

Review Article

## The Trends of *Staphylococcus aureus* Antibiotics Resistance in Iraq: A Narrative Review

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### Abstract

*Staphylococcus aureus* (*S. aureus*) is a major human pathogen that is able to develop resistance to multiple antibiotics with significant challenges in clinical treatment. The aims of this paper were to summarize the current understanding of *S. aureus* resistance to various antibiotic classes in Iraq, highlighting mechanisms of resistance, prevalence rates, and the need for further research. We conducted a narrative review using thematic approach to investigate the antibiotic sensitivity of *S. aureus* through searching two websites PubMed and Google Scholar. *S. aureus* resists  $\beta$ -lactam antibiotics through low-affinity PBP2a or  $\beta$ -lactamases. High resistance rates were observed in Iraq, with *BlaZ* gene sequences showing 100% similarity to those in other countries, suggesting a common origin or spread of genetic variants. Reports from Iraq revealed a high MRSA carriage rate among healthcare workers and the general community. Vancomycin resistance, mediated by *vanA* and *vanB* genes, has been reported globally. In Iraq, an 8% prevalence of VRSA was observed. Regarding MLS-B, tetracycline, and quinolone resistance, limited data from Iraq about the sensitivity pattern of these antibiotics is available. The available data are limited, highlighting significant gaps in understanding the full scope of resistance patterns. The high prevalence of antibiotic resistance in *S. aureus* in Iraq underscores the urgent need for comprehensive studies with international collaboration to develop effective public health strategies and improve antibiotic stewardship programs in Iraq.

**Keywords:** *Staphylococcus aureus*, Antibiotic resistance, Resistance mechanisms, *BlaZ* gene,  $\beta$ -lactam antibiotics.

### INTRODUCTION

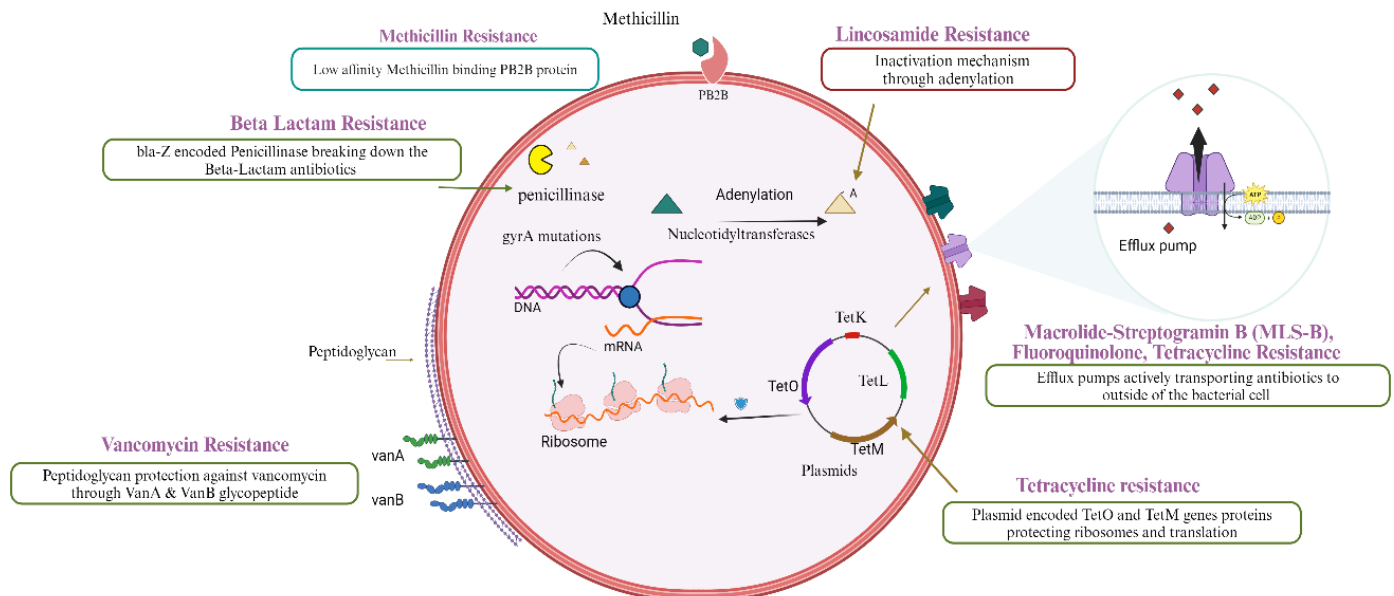
Infectious diseases are known as a significant concern for global public health and are widely recognized as a significant contributor to health problems<sup>1,2</sup>. Antibiotic resistance (AR) occurs when pathogens gain the ability to neutralize or evade the effects of antibiotics<sup>3</sup>. Recent studies on antimicrobial profiles have shown that bacteria responsible for both hospital-acquired and community-acquired infections are becoming resistant to multiple, or all groups of antibiotics which poses a serious clinical threat to public health<sup>4</sup>. The national pharmaceutical sales data revealed that antibiotic consumption increased in the most in the Low- and Middle-Income Countries including Iraq<sup>5</sup>. In addition to overuse of antibiotics, there are many other factors which contributes to AR issue including poor community

hygiene, poor infection control in hospitals and clinics, accumulation of antibiotics in the environment and their use in the animal and food industries<sup>6-8</sup>. Researchers believe that by 2050, the death toll of antibiotics resistance may soar to 10 million death annually<sup>9</sup>. Recent global burden research showed that a total of 7.7 million deaths were attributed to 33 different pathogens in 2019, of these 33 pathogens 5 key pathogens namely *S. aureus*, *Escherichia coli*, *Streptococcus pneumoniae*, *Klebsiella pneumoniae*, and *Pseudomonas aeruginosa* were responsible for 54.9% of these deaths<sup>1</sup>. Regarding *S. aureus*, the main mechanisms of antibiotic resistance are modifying the target site of the antibiotic, enzymatic inactivation of antibiotics, reduction of the inner and outer membrane permeability, active

pump system to pump out the antibiotic, and lastly using an alternative metabolic pathway as shown in (Figure 1) <sup>7,8</sup>. In this report we aimed to review the

mechanisms and the trends of antibiotics resistance in *S. aureus* in Iraq.

## Main Mechanisms of Antibiotic Resistance in *S. aureus*



**Figure 1.** An illustration of the main mechanisms in antimicrobial resistance in *S. aureus* which includes mechanism of Vancomycin, Tetracycline, Macrolide-Streptogramin B (MLS-B), Fluoroquinolone, Beta-Lactam, Methicillin, and Lincosamide resistance.

### PAPER SEARCH and SELECTION

We aimed to conduct a comprehensive review about *Staphylococcus aureus* in Iraq focusing on antibiotic resistance, sensitivity patterns, and relevant genetic factors. Therefore, a systematic literature search was performed. To ensure a focus on relevant studies addressing antibiotic resistance mechanisms and gene-related factors specific to *S. aureus* isolates, such a search was made using specific keywords, namely "*Staphylococcus aureus*," "antibiotic resistance," "sensitivity," "Iraq," and "genes." The search was performed using two primary databases: Google Scholar and PubMed. Our search was limited to articles published in English and only studies focused on *S. aureus* were included; studies involving other *Staphylococcus* species were excluded.

After the search, we initially screened the titles and abstracts relevant. In addition to essential papers from around the world, articles discussing antibiotic resistance mechanisms, prevalence, and sensitivity patterns in *S. aureus* in Iraq were included. Irrelevant studies, review articles, and

papers addressing topics outside the scope of *S. aureus* resistance in Iraq were excluded.

### ANTIBIOTIC RESISTANCE

#### Beta Lactam Resistance

*S. aureus* commonly resists  $\beta$ -lactam antibiotics via  $\beta$ -lactamases or low-affinity PBP2a.  $\beta$ -lactamase cleaves antibiotics, rendering them inactive <sup>10</sup>. Beta-lactam antibiotics target enzymes in peptidoglycan synthesis and *S. aureus* resists such an antibiotics via beta-lactamases, altered PBP genes, and the emergence of PBP2A <sup>11</sup>. Genetically, penicillin resistance in *S. aureus* involves two mechanisms: *BlaZ*-encoded penicillinase and altered penicillin-binding protein PBP2a via *mecA*. The process of regulation of *BlaZ* gene includes *BlaI* and *BlaR1* genes. Exposure to  $\beta$ -lactams triggers *BlaR1* cleavage, promoting *BlaZ* transcription. Four forms of penicillinase (Ambler class A) exist: the gene encoding form B is located on the chromosome, while the genes encoding A, C, and D forms are found on plasmids <sup>12</sup>. The prevalence of *BlaZ* in Germany, the US, Australia,

and Switzerland was 14.2%, 9.5%, 24.2%, and 40.9%, respectively, which is higher than the prevalence in Japan, which has been reported as 2.7%, 3.5%, and 1% in different studies. It is still unknown why the prevalence is lower in Japan<sup>12</sup>. In Iraq, previous studies shown a high percentage of B-lactam resistance<sup>13,14</sup>. However, the genetic makeup data of such resistances are sparse in Iraq. In a study conducted in Iraq to investigate the similarity of the *BlaZ* sequence, the *BlaZ* sequence found in Iraq showed 100% similarity to sequences isolated in China, France, South Korea, the UK, and Brazil<sup>15</sup>. This similarity may indicate a common origin, evolutionary relationship or spread of particular genetic variants across these countries. In a study conducted in Baquba Teaching Hospital, in the Middle of Iraq, between August 2020 and February 2021, urine samples were collected from individuals of both genders using sterile universal containers and subsequently analyzed using conventional microbiological methods. The presence of the *BlaZ* gene was identified in all *S. aureus* isolates examined in this study<sup>16</sup>. In another study conducted in Diyala Governorate in Iraq, the *BlaZ* gene was found in all *S. aureus* samples isolated from skin lesions in sheep<sup>17</sup>. These data are alarming as summarized in (Table 1), and further studies are needed to investigate and monitor B-lactam resistance spread in *S. aureus* through bio-surveillance.

### Methicillin Resistance

Globally, one of the main causes of nosocomial infections is *S. aureus* strains that are resistant to methicillin<sup>18</sup>. Methicillin-resistant *S. aureus* (MRSA) strains, which are particularly refractory to antibiotic treatment, used to be restricted to hospital settings without colonizing healthy individuals<sup>19</sup>. The prevalence of MRSA increased steadily to become one of the most deleterious hospital acquired infection (HA-MRSA)<sup>20</sup>. In the late 1990s, community-acquired MRSA (CA-MRSA) strains emerged with death toll of 400,000 annually<sup>20,21</sup>. The *mecA* gene, encoding the low-affinity penicillin-binding protein PBP 2A, confers methicillin resistance. It is part of the mobile genetic element SCCmec, which can also carry

genes for resistance to non- $\beta$ -lactam antibiotics like Tn554, pUB110, and pT181<sup>18</sup>.

Furthermore, *mecC* MRSA is a newly identified strain of MRSA that may colonize and infect a variety of host species, including humans. It carries a divergent *mec* gene. Even though *mecC* MRSA are currently uncommon and have only been documented in Europe, their appearance raises a number of problems for future research and poses a possible diagnostic challenge in situations where *mecA* or PBP2a/2' detection is the primary method used to diagnose MRSA infections<sup>22</sup>. The first official prospective prevalence study of *mecC* MRSA in the UK establishes a baseline for ongoing surveillance. While data on *mecC* MRSA prevalence abroad are limited, studies in Germany found a constant incidence of 0.06%, with one *mecC* isolate out of 1604 tested in 2004–05 and another out of 1603 tested in 2010–11. In contrast, Denmark has experienced a notable increase, with incidence rates rising from 1.91% in 2010 to 2.78% in 2011. The absence of *mecC* MRSA in a Swiss samples suggests a lower prevalence there. Overall, *mecC* MRSA prevalence varies between nations, highlighting the need for continued monitoring, especially in light of recent trends in Denmark<sup>23</sup>. MRSA strains' evolutionary origins have been explained by two theories. Based on preliminary analyses of restriction fragment length polymorphisms obtained for MRSA isolates collected globally using *mecA* and Tn554 probes, the single clone hypothesis postulates that *mecA* entered the *S. aureus* population once and produced a single MRSA clone that has since spread globally<sup>18</sup>. The second theory suggests that MRSA strains evolved multiple times through the horizontal transfer of *mecA* into phylogenetically distinct methicillin-susceptible *S. aureus* (MSSA) precursor strains. This theory is based on the detection of *mecA* in various *S. aureus* multilocus enzyme electrophoresis types. The *mecA* has been identified in at least five distinct lineages using DNA microarray technology, suggesting that horizontal *mecA* transfer has been a key factor in the evolution of MRSA. Recent in vivo observations of *mecA* transfer from *S. epidermidis* to *S. aureus* raise the possibility that *mecA* transfers

to MSSA more frequently<sup>18,24</sup>. In a meta-analysis study investigating 119 studies from 29 countries, the prevalence of MRSA was 14.69% among *S. aureus* strains<sup>25</sup>. In a study conducted in Iraq comparing the MRSA carriage rates between healthcare workers and non-healthcare workers, it was found that 22.5% of healthcare workers were *S. aureus* carriers compared with 18.7% of non-healthcare workers. Among the carriers, 61.0% of *S. aureus* strains isolated from healthcare workers were MRSA compared to 21.6% from non-healthcare workers<sup>26</sup>. In another study conducted in the Duhok province, samples were collected from Azadi and Bedari teaching hospitals. It was found that penicillin resistance was present in the majority of isolates from outpatients and healthcare professionals, 88 (100%) and 58(85.29%), respectively<sup>27</sup>. In a study conducted in Kirkuk Province investigating the prevalence of MRSA carriage in the community, MRSA carriage rate was found to be 27%<sup>28</sup>. In a study conducted in Duhok city recruiting preoperative patients, 27% were MRSA carrier. No significant differences was found between MRSA carriage and the associated risk factors including, gender and medical comorbidities<sup>29</sup>. Meanwhile in Muthanna Province, Iraq, 300 students were recruited from both rural and urban areas, the prevalence of MRSA was found to be 24%. The carriage rate was higher in rural schools compared to urban schools<sup>30</sup>. In agreement with this, another study from Iraq found that the carriage rate is ten times higher in rural areas than in urban areas<sup>31</sup>. The high carriage rate in rural area might be due to different factors including agriculture, population density and mobility, educations and access to healthcare services. The study in Muthanna found a higher MRSA carriage rate in males than females [28], whereas in the Kurdistan Region, females had a higher carriage rate than males [29]. These differences may be due to variations in population culture, behavior, sampling methods, and environmental factors.

Studies about MRSA in clinical samples are often simple, lacking depth, and usually investigating the prevalence of MRSA without examining the risk factors. Comprehensive

multidisciplinary studies are needed to explore this area. Longitudinal studies are recommended to track the MRSA carriage and outcome of such a carriage. The results of these studies (Table 1), can be used for public health prevention of the infection.

### Vancomycin Resistance

Glycopeptide antibiotic class, including vancomycin, is considered the drug of choice to treat infections caused by Gram-positive microorganisms including MRSA<sup>32</sup>. Through their binding to the C-terminal d-Ala-d-Ala of the pentapeptide precursors of peptidoglycan, glycopeptides prevent the transglycosylation and transpeptidation processes, hence inhibiting the formation of cell walls in gram-positive bacteria<sup>33</sup>. Conversely, the residual vancomycin-resistant *S. aureus* (VRSA) bacteria demonstrated elevated resistance to both glycopeptides (teicoplanin MIC > 32 µg/ml; vancomycin MIC > 256 µg/ml), and so, they were dubbed high-level-resistant VRSA (HLR-VRSA)<sup>33</sup>. VRSA may carry vancomycin resistance genes like *vanA* and *vanB*, acquired from Enterococci<sup>34</sup>. The first report of an MRSA isolate with intermediate resistance to vancomycin (VISA) was made in Japan in 1997<sup>35</sup>. Additionally, the first case of VRSA was reported in The USA in a clinical isolate<sup>20</sup>. In a recent meta-analysis report investigating 31 eligible studies recruiting 14,966 study participants and 2,348 *S. aureus* isolates, it was found that the overall pooled prevalence of VRSA was 14.52%<sup>36</sup>. In a study conducted in Iran, a neighboring country of Iraq, extremely high frequencies of vancomycin resistance genes (*vanA*, *vanB*) was revealed in *S. aureus* strains isolated from patients<sup>37</sup>. In Iraq, in a study conducted between December 2020 and April 2021, 150 samples were collected from individuals with infections across various age groups and clinical sources in Baghdad's primary hospitals. Isolates were diagnosed through biochemical tests, microscopic inspections, and morphological traits using blood agar and mannitol salt agar. Antibiotic susceptibility testing revealed 8% VRSA isolates. Vancomycin resistance genes were detected through polymerase interactions, with the *vanA* gene present in all isolates and the *vanB* gene in

66.6% of them <sup>38</sup>. While in a study conducted in Muthanna Province recruiting students in Iraq, the prevalence of vancomycin resistance was 4% <sup>30</sup>, a study conducted in Kirkuk Province showed that all strains from the community were sensitive to vancomycin <sup>28</sup>. In another study conducted in Iraq recruiting samples taken from Syrian refugees, the prevalence of vancomycin resistance was 11.4% <sup>39</sup>. In a study conducted in the Kurdistan Region of

Northern Iraq, where most Syrian refugee camps are located, the prevalence of vancomycin resistance was found to be 7.56% <sup>14</sup>. This higher rate of vancomycin resistance among Syrian refugees may pose a threat to the indigenous population. Further research is needed, recruiting large samples to explore the resistance pattern to vancomycin in contrast to available data in Table 1.

**Table 1.** Antibiotic Resistance Mechanisms in *Staphylococcus aureus* in Iraq.

Resistance Type	Gene(s)	Mechanism	Available Data	Iraqi Cities/Regions	Percentage of Resistance
<b>β-Lactam Resistance</b>	<i>BlaZ</i> , <i>BlaI</i> , <i>BlaR1</i>	Production of β-lactamase enzymes that hydrolyze β-lactam antibiotics	Found in <i>S. aureus</i> isolates from human and animal samples	Baquba, Diyala, Duhok, Kirkuk, Muthanna	Varies, e.g., 100% <i>BlaZ</i> in Baquba study
<b>Methicillin Resistance (MRSA)</b>	<i>mecA</i> , <i>mecC</i>	Modified penicillin-binding protein (PBP2a) confers resistance to methicillin and other β-lactam antibiotics	Data on MRSA carriage rates in healthcare and community settings; higher rates in rural areas	Duhok, Muthanna, Kirkuk	24% MRSA in Muthanna; 27% in Kirkuk and Duhok
<b>Vancomycin Resistance (VRSA)</b>	<i>vanA</i> , <i>vanB</i>	Altered peptidoglycan precursors (D-Ala-D-Lac) prevent vancomycin binding, inhibiting cell wall synthesis	VRSA prevalence and <i>vanA/vanB</i> genes presence studied	Baghdad, Muthanna, Kurdistan Region (Northern Iraq)	8% in Baghdad, 4% in Muthanna, 7.56% in Kurdistan Region
<b>MLS-B Resistance</b>	<i>erm</i> , <i>msrA</i> , <i>lnu</i> , <i>vga</i> , <i>vat</i>	Target site modification by methylases ( <i>erm</i> ), efflux pump ( <i>msrA</i> ), and enzymatic inactivation ( <i>lnu</i> , <i>vga</i> , <i>vat</i> )	Data on erythromycin, clindamycin, and streptogramin resistance; constitutive and inducible resistance profiles	Basrah, Baghdad, Kurdistan Region	54.1% in Basrah, 7.5%-45% varying resistance types in Baghdad, 2%-3% clindamycin resistance in Kurdistan Region
<b>Tetracycline Resistance</b>	<i>tetK</i> , <i>tetL</i> , <i>tetM</i> , <i>tetO</i>	Efflux pumps ( <i>tetK</i> , <i>tetL</i> ) and ribosomal protection ( <i>tetM</i> , <i>tetO</i> ); less commonly, enzymatic inactivation ( <i>tetX</i> )	Tetracycline resistance prevalence in MRSA and MSSA isolates studied; <i>tetK</i> , <i>tetL</i> , <i>tetM</i> detected in Iraqi isolates	Baquba (Diyala Province)	100% <i>tetK</i> , 53.3% <i>tetM</i> , 33.3% <i>tetL</i> in Baquba study
<b>Quinolone Resistance</b>	<i>NorA</i> , <i>gyrA</i> s	<i>NorA</i> efflux pump removes quinolones; mutations in topoisomerase IV and DNA <i>gyrA</i> se reduce binding efficiency	Quinolone resistance in <i>S. aureus</i> isolates with specific drug resistance levels; <i>gyrA</i> mutations identified in small sample size studies	Baghdad, Muthanna	50% nalidixic acid, 20% levofloxacin, 16%-18% norfloxacin, ofloxacin

## Macrolide-Lincosamide-Streptogramin B (MLS-B)

### Resistance

Resistance to antimicrobial agents in *S. aureus* is increasingly problematic <sup>40</sup>. Erythromycin, azithromycin, and spiramycin are examples of macrolide antibiotics that are frequently used to treat staphylococcal infections. The *msrA* gene in *S. aureus* encodes an ATP-dependent pump that actively effluxes the macrolides and streptogramin B (but not lincosamides) <sup>41</sup>. The presence of erythromycin resistance methylase (*erm*) genes, which encodes methylases that modify the structure

of 23S rRNA and decrease the binding of MLS antibiotics to the target site in the 50S ribosomal subunit, mediates target site modification reducing the binding affinity of macrolides, lincosamides, and streptogramin B leading to cross-resistance among these antibiotics <sup>42</sup>. Drug inactivation is another mechanism that confer resistance to MLS-B. The *lnu* genes that encode lincosamide nucleotidyltransferases that inactivate lincosamides by adenylation and it is specifically affects lincosamides <sup>43</sup>. Proteolytic inactivation is another mechanism of resistance in *S. aureus* for

this group of antibiotics. The *vga* and *vat* genes encode proteins that can inactivate streptogramin A antibiotics through acetylation, thus providing resistance<sup>44</sup>.

In a study conducted between January 2013 and December 2014, a total of 1456 blood culture bottles were supplied to the Kakas University Health Research and Application Hospital's Microbiology Laboratory. This study looked at the prevalence and antibiotic resistance of *S. aureus* isolated from blood cultures. The erythromycin resistance for MRSA infections in this study was %84, whereas resistance in MSSA strains was %19<sup>41</sup>. MLS-B-resistant staphylococci show varying rates among countries and species with limited data in the last decade. Otsuka et al.'s study (2001-2006) found 97% MRSA and 34.6% MSSA resistant to MLS-B agents<sup>45</sup>. In two Turkish hospitals, Cetin et al. reported 38.5% resistance, while Uzun et al. found 79% erythromycin resistance in Ismir during 2011-2012<sup>42,46</sup>. Greek and Cyprus hospitals reported MLS-B resistance rates of 44% and 67.61% in *S. aureus*, respectively<sup>47,48</sup>. MLS-B constitutive or inducible phenotypes are most common, with Japan showing a higher incidence of the MLSB-inducible phenotype than Europe, Turkey, and the USA, possibly reflecting differences in drug usage, gene carriage, and strain clonality<sup>49</sup>. In a study conducted in Basrah Province, Southern Iraq, it was shown that 54.1% of *S. aureus* isolates were resistant to erythromycin and clindamycin with D-test negative results<sup>50</sup>. In another study conducted in Baghdad, Iraq, it was shown that 7.5% of the *S. aureus* isolates were resistance to erythromycin, clindamycin and streptogramins (cMLS) whereas 22.5% were resistance to erythromycin, clindamycin and streptogramins (iMLS). In the same study, 25% of the isolates showed resistance to erythromycin and sensitive to clindamycin (M phenotype) and 45% of the strains were resistant phenotype to streptogramin A and B (SAB)<sup>51</sup>. In studies conducted in Kurdistan Region of Iraq, while the resistance rate of *S. aureus* to clindamycin was 2% in Syrian refugees<sup>39</sup>, 3% of the *S. aureus* strains isolated from healthy indigenous individual were resistant to clindamycin<sup>14</sup>. The limited data about

MLS-B sensitive pattern in Iraq make the choices for empirical therapy challenging. Ineffective management, due to the lack in data, may lead to increase mortality and morbidity because of antibiotics resistance and leads to high healthcare costs. Additionally, lack of data impedes the ability to tailor antibiotic stewardship program as shown in (Table 1). It is recommended to conduct local research, enhance surveillance and impose antibiotics stewardship.

### Tetracycline Resistance

*S. aureus* can resist tetracycline through active efflux that is encoded by genes such as *tetK* and *tetL*. The efflux reduces the concentrations of antibiotics intracellularly and negates its effectiveness. *TetK* and *TetL* are efflux proteins that actively transport tetracycline out of the bacterial cell, reducing its intracellular concentration and thereby its effectiveness<sup>52</sup>. These proteins are encoded by genes that are located on plasmids or transposons, which can be transferred between bacteria<sup>53</sup>. Ribosomal protection proteins, such as *TetO* and *TetM*, are other methods that confer resistance to tetracyclines. Strains with *tetK* are resistant to tetracycline but susceptible to minocycline, while *tetM* confers resistance to all tetracyclines<sup>53</sup>. The majority of human infections contain ribosome protection proteins and efflux pumps, which are the most prevalent forms of tetracycline clinical resistance<sup>54</sup>. Enzymatic inactivation is another mechanism of resistance, although it is less common. Enzymatic inactivation involves the production of enzymes that chemically modify tetracycline, rendering it ineffective. Tet(X) is an example of such an enzyme which can hydroxylate tetracycline and thereby inactivating it<sup>55</sup>. Mutations in the ribosomal binding site of tetracycline can reduce the binding affinity of the antibiotic preventing tetracycline from binding effectively<sup>56</sup>.

Previous study showed that the global tetracycline-resistance prevalence was 8.7% for MRSA<sup>57</sup>. In another study, the tetracycline susceptibility of *S. aureus* isolates collected from 25 university hospitals across Europe was assessed. The distribution of four tetracycline resistance genes in 600 tetracycline-resistant *S. aureus*

isolates, including 400 MRSA and 200 MSSA isolates was investigated. Among the MRSA isolates, 76% carried the *tetM* gene, 73% carried *tetK*, and 50.5% had both genes. The *tetL* gene was present in 1.5% of MRSA isolates. In MSSA isolates, *tetM* was found in 10%, *tetK* in 96%, and both genes in 6% of cases. *TetL* was not detected in any MSSA isolates, and *tetO* was absent in all tested isolates<sup>52</sup>. In a study conducted in Iran, recruiting samples recovered from the burn patients, 63.6% of MRSA isolates were resistant to tetracycline. Among the resistant strains 32.4% carried *tetM*, 17.2% carried *tetK* and 13.9% possessed both *tetM* and *tetK*. Regarding the only molecular study conducted in Iraq, in Baquba city, between December 2019 and August 2020, 75 samples were collected from various sources (burns, wounds, blood, nasal carriage, and urine). Molecular analysis using PCR targeting the 16SrRNA gene identified fifteen isolates as *S. aureus*. Subsequent PCR assays targeting tetracycline resistance determinants revealed that all the isolates were positive for the *tetK* gene, 33.3% of isolates harbored *tetL* genes, and 53.3% had *tetM* genes<sup>58</sup>. Regarding molecular studies in Iraq, the data are alarmingly sparse, and the available information is concerning (Table 1). This highlights an urgent need for more sequencing-based studies in this area.

### Quinolone Resistance

*S. aureus* fluoroquinolone resistance mechanisms involve efflux pump expression, gene mutations and fluoroquinolone inhibitory activities. The *NorA* gene, found in quinolone-resistant *S. aureus*, confers higher resistance to hydrophilic quinolones such as norfloxacin. While it also affects more hydrophobic quinolones, the resistance conferred is generally lower compared to the hydrophilic medications. It functions as an efflux pump, actively removing quinolones from the bacterial cell, reducing their effectiveness<sup>59</sup>. In a study explored the role of the *NorA* efflux pump in fluoroquinolone resistance, among 344 clinical isolates, it was shown that 40.4% overexpressed *NorA* resulting in variable norfloxacin MICs (1.56 to >800 µg/ml)<sup>60</sup>. Additionally, mutations in topoisomerase IV and DNA *gyrAse* proteins were

observed, suggesting a role in quinolone resistance. Complicated mutations may explain the rapid development of resistance. Sitafloxacin exhibited potent activity against resistant mutants due to its strong inhibitory effect on both topoisomerase IV and DNA *gyrAse*<sup>61</sup>. The range of mutations discovered provides insight into the swift emergence of resistance. Significantly, Sitafloxacin displays strong effectiveness against ciprofloxacin- or levofloxacin-resistant strains, highlighting its ability to target both topoisomerase IV and DNA *gyrAse*<sup>62</sup>. Globally, fluoroquinolone resistance ranged from 20% and 100% of MSSA and MRSA, respectively<sup>63</sup>. While in Turkey the resistance to quinolone was 41% in UTI samples<sup>64</sup>, in Canada the resistance rate was 20% in UTI samples<sup>65</sup>. In a study conducted in Iraq, the resistance patterns of *S. aureus* isolates were determined, the isolates showed a varied levels of resistance to; Levofloxacin (20%), norfloxacin (16%), ofloxacin (18%), ciprofloxacin (16%), lomofloxacin (14%) and nalidixic acid (50%)<sup>66</sup>. In a small genetic study conducted in Iraq, among 12 quinolone-resistant *S. aureus*, 8 (66.7%) carried mutations in the *gyrA* gene<sup>67</sup>. Although the data about the resistance rate to quinolones is alarming, the data in Iraq are sparse (Table 1). Only a few studies with small sample sizes have been conducted. More studies with larger sample sizes are needed. Collaboration within the country or with the international community is required to make comprehensive studies about antibiotic sensitivity patterns.

### NATIONAL ACTION PLAN of ANTIBIOTIC RESISTANCE in IRAQ

Iraq had an ambitious plan to combat AR between 2018 and 2022<sup>68</sup>. The plan set up five objectives including improve awareness of antimicrobial resistance; increase knowledge about the issue; reduce the infection rates; optimize use of antibiotics and develop economic case for sustainable investment. Applying a comprehensive strategy to battle AR faces numerous challenges. Raising awareness is critical but needs unceasing effort and effective communication strategies. Vigorous surveillance and research systems are vital, yet they depend on constant funding and precise data collection. Improving sanitation and

infection prevention includes upgrading infrastructure and endorsing consistent hygiene practices.

Optimizing antimicrobial use and prevention of antimicrobial abuse demands stronger legislations, and clear prescribing guidelines. Maintainable investment is another hurdle, requiring long-term funding and showing the economic benefits of AR initiatives. In addition to those challenges, the entire plan unfortunately slowed down and stopped during the COVID-19 pandemic. It is necessary to create another plan as soon as possible to combat this escalating issue in Iraq.

## CONCLUSIONS

In Iraq, the high rates of antibiotic resistance in *S. aureus* stresses an urgent need for research to investigate and explore this area. Current data are limited, deterring effective management of infections, particularly by empiric therapy. In Iraq,  $\beta$ -lactam resistance is widespread, with 100% prevalence of the *BlaZ* gene in some cities. Besides, MRSA linked to the *mecA* gene, also shows considerable presence, especially in rural areas.

Our data underscores the need for vigilant monitoring for VRSA that poses significant treatment challenges. Furthermore, resistance to macrolides, lincosamides, and streptogramin B (MLS-B) is evident, particularly the role of *erm* and *msrA* genes in modifying antibiotic targets or facilitating drug efflux.

Tetracycline resistance is notably high, with tet genes (*tetK*, *tetM*, *tetL*) highly prevalent in Iraq. Finally, quinolone resistance presents concerning levels of resistance to nalidixic acid and levofloxacin. Such a resistance is associated with *NorA* efflux pumps and *gyrA* mutations. Large multidisciplinary studies are needed to investigate resistance prevalence, identify risk factors, and evaluate treatment efficacy. To addressing the antibiotic resistance crisis in Iraq, collaboration with international research communities would provide valuable insights.

## Conflict of Interest

The authors declare they have no conflicting interests.

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