10–60 days before surgery. SA4Ag efficacy in preventing postoperative *S. aureus* bloodstream infection and/or deep incisional or organ/space SSIs was the primary end point. Safety evaluations included local reactions, systemic events, and adverse events (AEs). Immunogenicity and colonization were assessed.

Results. Study enrollment was halted when a prespecified interim efficacy analysis met predefined futility criteria. SA4Ag showed no efficacy (0.0%) in preventing postoperative *S. aureus* infection (14 cases in each group through postoperative day 90), despite inducing robust functional immune responses to each antigen compared with placebo. Colonization rates across groups were similar through postoperative day 180. Local reactions and systemic events were mostly mild or moderate in severity, with AEs reported at similar frequencies across groups.

Conclusions. In patients undergoing elective spinal fusion surgical procedures, SA4Ag was safe and well tolerated but, despite eliciting substantial antibody responses that blocked key *S. aureus* virulence mechanisms, was not efficacious in preventing *S. aureus* infection.

Clinical Trials Registration. NCT02388165.

Keywords. *Staphylococcus aureus*; vaccine; efficacy; spinal surgery; surgical site infection.

Staphylococcus aureus is a major cause of healthcare-associated infections worldwide [1] and is a leading cause of surgical site infections (SSIs) in healthcare settings, especially in high-risk orthopedic populations where SSIs can be debilitating [2]. *Staphylococcus aureus* is the most common cause of SSIs in spinal fusion surgeries [3, 4], with a 1.4%–2.3% prevalence [3–5]. Other common manifestations include bloodstream infection (BSI), endocarditis, pneumonia, and skin/soft tissue infections [6]. BSI-associated mortality rates are substantial, estimated at 16.5%–21.2% within 30 days of onset [7–9]. Further, SSIs cause considerable economic burden on healthcare systems [10].

Current preventive strategies include prophylactic antibiotics and infection prevention and control practices [11]. However, antibiotic effectiveness may be limited, with methicillin-resistant *S. aureus* causing the majority of infections in some

Received 02 November 2022; editorial decision 06 March 2023; published online 1 May 2023

[a]The STRIVE Investigators are listed in the Appendix.

Correspondence: H. Hassanzadeh, Department of Orthopaedic Surgery, Johns Hopkins University, 6420 Rockledge Dr, Suite 200 Bethesda, MD 20817 (hhmd06@gmail.com).

Clinical Infectious Diseases® 2023;77(2):312–20

https://doi.org/10.1093/cid/ciad218

settings [12] and increasing vancomycin resistance rates [13]. Vaccines, which represent effective tools for mitigating antimicrobial resistance [14], are critically needed and could prevent disease by providing functional antibodies to target key virulence mechanisms at infection risk onset [15]. Despite evidence of efficacy in preclinical models, investigational *S. aureus* vaccines aimed at generating high titers of antibodies against *S. aureus* surface antigens to prevent invasive infections (eg, V710, StaphVAX) have failed in human trials [16–18]. Proposed reasons underlying the lack of vaccine efficacy in clinical trials have included targeting of a single antigen or phase of pathogenesis, an inability to efficiently induce functional antibodies or other immune cells (eg, T cells) that could target *S. aureus*, and characteristics of the clinical population under study (eg, immunosuppressed patients) [16, 18–22]. An approach that comprehensively inhibits multiple bacterial virulence mechanisms may be required to effectively protect against *S. aureus* infection and disease in the clinical setting.

SA4Ag is an investigational *S. aureus* vaccine that targets 4 antigens carefully selected to disrupt the pathogenesis of *S. aureus* by blocking 3 key virulence mechanisms and eliciting functional immune responses with robust bacterial killing as determined in opsonophagocytic antibody (OPA) assays [21, 23]. The vaccine comprises 4 components [21]: capsular polysaccharide conjugates of serotypes 5 (CP5) and 8 (CP8); a recombinant version of clumping factor A (ClfA), an important virulence factor that mediates fibrinogen binding during early infection [24]; and rP305A, a recombinant, nonlipidated version of manganese transporter C (MntC), which is involved in evasion of neutrophil-mediated killing [25]. Each antigen showed promising results in preclinical animal models [26–28]. Initial clinical studies showed that SA4Ag was safe, tolerable, and rapidly induced robust and durable functional immune responses in healthy adults aged 18–85 years [14, 29–31].

In the *STaphylococcus aureus* suRgical Inpatient Vaccine Efficacy (STRIVE) study, we evaluated SA4Ag efficacy after elective open posterior multilevel instrumented spinal fusion procedures. This surgical population was chosen for its well-defined nature with a known, relatively high incidence and predictable period of risk for surgery-associated *S. aureus* infection among typically immunocompetent patients [3–5, 15].

METHODS

Study Design

This phase 2b, randomized, multicenter, placebo-controlled, double-blind study occurred between July 2015 and June 2019 in North America, Europe, and Japan (Supplementary Figure 1). Additional details are found in the Supplementary Appendix and study protocol, available at clinicaltrials.gov [32]. The study was conducted in accordance with the principles in the International Ethical Guidelines for Biomedical Research Involving Human Subjects, the International Conference on Harmonisation Guidelines for Good Clinical Practice, and the Declaration of Helsinki. All local legal and regulatory requirements were followed, and the study protocol and other relevant documents were prospectively approved by an institutional review board/independent ethics committee for each site. Patients were required to provide informed consent.

Patients

Eligible patients were adults aged 18–85 years scheduled to undergo an elective open posterior spinal fusion procedure with multilevel instrumentation (ie, surgical implantation of pedicular screws, rods, interbody implant material involving ≥2 motion segments; Supplementary Appendix) 10–60 days after study vaccination and able to participate in study procedures. Initial eligibility criteria were amended early during the study (June 2016) to include multilevel spinal fusions performed on any part of the spine (as opposed to lumbar only). Patients of childbearing potential had to use highly effective contraceptive methods throughout the study. The Supplementary Appendix lists exclusion criteria.

Randomization and Masking

Patients were randomized at the site level 1:1 via an interactive-voice/web-response system to receive single-dose SA4Ag or placebo (Supplementary Figure 1). Patients, investigators, and sponsors were blinded to group allocation; blinding codes were only broken in emergency situations for reasons of patient safety. Unblinded data reports were prepared by an unblinded, independent statistician under the direction of the blinded study statistician. A blinded independent Event Adjudication Committee (EAC) received, reviewed, and adjudicated blinded patient data only. The Data Monitoring Committee (DMC) reviewed blinded and unblinded data reports. Futility checks performed by the DMC were unblinded.

Procedures

Patients received a 0.5-mL intramuscular dose of SA4Ag or placebo into the deltoid of the nondominant arm. SA4Ag was a lyophilized preparation in a single-dose vial that contained 30 μg each of CP5 and CP8 individually conjugated to cross-reactive material (CRM_{197}), 60 μg of a recombinant mutated form of ClfA, and 200 μg of recombinant P305A. Selection of these dose levels was based on demonstration of robust and durable immunogenicity with a favorable tolerability profile in healthy adults [30]. The placebo was a lyophilized SA4Ag match with the same excipients (excluding active ingredients).

The EAC reviewed and adjudicated all suspected primary and secondary efficacy and exploratory end points of invasive *S. aureus* (ISA) disease according to criteria adapted from the Centers for Disease Control and Prevention [33] (https://www.cdc.gov/nhsn/PDFs/pscManual/validation/pcsManual-2014-valid.pdf).

The EAC adjudicated all multiple organ failure (MOF) events and deaths to determine association with *S. aureus* infection (Supplementary Appendix).

Outcomes

The primary efficacy objective was to assess SA4Ag efficacy in preventing postoperative *S. aureus* BSI and/or deep incisional or organ/space SSI (Supplementary Appendix) as confirmed by the EAC and occurring ≤90 days after surgery. Secondary efficacy end points were postoperative *S. aureus* BSI and/or deep incisional or organ/space SSI occurring ≤180 days after surgery and postoperative *S. aureus* SSI occurring 90–180 days after surgery. Exploratory efficacy end points included postoperative ISA disease occurring 90–180 days after surgery, and postoperative BSI and/or deep incisional or organ/space SSI of any cause occurring 90–180 days after surgery based on baseline *S. aureus* colonization status. Immunogenicity and *S. aureus* colonization evaluations were exploratory objectives (Supplementary Appendix).

The primary safety objective was to describe the safety and tolerability of SA4Ag. End points included the number and percentage of patients in each group who reported local reactions and systemic events ≤10 days after vaccination (Supplementary Appendix). Adverse events (AEs; through postoperative day 42), serious AEs (SAEs; through postoperative day 180), and newly diagnosed chronic medical conditions (NDCMCs; from postoperative day 42 through postoperative day 180) were evaluated.

Statistical Analyses

This event-driven study had a target of 48 *S. aureus* cases. Approximately 6000 patients were anticipated to accumulate the target cases assuming a 1.4% primary end point incidence among placebo recipients, vaccine efficacy (VE) of 70%, and 10% dropout rate. Total enrollment could have varied based on changes in these factors and a potential early stop for efficacy or futility. Based on assumed 70% VE, the study power was 88% for 48 cases. During the study (February 2018), the sample size was amended (from 2600 to 6000 patients and from 42 to 48 end point cases) due to a lower-than-predicted postoperative *S. aureus* infection rate and to increase statistical power. Missing values were not imputed for demographic, efficacy, immunogenicity, colonization, or safety variables. The Supplementary Appendix provides information on efficacy, immunogenicity, safety analyses, and evaluable populations.

RESULTS

Study Population and Index Surgeries

Study enrollment was halted in December 2018 when the prespecified 24-case interim primary end point analysis met predefined futility criteria; however, all patients continued to be followed for safety and efficacy evaluations through >6 months after vaccination. Of 3450 patients randomized, 3417 (99.0%) completed vaccination, 3311 (96.0%) completed the index surgery, and 3193 (92.6%) completed the study (Figure 1). Demographic and comorbidity characteristics were similar across groups (Table 1). Most patients had Charlson comorbidity index scores of ≤4, indicating a limited number of significant comorbidities, and American Society of Anesthesiologists (ASA) physical status classification of 1 (healthy) or 2 (mild systemic disease with no functional limitation) [34]. Characteristics of index surgeries were also similar between groups, including preoperative antimicrobial prophylaxis use (Supplementary Table 1). Approximately half of patients received intrawound/intra-articular antibiotics during surgery, most commonly vancomycin.

Efficacy

At the interim analysis, 12 primary end point cases occurred in each group, resulting in conditional power of 6.09%, meeting the predefined futility criteria (Supplementary Appendix). In the final analysis of the per-protocol efficacy population, SA4Ag VE against *S. aureus* BSI and/or deep incisional or organ/space SSI occurring ≤90 days after surgery was 0.0% (95% confidence interval [CI], −126.3% to 55.8%), with 14 cases in each group (Table 2). For BSI, VE was 36.4% (95% CI, −79.8% to 79.1%). Most patients with BSI also had *S. aureus* deep or organ/space SSIs (n/N, SA4Ag, 12/14; placebo, 12/14). The primary end point infection rate in the placebo group was 0.9%, lower than the anticipated 1.4%. Calculated VE of SA4Ag against *S. aureus* BSI and/or deep incisional or organ/space SSI occurring ≤180 days after surgery was similar; 1 additional case of deep incisional SSI was reported 90–180 days after surgery in a patient who previously experienced a BSI ≤90 days after surgery (Table 2). SA4Ag showed no efficacy against *S. aureus* SSI overall (superficial and invasive SSIs combined). SA4Ag did not appear to affect risk of ISA disease or BSI or SSI of any cause within 90 or 180 days after surgery (Supplementary Tables 2 and 3). There was no indication of SA4Ag efficacy based on baseline *S. aureus* colonization status (Supplementary Table 4).

Immunogenicity

For CP5 and CP8, functional immune responses measured using OPA assays were observed for the SA4Ag group after all vaccination time points, with geometric mean titer (GMT) ranges generally similar between cases (CP5, 8786.3–22 417.1; CP8, 8504.7–18 286.5) and noncases (CP5, 10 530.0–22 095.3; CP8, 12 023.2–23 281.5; Figure 2). OPA GMTs peaked on the day of the index surgery but remained elevated at day 90 compared with baseline. Similar results were observed for GMTs measured using a competitive Luminex assay for ClfA and

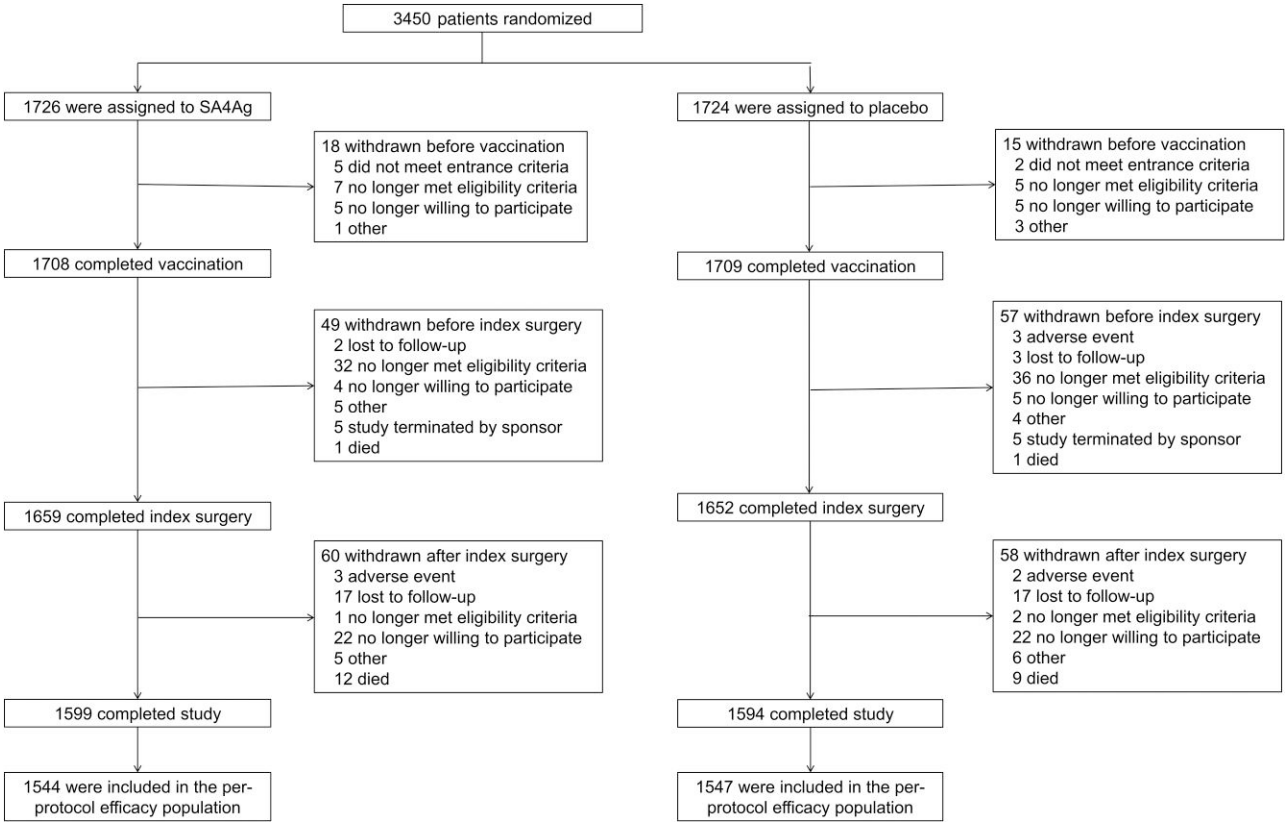

Figure 1. Patient disposition. Reasons for exclusion from the per-protocol efficacy population were as follows: had major protocol violation before reporting suspected *Staphylococcus aureus* infection (SA4Ag, n = 10; placebo, n = 9), did not meet all eligibility criteria (SA4Ag, n = 31; placebo, n = 30), did not undergo index surgery within 9–90 days after vaccination (SA4Ag, n = 19; placebo, n = 14), did not undergo spinal surgery (SA4Ag, n = 67; placebo, n = 72), had index surgery staged on separate days (SA4Ag, n = 18; placebo, n = 28), had infection or malignancy identified at index surgery (SA4Ag, n = 8; placebo, n = 10), was not vaccinated as randomized (SA4Ag, n = 18; placebo, n = 15), surgical procedure did not include ≥2 adjacent motion segments (SA4Ag, n = 52; placebo, n = 42), surgical procedure did not use implanted device(s) (SA4Ag, n = 14; placebo, n = 12), surgical procedure was not performed via an open posterior incision (SA4Ag, n = 5; placebo, n = 5). Abbreviation: SA4Ag, *Staphylococcus aureus* 4-antigen vaccine.

MntC, although ClfA responses peaked on the hospital discharge day.

Colonization

On the day of vaccination, 33.4%–35.0% of SA4Ag or placebo recipients, were *S. aureus*–positive based on nose or throat swabs (Supplementary Figure 2). Colonization rates were similar across groups, decreasing through the hospital discharge day to 19.4%–20.2% and then rising to 29.5%–30.0% through day 180.

Safety

Local reactions were more common in the SA4Ag group (28.9%) than in the placebo group (9.8%) ≤10 days after vaccination (Supplementary Figure 3). Most reactions were mild to moderate in severity with a median of 5 or fewer days duration per group; injection site pain the was most common. Systemic events, most commonly fatigue, were largely mild to moderate in severity and reported at similar frequencies across groups (SA4Ag, 62.3%; placebo, 60.4%) with median durations of fewer than 10 days per group.

Overall, AE reporting was generally similar across groups (Table 3). Most AEs and SAEs occurred after the index surgery. From vaccination until index surgery, urinary tract infection (UTI) was the only AE reported in ≥1% of patients per group (1.1%−1.3%). Related AEs during this time frame were more common in the SA4Ag group (1.2%) than in the placebo group (0.2%) and were mostly from the general disorders and administration site conditions system organ class. From index surgery until postoperative day 42, the most commonly reported AE was constipation (11.2% per group); other AEs reported after surgery in ≥5% of patients within each group included nausea, pyrexia, anemia, procedural pain, hypotension, UTI, and dural tear. Of individual AEs reported by ≥1% of patients, only cough was reported at different frequencies between groups (SA4Ag, 0.4%; placebo, 1.0%). Two related AEs (swelling, musculoskeletal pain) were reported in the SA4Ag group.

Severe and life-threatening AEs, most commonly cardiac disorders, occurring from vaccination to index surgery were infrequent in both groups (SA4Ag, 1.2%; placebo, 1.1%). Six (0.2%) patients experienced AEs considered related (2 patients

Table 1. Patient Demographic and Comorbidity Characteristics

Patient Demographics	SA4Ag ($N^a = 1726$) n^b (%)	Placebo ($N^a = 1724$) n^b (%)
Sex		
Female	960 (55.6)	947 (54.9)
Male	766 (44.4)	777 (45.1)
Race		
White	1311(76.0)	1294 (75.1)
Asian[c]	295 (17.1)	291 (16.9)
Japanese	280 (94.9)	281 (96.6)
Southeast Asian	5 (1.7)	3 (1.0)
Indian subcontinent Asian	3 (1.0)	2 (0.7)
Chinese	2 (0.7)	1 (0.3)
Korean	2 (0.7)	2 (0.7)
Other	2 (0.7)	2 (0.7)
Unknown	1 (0.3)	0 (0.0)
Black	92 (5.3)	114 (6.6)
Other	28 (1.6)	25 (1.5)
Ethnicity		
Non-Hispanic/Non-Latino	1652 (95.7)	1653 (95.9)
Hispanic/Latino	69 (4.0)	70 (4.1)
Age at vaccination, y		
n	1708	1709
Mean (SD)	62.7 (12.3)	62.6 (12.6)
Median	65.0	65.0
Min, max	18.0, 85.0	18.0, 85.0
Body mass index, kg/m^2		
n	1718	1719
Mean (SD)	28.9 (6.0)	28.9 (6.2)
Median	28.2	28.3
Min, max	15.6, 58.2	15.0, 61.0
Smoking status		
Never	772 (44.7)	812 (47.1)
Past	678 (39.3)	617 (35.8)
Current	274 (15.9)	292 (16.9)
Unknown	2 (0.1)	3 (0.2)

Comorbidity Characteristics	SA4Ag ($N^d = 1708$) n^b (%)	Placebo ($N^d = 1709$) n^b (%)
Charlson comorbidity index score		
n	1708	1709
0	181 (10.6)	189 (11.1)
1–2	692 (40.5)	639 (37.4)
3–4	660 (38.6)	685 (40.1)
≥5	175 (10.2)	196 (11.5)
American Society of Anesthesiologists physical status classification		
n	1656	1648
1, healthy	115 (6.7)	125 (7.3)
2, mild systemic disease with no functional limitation	953 (55.8)	883 (51.7)
3, severe systemic disease with definitive functional limitation	578 (33.8)	620 (36.3)
4, severe systemic disease that is a constant threat to life	10 (0.6)	20 (1.2)
5, moribund patient unlikely to survive 24 h with or without operation	0 (0.0)	0 (0.0)
Not evaluated	14 (0.8)	11 (0.6)

Abbreviations: SA4Ag, *Staphylococcus aureus* 4-antigen vaccine; SD, standard deviation.

[a]Number of patients in the specified group used as the denominators for the percentage calculations unless otherwise specified.

[b]Number of patients with the specified characteristic.

[c]Number of patients in this row used as denominators for the indented rows that follow.

[d]Number of patients in the safety population. These values were used as the denominators for the percentage calculations of the Charlson comorbidity index and American Society of Anesthesiologists physical status classification.

with chills; 1 patient each with muscle spasms, pain, pain in extremity, rheumatoid arthritis [RA]).

Two (0.1%) SAEs in the SA4Ag group (chills, RA) reported through day 180 were considered related. None of the 23 deaths (SA4Ag, 0.8%; placebo, 0.6%) or 82 NDCMCs (1.7% vs 2.4%) were considered related. One of 8 patients with AEs that led to withdrawal had an AE considered related (the SAE of RA previously noted). There was no difference across groups in EAC-confirmed MOF (SA4Ag, 0.59%, n = 10; placebo, 0.53%, n = 9). Seven patients reported infection-associated MOF (SA4Ag, n = 4; placebo, n = 3).

DISCUSSION

Preventive approaches against *S. aureus* infection remain a critical unmet medical need. Our randomized, double-blind, placebo-controlled study, one of the largest prospective studies of thoracolumbar spinal surgery, evaluated SA4Ag efficacy in adults undergoing elective multilevel open posterior spinal fusion surgeries with instrumentation. The study terminated early when prespecified futility criteria were met despite high study completion rates that, together with the large study population, enabled sufficient accrual of cases to evaluate efficacy. Primary efficacy end point analyses showed SA4Ag was not efficacious (VE, 0.0%) against *S. aureus* BSI and/or deep incisional or organ/space SSI occurring within 90 postoperative days. For BSI only, there was a trend toward low-level efficacy (VE, 36.36%), but the CI widely crossed 0%. Nevertheless, SA4Ag induced functional immune responses against all 4 antigens, remaining above baseline 90 days after surgery and eliciting similar immune responses in vaccinated patients regardless of infection status. SA4Ag was well tolerated and showed an acceptable safety profile. The STRIVE trial used a standardized, prospective collection of safety data and adjudication of all MOF events and deaths and did not identify any safety signals, marking a salient contribution to *S. aureus* vaccine development.

Table 2. Vaccine Efficacy of *Staphylococcus aureus* 4-Antigen Vaccine Against *S. aureus* Bloodstream Infection and Surgical Site Infection in the Per-Protocol Efficacy Population

	Vaccine Group			
	SA4Ag (N^a = 1544)	Placebo (N^a = 1547)	Vaccine Efficacy[c]	Vaccine Efficacy Adjusted for Follow-up Time[c]
Time Period/Efficacy Endpoint	n[b] (%)	n[b] (%)	% (95% CI)	% (95% CI)
90 days after index surgery	…	…	…	…
Patients completing 90 days of follow-up	1505 (97.5)	1504 (97.2)	…	…
Total follow-up time within 90 days, person-years[d]	374.1	375.1	…	…
Cases of *Staphylococcus aureus* BSI and/or deep incisional or organ/space SSI	**14 (0.9)**	**14 (0.9)**	**.0 (−126.3 to 55.8)**	**−.3 (−126.9 to 55.7)**
Cases of *S. aureus* BSI	**7 (0.5)**	**11 (0.7)**	**36.4 (−79.8 to 79.1)**	**36.2 (−80.3 to 79.0)**
Cases of *S. aureus* deep incisional or organ/space SSI	**12 (0.8)**	**12 (0.8)**	**.0 (−143.4 to 58.9)**	**−.3 (−144.0 to 58.8)**
Cases of *S. aureus* SSI	24 (1.6)	22 (1.4)	−9.1 (−104.1 to 41.4)	−9.4 (−104.6 to 41.2)
Cases of *S. aureus* deep incisional SSI	11 (0.7)	11 (0.7)	.0 (−154.4 to 60.7)	−.3 (−155.1 to 60.6)
Cases of *S. aureus* organ/space SSI	1 (0.1)	1 (0.1)	.0 (−7749.7 to 98.7)	−.3 (−7771.8 to 98.7)
Cases of *S. aureus* superficial SSI	12 (0.8)	10 (0.7)	−20.0 (−210.1 to 52.5)	−20.3 (−210.9 to 52.4)
180 days after index surgery	…	…	…	…
Patients completing 180 d of follow-up	1256 (81.4)	1246 (80.5)	…	…
Total follow-up time within 180 d, person-years[d]	739.0	739.5	…	…
Cases of *S. aureus* BSI and/or deep incisional or organ/space SSI	14 (0.9)	14 (0.9)	.0 (−126.3 to 55.8)	−.1 (−126.5 to 55.8)
Cases of *S. aureus* BSI	7 (0.5)	11 (0.7)	36.4 (−79.8 to 79.1)	36.3 (−79.9 to 79.1)
Cases of *S. aureus* deep incisional or organ/space SSI	13 (0.8)	12 (0.8)	−8.3 (−159.8 to 54.4)	−8.4 (−159.9 to 54.4)
Cases of *S. aureus* SSI	25 (1.6)	23 (1.5)	−8.7 (−100.4 to 40.8)	−8.8 (−100.6 to 40.8)
Cases of *S. aureus* deep incisional SSI	12 (0.8)	11 (0.7)	−9.1 (−172.9 to 55.9)	−9.2 (−173.1 to 55.9)
Cases of *S. aureus* organ/space SSI	1 (0.1)	2 (0.1)	50.0 (−860.5 to 99.2)	50.0 (−861.1 to 99.2)
Cases of *S. aureus* superficial SSI	13 (0.8)	11 (0.7)	−18.2 (−191.3 to 51.1)	−18.3 (−191.6 to 51. 1)

Primary end points are noted in bold type.

Abbreviations: BSI, bloodstream infection; CI, confidence interval; SA4Ag, *Staphylococcus aureus* 4-antigen vaccine; SSI, surgical site infection.

[a]Number of patients in the specified group vaccinated and completing the index surgery.

[b]Number of patients with the specified characteristic.

[c]Vaccine efficacy (VE) was calculated as follows: 1 − (P/[1 − P]); VE adjusted for follow-up time was calculated as 1 − (hP/[1 − P]), where P is the number of SA4Ag cases divided by the total number of cases and h is the ratio of total follow-up time in the placebo group to the total follow-up time in the SA4Ag group. 95% CIs were calculated using the Clopper–Pearson method.

[d]Calculated as total follow-up days divided by 365.25.

Evaluating vaccine efficacy in a surgical population presents substantial challenges, such as factors relating to surgical complexity and heterogeneity that could have affected antibody concentrations and/or surgical site access. The general health status of the study population may also have impacted immune responses and infection outcomes, with approximately one-third having ASA scores ≥3 (severe disease with functional limitation). Although these hypotheses could not be fully evaluated owing to inadequate statistical power, trends in increased efficacy were not observed for shorter-duration procedures or among patients with fewer comorbidities. Further, intrawound antibiotic use and other surgical variables likely did not confound results, as they were similar across groups and did not appear to obviously impact efficacy.

Mechanistically, lack of SA4Ag efficacy may be due to various reasons. Inhibition of virulence mechanisms by vaccine antibodies could have been circumvented by additional compensatory mechanisms or variable antigen expression in infecting *S. aureus* strains [19, 35], a possibility that is under active investigation. Similarly, the bacteria could be subverting immune responses required for the target antigens to be effective [36]. Alternatively, vaccine antigens may have insufficiently thwarted infection or vaccine-induced immune responses may have been inadequate. Notably, this study further supports that targeting gram-positive bacterial killing through anticapsular polysaccharide antibody-mediated opsonophagocytosis does not functionally prevent *S. aureus* infections.

Our study adds to a body of evidence that reiterates challenges in current approaches to *S. aureus* vaccine development. These include identification of reliable animal models for preclinical evaluation of *S. aureus* vaccine candidates and a lack of clinically validated correlates of protection [19, 20]. Despite efficacy of SA4Ag and other vaccine candidates in mouse models, vaccine efficacy has not yet been translated in human studies [20, 37]. Mice also require multiple doses of vaccine antigens owing to differences in immune mechanisms and prior exposure to *S. aureus* [19, 37]. The lack of clinically validated correlates of protection is reflected in the current study's finding of robust functional immune responses observed in the vaccinated participants with no differences in measurable immune

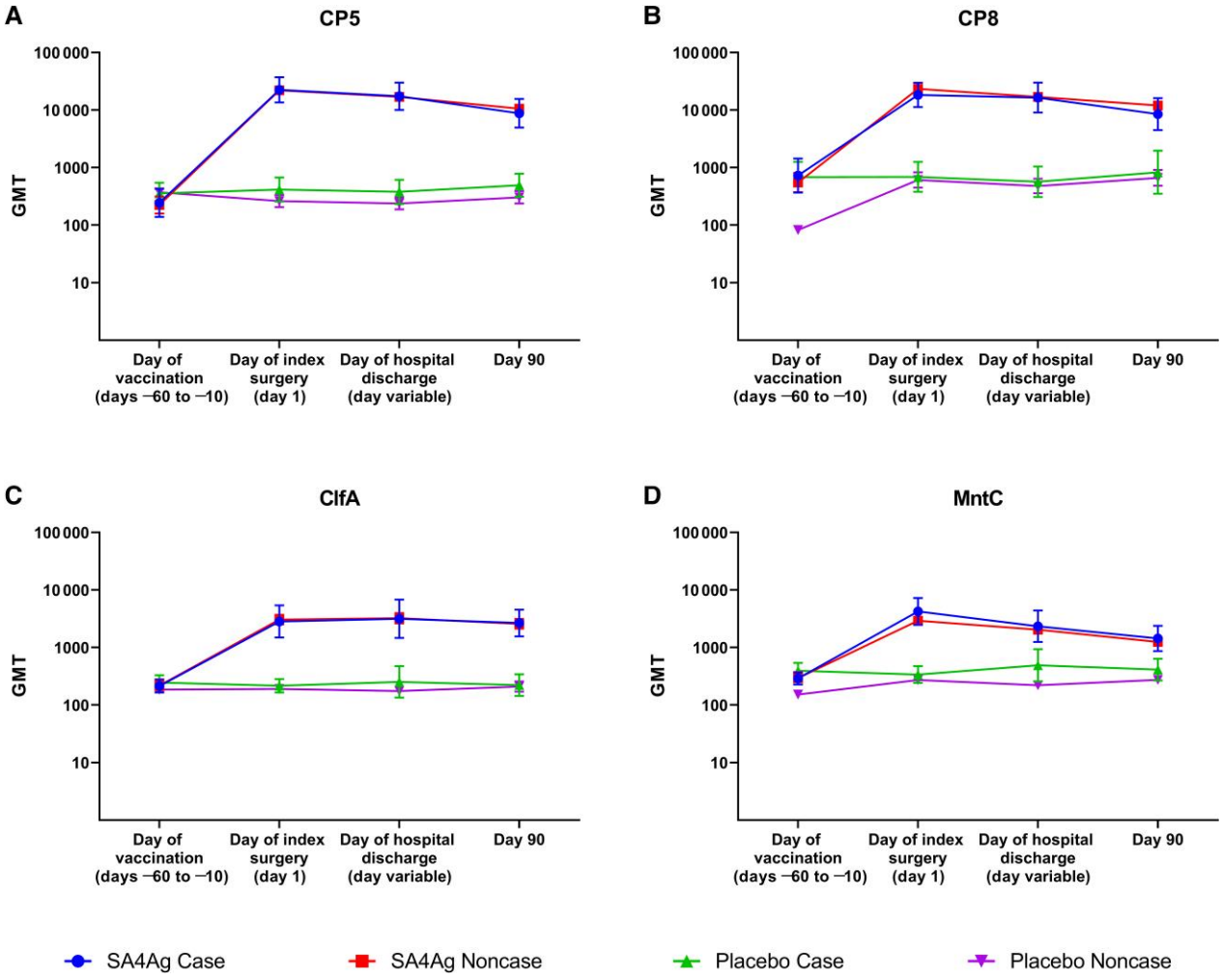

Figure 2. GMTs against all 4 vaccine antigens for cases and noncases in the SA4Ag and placebo groups. GMTs for CP5 (*A*) and CP8 (*B*), as measured using opsonophagocytic activity. GMTs for ClfA (*C*) and manganese transporter C (*D*), as measured using competitive Luminex immunoassay. All data shown are for the modified intent-to-treat immunogenicity population. For SA4Ag cases, n = 26–27 for day of vaccination; n = 27 for day of index surgery; n = 24 for day of hospital discharge; n = 22 for day 90. For SA4Ag noncases, n = 49–50 for day of vaccination; n = 246–252 for day of index surgery; n = 232–235 for day of hospital discharge; n = 242–248 for day 90. For placebo cases, n = 30–31 for day of vaccination; n = 28–29 for day of index surgery; n = 24–25 for day of hospital discharge; n = 20–22 for day 90. For placebo noncases, n = 1 for day of vaccination; n = 100–102 for day of index surgery; n = 96–97 for day of hospital discharge; n = 98–99 for day 90. Abbreviations: ClfA, clumping factor A; CP5, capsular polysaccharide serotype 5; CP8, capsular polysaccharide serotype 8; GMT, geometric mean titer; MntC, manganese transporter C; SA4Ag, *Staphylococcus aureus* 4-antigen vaccine.

responses between cases and non-cases (Figure 2). Additional challenges remain, including appropriate choice of study population for vaccine efficacy evaluation and optimal target antigen selection.

Although antibody-mediated clearance is clearly important [19], other mechanisms may be required for protection, and alternative strategies are warranted. The contribution of other undefined mechanisms, such as T cell–mediated immunity (in particular, γδ T cells, which play an important protective role in the immune response to *S. aureus* infection and may be induced by vaccination) or virulence mechanisms that enable infection progression despite robust antibody-mediated responses, should be considered [19, 20]. Additionally, adjuvants may be needed to enhance immunogenicity [20]. Other vaccine strategies under evaluation include a vaccine comprising 5 recombinant *S. aureus* antigens (rFSAV; Olymvax) that inhibits *S. aureus* immune-evasion strategies [20]. Another vaccine, targeting 5 antigens involved in different pathogenic mechanisms formulated with a Toll-like receptor 7-agonist adsorbed to aluminum hydroxide (GSK, NCT04420221), was recently announced as not continuing development [38–40]. An adjuvanted vaccine targeting the N-terminal portion of the *Candida albicans* cell-wall protein Als3p (NDV3-A; Novadigm) provided cross-protection against *S. aureus* in mouse models of bacteremia and skin infection but did not prevent nasal or oral acquisition of *S. aureus* or affect colonization prevalence in a randomized, double-blind, placebo-controlled phase 2 trial in military personnel, a population at high risk

Table 3. Summary of Adverse Events Reported by Patients per Group

Category of AE Interval Relationship[a]	*Staphylococcus aureus* 4-Antigen Vaccine (N[b] = 1708)		Placebo (N[b] = 1709)	
	n[c] (%)	Events, n[d]	n[c] (%)	Events, n[d]
AEs	1226 (71.8)	4456	1241 (72.6)	4447
Vaccination to day of index surgery	213 (12.5)	310	178 (10.4)	270
Related	20 (1.2)	28	4 (0.2)	5
Day of index surgery to day 42	1136 (66.5)	3923	1167 (68.3)	3929
Related	2 (0.1)	2	0 (0.0)	0
Serious AEs	406 (23.8)	666	425 (24.9)	668
Vaccination to day of index surgery	27 (1.6)	32	26 (1.5)	33
Related	1 (0.1)	1	0 (0.0)	0
Day of index surgery to day 180	384 (22.5)	627	401 (23.5)	629
Related	1 (0.1)	1	0 (0.0)	0
Severe and life-threatening AEs	280 (16.4)	498	281 (16.4)	456
Vaccination to day of index surgery	20 (1.2)	27	19 (1.1)	24
Related	5 (0.3)	7	1 (0.1)	1
Day of index surgery to day 42	223 (13.1)	369	213 (12.5)	328
Related	0 (0.0)	0	0 (0.0)	0
Deaths	13 (0.8)	13	10 (0.6)	10
Vaccination to day of index surgery	1 (0.1)	1	1 (0.1)	1
Related	0 (0.0)	0	0 (0.0)	0
Day of index surgery to day 180	12 (0.7)	12	9 (0.5)	9
Related	0 (0.0)	0	0 (0.0)	0
AEs leading to withdrawal	3 (0.2)	3	5 (0.3)	6
Related	1 (0.1)	1	0 (0.0)	0
Newly diagnosed chronic medical condition (day 42 to day 180)	29 (1.7)	32	41 (2.4)	50
Related	0 (0.0)	0	0 (0.0)	0

Abbreviation: AE, adverse event.

[a]Assessed by investigator as related to the investigational product.

[b]Number of patients in the specified group.

[c]Number of patients reporting ≥1 event of the type specified.

[d]Total number of occurrences of the event specified; patients could be represented more than once.

for *S. aureus* colonization and infection [20, 41]. In addition to vaccines, novel therapeutic approaches under consideration include monoclonal antibodies, bacteriophages, centyrins, and new antibiotic strategies [20].

Halting the study at the interim analysis precluded subgroup efficacy examinations due to inadequate statistical power. Additional limitations included a heterogeneous surgical population, single surgery type, and lower-than-anticipated infection rates among placebo recipients (0.9% vs 1.4%) in a clinical trial population that excluded those at high risk of infection (ie, immunocompromised), potentially affecting efficacy evaluations. Additionally, variable surgical methods were used, although this did not appear to affect efficacy.

Overall, while SA4Ag had an acceptable safety profile and elicited robust immunogenicity, the vaccine was not efficacious in preventing *S. aureus* infections. Despite these findings, efforts to develop a safe and effective vaccine to lower the substantial global burden of *S. aureus* infections should remain a priority.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author Contributions. J. B., E. B., C. S., I. M., D. C., D. R., A. J., M. P., W. C. G., K. U. J., A. S. A., and A. G. contributed to the conception or design of the work. Data collection was performed by H. H., D. C. N., H. K., Y. Y., M. Y. W., J. C. Le H., V. P., P. V., U. L., and J. C. All authors contributed to the drafting of the article and its critical revision for intellectual content as well as approved the final version to be published. All authors had access to the data presented in this article. J. B. and D. R. verified the underlying data of the article.

Acknowledgments. We thank all participants who volunteered to take part in the study and all subinvestigators, study coordinators, and site staff who contributed to the conduct of the study. The authors acknowledge Pfizer colleagues from Vaccine Clinical Research and Development, High-Throughput Clinical Testing, Clinical Development Operations, Pharmaceutical Sciences, Vaccine Regulatory, and Project Management for their contributions to this work. The authors acknowledge the independent Data Monitoring Committee members for the *STaphylococcus aureus* suRgical Inpatient Vaccine Efficacy (STRIVE) study for their contribution to safety oversight throughout the study: Jonathan Zenilman, MD (chair), Robert Salata, MD, William Schaffner, MD, William Blackwelder, PhD, and David Leaper, MD. We also acknowledge the independent Event Adjudication Committee members for their contribution to case adjudication throughout the study: Joseph S. Solomkin, MD, Lena M. Napolitano, MD, Steven P. LaRosa, MD, Gordon R. Bell, MD, Martin J. Llewelyn, PhD, FRCP, DTMH, and John Segreti, MD. Editorial/medical writing support was provided by Emily Stackpole, PhD, and Judith Kandel, PhD, both of ICON (Blue Bell, PA), and was funded by Pfizer.

Data sharing statement. On request and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions, and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

Financial support. This work was supported by Pfizer. Pfizer was involved with study concept and design; collection, analysis, and interpretation of the data; drafting of the manuscript; and the decision to submit the manuscript for publication. D. C. and J. B. report support for this work from ICON in the form of medical writing.

Disclaimer. All authors confirm that they had full access to all data in the study and accept responsibility to submit for publication.

Potential conflicts of interest. H. H. is a consultant for Medtronic, DePuy, Nuvasive, and Orthofix; has obtained research support from Orthofix, Nuvasive, Medtronic, SKK, and Pfizer; has taught/spoken for Nuvasive, Medtronic, Orthofix, and Globus; has received payment for expert testimony from the Expert Institute; has participated on an advisory board for MTF; and reports stock or stock options with Nuvasive and 4Web. V. P. is a consultant for Medtronic; has obtained research support from Pfizer, Orthofix, Medicrea, Mainstay Medical, SI Bone, and Premia Spine; reports grants or contracts from Spinal Kinetics; reports consulting

fees from DePuy Synthes, J&J SI-BONE, Mainstay Medical, Zimmer, Baxter, Stryker, and Aesculap; has filed multiple patents with the university office; and receives royalties from Stryker and Aesculap. H. K. has served as a consultant for Pfizer. D. N. is a consultant for Stryker. J. B., E. B., C. S., I. M., D. C., D. R., A. J., M. P., W. C. G., K. U. J., A. S. A., and A. G. are current employees of Pfizer and may hold stock or stock options. A. J. reports support for attending meetings as part of duties as a Pfizer employee and STRIVE team member. J. C. reports grants or contracts from the Canadian Institutes for Health Research and from Alberta Innovates; has received accommodations and airfare to attend and speak at a symposium from bioMerieux Canada; and is a member and chair of the World Health Organization (WHO) and a member of the WHO Health Emergencies Programme Ad-hoc COVID-19 IPC Guidance Development Group, both of which provide multidisciplinary advice to the WHO, for which no funding is received and from which no funding recommendations are made for any WHO contracts or grants; and works as an infectious diseases consultant at Alberta Health Services. K. J. reports consulting fees from and patents with Pfizer. M. W. reports royalties or licenses from Depuy-Synthes Spine; consulting fees from Depuy-Synthes Spine, Pacira, Stryker, NuVasive, Spineology, and Surgalign; and stock or stock options from Innovasive Surgical Devices, Kinesiomerics, and Medical Device Partners. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. Lowy FD. *Staphylococcus aureus* infections. N Engl J Med **1998**; 339:520–32.
2. Saadatian-Elahi M, Teyssou R, Vanhems P. *Staphylococcus aureus*, the major pathogen in orthopaedic and cardiac surgical site infections: a literature review. Int J Surg **2008**; 6:238–45.
3. Schimmel JJ, Horsting PP, de Kleuver M, Wonders G, van Limbeek J. Risk factors for deep surgical site infections after spinal fusion. Eur Spine J **2010**; 19:1711–9.
4. Rao SB, Vasquez G, Harrop J, et al. Risk factors for surgical site infections following spinal fusion procedures: a case-control study. Clin Infect Dis **2011**; 53: 686–92.
5. Patel H, Khoury H, Girgenti D, Welner S, Yu H. Burden of surgical site infections associated with select spine operations and involvement of *Staphylococcus aureus*. Surg Infect (Larchmt) **2017**; 18:461–73.
6. Tong SY, Davis JS, Eichenberger E, Holland TL, Fowler VG Jr. *Staphylococcus aureus* infections: epidemiology, pathophysiology, clinical manifestations, and management. Clin Microbiol Rev **2015**; 28:603–61.
7. Bassetti M, Trecarichi EM, Mesini A, et al. Risk factors and mortality of healthcare-associated and community-acquired *Staphylococcus aureus* bacteraemia. Clin Microbiol Infect **2012**; 18:862–9.
8. Goto M, Schweizer ML, Vaughan-Sarrazin MS, et al. Association of evidence-based care processes with mortality in *Staphylococcus aureus* bacteremia at Veterans Health Administration hospitals, 2003–2014. JAMA Intern Med **2017**; 177:1489–97.
9. Weber Z, Ariano R, Lagacé-Wiens P, Zelenitsky S. Multifaceted antibiotic treatment analysis of methicillin-sensitive *Staphylococcus aureus* bloodstream infections. Int J Antimicrob Agents **2016**; 48:674–9.
10. Calderone RR, Garland DE, Capen DA, Oster H. Cost of medical care for postoperative spinal infections. Orthop Clin North Am **1996**; 27:171–82.
11. Berrios-Torres SI, Umscheid CA, Bratzler DW, et al. Centers for Disease Control and Prevention guideline for the prevention of surgical site infection, 2017. JAMA Surg **2017**; 152:784–91.
12. Lee AS, de Lencastre H, Garau J, et al. Methicillin-resistant *Staphylococcus aureus*. Nat Rev Dis Primers **2018**; 4:18033.
13. McGuinness WA, Malachowa N, DeLeo FR. Vancomycin resistance in *Staphylococcus aureus*. Yale J Biol Med **2017**; 90:269–81.
14. Inoue M, Yonemura T, Baber J, et al. Safety, tolerability, and immunogenicity of a novel 4-antigen *Staphylococcus aureus* vaccine (SA4Ag) in healthy Japanese adults. Hum Vaccin Immunother **2018**; 14:2682–91.
15. Gurtman A, Begier E, Mohamed N, et al. The development of a *Staphylococcus aureus* four antigen vaccine for use prior to elective orthopedic surgery. Hum Vaccin Immunother **2019**; 15:358–70.
16. Fattom A, Matalon A, Buerkert J, Taylor K, Damaso S, Boutriau D. Efficacy profile of a bivalent *Staphylococcus aureus* glycoconjugated vaccine in adults on hemodialysis: phase III randomized study. Hum Vaccin Immunother **2015**; 11:632–41.
17. Fattom AI, Horwith G, Fuller S, Propst M, Naso R. Development of StaphVAX, a polysaccharide conjugate vaccine against *S. aureus* infection: from the lab bench to phase III clinical trials. Vaccine **2004**; 22:880–7.
18. Fowler VG, Allen KB, Moreira ED, et al. Effect of an investigational vaccine for preventing *Staphylococcus aureus* infections after cardiothoracic surgery: a randomized trial. JAMA **2013**; 309:1368–78.
19. Miller LS, Fowler VG, Shukla SK, Rose WE, Proctor RA. Development of a vaccine against *Staphylococcus aureus* invasive infections: evidence based on human immunity, genetics and bacterial evasion mechanisms. FEMS Microbiol Rev **2020**; 44:123–53.
20. Clegg J, Soldaini E, McLoughlin RM, Rittenhouse S, Bagnoli F, Phogat S. *Staphylococcus aureus* vaccine research and development: the past, present and future, including novel therapeutic strategies. Front Immunol **2021**; 12:705360.
21. Scully IL, Liberator PA, Jansen KU, Anderson AS. Covering all the bases: preclinical development of an effective *Staphylococcus aureus* vaccine. Front Immunol **2014**; 5:109.
22. Zorman JK, Esser M, Raedler M, et al. Naturally occurring IgG antibody levels to the *Staphylococcus aureus* protein IsdB in humans. Hum Vaccin Immunother **2013**; 9:1857–64.
23. Anderson AS, Miller AA, Donald RG, et al. Development of a multicomponent *Staphylococcus aureus* vaccine designed to counter multiple bacterial virulence factors. Hum Vaccin Immunother **2012**; 8:1585–94.
24. McDevitt D, Nanavaty T, House-Pompeo K, et al. Characterization of the interaction between the *Staphylococcus aureus* clumping factor (ClfA) and fibrinogen. Eur J Biochem **1997**; 247:416–24.
25. Handke LD, Hawkins JC, Miller AA, Jansen KU, Anderson AS. Regulation of *Staphylococcus aureus* MntC expression and its role in response to oxidative stress. PLoS One **2013**; 8:e77874.
26. Scully IL, Timofeyeva Y, Keeney D, et al. Demonstration of the preclinical correlate of protection for *Staphylococcus aureus* clumping factor A in a murine model of infection. Vaccine **2015**; 33:5452–7.
27. Scully IL, Pavliak V, Timofeyeva Y, Liu Y, Singer C, Anderson AS. O-acetylation is essential for functional antibody generation against *Staphylococcus aureus* capsular polysaccharide. Hum Vaccin Immunother **2018**; 14:81–4.
28. Anderson AS, Scully IL, Timofeyeva Y, et al. *Staphylococcus aureus* manganese transport protein C is a highly conserved cell surface protein that elicits protective immunity against *S. aureus* and *Staphylococcus epidermidis*. J Infect Dis **2012**; 205:1688–96.
29. Frenck RW J, Creech CB, Sheldon EA, et al. 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. Vaccine **2017**; 35:375–84.
30. Creech CB, Frenck RW Jr, Sheldon EA, et al. Safety, tolerability, and immunogenicity of a single dose 4-antigen or 3-antigen *Staphylococcus aureus* vaccine in healthy older adults: results of a randomised trial. Vaccine **2017**; 35:385–94.
31. Begier E, Seiden DJ, Patton M, et al. SA4Ag, a 4-antigen *Staphylococcus aureus* vaccine, rapidly induces high levels of bacteria-killing antibodies. Vaccine **2017**; 35: 1132–9.
32. ClinicalTrials.gov. NCT02388165. Safety and efficacy of SA4Ag vaccine in adults having elective open posterior spinal fusion procedures with multilevel instrumentation (STRIVE). Accessed 24 April 2023.
33. Centers for Disease Control. National Healthcare Safety Network (NHSN) overview. 2014. Available at: https://www.cdc.gov/nhsn/PDFs/pscManual/validation/pcsManual-2014-valid.pdf. Accessed 21 April 2023.
34. American Society of Anesthesiologists. ASA physical status classification system. Available at: https://www.asahq.org/standards-and-guidelines/asa-physical-status-classification-system. Accessed 28 May 2020.
35. Pier GB. Will there ever be a universal *Staphylococcus aureus* vaccine? Hum Vaccin Immunother **2013**; 9:1865–76.
36. Sun Y, Emolo C, Holtfreter S, et al. Staphylococcal protein A contributes to persistent colonization of mice with *Staphylococcus aureus*. J Bacteriol **2018**; 200:e00735-17.
37. Scully IL, Timofeyeva Y, Illenberger A, et al. Performance of a four-antigen *Staphylococcus aureus* vaccine in preclinical models of invasive *S. aureus* disease. Microorganisms **2021**; 9:177.
38. Bagnoli F, Fontana MR, Soldaini E, et al. Vaccine composition formulated with a novel TLR7-dependent adjuvant induces high and broad protection against *Staphylococcus aureus*. Proc Natl Acad Sci U S A **2015**; 112:3680–5.
39. GSK Pipeline. Available at: https://www.gsk.com/en-gb/innovation/pipeline/#phase-i. Accessed 8 February 2023.
40. ClinicalTrials.gov. Safety, immunogenicity and efficacy of GSK *S. aureus* candidate vaccine (GSK3878858A) when administered to healthy adults (dose-escalation) and to adults 18 to 64 years of age with a recent *S. aureus* skin and soft tissue infection (SSTI). Available at: https://clinicaltrials.gov/ct2/show/NCT04420221. Accessed 8 February 2023.
41. Millar EV, Bennett JW, Barin B, et al. Safety, immunogenicity, and efficacy of NDV-3A against *Staphylococcus aureus* colonization: a phase 2 vaccine trial among US Army infantry trainees. Vaccine **2021**; 39:3179–88.