Policy Number	**RX504.006**
Policy Effective Date	**10/15/2024**
Policy End Date	**05/31/2025**

Staphylococcal Vaccines

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Related Policies (if applicable)
None

Disclaimer

Medical policies are a set of written guidelines that support current standards of practice. They are based on current peer-reviewed scientific literature. A requested therapy must be proven effective for the relevant diagnosis or procedure. For drug therapy, the proposed dose, frequency and duration of therapy must be consistent with recommendations in at least one authoritative source. This medical policy is supported by FDA-approved labeling and/or nationally recognized authoritative references to major drug compendia, peer reviewed scientific literature and acceptable standards of medical practice. These references include, but are not limited to: MCG care guidelines, DrugDex (IIa level of evidence or higher), NCCN Guidelines (IIb level of evidence or higher), NCCN Compendia (IIb level of evidence or higher), professional society guidelines, and CMS coverage policy.

Carefully check state regulations and/or the member contract.

Each benefit plan, summary plan description or contract defines which services are covered, which services are excluded, and which services are subject to dollar caps or other limitations, conditions or exclusions. Members and their providers have the responsibility for consulting the member's benefit plan, summary plan description or contract to determine if there are any exclusions or other benefit limitations applicable to this service or supply. **If there is a discrepancy between a Medical Policy and a member's benefit plan, summary plan description or contract, the benefit plan, summary plan description or contract will govern.**

Legislative Mandates

EXCEPTION: For HCSC members residing in the state of Ohio, § 3923.60 requires any group or individual policy (Small, Mid-Market, Large Groups, Municipalities/Counties/Schools, State Employees, Fully-Insured, PPO, HMO, POS, EPO) that covers prescription drugs to provide for the coverage of any drug approved by the U. S. Food and Drug Administration (FDA) when it is prescribed for a use recognized as safe and effective for the treatment of a given indication in one or more of the standard medical reference compendia adopted by the United States Department of Health and Human Services or in medical literature even if the FDA has not approved the drug for that indication. Medical literature support is only satisfied when safety and efficacy has been confirmed in two articles from major peer-reviewed professional medical journals that present data supporting the proposed off-label use or uses as generally safe and effective. Examples of accepted journals include, but are not limited to, Journal of

American Medical Association (JAMA), New England Journal of Medicine (NEJM), and Lancet. Accepted study designs may include, but are not limited to, randomized, double blind, placebo controlled clinical trials. Evidence limited to case studies or case series is not sufficient to meet the standard of this criterion. Coverage is never required where the FDA has recognized a use to be contraindicated and coverage is not required for non-formulary drugs.

Coverage

This medical policy has become inactive as of the end date above. There is no current active version and this policy is not to be used for current claims adjudication or business purposes.

Staphylococcal vaccines **are considered experimental, investigational and/or unproven.**

Policy Guidelines

None.

Description

The staphylococcus species are well-adapted parasites. In humans, they colonize on the skin and in the nose. These organisms are involved in common skin disorders including eczema, psoriasis, acne, boils and infections of cuts and burns. They can invade and cause more serious infections of the skin, mammary glands, respiratory tree, blood, joints and bones. Their toxins can cause food poisoning and toxic shock syndrome. Those staphylococci that synthesize coagulase, including staphylococcus aureus, are more invasive. By contrast, coagulase negative species are particularly good at colonizing implanted materials such as long intravenous lines, heart valves, and orthopedic prostheses.

Background

The mortality of Staphylococcus aureus (S. *aureus*) invasive infections has fallen from ~80% in the pre-antibiotic era to 16%–30% over the past two decades. (1) Further reductions in mortality below 20% have remained elusive despite the introduction of new antibiotics to address antibiotic-resistant isolates, rapid diagnostic and susceptibility testing, widespread antibiotic stewardship programs and improvements in therapeutic supportive care. While vaccine development has lowered the mortality of other bacterial infections, all vaccination attempts aimed at preventing S. *aureus* invasive infections have failed in human trials, especially all vaccines aimed at generating high titers of opsonic antibodies against S. *aureus* surface antigens to facilitate antibody-mediated bacterial clearance. A major impediment to the development of a successful vaccine against S. *aureus* is an incomplete understanding of protective immune mechanisms and biomarkers that clearly indicate durable and long-term protective immunity against S. *aureus* infections in humans. This impediment stems in part from relatively limited information about the specific immune responses in humans that protect against invasive S. *aureus* infections.

Regulatory Status
At the present time, no staphylococcal vaccine has received approval from the U.S. Food and Drug Administration (FDA). There have been several vaccines coined with brand/generic names, e.g., StaphVAX and PentaStaph (Nabi Biopharmaceuticals: Rockville, MD and GlaxoSmithKline: Brentford, London, England), V710, VRi, SA75 (Intercell: Vienna, Austria and Merck & Co., Inc.: Kenilworth, New Jersey).

Rationale

This policy was originally created in 1995 and was periodically updated with searches of the PubMed database. The most recent literature search was performed through August 13, 2024.

There are no current U.S. Food and Drug Administration (FDA) approved staphylococcal vaccines. (2-5, 7-13, 23)

An article published in the Journal Trends of Immunology, by Colin A. Michie stated (6), "Vaccination has proved relatively unsuccessful against the common bacteria staphylococcus, despite almost a century of experimentation." "It is hoped that one day a vaccine will be developed to help combat the prevalence and incidence of staphylococcus infection."

Fowler et al. (2013) performed a double-blind, randomized event-driven trial to evaluate the efficacy and safety of preoperative vaccination in preventing serious postoperative staphylococcus aureus (*S. aureus*) infection in patients undergoing cardiothoracic surgery. (14) Participants were randomly assigned to receive a single 0.5mL intramuscular injection of either V710 vaccine, 60 µg (n = 4015), or placebo (n = 4016). The primary efficacy end point was prevention of *S. aureus* bacteremia and/or deep sternal wound infection (including mediastinitis) through postoperative day 90. Secondary end points included all *S. aureus* surgical site and invasive infections through postoperative day 90. Three interim analyses with futility assessments were planned. After the second interim analysis, an independent data monitoring committee recommended termination of the study because of safety concerns and low efficacy.

Schwameis et al. (2016) published a randomized, double-blind, adjuvant-controlled, dose-escalation, first-in-human trial. Healthy adults aged 18-64 years were enrolled from the Medical University of Vienna, Austria (NCT02340338). (15) Participants were randomly assigned (2:1 and 3:1) by block randomization (block sizes of three and 12) to receive increasing doses of recombinant detoxified toxic shock syndrome toxin-1 variant (rTSST-1v) (100 ng to 30 µg) or the adjuvant comparator aluminum hydroxide (Al(OH)3) (200 µg, 600 µg, or 1 mg). Investigators and participants were masked to group allocation. The per-protocol population received booster immunization 42 days after the first vaccination. The primary endpoint was safety and tolerability of rTSST-1v. The per-protocol population included all participants who had adhered to the study protocol without any major protocol deviations. The per-protocol population was

the primary analysis population for immunogenicity. Between August 19, 2014 and April 14, 2015, 46 participants were enrolled (safety population), of whom three were assigned to cohort 1 (two to receive 100 ng rTSST-1v and one to receive 200 µg Al(OH)3, three to cohort 2 (two to receive 300 ng rTSST-1v and one to receive 600 µg Al(OH)3, four to cohort 3 (three to receive 1 µg rTSST-1v and one to receive 1 mg Al(OH)3, 12 to cohort 4 (nine to receive 3 µg rTSST-1v and three to receive 1 mg Al(OH)3, 12 to cohort 5 (nine to receive 10 µg rTSST-1v and three to receive 1 mg Al(OH)3, and 12 to cohort 6 (nine to receive 300 µg rTSST-1v and three to receive 1 mg Al(OH)3. Forty-five participants (98%) were included in the per-protocol population. rTSST-1v had a good safety profile, and no vaccination-related severe or serious adverse events occurred. Adverse event rates were similar between participants who received rTSST-1v and those who received placebo (26 [76%] vs 10 [83%]; p=0·62) independent of pre-existing toxic shock syndrome toxin-1 (TSST-1) immunity. The authors concluded that rTSST-1v was safe, well-tolerated, and immunogenic. The trial was limited by recruitment of primarily white volunteers. Extended trials will have to confirm the safety of rTSST-1v and the persistence of functional anti-TSST-1 antibodies in a larger, more heterogeneous population. Although randomization was used to equally distribute unknown confounders, residual confounding cannot be reliably ruled out due to the small sample size of this trial. Furthermore, the sample size of a phase 1 study is insufficient to detect rare adverse events. This first-in-human study included healthy young individuals. Future studies on immunocompromised patients will indicate whether the dose regimen used is adequate or higher doses need to be given. Finally, major histocompatibility complex class II (MHC II) variability in peripheral blood mononuclear cells (PBMCs) was not assessed. Genetic diversity, time, specificity, and intensity of priming are variables, which cannot be addressed other than in large clinical trials planned to focus or stratify for these variables.

Hassanzadeh et al. (2023) 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. (16) 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 surgical site infections (SSIs) was the primary end point. Safety evaluations included local reactions, systemic events, and adverse events (AEs). Immunogenicity and colonization were assessed. 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. The authors concluded that 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.

Recently published literature reiterated the history of failed clinical trials of *S. aureus* vaccines. (17-22) Numerous animal trials continue to work, by exploring active or passive models for vaccine development, towards a human immunity pathway protecting against the increasing incidence of the pathogen. One major barrier to *S. aureus* bacterial vaccine development comes from the issue of this organism being a part of the normal human flora. (20) This allows the bacteria to adapt to the host environment and its defenses. Thus, the number of opportunistic infections remains on the rise, such as sepsis and pneumonia. (21) The researchers' current strategy is to focus on the understanding of the pathogen itself and the future of a potential vaccine. The issues the researchers face are:

- The nature of the driving forces behind the rise and decline of methicillin-resistant *S. aureus* (MRSA) clones;
- The mechanisms by which a commensal becomes a pathogen;
- The molecular underpinnings of toxin overexpression in hyper virulent MRSA clones; and
- The repeated failures of anti-*S. aureus* vaccine approaches. (22)

Until these issues are resolved, the development of a vaccine and methods to combat the pathogen remain elusive.

Summary of Evidence

For the use of staphylococcus aureus vaccines, there is currently no approval from the U.S. Food and Drug Administration (FDA). There were no peer-reviewed scientific published data identified that would prompt reconsideration of the coverage position. The evidence is insufficient and therefore considered experimental, investigational and/or unproven.

Practice Guidelines and Position Statements

There are no practice guidelines or position statements issued by professional organizations which address the development or utilization of the staphylococcus aureus vaccine.

Ongoing and Unpublished Clinical Trials

A search of ClinicalTrials.gov in August 2024 did not identify any ongoing or unpublished trials that would likely influence this policy.

Coding

Procedure codes on Medical Policy documents are included **only** as a general reference tool for each policy. **They may not be all-inclusive.**

The presence or absence of procedure, service, supply, or device codes in a Medical Policy document has no relevance for determination of benefit coverage for members or reimbursement for providers. **Only the written coverage position in a Medical Policy should be used for such determinations.**

Benefit coverage determinations based on written Medical Policy coverage positions must include review of the member's benefit contract or Summary Plan Description (SPD) for defined coverage vs. non-coverage, benefit exclusions, and benefit limitations such as dollar or duration caps.

CPT Codes	90749
HCPCS Codes	None

*Current Procedural Terminology (CPT®) ©2023 American Medical Association: Chicago, IL.

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Centers for Medicare and Medicaid Services (CMS)

The information contained in this section is for informational purposes only. HCSC makes no representation as to the accuracy of this information. It is not to be used for claims adjudication for HCSC Plans.

The Centers for Medicare and Medicaid Services (CMS) does not have a national Medicare coverage position. Coverage may be subject to local carrier discretion.

A national coverage position for Medicare may have been developed since this medical policy document was written. See Medicare's National Coverage at <https://www.cms.hhs.gov>.

Policy History/Revision	
Date	**Description of Change**
05/31/2025	Document became inactive.
10/15/2024	Document updated with literature review. Coverage unchanged. Added references 1 and 16.
07/15/2023	Reviewed. No changes.
01/15/2023	Document updated with literature review. Coverage unchanged. No new references added.
09/15/2021	Reviewed. No changes.
11/15/2020	Document updated with literature review. Coverage unchanged. Reference 14 was added.
01/15/2019	Reviewed. No changes.
01/15/2018	Document updated with literature review. Coverage unchanged.
01/15/2017	Reviewed. No changes.
04/01/2016	Document updated with literature review. Coverage unchanged.
10/01/2015	Reviewed. No changes.
07/01/2014	Document updated with literature review. Coverage unchanged.
03/01/2014	Document updated with literature review. Coverage unchanged.
04/01/2008	Policy reviewed.
05/15/2006	References revised
01/01/2004	Revised/updated entire document
05/01/1995	New medical document