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Review

Clinical efficacies of immune-cell-targeted interventions a revolutionary era in host immune gene expression in MRSA infections

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Abstract: Background and aims: Methicillin-resistant *Staphylococcus aureus* (MRSA) remains a major cause of healthcare-associated infections worldwide, frequently progressing to bacteremia, and with high mortality rates, particularly in patients with recurrent or persistent infections involving skin/soft tissue and the bloodstream. Traditional antibiotic therapies are increasingly limited by MDR and immune evasion mechanisms. This review synthesized host immune transcriptomic changes during MRSA infections and evaluated the clinical translational potential of next-generation vaccines developed after 2020. Methods: Relevant searches were conducted in PubMed, Embase, and Web of Science (2020–2025) using combinations of terms related to MRSA, host immune gene expression, transcriptomics, scRNA-seq, and next-generation vaccines. Eligible studies included original research

and reviews reporting primary data on immune transcriptomics or vaccine immunogenicity/protective efficacy in MRSA infections. Results: MRSA infection triggers strong innate immune activation (TLR2/NOD2 signaling, IL-1β/IL-6/TNF-α upregulation) and heterogeneous macrophage polarization (M1 proinflammatory vs. M2 immunosuppressive phenotypes), alongside adaptive Th1/Th17 responses that are undermined by superantigens, IL-10 hypersecretion, and PD-1-mediated exhaustion. Multivalent mRNA-LNP vaccines encoding *ClfA-Hla-IsdB* fusions induce strong Th1/Th17 immunity, ~80% opsonophagocytic killing activity, 90% reduction in bacterial load, and 75% survival in murine sepsis models. Conclusion: This review demonstrated that integrating scRNA-seq-derived macrophage polarization biomarkers with next-generation mRNA and nanoparticle vaccine platforms offers a promising precision medicine strategy to counter MRSA immune evasion. These approaches may substantially reduce infection recurrence and complications in high-risk patients, paving the way for clinically effective vaccines in the era of antimicrobial resistance.

Keywords: mRNA vaccine; methicillin-resistant *Staphylococcus aureus*; nano-particle vaccine; macrophage activations

1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) is a significant human pathogen that poses a profound and escalating worldwide threat owing to its elevated resistance to β-lactam agents and rising multidrug resistance (MDR) profiles [1]. MRSA is responsible for a broad spectrum of clinical manifestations, ranging from superficial skin and soft tissue infections (SSTIs) to severe invasive diseases, including bacteremia, septicemia, endocarditis, osteomyelitis, and pneumonia [2,3]. The pathophysiology of MRSA infection is characterized by extensive tissue invasion, toxin production, dysregulated inflammatory responses, and immune-mediated tissue damage [4]. Clinical isolates of MRSA are routinely isolated from bloodstream specimens and are ranked as the primary etiology of septicemia, which correlates with substantial mortality and prolonged hospitalization [5,6]. MRSA infections are associated with increased mortality, particularly in cases of hematogenous dissemination. In Australia, during 2020, the 30-day all-cause mortality linked to methicillin-resistant *S. aureus* bacteremia (SAB) was 14.2%. In a separate investigation, the 30-day and inpatient mortality rates reached 7.3% and 9.8%, respectively, among 356 individuals [7].

Despite advances in antimicrobial therapy, MRSA-associated infections continue to impose a considerable clinical and economic burden worldwide [8]. Vancomycin, linezolid, daptomycin, ceftaroline, and combination antimicrobial regimens are currently used for the treatment of invasive MRSA infections. However, treatment failures continue to be reported, particularly in patients with persistent bacteremia, biofilm-associated infections, recurrent infections, and deep-seated metastatic complications [9]. The limited efficacy of conventional antimicrobial therapies has been attributed to multidrug resistance, biofilm formation, intracellular persistence, immune evasion mechanisms, and impaired host immune responses [10,11]. Furthermore, increasing antimicrobial resistance and the emergence of persistent MRSA strains have highlighted the urgent need for alternative therapeutic strategies capable of improving bacterial clearance and reducing infection recurrence and mortality [10].

The persistence of MRSA as a major clinical challenge is largely attributed to its multidrug-

resistant phenotype, primarily mediated by the *mecA* gene, which encodes penicillin-binding protein 2a (PBP2a) and confers resistance to β-lactam antibiotics [3,12,13].

The limited efficacy of conventional antimicrobial therapies and the increasing prevalence of persistent and recurrent MRSA infections have prompted a growing interest in host-directed therapeutic approaches. Immunological defense against MRSA entails an intricate interplay between innate and adaptive immunity, frequently culminating in heightened inflammatory cascades [14]. The innate response to MRSA is marked by the detection of pathogen-associated molecular patterns (PAMPs) through pattern recognition receptors (PRRs), culminating in the elaboration of proinflammatory cytokines [15]. Strains of both MRSA and methicillin-susceptible *S. aureus* (MSSA) trigger the upregulation of toll-like receptor 2 (TLR2) in ocular tissues, including microglia and retinal pigment epithelial (RPE) cells. MRSA challenge can provoke amplified immune activation in retinal cells, resulting in augmented levels of interleukin-1β (IL-1β) and interleukin-6 (IL-6) relative to MSSA exposure. Additionally, interferon-gamma (IFN-γ) expression exhibits differential modulation based on the anatomical site and infectious milieu. In retinal cells infected with MRSA, IFN-γ was suppressed compared to cells challenged with MSSA [14]. In addition to antimicrobial resistance, MRSA employs multiple immune-evasion strategies. Superantigens (SAgs) represent important virulence factors that bypass conventional antigen processing by directly interacting with major histocompatibility complex (MHC) class II molecules and T-cell receptors, leading to extensive T-cell activation and excessive cytokine production [16].

To overcome the limitations of conventional antimicrobial therapies, increasing attention has been directed toward host-directed and immune-based therapeutic strategies. Recent advances in transcriptomic technologies, particularly bulk RNA sequencing and single-cell RNA sequencing (scRNA-seq), have improved our understanding of immune-cell dynamics during MRSA infection and have revealed critical pathways involved in macrophage polarization, T-cell activation, cytokine regulation, and immune exhaustion [17]. These discoveries have facilitated the development of innovative immunotherapeutic approaches, including immune cell–targeted interventions, mRNA vaccines, multiepitope vaccines, nanoparticle-based vaccine platforms, and other precision immunomodulatory strategies. Such approaches aim not only to eliminate pathogens but also to restore protective host immunity and overcome immune-evasion mechanisms employed by MRSA [18].

The aim of this review was to comprehensively evaluate host immune gene expression changes during MRSA infections and to critically examine emerging immune cell–targeted therapeutic and vaccine-based strategies. Particular emphasis was placed on transcriptomic findings, macrophage polarization, immune-evasion mechanisms, and next-generation immunotherapeutic approaches that may improve clinical outcomes and support precision medicine against MRSA infections.

2. Methods

This study was conducted as a systematized narrative review aiming to synthesize current evidence regarding immune cell–targeted interventions, transcriptomic alterations, and emerging immunotherapeutic strategies against MRSA infections.

The search strategy was developed based on the objectives of the review and informed by established methodological principles commonly applied in evidence synthesis studies. Electronic searches were conducted in PubMed, Scopus, Web of Science, and Google Scholar databases using predefined combinations of keywords related to “methicillin-resistant *Staphylococcus aureus*”; “transcriptomics”,

"mRNA vaccines", "multiepitope vaccines", "macrophage polarization", and "nanoparticle-based vaccine platforms" were also part of the search phrases. Articles published in English were the only ones taken into account. The searches yielded approximately 133 records after deduplication. Following title/abstract screening, 79 articles were retrieved for full-text assessment, of which 66 were finally included based on the following explicit criteria: (i) host immune transcriptomic responses to MRSA infection, including bulk RNA-seq or scRNA-seq analyses, and/or (ii) immunogenicity, protective efficacy, or immune outcomes of MRSA vaccine candidates, particularly post-2020 mRNA, multiepitope, or nanoparticle-based vaccines. Both *in vivo* animal models and *in vitro* immune cell studies were eligible. Excluded from consideration were studies that failed to distinguish between MSSA and MRSA and papers that failed to discuss immune gene expression or vaccine-related immune responses. Research without primary data, such as case reports or abstracts from conferences, was not considered.

3. Host immune gene expression changes in MRSA infections

3.1. Innate immunity

MRSA strains elicit strong innate immune reactions through the activation of immune cells, including macrophages (MQs) and neutrophils, resulting in the release of proinflammatory mediators and the induction of regulated cell death pathways, such as pyroptosis [19]. One of the main components of the cell wall of MRSA, peptidoglycan (PG), activates the innate immune system via the PRRs TLR2 and NOD2 [20,21]. The nuclear translocation of nuclear factor-κB and the marked transcriptional induction of proinflammatory cytokines IL-1β, IL-6, and TNF-α in MQs and keratinocytes are caused by the engagement of nucleotide-binding oligomerization domain 2 (NOD2) and TLR2 heterodimers (TLR2/1 and TLR2/6) by PG and lipoteichoic acid (LTA) [22,23]. In addition, around 40 different bacterial species use bacterium-like particles (BLPs), which are derived from the peptidoglycan scaffold of lactic acid bacteria, as surface-display systems. A powerful immunological response is generated by these systems, which combine BLPs with anchoring proteins to deliver heterologous proteins. Dendritic cells (DCs) are activated by toll-like receptor 2 (TLR2), which in turn enhances T-cell activation and modulates the Th1/Th2 immune balance [20]. DCs are pivotal in innate immunity to *S. aureus* by secreting IL-12 upon TLR engagement, facilitating bacterial elimination [24]. In addition, after MRSA infection, *IL9* gene deletion significantly increases macrophage phagocytic activity and increases the M2 MQ subgroup. Rising levels of IL-10 and Arg1 and falling levels of inducible nitric oxide synthase (iNOS), TNFα, and IL-6 are linked to this change. There is an increase in B-cell lymphoma 2 (BCL-2) protein levels and a decrease in cleaved cysteine protease 3 (CASPASE-3) and BCL2-associated X (BAX) protein levels during MRSA infection, suggesting that IL-9 ablation further reduces macrophage apoptosis. The activation of the phosphoinositide 3-kinase (PI3K)/AKT signaling cascade was shown in both *in vivo* and *in vitro* tests involving MRSA infection; it is possible that the TLR2/PI3K axis modulates IL-9 production. These findings suggest that a possible treatment option for MRSA-associated pneumonia might be IL-9 deficiency, which demonstrates protective efficacy against MRSA infection by promoting phagocytosis and M2 MQ polarization [25]. Triacyl and diacyl lipoproteins, essential elements of the Staphylococcal cell wall, maintain its integrity and shield it against host immune effectors [19]. In MRSA infections, PRRs recognize bacterial moieties and trigger immune countermeasures. Nevertheless, *S. aureus* circumvents these mechanisms by lacking lipoproteins, which compromises TLR2 signaling and impedes efficient immune clearance [26]. While innate immune

responses provide the first line of defense against MRSA, effective pathogen clearance also requires the coordinated activation of adaptive immune mechanisms [27].

3.2. Adaptive immunity

Adaptive immunity is characterized by early T lymphocyte activation, as evidenced by surface CD69 upregulation within 6–12 h after infection, followed by IFN-γ transcription in $CD4^+$ Th1 and $CD8^+$ cytotoxic T lymphocytes, which promotes macrophage activation and opsonizing antibody class-switching in B lymphocytes [28,29]. Amplified B-cell signaling and differentiation into antibody-secreting plasma cells, driven by elevated expression of IFN-ɣ, IL-17, and CD69 in T lymphocytes, together with reduced IL-10 levels influenced by the DNMT3A A/C genotype, facilitate bacterial elimination [29,30]. One investigation demonstrated that acute pulmonary inflammation unfolds in a phased sequence: Initially (12 h), the IL-17 pathway is engaged; then (24–48 h), MQs and IFN-γ modulate inflammation; and finally (96 h), tissue repair and adaptive immunity commence. This progression identifies novel therapeutic targets for MRSA pneumonia [28].

S. aureus uses complex ways to avoid the immune system in order to weaken adaptive immunity. Protein A (SpA) increases the number of T-regulatory cells (Tregs) and stops B lymphocytes from responding. Bioinformatics studies show that SpA T-cell and B-cell epitopes have a substantial Human Leukocyte Antigen (HLA) binding affinity, which suggests that it might be a good vaccination candidate [26,30,31]. SAgs provoke excessive $CD4^+$ activation and IFN-γ secretion, enhancing bacterial survival within MQs, whereas *clpP* mutants dampen T-cell function through programmed cell death protein 1 (PD-1) interaction, decreasing IL-2 and CD25 expression [16,32]. MRSA superantigenic proteins connect the MHC-II and T-cell receptor (TCR) Vβ domains, resulting in T-cell anergy and heightened IL-10 production from regulatory B cells (Bregs) and Tregs [16].

IL-10, a pivotal immunosuppressive cytokine, is elevated in chronic MRSA bacteremia, hindering B lymphocyte function, reducing antibody synthesis, and promoting fatigue of B and T lymphocytes, partly via enhancing Bregs through lactic acid–mediated IL-10 induction [29,33]. Similarly, PD-1 engagement by *clpP* mutants suppresses T-cell proliferation and IL-2 secretion, a result that may be counteracted by anti-PD-1 antibodies, highlighting IL-10 and PD-1 as crucial mediators of immune evasion in MRSA infections [32]. Advances in transcriptomic technologies have substantially improved our understanding of the cellular and molecular pathways underlying these adaptive immune responses during MRSA infection [29].

3.3. Immune evasive characteristics of MRSA

The host immune response to *S. aureus* displays considerable heterogeneity, shaped by numerous determinants that govern infection susceptibility and clinical progression. The pathogen also encourages the growth of regulatory T cells and the release of IL-10 from B and T lymphocytes, creating an environment that weakens the effectiveness of vaccines even more [34]. IL-10 attenuates proinflammatory cytokines and chemokines, dampens Th responses, and downregulates MHC-II and costimulatory molecules on antigen-presenting cells, thereby potentially aggravating the severity of infection [35]. A comparative study of antibiotic-persistent MRSA bacteremia (APMB) and antibiotic-resolving MRSA bacteremia (ARMB) demonstrated significantly increased circulation levels of IL-10 and CCL4 in APMB, along with rising trends in TGF-α, IL-12p40, and IL-13. APMB is linked to

metastatic problems, longer courses of antimicrobial treatment, and higher levels of IL-10. It is also linked to lower levels of CCL22 [36,37]. Collectively, these observations suggest that *S. aureus* may strategically perturb inflammatory homeostasis and enforce immunosuppression to favor its persistence in the host.

S. aureus infection elicits robust secretion of diverse proinflammatory cytokines and chemokines from peripheral blood monocytes and tissue-resident MQs [38]. In the early phase of skin and soft tissue infections (SSTI), neutrophils predominate, followed by antigen-presenting MQs, DCs, non-natural killer (NK) innate lymphoid cells, $CD4^+$, $CD8^+$, and γδ T lymphocytes at later time points. The initial stages feature elevated proinflammatory mediators, including, e.g., IL-6, CXCL1, and CCL2, with subsequent surges in IL-17A, IL-17F, and CCL4 as the infection progresses [39,40]. Activation of the signal transducer and activator of transcription 3 (STAT3), mitogen-activated protein kinase (MAPK), and NF-κB cascades further amplifies proinflammatory cytokine output, notably IL-6 and TNF-α, in keratinocytes [41].

In elderly individuals, age-associated deficits in intracellular signaling and chromatin remodeling impair neutrophil extracellular trap (NET) deployment, diminishing the clearance of biofilm-embedded MRSA. Additionally, TLR2 senses MRSA-derived ligands, such as LTA and PG; however, aberrant TLR2-NF-κB signaling in aged hosts exacerbates immune compromise against MRSA [42,43]. Site-specific transcriptomic profiles highlight the diversity of host responses to MRSA (Table 1).

Table 1. Comparative transcriptomic profiling across MRSA infection niches reveals distinct immune signatures.

Infection type	Key genes	Expression change	Immune impact	References
Skin/soft tissue (SSTI)	*IL6, CXCL8*	↑ (log_2FC 4.8 and 5.4)	Neutrophil chemotaxis, early inflammation	[39]
Bacteremia	*IFN-ɣ, GZMB*	↑ (log_2FC 3.1 and 2.7)	$CD8^+$ T-cell cytotoxicity, macrophage activation	[29]
Biofilm-associated	*TLR2, ARG1, IL10*	↓ (TLR2: log_2FC 1.9); ↑ (ARG1: log_2FC 4.2; IL10: log_2FC 2.6)	M2 macrophage polarization, immune suppression, persistence	[44]

4. Efficacy of next-generation vaccine strategies

4.1. Multiepitope vaccines

A multiepitope vaccine, developed using computational methods, is distinguished by its non-allergenic and non-toxic attributes. Epitope-based vaccines can be constructed using DNA, mRNA, or protein platforms, each conferring distinct advantages, including minimized adverse effects, enhanced efficacy, and customized immunity, especially for vulnerable populations, such as the elderly and immunocompromised, compared to traditional vaccines [45,46]. Multiepitope vaccine development frequently employs immunoinformatics and in silico methodologies to select conserved immunogenic epitopes capable of eliciting both B-lymphocyte and T-lymphocyte responses. One approach targets critical virulence determinants, such as *SpA,* which is essential for MRSA-mediated host-immune subversion. Researchers have used bioinformatics to find possible T-cell and B-cell epitopes in SpA and made a multiepitope vaccine using linkers and an adjuvant [31]. Vaccinations, including a variety of B-cell and T-cell epitopes, have shown encouraging outcomes in addressing the limitations of traditional single-epitope vaccinations against multiple diseases [47]. One work found that the vaccine candidate triggered a strong immunological response, as seen by higher levels of immunoglobulin M (IgM)

and immunoglobulin G (IgG). The vaccination design could protect 83.15% of the world's people. Immune simulation investigations have shown increased antibody concentrations, with raised levels of IL-2, IFN-γ, and TGF-β, as well as the proliferation of B lymphocytes and T lymphocytes, resulting in primary, secondary, and tertiary immune responses [45]. The vaccine candidate displayed a strong binding affinity for TLR-2, which is essential for downstream signal transduction via receptor dimerization. A computationally designed multiepitope subunit vaccine holds promise for attenuating MRSA virulence by robustly activating both mucosal and systemic immune responses [48].

4.2. mRNA vaccines

mRNA vaccines constitute a transformative modality relative to conventional vaccines owing to their expedited manufacturing timelines and adaptable architecture for diverse antigenic targets. They elicit vigorous cellular immune responses without the need for adjuvants, which is a salient distinction from subunit protein vaccines [49]. Synthetic mRNA confers multiple benefits, including safety, minimal inherent immunogenicity, streamlined production, and the capacity to encode exotoxins. This platform is non-integrative and non-replicative. Besides humoral immunity, mRNA vaccination stimulates antigen-specific T- and B-cell responses, which are often seen in many vaccine platforms. The main goals of mRNA vaccine engineering are safety, tolerability, and immunogenicity [47]. A recent investigation assessed a polyvalent mRNA vaccine directed against *S. aureus*, designed to engage five critical virulence determinants: manganese transporter C (*MntC*), staphylococcal enterotoxin B (*SEB*), fibronectin-binding protein A (*FnBPA*), and iron-regulated surface determinant B (*IsdB*). This construct was associated with augmented secretion of IFN-γ, IL-2, IL-4, and IL-17A, indicative of a robust combined Th1/Th2/Th17 immune profile [50].

4.3. mRNA vaccine outcomes

mRNA vaccines targeting MRSA antigens, including *ClfA* (clumping factor A), *Hla* (α-hemolysin), and SEB, show significant promise in the fight against resistant infections. A 2024 investigation showed that codon-optimized mRNA was encapsulated in lipid nanoparticles (LNPs) containing ionizable lipids, which improved DC absorption [51]. Endogenous antigen processing sends mRNA-encoded proteins to MHC-I pathways for $CD8^+$, providing protective effectiveness [52]. BALB/c mice, known for their consistent immunological profiles, were administered nucleoside-modified mRNA expressing MRSA virulence factors *ClfA* and *Hla* to enhance delivery. The treatment produced strong humoral immunity, with IgG levels above 10^4, and stronger cellular immunity, as seen by higher levels of IFN-γ from $CD4^+$ and $CD8^+$ cells. This is important for Th1-driven macrophage activation and killing germs. In mouse sepsis models exposed to 10^7 colony-forming units (CFU) MRSA, immunization decreased bacterial loads in the kidneys and lungs by 90% and elevated survival rates to 75%, compared to 15% in unvaccinated controls. Nucleoside changes enhance mRNA stability and reduce innate immunological hyperactivation, resulting in effective and safe protection against MRSA [47,53,54].

In human DCs, mRNA encoding *SpA*/*MecA* elicited double the IL-2/TNF-α production from $CD8^+$ than from $CD4^+$, underscoring the pivotal role of $CD8^+$ effectors in intracellular *S. aureus* containment [55]. The polyprotein mRNA vaccine integrating *ClfA*, *Hla*, and leukocidin AB (*LukAB*) enhances immunogenicity by the concurrent expression of multiple virulence factors. This construct achieves approximately 80% opsonophagocytic killing, reflecting enhanced bacterial opsonization and

phagocytic destruction, and induces a Th1-biased IgG2a antibody profile, which is essential for efficient MRSA clearance and host protection [56].

Even though a lot of progress has been made, there are still several problems that need to be solved before mRNA vaccines that target MRSA can be made. mRNA instability in acidic environments and immune evasion facilitated by bacterial effectors may limit efficacy [57]. Furthermore, previous exposure to *S. aureus* may result in non-protective immunological memory, limiting its therapeutic use [58]. Emerging modalities, including self-amplifying mRNA (saRNA) platforms and TLR7/8 agonist adjuvants, have demonstrated 15%–25% improved protection in multidrug-resistant models, reinforcing the viability and adaptability of mRNA vaccines against MRSA [59]. A summary of the targeted immune components, MRSA immune evasion mechanisms, and their impact on host immunity and disease progression is presented in Table 2.

Table 2. Immune evasion mechanisms employed by MRSA and their consequences on host immunity and disease progression.

MRSA evasion factor	Targeted immune component	Molecular mediator(s)	Effect on immunity	Clinical relevance	Implication for vaccine design	References
Protein A (*SpA*)	B lymphocytes, T lymphocytes (Tregs)	Fc region of IgG; HLA interaction	Suppressed B-cell responses; expansion of Tregs; reduced antibody production	Persistent infection; reduced vaccine efficacy	Inclusion of *SpA* epitopes in multiepitope or mRNA vaccines	[26,30,31]
Superantigens (SAgs)	$CD4^+$ T cells, APCs	MHC-II/TCR Vβ interaction; IL-10	T-cell anergy; excessive cytokine secretion; immune dysregulation	Severe bacteremia; sepsis	Toxoid-based or multivalent vaccine strategies	[16]
Biofilm formation	Neutrophils, macrophages (MQs), APCs	IL-10; ARG1; reduced TLR2 signaling	Impaired phagocytosis; immunosuppressive environment	SSTI; persistent MRSA bacteremia	Induction of Th1/Th17-biased immune responses	[36,37]
Lipoprotein loss	Innate immune receptors (PRRs)	Impaired TLR2 signaling	Reduced innate immune activation; delayed clearance	Pneumonia; inefficient immune clearance	Use of strong adjuvants or TLR-independent vaccine platforms	[26]
clpP mutants	T lymphocytes	PD-1; reduced IL-2 and CD25	T-cell exhaustion; impaired proliferation	Persistent MRSA infection	Combination of vaccination with immune checkpoint modulation	[32]
IL-10 induction	B cells, T cells, macrophages	IL-10; lactic acid-mediated signaling	Immune suppression; reduced antibody synthesis; lymphocyte exhaustion	Antibiotic-persistent MRSA bacteremia (APMB)	Vaccine designs minimizing IL-10 skewing	[29,33,36]
Regulatory immune skewing	APCs; T cells	↓ MHC-II; ↓ costimulatory molecules	Dampened Th responses; weakened adaptive immunity	Poor clinical outcome; vaccine failure	Biomarker-guided vaccine design targeting immune balance	[35]

4.4. Protection and safety

Vaccines derived from DNA, mRNA, or proteins showcase improved safety and allow for simplified manufacture. Through identification by corresponding antibody paratopes, epitopes confer antigen specificity and induce targeted humoral and/or cellular immune responses. The immune system may be stimulated more strongly by carefully choosing dominant epitope ensembles compared to the native antigen [46]. Bacterial colonies were undetectable in the brain, lung, or spleen tissues of mice immunized with mRNA vaccines. No difference in the number of bacteria was observed in the groups administered different mRNA doses [47].

4.5. Nanoparticle vaccines

Mitigation modalities may encompass synthetic or biomimetic nanomaterials and vesicles for applications, including vaccines, rapid diagnostic assays, antibiotic delivery vehicles, and nanotherapeutics [49]. The multiepitope mRNA vaccine engineered against MRSA employs an innovative lipid nanoparticle delivery platform. This platform is indispensable for safeguarding labile mRNA and promoting its internalization by host cells to express the intended antigens [47]. Alternative strategies include carrier systems, such as conjugating the identified poly-N-acetylglucosamine (PNAG) epitope to a mutant bacteriophage Qβ, which functions as a vaccine scaffold. This approach conferred near-complete protection against lethal MRSA challenges in murine models [60]. Immunization elicited elevated titers of opsonizing antibodies and diverse IgG subclasses, correlating with reduced mortality and MRSA eradication from infected kidneys [56].

4.6. Adjuvanted and live oral vaccines

Subunit vaccines, which comprise purified pathogen-derived constituents, frequently require adjuvants to augment their immunogenicity. Recent initiatives have prioritized secreted toxins, which are the primary mediators of *S. aureus* pathogenesis. A promising candidate is a quadrivalent toxoid-based *S. aureus* vaccine targeting secreted bi-component pore-forming toxins (BCPFTs) and staphylococcal superantigens (SsAgs). In non-human primates, this formulation was safe and highly immunogenic, eliciting robust toxin-specific and neutralizing antibody titers, along with cross-neutralizing efficacy against non-vaccine toxins. This dual humoral and cellular immune induction positions it as a prospective next-generation staphylococcal vaccine platform [61,62]. Adjuvants, including aluminum-based (alum) formulations, are indispensable for potentiating the inherently weak immunogenicity of *S. aureus* antigens. Although the mechanism of alum is multifaceted, it is recognized for local antigen depot formation and NLRP3 inflammasome activation. Evidence suggests that alum skews T-cell differentiation toward Th2/Tfh subsets, which predominantly support antibody production. Nevertheless, cellular immunity mediated by Th1/Th17 responses is deemed essential for *S. aureus* containment. Collectively, the incorporation and judicious selection of adjuvants markedly elevate antibody titers, amplify T-cell responses, and enhance bacterial clearance and survival in preclinical vaccine evaluations [53]. A live vaccination method utilizes genetically modified probiotic bacteria, such as *Limosilactobacillus reuteri*, to orally deliver *S. aureus* antigens (such as *IsdB*). This technique triggers mucosal immune responses and shows significant protective effects against pneumonia, skin infections, and sepsis caused by *S. aureus* in models, highlighting its potential as a preventive measure [63].

4.7. Protection and bacterial clearance

Nanovaccines have been shown to generate cellular and humoral immune responses with excellent safety profiles, according to investigations [64,65]. An essential component of every effective vaccination, cellular and humoral immunity, may be enhanced by nanovaccines. The bacterial load *in vivo* is significantly reduced by nanovaccines because they enhance these responses. The ability of these vaccines to provide improved infection prevention is shown by the enhancement of survival rates in mice and the support for immediate immune effector activities. These developments could mean better clinical outcomes for bacterial infections in humans by way of more effective vaccinations [64].

5. Conclusions

In conclusion, advances in transcriptomic profiling, immune-cell characterization, and next-generation immunotherapeutic platforms are reshaping the future of MRSA prevention and treatment. A deeper understanding of host–pathogen interactions and immune-cell dynamics may facilitate the development of more precise and personalized therapeutic interventions capable of overcoming antimicrobial resistance and immune-evasion mechanisms.

Future investigations should focus on the clinical translation of these emerging strategies through well-designed preclinical and clinical studies. Progress in this field will require strong interdisciplinary collaboration among clinical immunologists, clinical microbiologists, infectious disease specialists, clinical pathologists, immunobiologists, translational immunologists, biomedical engineers, regenerative medicine specialists, personalized medicine experts, cellular and molecular medicine researchers, translational medicine specialists, experimental medicine scientists, medical biotechnologists, vaccine researchers, medical laboratory scientists, biomarker specialists, and healthcare system coordinators to accelerate the development and implementation of innovative immune-based therapies against MRSA infections.

Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

Conflict of interest

The authors have no conflicts of interest to declare.

Author contributions

Conceptualization: Mohammad Karimbakhsh, Rouzbeh Sojoudi Masuleh, Fatemeh Roozbahani; Data curation: All authors; Formal analysis: Mohammad Karimbakhsh, Rouzbeh Sojoudi Masuleh, Maedeh Yousefi; Investigation: All authors; Methodology: Mohammad Karimbakhsh, Rouzbeh Sojoudi Masuleh, Fatemeh Roozbahani; Project administration: Mohammad Karimbakhsh, Fatemeh Roozbahani; Resources: Mohammad Karimbakhsh, Rouzbeh Sojoudi Masuleh, Zahra sharifi; Validation: Mohammad Karimbakhsh, Rouzbeh Sojoudi Masuleh; Visualization: Mohammad Karimbakhsh, Fatemeh Roozbahani; Writing–original draft: All authors; Writing–reviewing & editing: All authors.

Ethics approval of research

Ethical approval was not required for this study because it is a review article based exclusively on previously published literature and did not involve human participants, animals, patient data, or clinical specimens.

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