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A review and meta-analysis of *Staphylococcus aureus* prevalence in foods

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ABSTRACT

We present the review and meta-analysis of the prevalence of *Staphylococcus aureus* isolates from various food sources. PubMed, Google Scholar, Scopus, and Science Direct were searched for articles from 2012 to 2022. *S. aureus* is a pathogenic bacterium present in natural skin flora, that can cause a variety of diseases with different degrees of severity. Although its natural habitat are humans and animals, *S. aureus* can be found in water, soil and contaminated surfaces. Consequently, multiple routes can be involved in food contamination by *S. aureus*. The bacterium was most prevalent in ready-to-eat food (35.1 %), meat (21.7 %) and dairy products (18.5 %). Among contaminated products, meat products represented 59.51 % and were distributed as such: 44 % for beef meat, 28 % for pork meat, 22 % for chicken meat, 6 % for turkey meat. Antibiotic resistance studies showed resistance to penicillins is the most common (61 %) while resistant to quinolones, amphenicols and rifamycins were found to be low (<10 %). Pooled prevalence of antimicrobial resistance in isolated strains revealed that 68 % of all isolates carried resistance to at least one antibiotic in clinical use. Future studies are needed to assess antimicrobial resistance, food-associated stress and biofilm formation of the foodborne pathogen *S. aureus*. Furthermore, improved diagnostic tools and implementation of surveillance programs could lead to reduction of the burden caused by *S. aureus*.

1. Introduction

Staphylococcus aureus is a Gram-positive bacterium, typically arranged in grape-form clusters that can colonize humans, animals, and the environment (Cheung, Bae, & Otto, 2021). It can be transmitted by contact with infected individual or contaminated surfaces, but also by contact with sick animals or contaminated food and water. In addition to infections, this pathogen can be responsible for intoxications which occurs after the consumption of foods containing toxins, like staphylococcal enterotoxins, which resist to thermal treatments used by the food industries to eliminate bacteria from food products.

S. aureus infections range from localized infections to more severe conditions like sepsis and pneumonia. Examples of easily manageable pathologies are folliculitis, blister bubble formation, and diarrhea, while more severe disorders include osteomyelitis, mastitis, endocarditis, and toxic shock syndrome, which, if left untreated or mismanaged, can lead to death (Ford, Hurford, & Cassat, 2021).

S. aureus is one of the most problematic pathogens and one of the six ESKAPE pathogens (*Enterococcus faecium, Staphylococcus aureus, Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* and *Enterobacter species)* that are increasingly associated with therapeutic failures. Antimicrobial resistance (AMR) is a mechanism by which microorganisms undergo adaptive changes to become partially, or totally resistant to antimicrobial agents that were previously efficient (Darby et al., 2023; Guo, Song, Sun, Wang, & Wang, 2020; Urban-Chmiel et al., 2022). The easy adaptation of *S. aureus* to various environments and its high genetic flexibility contribute to its ability to survive against anti-staphylococcal drugs.

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In 1940s and 1950s, the emergence of penicillin- and methicillin-resistant *S. aureus* (PRSA and MRSA) strains detected in hospitals was a consequence of the antibiotic introduction (EFSA). For many years, treatment against MRSA relied on glycopeptides, particularly vancomycin, contributing to the emergence of vancomycin-resistant strains (VRSA). Nowadays, despite introduction of new antibiotics with different modes of action, new resistance systems have emerged, causing a serious public health and safety issue (Foster, 2017; Hughes & Andersson, 2017). Among glycopeptide antibiotics teicoplanin and vancomycin are still used as efficient for MRSA infections. Ceftobiprole and ceftaroline are new cephalosporins that seem to overcome the limits of cefazolin and other cephalosporins as they have a wide spectrum of antimicrobial activity. In addition, we can mention telavancin, oritavancin (lipoglycopeptides), dalbavacin (which is similar to teicoplanin) and oxazolidinones (linezolid and tedizolid) that are all effective against MRSA isolates (Esposito et al., 2023). Nevertheless, the extensive use of antibiotics for medicine and veterinary purposes and its consequent antibiotic selection pressure led to the selection of multidrug resistant *S. aureus* strains (MDR), able to resist to all clinically used antibiotics.

Besides *S. aureus* can form biofilms, enter in a transient phenotype of non-growing persister, and produce toxins after tissue colonization (Peyrusson et al., 2020). In some cases, host innate immunity alone is inefficient against staphylococcal infections, and a long-term treatment by antibiotics is necessary to clear out this rapidly multiplying bacterium. Consequently, *S. aureus* is one of the most noticeable causes of nosocomial and community acquired bacterial infections worldwide.

In this review we analyzed the prevalence of *S. aureus* in different foods, with particular focus on AMR stains and the resistance mechanisms. We based the study on existing publications from January 2012 to December 2022, using the meta-analytical approach. Besides, we critically present analytical methods used to detect *S. aureus* in different foods, mostly meat and milk, and the main preventive actions available to improve microbiological food safety and risk mitigation regarding *S. aureus*.

2. Methodology

Meta-analysis of *S. aureus* incidence in food products was applied on a collection of results from published primary studies with the objective to generate conclusions that the individual studies alone would not interpret and integrate clearly.

2.1. Search methodology

We examined data from different Medline search engines, including PubMed, Google Scholar, Web of Science, Scopus, and Science Direct, using preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guideline (http://www.prisma-statement.org/). To search the articles, MeSH terms and Boolean Logic tools with the connectors 'AND' and 'OR' were used, including (antimicrobial resistance OR antibiotic resistance OR AMR) AND (*Staphylococcus aureus* OR *S. aureus*) AND (food sources), OR (chicken Grilled fish and meat (barbecues)), OR sea food, OR dairy products, OR ready to eat food, OR pork, OR beef, OR turkey OR vegetables OR pastries OR pasta), AND (Multi drug resistance OR MDR) AND (Drug susceptibility tests of *Staphylococcus aureus*).

2.2. Selection criteria

In the process of assessing data from various articles, several criteria were meticulously applied: (i) availability of the full text and abstract of the article; (ii) examination of *Staphylococcus aureus* in different food sources; (iii) inclusion of studies specifying author names, publication year and total number of isolates of *S. aureus*; (iv) identification of sample sources (e.g., chicken, seafood, dairy products, ready-to-eat food, pork, beef, and turkey, vegetables, egg products, pastries, pasta, rice, spices); and (v) AMR assessment method were applied, including different molecular techniques, disk diffusion (DD), minimum inhibitory concentration (MIC), and (vi) sample size and susceptible/resistant organism, multidrug resistant.

Studies were excluded if they (a) were review articles, perspectives, case studies, thesis, editorial notes and book chapters, (b) did not mention antimicrobial susceptibility tests using the Clinical Laboratory Standard Institute (CLSI) guidelines studies, (c) had missing essential statistics, or (d) not written in English.

2.3. Data extraction and statistical analysis

To establish a baseline, complete versions of purportedly relevant articles were acquired. Author names, publication years, the total number of *S. aureus* isolates, and total samples from each article were independently gathered and documented in a spreadsheet (Microsoft Excel® 2023) (Table S1.) for preliminary testing before full extraction. Data extraction involved utilizing text, tables, and figures. The findings were scrutinized, and AMR pie charts were generated to present the data using GraphPad Prism®. Citations from the compiled papers were done by using Endnote software.

To adequately address potential biases stemming from heterogeneity, a random-effects model analysis was conducted. The results were presented using effect size estimates along with corresponding 95 % confidence intervals (95 % CIs). The entire analysis was performed using the "metafor" package in R (version 4.1.2; R Foundation for Statistical Computing, Vienna, Austria) within Rstudio (build 4.4.3). Proportions and pooled 95 % CIs were calculated within the framework of a random-effects model to evaluate the prevalence of *S. aureus* isolates in food samples. Heterogeneity was assessed using the I2 statistic, and value of $p < 0.05$ was defined as the threshold for statistical significance.

3. Food contamination by *S. aureus*

S. aureus is found in various protein-rich foods, including raw meat and meat products, milk and dairy products, bakery products, and fresh vegetables (Grispoldi, Karama, Armani, Hadjicharalambous, & Cenci-Goga, 2021; Gunjan et al., 2023; Mukherjee, Vidic, Auger, Wen, Pandey, & Chang, 2023; Vidic, Manzano, Raj, Pandey, & Chang, 2023). Food contaminated with *S. aureus* poses a particularly high risk for consumers if strains produce enterotoxins. While *S. aureus* is inactivated by cooking or pasteurization processing, toxins are heat-stable and remain active reaching the human gastrointestinal tract. The enterotoxin production increases within an optimal temperature range of 20–37 °C and pH 4–7.4 with consequent release in foods (Al-Nabulsi et al., 2020). Furthermore, any food, which preparation requires warm temperatures, or low-salt solution after preparation and considerable handling, such as dairy products, are also commonly implicated in staphylococcal enterotoxins food poisoning.

The ability of *S. aureus* to adhere to abiotic surfaces and form biofilms is one of the main concerns in the food industry as it increases the riskiness of this species for the microbial cross-contamination of food products. The presence of other pathogenic microorganisms, which may co-exist with *S. aureus* in biofilm, potentiates disease transmission. Biofilms are mainly composed on an extracellular matrix of exopolysaccharides (EPS), which help bacteria resisting to their environment by limiting mobility and penetration of biocides deeper into the biofilm matrix (Kaplan et al., 2018; Tuon, Suss, Telles, Dantas, Borges, & Ribeiro, 2023). The resistance of *S. aureus* cells to cleaning and disinfection procedures within biofilms poses continuous risk for food deterioration and reduced food shelf life. This problem is of high concern for industries involved in meat production and processing (Wagner et al., 2020).

Fig. 1 illustrates possible diffusion routes of *S. aureus* in the food chain. The bacterium can grow in different food products, including foods with high salt or sugar content and low water activity (Beuchat

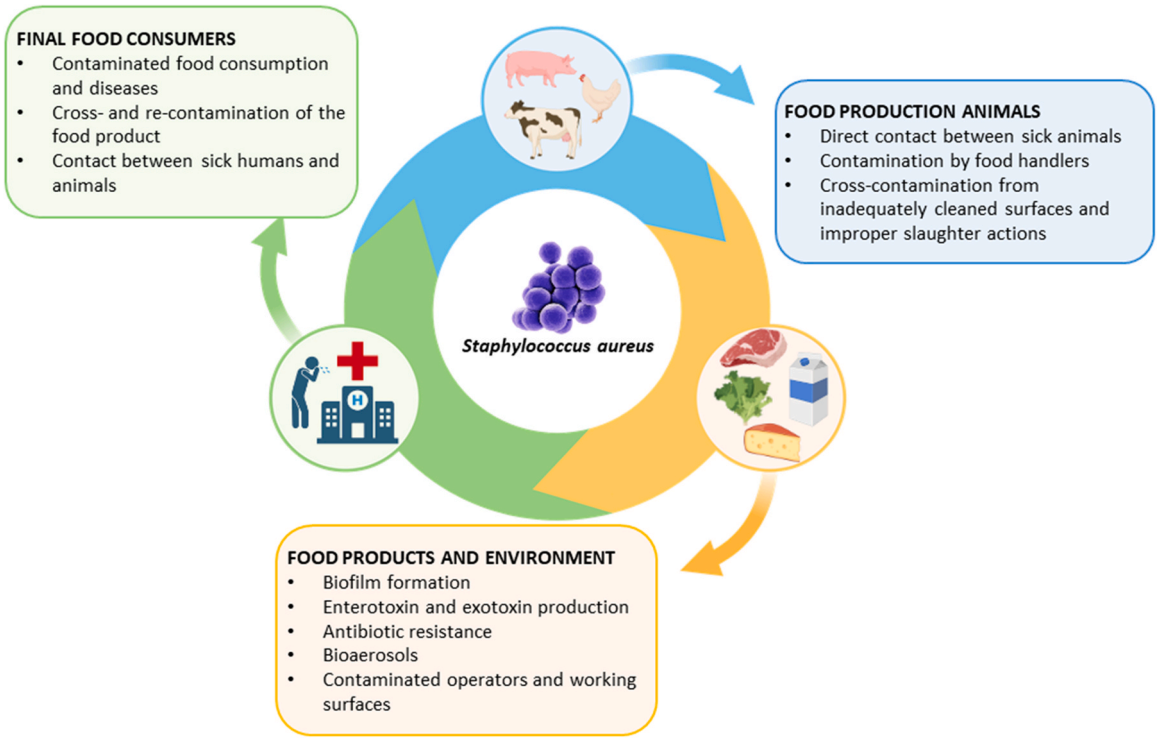

Fig. 1. Critical elements in *Staphylococcus aureus* diffusion within the food chain. The transmission of *S. aureus* starts during primary production, especially in livestock farming, then extends through food products and work environments to finally affect human health among final consumers.

et al., 2013; Castro, Santos, Meireles, Silva, & Teixeira, 2016). In these environments, inadequately cleaned surfaces promote dirt accumulation, which, in the presence of water, favorize bacterial biofilm development. Furthermore, climate change leads to changes in temperature and precipitation patterns, increased frequency and intensity of extreme weather events, ocean warming and acidification. All these changes modify environmental dispersal and persistence of *S. aureus,* with consequences for food safety (Hellberg & Chu, 2016; Kadariya, Smith, & Thapaliya, 2014).

Pathogenic and epidemiological characteristics of MRSA indicated that food can be contaminated with community associated-MRSA, livestock associated-MRSA and even hospital associated-MRSA (Sergelidis & Angelidis, 2017). Agricultural intensification and simplification and livestock density are key drivers of MRSA reservoir in livestock animals which role in human invasive infections is difficult to assess (Fetsch, Etter, & Johler, 2021). Human invasive *S. aureus* infections are declining in regions with advanced surveillance systems such as in the EU member states with the centralized European Antimicrobial Resistance Surveillance Network (EARS-Net) hosted by the European Centre for Disease Prevention and Control (ECDC) and in the USA with Centers for Disease Control and Prevention (CDC) and Centers for Medicare and Medicaid Services relying on National Healthcare Safety Network Reports, the Emerging Infections Program (Authority, 2021; Fetsch et al., 2021). However, it is not a general trend at the global level. For example, the significant increase of infections caused by methicillin-resistant *S. aureus* in Asia-Pacific region is evidenced since the 1980s (W. W. Lim et al., 2019).

3.1. Food screening for S. aureus presence

To assess the safety of food products, the European Commission has defined the food safety and hygiene criteria (Regulation (EC) No. 2073/2005) which comprehends a well-defined guideline to identify and quantify foodborne pathogens, as *S. aureus*, and the toxin that they can produce in food (Cossettini, Vidic, Maifreni, Marino, Pinamonti, & Manzano, 2022; De Medici et al., 2015). The conventional approach used to detect *S. aureus* in food is based on bacterial culturing and includes sample preparation, enrichment, plating, isolation, and confirmation of the colonies as illustrated in Fig. 2. Even though the culture-based methods are still reported as the gold standard, due to the sensitivity and efficiency, they do not fit the need of the food industry because of the long time required to obtain the results.

Recently, Gizaz et al. (2023) reports the collection of 1001 samples of raw milk, and tank milk, buckets, farm tanks, milkers' hands, and nasal swabs to evaluate the presence of *Staphylococcus aureus* (Gizaw et al., 2023). A non-selective pre-enrichment, plating for identification, Gram-stain test, and biochemical tests (coagulase, catalase, indole production, methyl red test, Voges-Proskauer reaction, urease production, citrate utilization, and sugar fermentation) were needed to identify the presence of *S. aureus*. The overall analysis take several days. Similar timing was reported for detection of *Staphylococcus* species from alkaline fermented foods (Ouoba et al., 2019). In this study, along with the identification steps (including the homogenization, the plating on nutrient agar, and the plating on Baird Parker), detection of AMR and toxin genes were added, demanding for 5 days to provide results. These studies illustrate the complexity and time- and efforts- associated challenges of the traditional methods to provide conclusive outcomes.

Given these limitations, the attention has shifted towards the development of molecular methods capable of providing results rapidly (Vidic et al., 2019). Besides, the emergency of bacteria carrying AMR has led to extensive development of tests to detect resistance to antibacterial drugs because many of these resistance mechanisms are driven by specific genes. Polymerase Chain Reaction (PCR) stands out as the most widely used molecular method for detecting the presence of *S. aureus* species by amplifying usually the *nuc* or 16 S rRNA gene. By selecting primers specifically designed for genes associated with AMR, PCR enables to assess the presence of antibiotic resistance in the bacterial pathogens detected in food samples. PCR is a gold-standard technique to detect the gene carrying resistance to methicillin (*mecA* is the most diffused methicillin-resistance gene) and consequently

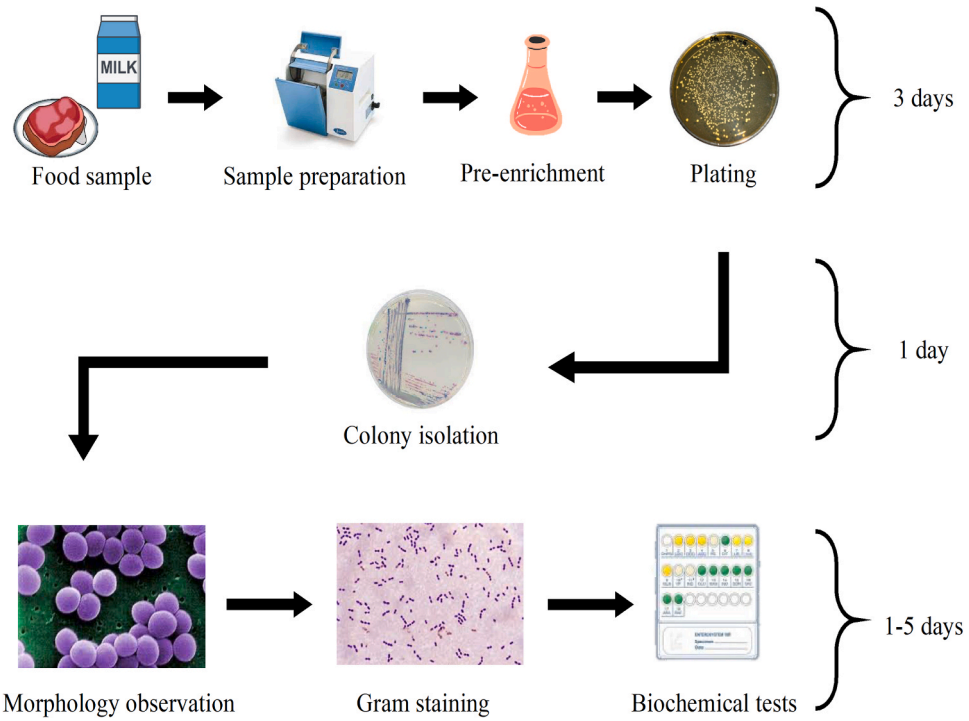

Fig. 2. Detection of *Staphylococcus aureus* in foods by classical microbiological techniques: steps including food sampling, homogenization, pre-enrichment, and plating, followed by colony isolation are required to evidence suspicious *S. aureus* strains. Furthermore, biochemical and morphological tests are needed for the final confirmation.

MRSA. We found that most of the studies using PCR method examined the presence of either *mecA, mecC, ermA, ermB, ermC, blaZ, tetK, tetM, tetS, tet L, vanA, vanB, vatA, vatB,* or *vatC* resistance genes. To increase the sensitivity and selectivity of detection, PCR is usually performed on isolated colonies for confirmation. For instance, PCR was applied to amplify the *nuc* gene and resistance genes for methicillin, *mecA* and *mecC*, in isolates from raw cow's milk collected from bulk cooling tanks on dairy farms (Oliveira, Pinho, Almeida, Azevedo, & Almeida, 2022). Moreover, a multiplex PCR can be employed on positive samples to simultaneously detect different genes of antibiotic resistance and toxins. Parco et al. (2021) investigated the antimicrobial resistance of *S. aureus* strains isolated from milk of sheep and goats using specific primers for *mecA, tetK, tetM, ermA, and ermC*. After isolation, dilution, homogenization, identification, and DNA extraction, PCR results were obtained within approximately 3 days (Parco et al., 2021) indicating molecular methods are an attractive alternative to traditional methods. Real-time PCR is used for quantitative gene detection. For instance, real-time PCR was applied in routine microbiome surveillance of genes associated with resistance to different antibiotics in the human gut (glycopeptides, beta-lactams, and macrolides), including *ermB*, *mefA*, *vanB,* and *mecA*, belonging to resistant species such as *Staphylococcus* (Burcham et al., 2019). When used to detect genes associated with resistance, real-time PCR and multiplex PCR show sensitivity between 95.7 % and 100 % (Sanchini, 2022).

Table 1
Prevalence and sample size for the detection methods of *S. aureus*.

Method	Total sample number	Case number	% Prevalence	% Weight
Culture	12,912	2328	18.03	65.31
Culture/biochemical	1414	466	32.96	7.15
Culture/PCR	4627	1365	29.50	23.40
Culture/ biochemical/PCR	818	340	41.56	4.14
Total	19,771	4504	22.78	100

Although the PCR-based methods are well-developed, they are still less standard than culture-based method, as shown in Table 1. We found that less than 30 % of the studies used PCR. It is worth noting that molecular methods are highly sensitive, specific, and able to provide quantitative results, but also have limitations since they are costly, complex and require isolated genetic materials, manipulation with special care and sophisticated equipment. Moreover, PCR may miss novel or less common genes, which highlights the need for complementary methods like next-generation sequencing for comprehensive surveillance.

In recent years there was a shift towards specific detection tools like biosensors (McNaught & Wilkinson, 1997) that offer the advantage of further reducing the time of analysis and allowing for *in-situ* working. These specialized tools are composed of two main components: a biological element designed to specifically interact with the target of interest, and a transducer that converts the biorecognition event into a measurable signal. Biosensors may be categorized according to the transducer element employed in the construction (electrochemical, piezoelectrical, and optical) or to the bioreceptor (DNA probes, aptamers, antibodies, enzymes, etc.). Once the target is detected, biosensors generate a signal directly proportional to the concentration of the analyte of interest. Due to their sensitivity, specificity, ease of use, and short time of analysis, biosensors find applications across various fields, including the detection of microorganisms, toxins and antimicrobial resistance genes (Balbinot, Srivastav, Vidic, Abdulhalim, & Manzano, 2021; Ionescu et al., 2020; Kotsiri, Vidic, & Vantarakis, 2022; Novakovic et al., 2024; Poggesi, Zhou, Bariani, Mittapalli, Manzano, & Ionescu, 2021; Rizzotto et al., 2023).

Marin *et al.* (2017) developed a colorimetric biosensor that enabled a naked-eye detection of *S. aureus* in milk and infant formula (Marin, Rizzotto, Léguillier, Péchoux, Borezee-Durant, & Vidic, 2022). This tool combines gold nanoparticles functionalized with specific aptamers that bind *S. aureus* cells, and phenomenon of localized surface plasmon resonance. Under optimized conditions, *S. aureus* was visually detected within only 30 min. However, the sensitivity was low since the detection

limit was 7.5 × 10^4 CFU/mL in milk and 8.4 × 10^4 CFU/mL in infant formula, respectively. This study highlights the benefits that can be obtained by adopting biosensors for food microbiological safety assessment regarding a considerable reduction of the overall time required for the analysis, and possibility to detect pathogen directly in food sample and *on-site*. However, further optimizations are needed to reach the end-users compliance and regulatory guidelines on food microbiological quality.

Biosensors have been also developed to replace common antibiotic susceptibility tests. For instance, resistances to ampicillin, ciprofloxacin, daptomycin, erythromycin, vancomycin, and methicillin can be accessed by measuring the impedance generated by *S. aureus* cells cultured on plastic microchips (Safavieh et al., 2017). Alternatively, biosensors can be employed on bacterial DNA to detect antibiotic resistant genes. Although DNA extraction from bacterial cells is needed prior to analysis, the gene detection by biosensors is achieved quickly, taking less than 2 hours for the hybridization between the DNA probe and the target gene. The *nuc* and *mecA* genes were simultaneously detected within 1 hour using target-specific ssDNA probes immobilized on the N-doped porous carbon materials with limits of detection of 1.6 fM and 3.6 fM, respectively (Dai et al., 2021). Similar strategies with analogous timing were applied in other studies to detect simultaneously *nuc* and *mecA* genes, such as the streptavidin-graphite-epoxy bio--composited geno-biosensor (Zacco, Pividori, & Alegret, 2006), or argonaute-centered portable and visual biosensor (Kou et al., 2024).

Although in dynamic development, biosensors are still rarely used for food items screening. The large majority of publications on *S. aureus* detection in food used culturing and PCR-based methods (Table 1).

3.2. Origin of food products contaminated with S. aureus

The meta-analysis conducted on research rapports dealing with 19771 different food samples revealed that *S. aureus* is most frequently reported in ready-to-eat, meat and dairy products (Fig. 3). The publications were classified into two categories, one dealing with 'raw and cooked meat' comprising all references that precise or not the animal origin of meat (Fig. 3A and 3C) and the other with animal origin 'chicken', 'beef', 'pork', and 'turkey' (Figs. 3B and D). The study employed a random effects model to examine food consumption proportions, encompassing sea food, dairy products, chicken, pork, turkey, beef, ready-to-eat foods, vegetables, egg products pastries, starchy foods and spices. Prediction intervals were calculated for each category, showing varying proportions with corresponding confidence intervals. The analysis revealed high heterogeneity (I^2 = 100 %) and low variability between studies ($\tau^2 = 0.0699$, p = 0). The overall proportion and 95 % confidence interval under the random effect model was calculated as 0.37 (0.20: 0.53). The sample size of food types ranged from 60 to 10606, and the prevalence of *S. aureus* ranged from less than 1–35.1 % with the highest prevalence for ready-to-eat food (35.1 %, 95 % CI: 33.3; 36.9) followed by raw and cooked meat (21.7 %, 95 % CI: 20.6; 22.8) and dairy products (18.5 %, 95 % CI: 17.6; 19.4). The lowest prevalence of *S. aureus* was found in pastries (0.57 %, 95 % CI: 0.54; 0.60), starchy foods (0,6 %, 95 % CI: 0.57; 0.63) and spices 2.3 (95 % CI: 2.19; 2.42). Among meat samples analyzed, the highest prevalence of *S. aureus* was found in turkey (42.8 %), followed by pork (36 %), beef (34.5 %) and chicken (31 %), as shown in Fig. 3B.

Among all samples positive to *S. aureus*, the raw and cooked meat was the most represented food category (59.51 %) followed by dairy

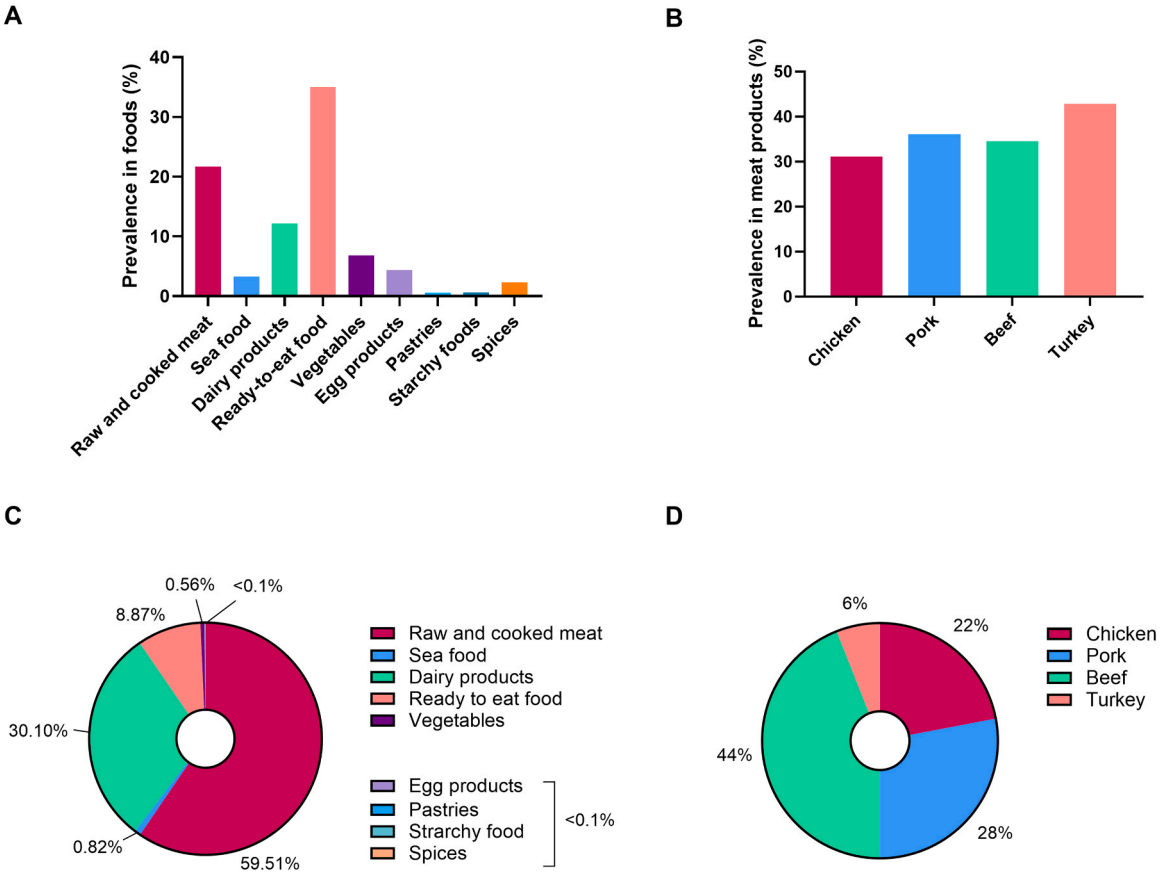

Fig. 3. Prevalence of *Staphylococcus aureus* isolates in all kinds of foods. (**A**) The prevalence of *S. aureus* in all kinds of foods. The highest prevalence was found in ready-to-eat foods. (**B**) The prevalence of *S. aureus* in meat products of different origin seem to be similar. (**C**) The food sources of *S. aureus* isolates are very diverse, but raw and cooked meat seem to be at high risk of contamination compared to other food products. (**D**) Meat products contaminated by *S. aureus* were separated depending on their animal origin and beef is the main source of contamination.

products (30.10 %), ready-to-eat food (8.87 %), sea food (0.82 %), vegetables (0.56 %), and finally egg products, pastries, starchy food and spices with less than 0.1 % of positive samples (Fig. 3C). Interestingly, among meat positive samples, beef was the most represented meat (44 %) followed by pork (28 %), chicken (22 %) and turkey (6 %), as shown in Fig. 3D. It is to note that the majority of studies focused on meat and dairy products because these categories are known as high risk.

S. aureus is a well-known raw and cooked meat contaminant. The bacterium is responsible for mastitis in bovines, and makes milk from infected cows not useful for human consumption. Indeed, *S. aureus* is a primary cause of mastitis in small ruminants, causing significant losses in dairy industries. Mastitis is a challenge in dairy cattle farming due to the high diffusion of *S. aureus* and the easy dissemination through contaminated animals, which can lead contamination of meat products. Cross-contamination from inadequately cleaned surfaces or improper actions of workers during slaughter or preparation processes can produce bioaerosols responsible for *S. aureus* spread.

Milk, a common food in many diets and ingredient in numerous food products can be a route for the transmission of antibiotic-resistant bacteria to humans. *S. aureus* can contaminate raw milk in different ways including soil and grass in contact with cow but also during transport from the farm to the dairy plants or via contaminated milking processing equipment if hygienic conditions are not fully respected (Doyle, Hartmann, & Wong, 2012). Previous studies indicated the presence of *S. aureus* in pasteurized or heated milk, which may result from insufficient heat treatment or post-treatment contamination by food handlers. It can also be contaminated along the retail chain or during storage, consequence of an insufficient temperature control (More O'Ferrall--Berndt, 2007; Ou et al., 2018). In addition, dairy industry production lines often contain residues of proteins and minerals such as calcium and phosphate, which promote the formation of biofilms by *S. aureus* (Shen, Wang, Zhu, Zhang, Shang, & Xue, 2021). These various contamination routes may partly explain the 18.5 % prevalence of milk and dairy products with *S. aureus* in this study. The presence and transmission of pathogenic MRSA in milk samples indicates a significant risk to human health, that need to be assessed and controlled.

Although *S. aureus* is generally susceptible to disinfectants, some strains are resistant in poultry processing plants, dehydrated products, and food rich in fat and salt (Bertolatti, O'BRIEN, & Grubb, 2003). In addition to cleaning, disinfection and thermal treatments, *S. aureus* can also survive unconventional treatments used in the food industries. Referring to non-thermal technologies, acidification is acknowledged as a method to control the proliferation of undesirable microorganisms, including pathogens, while also enhancing the shelf life, texture, and flavor of food products.

The overall prevalence of *S. aureus* was investigated in 26 studies originated from China, USA, Italy, Portugal, Thailand, Malaysia, Portugal and Egypt. Since the food production practices vary across these countries, we compared the differences in the pooled prevalence of *S. aureus* among different countries. The lowest prevalence was found in Italy (8.3 %), followed by Malaysia (15 %), China (27.8 %) and Thailand (30.6 %), while the highest prevalence was reported in Egypt (32.2 %), Portugal (53 %) and USA (46.0 %). Regarding the simple size, the number of tested samples was highly variable with the largest size for Italy (11794 samples), and the smallest for Portugal (100 samples).

Some studies suggested that AMR strains are more tolerant to food-associated stresses and can adapt to nonthermal treatments used by the food industries (Liao et al., 2020). For instance, Ma et al., found that *S. aureus* strains resistant to antibiotics exhibited high resistance to strong acid exposure (HCl, pH 1.5, 40 min) compared to antibiotic-susceptible counterparts (Ma et al., 2019). Another study showed that antibiotic-resistant strains were more resistant to gamma radiation and high energy electron beam (Skowron et al., 2018), methods used to eliminate microorganisms and food preservation. Several molecular mechanisms involving *S. aureus* sigma factors, SOS response, mutations, and two-component system were reported for the cross protection between antibiotics and food-associated stresses (Liao et al., 2020). These findings indicate that the food chain can be a vector for dissemination of AMR strains. However, further investigations are necessary to fully understand the relationship between AMR and bacterial resistance to food-associated stress.

4. Antimicrobial resistance of *S. aureus*: burden, mechanisms and prevalence in food products

Antibiotic resistance is mainly attributed to the selection pression caused by the misuse and overuse of antibiotics. Although antibiotics are one of the most important advances in medicine, their overprescribing has led to resistant bacteria (Bell, Schellevis, Stobberingh, Goossens, & Pringle, 2014). The escalating demand for animal proteins and the intensification of food animal production resulted in greater antibiotic utilization since their initial deployment as growth promoters (Dibner & Richards, 2005). Besides, antibiotics are commonly used to treat livestock in order to prevent animal diseases, which favors the development of AMR in foodborne bacteria (Gao et al., 2020). However, antibiotics cannot be completely absorbed by animal intestines and enter into the environment through the urine and feces. Because of their low biodegradability, antibiotics are further released and spread into soils, sediments and sewage through the application of fertilizers and the use of recycled water. A study conducted on cereals cultivated using wastewater indicated the presence of 19 different antibiotics in wheat, barley oats and rice (Albero, Tadeo, Miguel, & Pérez, 2019).

The increased prevalence of antibiotic-resistant foodborne bacteria is linked not only to their exposure to corresponding antibiotics but also to environmental chemical pollutants such as heavy metals, per- and polyfluoroalkyl compounds (PAFS), disinfectants, and pesticides. Moreover, this excessive release of pollutions in the environment can induce selective pression of two or more chemical compounds on bacteria by co-selection mechanisms including co-resistance, cross-resistance, co-regulation and biofilm resistance (Huo et al., 2023; Murray, Hayes, Snape, Kasprzyk-Hordern, Gaze, & Murray, 2024; Sentic et al., 2023). For instance, the coexisting of heavy metals and antibiotics in manures and manure-amended agricultural soils were shown to exert a strong selection pressure and acted as complementary factors for abundance of antibiotic resistance genes (Ji et al., 2012). These co-selection mechanisms makes bacteria resistant to multiple antibiotics, heavy metals and chemical substances (Imran, Das, & Naik, 2019; Murray et al., 2024). It was shown that soil from mining sites rich in zinc and iron contained numerous isolates with multiple co-resistance to antibiotics and heavy metals such as mercury, zinc and nickel (Sinegani & Younessi, 2017). In addition, the co-transmission mechanism of resistance genes among microbial populations through the vertical and horizontal gene transmission allow bacteria to indirectly obtain resistance. The horizontal gene transmission can be enhanced by chemical pollutants in the environment in various mechanisms: conjugation transfer, membrane vesicles transport, bacterial transformation and bacteriophage transduction (Huo et al., 2023; Lu, Wang, Jin, Yuan, Bond, & Guo, 2020).

Altogether, the presence of antibiotic residues and pollutants in the environments surrounding food production sites promotes the emergence of AMR, contributes to food contamination with resistant strains and poses a serious risk to humans and animals (Hazards et al., 2021). Especially, *S. aureus* adaptability to diverse environments and regulation of gene expression contribute to its ability to survive against anti-staphylococcal drugs (O'Gara, 2017). Indeed, *S. aureus* possesses a high genetic flexibility, and can easily develop novel defense mechanisms. The co-selection pressure may play a significant role in the emergence and persistence of multi-drug resistant *S. aureus* strains in industrial plants and farms. A CC398 LA-MRSA strain that potentially acquired resistance to tetracycline and zinc in feed by the co-selection mechanism was shown to be highly prevalent in pig farms in Korea (Back, Eom, Lee, Lee, Park, & Yang, 2020). Depending on the

antimicrobial used, the pathogen can use one or more specific resistance mechanisms as illustrated in Fig. 4.

Based on data from the scientific literature, a meta-analysis of *S. aureus* isolates detected in food products and their AMR profiles was conducted in order to estimate the prevalence of resistant strains. In the present study, we grouped the reported antibiotics into eight categories based on the classification of the World health Organization (WHO). We found that over the 3900 *S. aureus* isolated from 19771 food samples, 68 % were resistant to at least one antibiotic in clinical use. The highest overall prevalence of resistant *S. aureus* was against penicillins (61 %), followed by tetracyclines (49 %), and macrolides (37 %), aminoglycosides (26 %), cephalosporins (21 %), fluoroquinolones (16 %), glycopeptides and lincosamides (10.5 %), as shown in Fig. 5A. Besides, as shown in Fig. 5B, among all these resistant isolates detected in foods, 26 % were resistant to penicillins, 22.6 % to tetracyclines, 10 % to aminoglycosides and 8 % to cephalosporins. Less than 10 % of isolates were found resistant to quinolones, amphenicols and rifamycins. Table 2 presents mode of action of antibiotics and the most prevalent bacterial resistance mechanism acquired by *S. aureus* strains isolated from food, based on Fig. 5. This high prevalence of AMR strains indicates that through the food, humans can be exposed to resistant *S. aureus*, that is difficult to treat.

The resistance to penicillin is the first resistance to emerged rapidly after the introduction of penicillin G in the 1940s (Kirby, 1944). The antibiotic targets the transglycosylase-transpeptidase PBP2 in the cell envelope and blocks peptidoglycan synthesis. *S. aureus* inhibits the action of this antibiotic by expressing a β-lactamase BlaZ which hydrolyses the amide bond of the four-membered β-lactam ring of the penicillin. The *blaZ* gene is regulated by an inducible system activated by β-lactams involving a repressor DNA-binding protein (BlaI) and a transmembrane protein (BlaR1), which serves as both a receptor and a signal transducer (Hao, Dai, Wang, Huang, & Yuan, 2012). The *bla* genes may be located on transposons or in the chromosomal DNA. Other β-lactam antibiotics, such as methicillin and oxacillin, are inactivated via the *mecA* gene encoding a novel Penicillin-Binding Protein, PBP2. This mechanism has caused the emergence of MRSA strains. The enzyme has low affinity for β-lactams and in consequence is not sensitive to these drugs (D. Lim & Strynadka, 2002; Turner et al., 2019). Nevertheless, MRSA strains growing in the presence of β-lactam generally have a less cross-linked peptidoglycan, giving them much more pro-inflammatory properties (D. Lim & Strynadka, 2002; Müller, Wolf, Iliev, Berg, Underhill, & Liu, 2015).

Several mechanisms can provide tetracycline resistance to *S. aureus*. Tetracycline is a bacteriostatic compound that binds to 30 S ribosomal subunits and blocks the protein production. *S. aureus* may develop ribosomal protection due to the *tetM* gene (Nguyen, Starosta, Arenz, Sohmen, Dönhöfer, & Wilson, 2014). Alternatively, mutation in efflux pump systhem coded by the *tetK* gene may limit the uptake of the drug (Wilson, 2016). Additionally, the overexpression of specific efflux pumps encoded by *tetK* and *telL* genes increases strongly the resistance to the tetracyclines by facilitating their expulsion from the bacterium (Hooper & Jacoby, 2015). Similarities have been observed in resistance

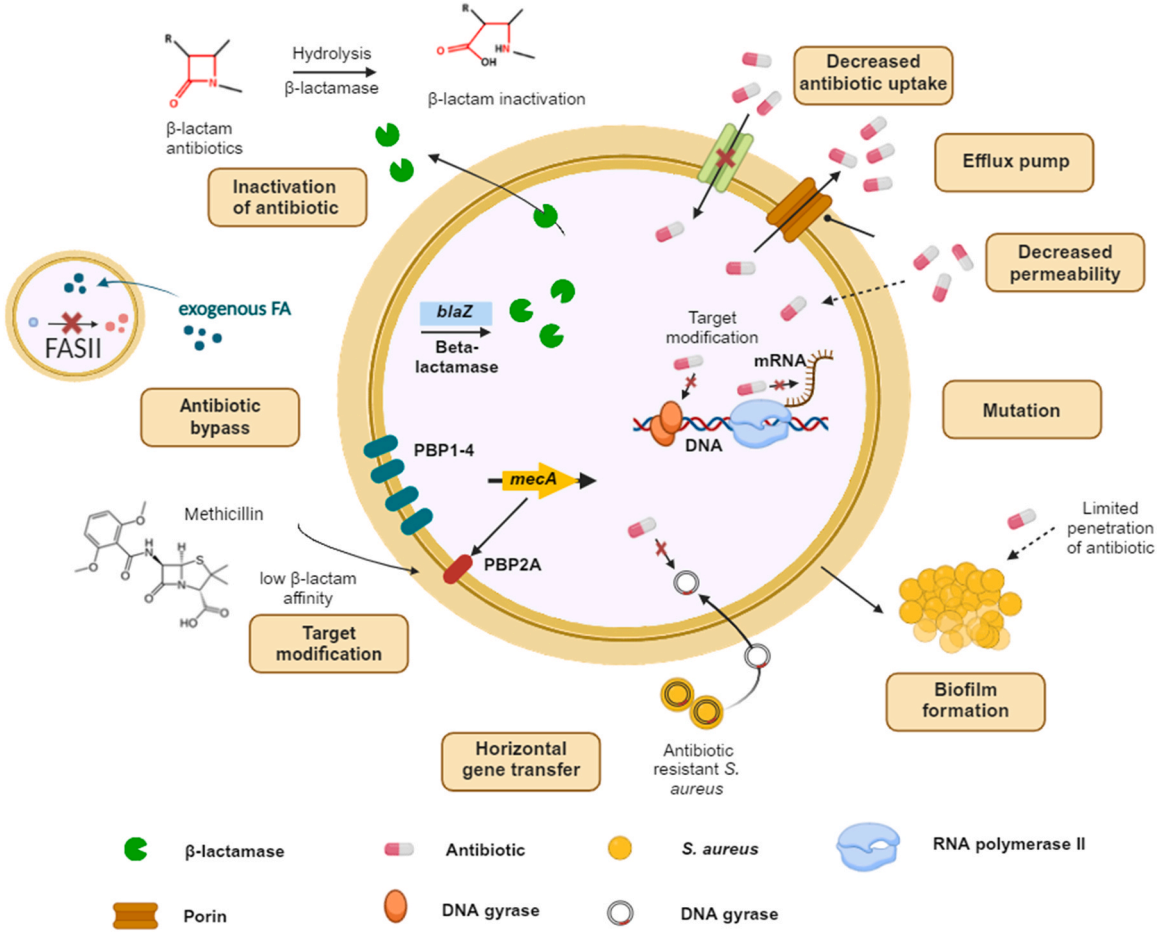

Fig. 4. Molecular mechanisms of *Staphylococcus aureus* adaptation to antibiotics. The bacterium can degrade or modify the antibiotic molecule, alter the binding site of the antibiotic, bypass the antibiotic activity by producing or incorporating the target molecule of the antibiotic, decrease the influx, decrease the permeability of the envelop to block the passive transport of the antibiotic molecule into the cell, activate efflux to export the antibiotic from the cell or mutate the gene encoding the antibiotic's target.

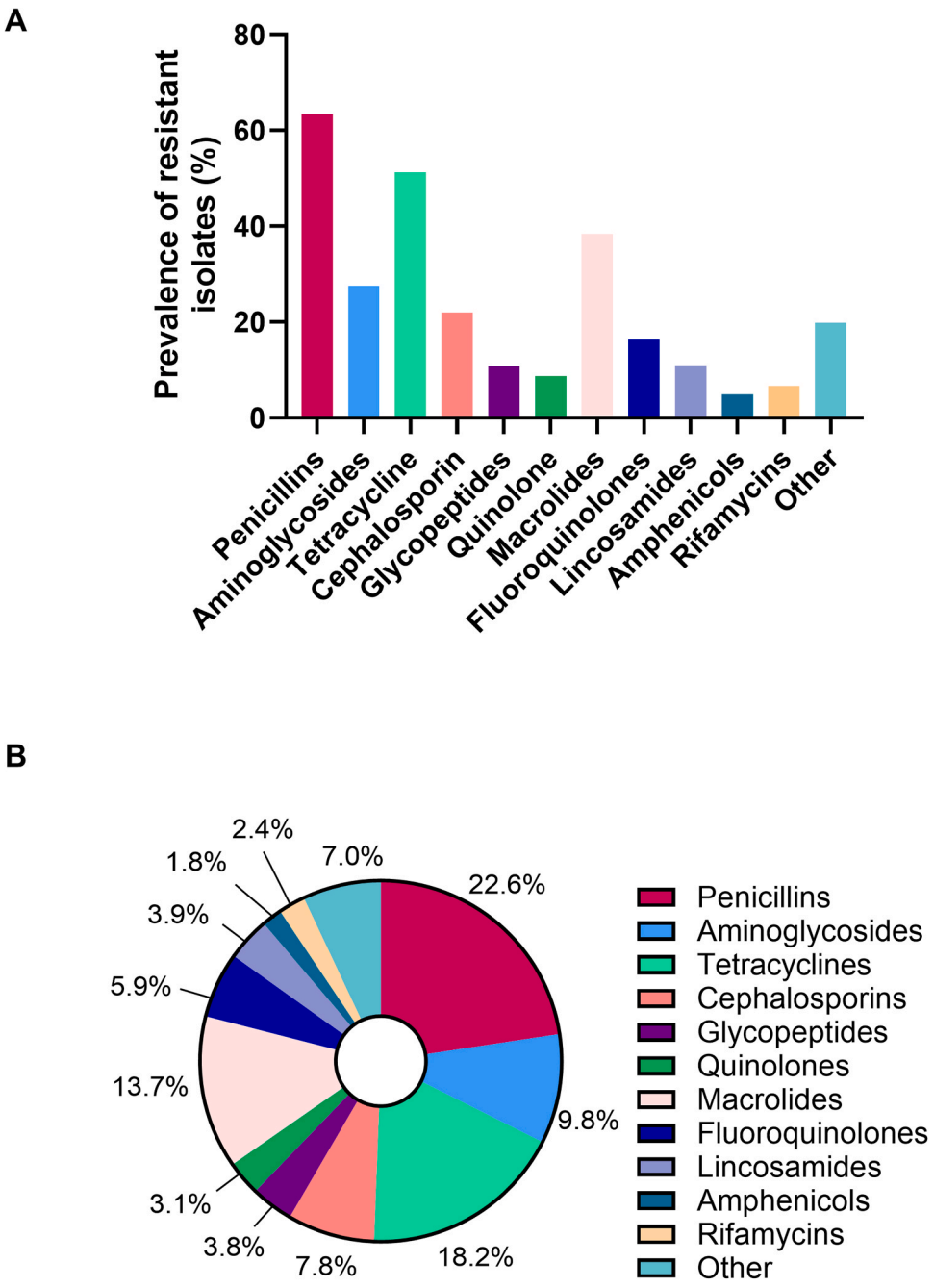

Fig. 5. Overview of antimicrobial resistance of *S. aureus* isolated in food products. (**A**) Prevalence of *S. aureus* resistant isolates to specific class of antibiotics from food products. (**B**) Antimicrobial resistance of *S. aureus* food isolates in this study. The data were obtained via a meta-analysis approach compiling publications from 2012 to 2022. More than 50 % of isolated were resistant to penicillins and tetracyclines.

to fluoroquinolones with the mutations in the topoisomerase IV genes *gyrA* and *gyrB* (Mlynarczyk-Bonikowska, Kowalewski, Krolak-Ulinska, & Marusza, 2022).

As mentioned above, horizontal gene transfer plays an important role of bacterial evolution and AMR spreading. *S. aureus* relies on mobile genetic elements (MGEs) such as plasmids, transposons, chromosomal cassettes, bacteriophages or Staphylococcal pathogenicity islands (SaPIs). These elements act as crucial facilitators for genetic exchange between bacteria through horizontal gene transfer, one of the main mechanisms of adaptation and evolution (Malachowa & DeLeo, 2010). Interestingly, this pathogen is capable of rapidly acquiring MGEs following a host-switching event, to get the capacity for survival and adaptation to a new environment. For instance, a strong antibacterial selective pressure targeting the innate immune response via bacterial effectors in acute mastitis can confer resistance to antibiotics and heavy metal (Campos et al., 2022).

Phages have an important impact on Staphylococcal diversity and evolution. For example, the ciprofloxacin can induce the SOS response, which can stimulate the gene transfer by phages and lead to the acquirement new resistance genes (Úbeda, Maiques, Knecht, Lasa, Novick, & Penadés, 2005), or the transfer of Staphylococcal cassette chromosome carrying the *mecA* gene (SSC*mec*) (Ray, Boundy, & Archer, 2016). Moreover, phages can participate in other MGEs. The helper phage 80α can mediate excision, replication, encapsidation and transduction to transfer SaPIs to other staphylococci (Mir-Sanchis et al., 2012).

Table 2
Main antibiotics to which *S. aureus* isolates from food products have developed resistance and mechanisms implicated.

Antibiotic class	Antibiotics	Mechanism of action	Resistance mechanism
Penicillins	Cloxacillin, ampicillin, penicillin G, amoxicillin/ clavulanic acid, methicillin, oxacillin	Inhibit PBP transpeptidases catalyzing the final step in cell wall synthesis (peptidoglycan cross-linking)	• Production of β-lactamases • Mutations accumulation in PBP leading to reduced binding affinities • Reduced permeability • Efflux
Cephalosporins	Cefoperazone, cefoxitin, cefazolin, ceftaroline-fosamil, ceftriaxone, cefalexin, cefuroxime, cefotaxime, cefalotin		
Carbapenems	Imipenem		
β-Lactam/ β-lactamase inhibitor	Ampicillin/ sulbactam, amoxicillin/ clavulanic-acid	Combination of a β-Lactam (blocking cell wall synthesis) and a β-lactamase inhibitor (inhibiting the β-lactamase responsible for β-Lactam inactivation by hydrolysis)	• Mutation in β-lactamase
Aminoglycosides	Gentamycin, amikacin, erythromycin, kanamycin, streptomycin	Inhibit protein synthesis by binding to the 16 S rRNA of the 30 S ribosome, causing misreading or truncated proteins	• Enzymes modifying aminoglycosides • Decreased influx • Increased efflux • 16 S ribosomal methylases
Tetracyclines	Tetracycline, doxycycline	Inhibit protein synthesis by binding the 16 S rRNA of the 30 S ribosomal unit, blocking the binding of tRNA at the A-site of the ribosome	• Ribosome protection • Mutations in ribosome • Enzymatic inactivation of drug • Efflux
Glycopeptides	Vancomycin	Inhibits the cell wall biosynthesis by binding the D-alanyl-D-alanine portion of the lipid II (peptidoglycan precursor)	• Enzymatic modification and hydrolyse of peptidoglycan precursors • Mutations leading to low permeability
Macrolides	Azithromycin, erythromycin, tilmicosin	Inhibit bacterial protein synthesis by targeting the 23 S rRNA of the 50 S ribosomal subunit, causing truncated peptide chains	• Modification of the 23 S rRNA by methytransferases • Protection of the ribosome via ABC-F proteins
Fluoroquinolones	Ciprofloxacin, levofloxacin, enrofloxacin	Inhibit DNA replication by blocking DNA gyrase and topoisomerase IV	• Mutations in DNA gyrase or topoisomerase IV • Proteins protecting DNA • Efflux of antibiotic
Quinolones	Nalidixic acid		
Lincosamides	Clindamycin, lincomycin	Inhibit bacterial protein synthesis by targeting the 23 S rRNA of the 50 S ribosomal subunit, causing truncated proteins	• Modification of the 23 S rRNA by methytransferases • Inactivation of antibiotic • Efflux
Amphenicols	Chloramphenicol, florophenicol	Inhibit bacterial protein synthesis by binding the 50 S ribosomal subunit	• Mutations in the 50 S ribosomal subunit • Enzymatic inactivation • Efflux
Rifamycins	Rifampicin	Inhibit transcription by binding to RNA polymerase	• Mutations in *rpoB*, encoding RpoB, target of the antibiotic • Enzymatic ribosylation or inactivation of drug

Together, different *S. aureus* food isolates carried various antibiotic resistance suggesting that all mechanisms of resistance described for clinical strains can be also found in food. Consequently, food seems to be one of the most important vehicles for spreading resistant *S. aureus* strains.

5. Conclusions and future outlook

The aim of this review was to search available literature in order to identify the prevalence of *S. aureus* in food, highlight risk factors for food contamination, methods to detect foodborne *S. aureus*, and its resistance to antibiotics.

The WHO has classified *S. aureus* as a high-tier priority II pathogen. Foods are favorable environment for *S. aureus* survival and proliferation. Based on the selected publications in this study, ready-to-eat foods, meat, and milk are the most contaminated. In addition, the meta-analysis revealed the high antibiotic rates of *S. aureus* isolates. These findings of high prevalence of *S. aureus* including resistant strains in various foods impose a potential hazard to consumers, and also food handlers. Moreover, it is possible that *S. aureus* in meat and milk was identified because they were most often sampled. While there are many studies that assessed *S. aureus* presence in protein-rich foods, there is a need for additional analysis of other food categories together with food production facilities and environmental monitoring. Indeed, the spreading of *S. aureus* should be considered using a One health approach, as recommended by the WHO (Garcia, Osburn, & Jay-Russell, 2020; Mukherjee et al., 2023).

Improved diagnostic methods could significantly contribute to improve food safety. We found that most studies used culture alone while others combine culturing with PCR or biochemical testing. *mecA* is the most diffused methicillin-resistance gene in *S. aureus* and PCR is a gold-standard technique to detect the gene and consecutively MRSA. PCR-based methods have high sensitivity and selectivity, and their specificity can reach 100 % accordance when compared to culturing methods. However, PCR methods are expensive, labor intense and

require complex sample preparation, DNA extraction and amplicon analysis that significantly increase the overall time of analysis. Molecular methods are still lacking quality reagents, standardized equipment and analysis methods, which affect results between studies. Consequently, the food industry has a strong interest for advanced technologies for *S. aureus* detection to provide quality products and minimize the health risks. Biosensors can represent an alternative to culture-based and molecular methods as they provide needed sensitivity, specificity, and rapidity in pathogen detection. In addition to being affordable and user-friendly, biosensors can work in real-time, require no instrumentation and are suitable for point-of-care testing. The major challenge associated with the development of a biosensor for *S. aureus* detection in the food industry is the complexity of food matrices that may affect the accuracy and detection probability.

Prevention of food contamination by *S. aureus* requires rapid methods of microbiological surveillance and routine analysis for the bacterial cells, their toxins and AMR genes presence in food products. The surveillance of *S. aureus* should be performed in humans, animals, food and farm environments. Besides, it is necessary to develop programs to promote rational use of antimicrobial agents, infection prevention and control to reduce the incidence of resistance *S. aureus* strains. The surveillance along with the caution in the use of antibiotics in both human and animal health are related to the implementation of global and national One Health antimicrobial resistance programs. Moreover, to control MRSA strains spreading, prevention strategies and monitoring programs need to be implemented from farm to distribution posts. Besides, prevention of contamination from livestock to human via foods requires good farming practice and biosecurity and rigorous hygiene control measures together with the rational use of antibiotics. Prevention of food contamination by *S. aureus* requires strict hygiene standards for food industry staff in contact with raw food such as meat and milk. Finally, consumers need to be aware of potential risks. Cooking food thoroughly and maintaining good sanitation conditions in kitchen would help to prevent contamination and cross-contamination.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data Availability

No data was used for the research described in the article.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.microb.2024.100131.

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