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### METHICILLIN-RESISTANT STAPHYLOCOCCUS AUREUS (MRSA) IN COMMUNITY AND HEALTHCARE SETTINGS: A SYSTEMATIC REVIEW OF EVOLVING RESISTANCE MECHANISMS

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#### ABSTRACT

Methicillin-resistant *Staphylococcus aureus* (MRSA) is an efficient community and healthcare-associated pathogen due to its ability to transmit, colonize, be virulent, and have a high degree of genomic plasticity. This systematic narrative review compiles the latest evidence on the changing MRSA resistance mechanisms, focusing on the development of a larger adaptive phenotype of classical *mecA*-mediated beta-lactam resistance, appearance of *mecC*, GIP, transferable vancomycin resistance, daptomycin non-susceptibility, linezolid resistance, biofilm-associated tolerance, multidrug resistance through efflux, and clonal genomic adaptation. The review was conducted following PRISMA 2020 guidelines for reporting a review transparently and included landmark studies, recent reviews, public health surveillance data and authoritative guidance. The evidence suggests that rather than having one single mechanism, MRSA evolution is stimulated by multiple pressures or pressures acting together such as the effect of antibiotic exposure, the presence of biofilm associated with the use of medical devices, host immune selection, the presence of livestock and environmental reservoirs, and the spread of high-risk clones between community and healthcare settings. Community-associated lineages have established themselves in healthcare networks, while multidrug-resistance determinants have been introduced into healthcare-associated lineages, making empiric treatment more challenging. While vancomycin, daptomycin, linezolid, ceftaroline, and combination therapies continue to be clinically relevant, the importance of rapid diagnostics, source control, infection prevention, stewardship, and genomic surveillance are emerging as keys to therapeutic success. The review will conclude that high impact research on MRSA must go beyond just cataloguing resistance genes to integrated One Health surveillance, mechanism-driven diagnostics, prediction of resistance from whole genome sequencing and approaches to target tolerance, colonization and transmission as well as conventional susceptibility.

**Keywords:** *Staphylococcus aureus* methicillin-resistant; resistance; MRSA

#### Introduction

*Staphylococcus aureus* is an extremely adaptable commensal and opportunistic pathogen that can infect the skin and soft tissue and lead to pneumonia, osteomyelitis, endocarditis, bacteremia, sepsis, and infection of medical devices. Soon after the introduction of methicillin for clinical use, methicillin-resistant *Staphylococcus aureus* (MRSA) appeared and proved to be one of the most important examples of bacterial adaptation to antimicrobial pressure. In the center of the biochemical logic of methicillin resistance is the acquisition of an altered

penicillin-binding protein (PBP2a) that allows the maintenance of peptidoglycan cross-linking while the native penicillin binding proteins are inhibited by beta-lactam antibiotics, as described by Chambers (1997). This mechanism is still the basis of MRSA, but contemporary MRSA biology is far more complex than just resistance to methicillin.

MRSA's public health impact is compounded by the worldwide problem of antimicrobial resistance. In 2019,

*Staphylococcus aureus* was one of the most important bacterial causes of deaths caused by antimicrobial resistance, according to the Antimicrobial Resistance Collaborators (2022). The World Health Organization (WHO) (2024) has kept *Staphylococcus aureus* (*S. aureus*) in the current list of priority pathogens for bacteria, highlighting the ongoing demand for diagnostics, therapeutics, vaccines and prevention strategies. Besides failing therapy with beta-lactams, MRSA is important in clinical practice due to the fact that invasive disease is common, colonization can last for months, bacteria can form a biofilm on devices and multidrug resistance limits therapy options.

MRSA historically has been classified as hospital-associated MRSA (HA-MRSA) and community-associated MRSA (CA-MRSA). Classically HA-MRSA strains were associated with hospitalizations, surgeries, indwelling devices, dialysis, long-term care, and prior antibiotic use, while CA-MRSA strains were associated

with skin infection in healthy people. This border has become porous. David and Daum (2010) reported that community-associated MRSA had rapidly proliferated in the United States, and that USA300 had emerged as a predominate community-associated cause and an increasing healthcare-associated lineage (David et al., 2015). Later, genomic epidemiology studies conducted by Thiede et al. (2022) suggested that community reservoirs can contribute to the seeding of MRSA in HAIs, and that hospitals must account for community transmission to effectively control MRSA.

This review collates new and evolving mechanisms of MRSA resistance in both community and healthcare settings. In contrast to resistance as a collection of genes, the review sees MRSA as an adaptive system, with the interrelationships of mobile genetic elements, antibiotic exposure, host ecology, biofilm physiology, clonal success, and healthcare networks.

**Table 1. Systematic review framework and eligibility logic**

| Element             | Operational approach in this review                                                                                                                                                                                       |
|---------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Review question     | How have MRSA resistance mechanisms evolved across community and healthcare settings, and what implications follow for diagnostics, treatment, surveillance, and prevention?                                              |
| Population/pathogen | Methicillin-resistant <i>Staphylococcus aureus</i> affecting humans, with One Health attention to animal and environmental reservoirs when mechanistically relevant.                                                      |
| Concepts            | <i>mecA/mecC</i> , <i>SCCmec</i> , <i>PBP2a</i> , glycopeptide adaptation, <i>vanA</i> -mediated resistance, daptomycin non-susceptibility, linezolid resistance, biofilm, efflux, tolerance, clonal evolution, genomics. |
| Context             | Community, hospitals, long-term care, outpatient care, livestock-associated reservoirs, and transmission interfaces.                                                                                                      |
| Synthesis method    | Structured qualitative synthesis, mechanism tables, setting comparison, conceptual mechanism map, and research agenda.                                                                                                    |
| Limitations         | This draft is not a registered PROSPERO protocol and does not include formal database-export counts. Journal submission should add reproducible search strings, screening logs, and risk-of-bias decisions.               |

### Epidemiological transition: From hospital pathogen to community-healthcare continuum

The medical setting has been the source of the initial emergence of MRSA as a health-care-associated organism, since it is at the medical center where antimicrobial exposure is concentrated, invasive devices are used, host defenses are compromised, and opportunities for cross-transmission are available. Under this condition, strains with bigger *SCCmec* elements and multiple resistance

determinants were at a selective advantage. According to Lee et al., 2018, MRSA is a disease entity resulting from colonization, host susceptibility, virulence, antimicrobial exposure and infection-control context. This multi-dimensional perspective is needed because the same resistance determinant may pose various risks in a different

environment, such as an intensive-care unit, a household, a sports team, a prison, a dialysis unit or a livestock facility.

The CA-MRSA caused a paradigm shift in the epidemiology model. CA-MRSA lineages often included smaller SCCmec elements, were resistant to fewer non-beta-lactam antibiotics and had virulence factors associated with skin and soft tissue disease. In addition, Lakhundi and Zhang (2018) stated that MRSA evolution is not necessarily linear and occurs through the gain and loss and recombination of mobile genetic elements. Because it has been an example of efficient community transmission and the spread of the lineage into hospitals, it was deemed a paradigmatic example. USA300 was responsible for the majority of community-acquired MRSA infections in the United States, and was becoming more common in healthcare-associated disease, said David et al. (2015).

**Table 2. Community and healthcare MRSA as overlapping ecological states**

| Feature                          | Community-associated MRSA                                                                        | Healthcare-associated MRSA                                                                                               | Current interpretation                                                                                |
|----------------------------------|--------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------|
| <b>Typical setting</b>           | Households, schools, sports teams, prisons, military groups, outpatient skin infection clusters. | Hospitals, ICUs, surgery, dialysis, long-term care, device-associated infections.                                        | Increasing overlap; community clones enter hospitals and healthcare clones circulate after discharge. |
| <b>Common clinical syndromes</b> | Skin and soft-tissue infections, abscesses, necrotizing pneumonia in selected outbreaks.         | Bacteremia, pneumonia, surgical-site infection, catheter/device infection, osteomyelitis, endocarditis.                  | Clinical syndrome depends on host, site, inoculum, source control, and clone.                         |
| <b>Resistance profile</b>        | Historically fewer non-beta-lactam resistances, but local variation is substantial.              | Often multidrug resistant due to prolonged antibiotic selection.                                                         | Distinction is weakening as mobile genes and clones move between reservoirs.                          |
| <b>Key genetic features</b>      | Often smaller SCCmec types and successful clones such as USA300 in North America.                | Often larger SCCmec types, hospital-adapted lineages, and resistance accumulation.                                       | Genomic surveillance is preferred over setting labels alone.                                          |
| <b>Control priorities</b>        | Household hygiene, wound care, decolonization in selected clusters, outpatient stewardship.      | Screening in high-risk contexts, contact precautions, device bundles, environmental cleaning, antimicrobial stewardship. | Integrated community-healthcare surveillance and infection prevention.                                |

### Core and evolving resistance mechanisms

MRSA resistance must be considered as a multi-layered phenotype. The first line is beta-lactam resistance – mecA, mecC and PBP2a. The second layer consists of accessory regulatory and cell-wall factors that affect expression and fitness. The third layer consists of other forms of antimicrobial resistance, such as glycopeptides, lipopeptides, oxazolidinones, aminoglycosides, macrolides, tetracyclines, mupirocin, antiseptics, biofilm physiology, and tolerance. Basic microbial biology needs

Support for community source of origin of some HA-USA300 cases was also provided by Thiede et al. (2022) who noted that infection prevention needs to go beyond the walls of the hospital.

The livestock-associated MRSA (LA-MRSA) is added on. García-Álvarez et al. (2011) found a mecA homologue, now called mecC, in MRSA from human and bovine populations which were not detected by conventional mecA assays in animal reservoirs. MecC MRSA is less prevalent than mecA MRSA, but it led to a change in diagnostic thinking because it was found that phenotypic methicillin resistance can occur without the traditional mecA test. One Health surveillance is thus not an option, but a reality: the need to identify new resistance determinants before they are widely spread.

to be combined with clinical and epidemiological data in MRSA research, as resistance, virulence and transmission are interconnected, as stressed by Turner et al. (2019).

### The principal mechanism of MRSA on mecA

The principal mechanism of MRSA is acquisition of mecA, which codes the protein PBP2a, a transpeptidase with decreased affinity for beta-lactam antibiotics. If the beta-lactams block native PBPs, PBP2a can still cross-link the cell wall, so the cells can survive when exposed to the drug.

Lim and Strynadka (2002) determined the structure of PBP2a and demonstrated that its low affinity for beta-lactams is due to steric hindrance of the antibiotic binding site. Peacock and Paterson (2015) later reviewed the link between *mecA* expression, PBP2a function and cell-wall physiology in the development of clinically significant resistance.

The *mecA* gene is within a mobile genetic element called staphylococcal cassette chromosome *mec* (SCC*mec*), which is integrated into a chromosome. Katayama et al. (2000) found SCC*mec* to be a genetic element that carries the methicillin-resistance and the International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements (2009) classified SCC*mec*. SCC*mec* is not just a carrier of *mecA* but it also affects fitness, mobility and related resistance. Fitness costs may be associated with larger types, which often carry other resistance determinants, while smaller types are often linked to CA-MRSA.

Homologues are important for diagnostic and evolutionary reasons like in the case of *mecC*. Although the *mecA*/*mecC* test can detect *mecA*, *mecC*-positive MRSA have been found in human and bovine populations by García-Álvarez et al. 2011. CDC laboratory guidance states that PBP2a encoded by *mecA* is the most common mechanism of oxacillin/methicillin resistance, but also notes about rare non-*mecA* mechanisms and heteroresistance (Centers for Disease Control and Prevention, 2025). In the case of high impact diagnostics, it means that looking for phenotypic susceptibility should be combined with *mec* gene detection, PBP2a detection, and whole genome sequencing, not done at the exclusion of the other.

### **The reduced susceptibility to glycopeptides and *vanA* resistance**

Vancomycin has always had a major role in the treatment of invasive MRSA, but there are multiple routes to reduced glycopeptide susceptibility in MRSA. The clinical significance of vancomycin-intermediate *S. aureus* (VISA) has been described by Hiramatsu et al. (1997). The VISA phenotype is commonly associated with the presence of thickened cell walls, regulatory mutations in cell envelope stress response pathways, and altered autolysis and increased D-Ala-D-Ala targets that trap vancomycin. hVISA is a resistant subpopulation within an apparently susceptible isolate, and can be hard to detect and may also lead to treatment failure.

True high-level vancomycin-resistant *S. aureus* (VRSA) is less common but is mechanistically alarming; it can be the acquisition of *vanA* from enterococci. Horizontal transfer of a resistance module remodelling the peptidoglycan terminus and decreasing vancomycin binding has been reported by Chang et al. (2003) for *vanA* containing VRE *S. aureus*. VRSA is rare, but the fact that it exists

demonstrates that MRSA can develop significant resistance mechanisms to VRSA across genus.

### **The susceptibility of Daptomycin**

Daptomycin is a significant alternative to vancomycin in treating MRSA bacteremia and RSE, particularly when vancomycin is not effective. Rarely, resistance is due to a single transferable gene. Rather, it tends to be developed in the bacterial membrane and cell envelope via mutation. Bayer et al. (2013) reported “daptomycin resistance is a complex phenotype of cell-membrane charge, phospholipid metabolism, mutations in *mprF*, effects of the *dlt* pathway, and cell-wall changes”. Most recent in vivo observations by Boutet-Dubois et al., 2023, also confirm the model of a genomic and phenotypic adaptation that progresses by steps during bloodstream infection in the presence of daptomycin.

This mechanism has clinical relevance. Resistance to daptomycin may develop during chronic bacteremia in the absence of good source control or when there is significant bacterial burden. Membrane remodelling can also influence susceptibility to antimicrobials such as host defence peptides, and therefore, resistance to daptomycin may be linked to immune escape. Therefore, in high impact studies, daptomycin non-resistance should be studied in conjunction with host-pathogen interactions and infection source control, and not as an end-point in the laboratory.

### **The mechanism of Linezolid resistance**

Linezolid is clinically useful for some MRSA infections such as pneumonia and skin infection, while it targets the 50S ribosomal subunit. Beta-lactam resistance is becoming more common, but clinically significant as linezolid is frequently used for highly virulent Gram-positive infections. Gu et al. (2024) summarized the major mechanisms such as mutation in the 23S rRNA domain V, mutation in genes coding for ribosomal proteins *rplC*, *rplD* and *rplV*, acquisition of *cfr* methyltransferase genes, ribosomal protection genes (*optrA*, *poxtA*) and efflux contribution (*LmrS*). In the case of the *cfr* gene, it can be responsible for cross-resistance against different classes of drugs and may be carried by mobile elements.

The example of linezolid shows that resistance can develop via both mobile-gene and chromosomal routes. Mutations may occur in the 23S rRNA during therapy, and plasmid-associated *cfr*, *optrA* and *poxtA* can be disseminated between strains, species and ecological reservoirs. This dual risk is beneficial to antimicrobial stewardship and molecular surveillance in the food-chain environment, livestock production, and in hospitals.

### **Biofilm, efflux, persistence, and tolerance**

MRSA persistence in healthcare environments is key to the development of biofilm. MRSA can attach to and form an extracellular matrix on a variety of surfaces such as

catheters, prosthetic joints, cardiac devices, wounds, and endotracheal tubes, and can enter into the physiological state that decreases antimicrobial killing. Otto (2018) stressed that staphylococcal biofilms are not a random assembly of cells but an organized community where cells adhere, produce matrix, evade immune system, disperse,

and are metabolically diverse. Biofilm does not always lead to an increase in MIC during standard planktonic testing but it can drastically decrease treatment success by protecting bacteria from host immunity and inducing tolerance.

**Table 3. Mechanistic synthesis of evolving MRSA resistance**

| <b>Mechanism</b>              | <b>Main genetic/physiological basis</b>                                                                  | <b>Most relevant setting</b>                                      | <b>Clinical or surveillance implication</b>                                                            |
|-------------------------------|----------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------|
| Beta-lactam resistance        | mecA or mecC encoding PBP2a/PBP2c within SCCmec; regulatory effects from mecI/mecR1 and accessory genes. | All MRSA settings.                                                | Cefoxitin/oxacillin screening, mec/PBP2a detection, and WGS improve identification.                    |
| SCCmec diversification        | Different cassette types vary in mec complex, ccr recombinases, cargo genes, size, and mobility.         | Community-healthcare continuum.                                   | Setting labels are insufficient; molecular typing clarifies clone movement.                            |
| hVISA/VISA                    | Cell-wall thickening, altered autolysis, regulatory mutations, reduced vancomycin penetration.           | Persistent bacteremia, deep infection, prior vancomycin exposure. | Routine MIC may miss heteroresistance; persistent bacteremia requires reassessment and source control. |
| VRSA                          | vanA-mediated alteration of peptidoglycan terminus after horizontal transfer, usually from enterococci.  | Rare but high-consequence healthcare events.                      | Requires urgent infection control and molecular confirmation.                                          |
| Daptomycin non-susceptibility | mprF, dlt, graRS, walKR, membrane charge and phospholipid remodeling; cell-envelope adaptation.          | Persistent bloodstream infection and endocarditis.                | Monitor MIC during treatment failure; optimize dosing and source control.                              |
| Linezolid resistance          | 23S rRNA mutations, rplC/rplD/rplV mutations, cfr, optrA, poxtA, LmrS efflux.                            | Hospitals, long-term treatment, livestock/food reservoirs.        | Molecular surveillance for mobile genes is needed when linezolid use increases.                        |
| Biofilm/tolerance             | Adhesion, extracellular matrix, persister cells, metabolic heterogeneity, agr shifts.                    | Devices, wounds, implants, chronic infection.                     | Standard MIC can underestimate recalcitrance; device removal and anti-biofilm strategies are critical. |
| Efflux/biocide tolerance      | Multidrug efflux pumps and qac determinants affecting antiseptic susceptibility.                         | Healthcare surfaces, decolonization, environmental reservoirs.    | Stewardship should cover disinfectants and topical agents, not only systemic antibiotics.              |

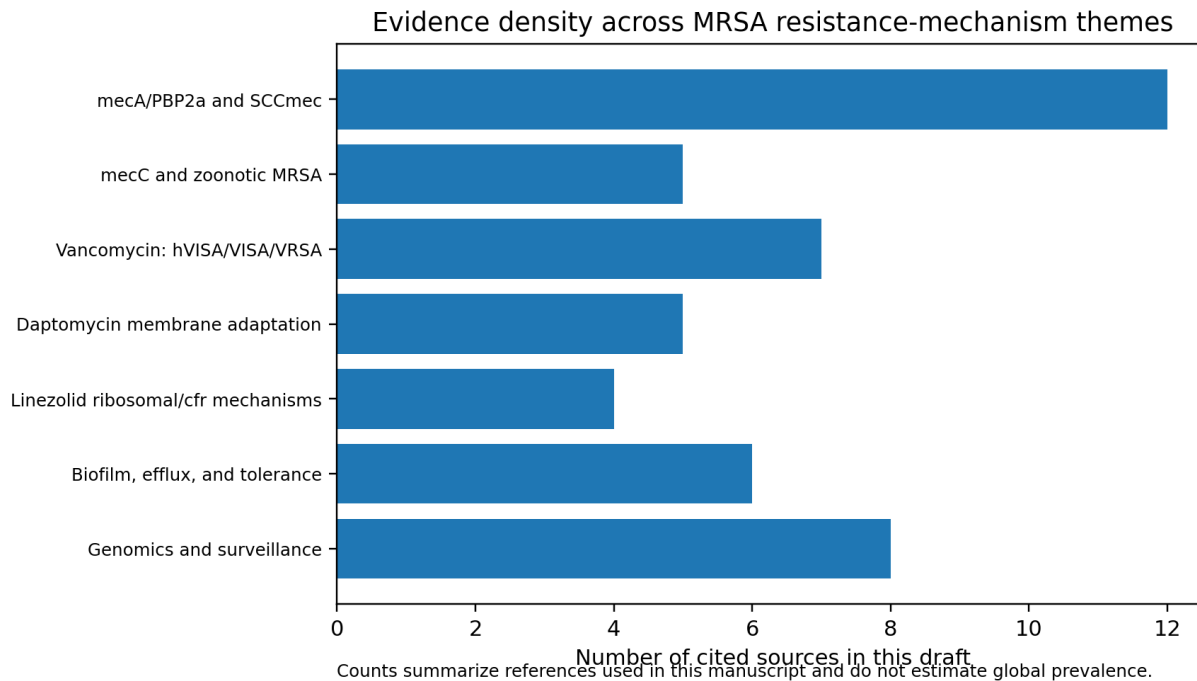


Figure 1. Evidence density across resistance-mechanism themes

### Diagnostic implications

Accurate MRSA detection is the foundation of both treatment and infection prevention. Phenotypic methods such as ceftioxin or oxacillin susceptibility testing remain practical and widely used, while molecular methods detect *mecA*, *mecC*, *SCCmec* markers, and clonal lineages. CDC guidance notes that *mecA*-encoded PBP2a is the usual explanation for oxacillin/methicillin resistance, and that heteroresistance can complicate *in vitro* expression (Centers for Disease Control and Prevention, 2025). A high-impact diagnostic framework should therefore combine phenotypic susceptibility testing with mechanism detection when results are discordant or when high-risk settings are involved.

Whole-genome sequencing (WGS) increasingly changes how MRSA is understood. WGS can identify resistance determinants, infer strain relatedness, detect outbreaks, reconstruct transmission, and reveal community introductions into hospitals. However, genotype-phenotype prediction is not perfect. Resistance can depend on expression, copy number, promoter mutations, cell-envelope regulation, or mixed populations. For this reason, WGS should augment rather than replace high-quality microbiology and clinical interpretation. The next generation of MRSA diagnostics should predict resistance, virulence, transmissibility, and treatment failure risk in a single clinically actionable report.

### Therapeutic implications of evolving resistance

Therapy for MRSA depends on infection site, severity, susceptibility, source control, host factors, and local epidemiology. Vancomycin remains widely used for serious MRSA infection, but persistent bacteremia, elevated MICs within the susceptible range, nephrotoxicity concerns, and hVISA/VISA phenotypes require careful reassessment. Daptomycin is important for bloodstream infection but is not suitable for pneumonia because pulmonary surfactant inactivates it. Linezolid has excellent oral bioavailability and lung penetration but requires attention to duration-related toxicity and resistance selection. Ceftaroline restores beta-lactam activity against MRSA by binding PBP2a and has become important in selected salvage or combination strategies, although resistance can occur through PBP2a alterations.

Mechanism-informed therapy requires more than selecting a drug from a susceptibility panel. In biofilm-associated infection, device removal or drainage may determine success. In persistent bacteremia, repeated blood cultures, echocardiography when indicated, evaluation for metastatic foci, and antimicrobial reassessment are essential. In recurrent community infection, household decolonization, wound hygiene, and management of close-contact reservoirs may be more important than repeated antibiotic courses. Antimicrobial stewardship must be integrated with infection prevention because antibiotic exposure drives resistance while transmission spreads successful clones.

**Table 4. Mechanism-informed clinical and infection-control responses**

| Clinical challenge                    | Resistance/tolerance mechanism to consider                                         | Management implication                                                                                    |
|---------------------------------------|------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------|
| Persistent MRSA bacteremia            | hVISA/VISA, daptomycin adaptation, high inoculum, biofilm, source-control failure. | Repeat cultures, search for endocarditis/metastatic foci, optimize source control, reassess therapy.      |
| Device or implant infection           | Biofilm-mediated tolerance and persister cells despite susceptible MIC.            | Removal or exchange often required; prolonged therapy alone may fail.                                     |
| Recurrent skin infection in household | Colonization, environmental contamination, community clone circulation.            | Wound care, hygiene, targeted decolonization, household assessment, avoid unnecessary antibiotics.        |
| Linezolid exposure or failure         | 23S rRNA mutation, cfr, optrA, poxtA, ribosomal protein mutations.                 | Confirm susceptibility, consider molecular testing where available, avoid prolonged unnecessary exposure. |
| Decolonization failure                | Mupirocin resistance, qac-mediated antiseptic tolerance, recolonization.           | Use decolonization selectively and monitor resistance in repeated programs.                               |
| Hospital outbreak                     | Clonal spread, community introduction, environmental persistence.                  | Combine WGS, screening, contact precautions, environmental cleaning, device bundles, and stewardship.     |

### Infection prevention, surveillance, and One Health control

MRSA control requires preventing both infection and transmission. In hospitals, central-line bundles, surgical-site infection prevention, hand hygiene, environmental cleaning, chlorhexidine bathing in selected high-risk units, contact precautions according to local policy, and antimicrobial stewardship remain core tools. AHRQ emphasizes that MRSA surveillance helps identify prevalence, transmission locations, and patient populations at risk (Agency for Healthcare Research and Quality, 2024). Surveillance is most useful when it informs action: targeted screening, outbreak investigation, decolonization policy, device-associated infection prevention, and stewardship feedback.

Community prevention requires different tools. Skin infection education, wound coverage, hygiene, avoidance of shared personal items, timely drainage of abscesses, and stewardship for outpatient antibiotics are central. Because

### Research gaps and future directions

**Table 5. Research agenda for a high-impact MRSA review**

| Priority gap | Why it matters | High-impact study design |
|--------------|----------------|--------------------------|
|--------------|----------------|--------------------------|

community strains may seed hospital cases, community surveillance can support hospital prevention. Thiede et al. (2022) illustrated this connection with USA300, showing why hospital-onset metrics alone cannot capture MRSA ecology.

One Health surveillance is increasingly important. *mecC* discovery in bovine and human populations by García-Álvarez et al. (2011) demonstrated that animal reservoirs can reveal resistance mechanisms relevant to humans. Livestock-associated MRSA, wastewater surveillance, food-chain monitoring, and occupational screening are therefore not peripheral topics; they are early-warning systems for mobile determinants and adaptive clones. WHO (2024) positioned antimicrobial-resistant pathogens within a global prioritization framework that links public health, research and development, and stewardship, reinforcing the need for integrated surveillance.

|                                |                                                                                     |                                                                                                             |
|--------------------------------|-------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------|
| Resistance versus tolerance    | Standard MIC testing misses biofilm and persister-mediated treatment failure.       | Prospective cohorts integrating MIC, time-kill, biofilm assays, WGS, transcriptomics, and outcomes.         |
| Genotype-phenotype prediction  | WGS is powerful but expression and regulation complicate prediction.                | Large multi-country datasets linking genome, MIC, treatment, source control, and outcome.                   |
| Community-healthcare interface | Hospitals may receive MRSA from households and community networks.                  | Paired community-hospital genomic surveillance with contact-network modeling.                               |
| One Health reservoirs          | Livestock, companion animals, food, and wastewater can carry emerging determinants. | Coordinated human-animal-environment sampling with harmonized typing and AMR testing.                       |
| Anti-biofilm therapy           | Device infections remain difficult despite in vitro susceptibility.                 | Randomized or pragmatic trials of device management, anti-biofilm adjuncts, and optimized duration.         |
| Decolonization resistance      | Mupirocin and antiseptic resistance can undermine prevention programs.              | Cluster studies monitoring colonization, qac/mupirocin resistance, recolonization, and infection outcomes.  |
| Equity in MRSA control         | AMR burden and access to diagnostics vary by region and health system.              | Implementation studies in low-resource hospitals linking IPC, stewardship, rapid diagnostics, and outcomes. |

Future MRSA research should shift from gene cataloging to systems-level explanation. First, resistance mechanisms should be evaluated in clinically meaningful contexts such as persistent bacteremia, pneumonia, prosthetic-joint infection, diabetic foot infection, and recurrent household transmission. Second, diagnostics should report actionable mechanisms rather than isolated gene lists. Third, stewardship should include systemic antibiotics, topical decolonization agents, and antiseptics. Fourth, surveillance should connect hospital data with community and One Health reservoirs. Finally, research should consider inequity: many regions with high antimicrobial-resistance burden have limited access to rapid diagnostics, infection-control infrastructure, and second-line therapy.

## Conclusion

MRSA remains a high-priority antimicrobial-resistant pathogen because it evolves through converging mechanisms: *mecA/mecC*-mediated beta-lactam resistance, *SCCmec* diversification, glycopeptide adaptation, transferable vancomycin resistance, daptomycin-associated membrane remodeling, linezolid resistance, efflux, biofilm tolerance, and clonal movement

across community, healthcare, animal, and environmental reservoirs. The practical lesson is that MRSA cannot be controlled by treating susceptibility as a static laboratory result. Effective response requires mechanism-aware diagnostics, genomic and One Health surveillance, infection prevention, antimicrobial stewardship, source control, and research that connects molecular adaptation with real clinical outcomes. High-impact work in this field will be defined by its ability to explain not only how MRSA resists antibiotics, but how resistance, transmission, virulence, and healthcare systems interact to produce preventable disease.

## Declarations

**Ethics approval and consent to participate:** Not applicable for this review article.

**Consent for publication:** Not applicable.

**Availability of data and material:** Not applicable.

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## References

- Agency for Healthcare Research and Quality. (2024). MRSA surveillance. <https://www.ahrq.gov/hai/tools/mrsa-prevention/toolkit/surveillance.html>
- Antimicrobial Resistance Collaborators. (2022). Global burden of bacterial antimicrobial resistance in 2019: A systematic analysis. *The Lancet*, 399(10325), 629-655. [https://doi.org/10.1016/S0140-6736\(21\)02724-0](https://doi.org/10.1016/S0140-6736(21)02724-0)
- Bayer, A. S., Schneider, T., & Sahl, H. G. (2013). Mechanisms of daptomycin resistance in *Staphylococcus aureus*: Role of the cell membrane and cell wall. *Annals of the New York Academy of Sciences*, 1277(1), 139-158. <https://doi.org/10.1111/j.1749-6632.2012.06819.x>
- Boutet-Dubois, A., Magnan, C., Lienard, A., Pouget, C., Bouchet, F., Marchandin, H., Larcher, R., Lavigne, J. P., & Pantel, A. (2023). In vivo-acquired resistance to daptomycin during methicillin-resistant *Staphylococcus aureus* bacteremia. *Antibiotics*, 12(12), 1647. <https://doi.org/10.3390/antibiotics12121647>
- Centers for Disease Control and Prevention. (2025). Laboratory testing for methicillin (oxacillin)-resistant *Staphylococcus aureus*. <https://www.cdc.gov/mrsa/php/laboratories/index.html>
- Chambers, H. F. (1997). Methicillin resistance in staphylococci: Molecular and biochemical basis and clinical implications. *Clinical Microbiology Reviews*, 10(4), 781-791. <https://doi.org/10.1128/CMR.10.4.781>
- Chang, S., Sievert, D. M., Hageman, J. C., Boulton, M. L., Tenover, F. C., Downes, F. P., Shah, S., Rudrik, J. T., Pupp, G. R., Brown, W. J., Cardo, D., & Fridkin, S. K. (2003). Infection with vancomycin-resistant *Staphylococcus aureus* containing the vanA resistance gene. *The New England Journal of Medicine*, 348(14), 1342-1347. <https://doi.org/10.1056/NEJMoa025025>
- David, M. Z., & Daum, R. S. (2010). Community-associated methicillin-resistant *Staphylococcus aureus*: Epidemiology and clinical consequences of an emerging epidemic. *Clinical Microbiology Reviews*, 23(3), 616-687. <https://doi.org/10.1128/CMR.00081-09>
- David, M. Z., Cadilla, A., Boyle-Vavra, S., & Daum, R. S. (2014). Replacement of HA-MRSA by CA-MRSA infections at an academic medical center in the midwestern United States, 2004-5 to 2008. *PLoS ONE*, 9(4), e92760. <https://doi.org/10.1371/journal.pone.0092760>
- David, M. Z., Glikman, D., Crawford, S. E., Peng, J., King, K. J., Hostetler, M. A., Boyle-Vavra, S., & Daum, R. S. (2008). What is community-associated methicillin-resistant *Staphylococcus aureus*? *The Journal of Infectious Diseases*, 197(9), 1235-1243. <https://doi.org/10.1086/533502>
- García-Álvarez, L., Holden, M. T. G., Lindsay, H., Webb, C. R., Brown, D. F. J., Curran, M. D., Walpole, E., Brooks, K., Pickard, D. J., Teale, C., Parkhill, J., Bentley, S. D., Edwards, G. F., Girvan, E. K., Kearns, A. M., Pichon, B., Hill, R. L. R., Larsen, A. R., Skov, R. L., ... Holmes, M. A. (2011). Methicillin-resistant *Staphylococcus aureus* with a novel mecA homologue in human and bovine populations in the UK and Denmark: A descriptive study. *The Lancet Infectious Diseases*, 11(8), 595-603. [https://doi.org/10.1016/S1473-3099\(11\)70126-8](https://doi.org/10.1016/S1473-3099(11)70126-8)
- Gu, B., Kelesidis, T., Tsiodras, S., Hindler, J., & Humphries, R. M. (2013). The emerging problem of linezolid-resistant *Staphylococcus*. *Journal of Antimicrobial Chemotherapy*, 68(1), 4-11. <https://doi.org/10.1093/jac/dks354>
- Gu, Y., Xu, X., Zhang, X., & Wang, H. (2024). Resistance to linezolid in *Staphylococcus aureus* by mutation, methylation, and acquisition of resistance genes. *The Journal of Antibiotics*, 77, 1-13. <https://doi.org/10.1038/s41429-024-00778-4>
- Hiramatsu, K., Hanaki, H., Ino, T., Yabuta, K., Oguri, T., & Tenover, F. C. (1997). Methicillin-resistant *Staphylococcus aureus* clinical strain with reduced vancomycin susceptibility. *The Journal of Antimicrobial Chemotherapy*, 40(1), 135-136. <https://doi.org/10.1093/jac/40.1.135>
- International Working Group on the Classification of Staphylococcal Cassette Chromosome Elements. (2009). Classification of staphylococcal cassette chromosome mec (SCCmec): Guidelines for reporting novel SCCmec elements. *Antimicrobial Agents and Chemotherapy*, 53(12), 4961-4967. <https://doi.org/10.1128/AAC.00579-09>
- Katayama, Y., Ito, T., & Hiramatsu, K. (2000). A new class of genetic element, staphylococcus cassette chromosome mec, encodes methicillin resistance in *Staphylococcus aureus*. *Antimicrobial Agents and Chemotherapy*, 44(6), 1549-1555. <https://doi.org/10.1128/AAC.44.6.1549-1555.2000>
- Lakhundi, S., & Zhang, K. (2018). Methicillin-resistant *Staphylococcus aureus*: Molecular characterization, evolution, and epidemiology. *Clinical Microbiology*

- Reviews, 31(4), e00020-18. <https://doi.org/10.1128/CMR.00020-18>
- Lee, A. S., de Lencastre, H., Garau, J., Kluytmans, J., Malhotra-Kumar, S., Peschel, A., & Harbarth, S. (2018). Methicillin-resistant *Staphylococcus aureus*. *Nature Reviews Disease Primers*, 4, 18033. <https://doi.org/10.1038/nrdp.2018.33>
- Lim, D., & Strynadka, N. C. J. (2002). Structural basis for the beta-lactam resistance of PBP2a from methicillin-resistant *Staphylococcus aureus*. *Nature Structural Biology*, 9(11), 870-876. <https://doi.org/10.1038/nsb858>
- McKinney, T. K., Sharma, V. K., Craig, W. A., & Archer, G. L. (2001). Transcription of the gene mediating methicillin resistance in *Staphylococcus aureus* (*mecA*) is corepressed but not coinduced by cognate *mecA* and beta-lactamase regulators. *Journal of Bacteriology*, 183(23), 6862-6868. <https://doi.org/10.1128/JB.183.23.6862-6868.2001>
- Otto, M. (2018). *Staphylococcal biofilms*. *Microbiology Spectrum*, 6(4), 10.1128/microbiolspec.GPP3-0023-2018. <https://doi.org/10.1128/microbiolspec.GPP3-0023-2018>
- Page, M. J., McKenzie, J. E., Bossuyt, P. M., Boutron, I., Hoffmann, T. C., Mulrow, C. D., Shamseer, L., Tetzlaff, J. M., Akl, E. A., Brennan, S. E., Chou, R., Glanville, J., Grimshaw, J. M., Hróbjartsson, A., Lalu, M. M., Li, T., Loder, E. W., Mayo-Wilson, E., McDonald, S., ... Moher, D. (2021). The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. *BMJ*, 372, n71. <https://doi.org/10.1136/bmj.n71>
- Peacock, S. J., & Paterson, G. K. (2015). Mechanisms of methicillin resistance in *Staphylococcus aureus*. *Annual Review of Biochemistry*, 84, 577-601. <https://doi.org/10.1146/annurev-biochem-060614-034516>
- Popovich, K. J., Snitkin, E. S., Green, S. J., Aroutcheva, A., Hayden, M. K., Hota, B., & Weinstein, R. A. (2016). Genomic epidemiology of USA300 methicillin-resistant *Staphylococcus aureus* in an urban community. *Clinical Infectious Diseases*, 62(1), 37-44. <https://doi.org/10.1093/cid/civ794>
- Rybak, M. J., Le, J., Lodise, T. P., Levine, D. P., Bradley, J. S., Liu, C., Mueller, B. A., Pai, M. P., Wong-Beringer, A., Rotschafer, J. C., Rodvold, K. A., Maples, H. D., & Lomaestro, B. M. (2020). Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline. *American Journal of Health-System Pharmacy*, 77(11), 835-864. <https://doi.org/10.1093/ajhp/zxaa036>
- Sati, H., Carrara, E., Savoldi, A., Hansen, P., Garlasco, J., Campagnaro, E., Boccia, S., Castillo-Polo, J. A., Magrini, E., Garcia-Vello, P., Wool, E., Gigante, V., Duffy, E., Cassini, A., Huttner, B., Ramon Pardo, P., Naghavi, M., Mirzayev, F., Zignol, M., ... Tacconelli, E. (2025). The WHO bacterial priority pathogens list 2024: A prioritisation study to guide research, development, and public health strategies against antimicrobial resistance. *The Lancet Infectious Diseases*. [https://doi.org/10.1016/S1473-3099\(25\)00118-5](https://doi.org/10.1016/S1473-3099(25)00118-5)
- Thiede, S. N., Snitkin, E., Trick, W., Payne, D., Aroutcheva, A., Weinstein, R. A., & Popovich, K. J. (2022). Genomic epidemiology suggests community origins of healthcare-associated USA300 methicillin-resistant *Staphylococcus aureus*. *The Journal of Infectious Diseases*, 226(1), 157-166. <https://doi.org/10.1093/infdis/jiac056>
- Tong, S. Y. C., Davis, J. S., Eichenberger, E., Holland, T. L., & Fowler, V. G., Jr. (2015). *Staphylococcus aureus* infections: Epidemiology, pathophysiology, clinical manifestations, and management. *Clinical Microbiology Reviews*, 28(3), 603-661. <https://doi.org/10.1128/CMR.00134-14>
- Turner, N. A., Sharma-Kuinkel, B. K., Maskarinec, S. A., Eichenberger, E. M., Shah, P. P., Carugati, M., Holland, T. L., & Fowler, V. G., Jr. (2019). Methicillin-resistant *Staphylococcus aureus*: An overview of basic and clinical research. *Nature Reviews Microbiology*, 17(4), 203-218. <https://doi.org/10.1038/s41579-018-0147-4>
- World Health Organization. (2024). WHO bacterial priority pathogens list, 2024: Bacterial pathogens of public health importance to guide research, development and strategies to prevent and control antimicrobial resistance. <https://www.who.int/publications/i/item/9789240093461>