frontiers | Frontiers in Food Science and Technology

TYPE Review
PUBLISHED 05 May 2023
DOI 10.3389/frfst.2023.1165871

OPEN ACCESS

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RECEIVED 14 February 2023
ACCEPTED 14 April 2023
PUBLISHED 05 May 2023

CITATION
Chieffi D, Fanelli F and Fusco V (2023), Antimicrobial and biocide resistance in *Staphylococcus aureus*: genomic features, decontamination strategies, and the role of *S. aureus* complex-related species, with a focus on ready-to-eat food and food-contact surfaces. *Front. Food. Sci. Technol.* 3:1165871. doi: 10.3389/frfst.2023.1165871

Antimicrobial and biocide resistance in *Staphylococcus aureus*: genomic features, decontamination strategies, and the role of *S. aureus* complex-related species, with a focus on ready-to-eat food and food-contact surfaces

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Staphylococcus (S.) aureus can proliferate in a broad range of food and contact surfaces. The ability to grow as a biofilm enhances its resistance to cleaning agents and the chance to persist on food facility contact surfaces and enter the food chain. This presents a risk to the health of food workers and consumers, considering that this pathogen has been associated with a wide variety of local and systemic human infections, as well as with food poisoning caused by the production of enterotoxins. In particular, ready-to-eat (RTE) food, that does not undergo further processing capable of reducing bacterial contamination, may be of particular concern since its consumption poses a direct microbiological risk to consumers. To worsen this scenario, *S. aureus* harbors several biocide and antimicrobial resistance genes (BRGs and ARGs), which, respectively, reduce the efficacy of sanitizing agents during cleaning procedures and antimicrobial treatments when infections occur. Considering this, several novel methods have recently been investigated to control *S. aureus* contamination in food and contact surfaces in food facilities in order to overcome the limitations of traditional sanitizing protocols and improve the safety of the produced food products. In this review, we will provide an overview of *S. aureus* ARGs and BRGs and whole-genome sequence (WGS)-based methods recently implemented for their surveillance. Furthermore, we will describe the presence of antimicrobial-resistant *S. aureus* in RTE food and food-contact surfaces and present novel natural or chemical compounds, new food-contact materials, and innovative physical methods to control the contamination of this pathogen in the food sector. Finally, we will also discuss if *S. aureus* complex-related species are emerging as new antimicrobial-resistant pathogens of the food chain.

KEYWORDS

***Staphylococcus aureus*, ready-to-eat food, food-contact surfaces, co-selection, cgWGS, antimicrobial resistance, biocide resistance, biofilm**

Introduction

Staphylococcus aureus is an opportunistic pathogen that causes several diseases such as skin and soft tissue infections (Lacey et al., 2016), food poisoning, and life-threatening complications, such as pneumonia, endocarditis (Grapsa et al., 2021), osteomyelitis, and toxic shock syndrome, due to its large arsenal of exotoxins, including enterotoxins, as well as invasion, immune evasion, and antibiotic resistance mechanisms (Fusco et al., 2011; Chieffi et al., 2020).

Due to its ability to proliferate in a wide range of temperatures, pH levels, and salt concentrations, *S. aureus* can contaminate a wide variety of food and contact surfaces in the food facility environment. Indeed, it has been reported in meat products (Silva-de-Jesus et al., 2022), fruit juices, ready-to-eat (RTE) food, salad dressings, milk and dairy products (Chieffi et al., 2020; Mekhloufi et al., 2021), seafood, and freshwater fish (Kukułowicz et al., 2021; Rashid et al., 2021). In particular, RTE food that does not undergo further processing capable of reducing bacterial contamination is of particular concern, and their consumption may pose a direct risk to consumer health.

S. aureus can aggregate and form biofilm on food facility surfaces becoming less susceptible to biocides, sanitizers, and antimicrobials in general (Fux et al., 2004) than planktonic cells dispersed in the environment. This increases the persistence of the bacterial cells on such surfaces and the possibility of cross-contamination with other materials and food (Van-Houdt and Michiels, 2010; Vázquez-Sánchez et al., 2014; Bridier et al., 2015; Gutiérrez et al., 2021).

Pathogenic foodborne bacteria can acquire resistance to antimicrobial agents and biocides through horizontal gene transfer from antimicrobial-resistant bacteria, or via adaptive mutation. The growth of *S. aureus* as a biofilm enhances the possibility of transferring antimicrobial resistance genes (ARGs) and biocide resistance genes (BRGs) to both pathogenic and non-pathogenic bacteria in food products and contact surfaces in food facility environments and, being a reservoir of these genes, presents a serious health risk for consumers (Savage et al., 2013). In addition, the presence of ARGs and BRGs has been demonstrated to be correlated with an increase in pathogenicity (Beceiro et al., 2013; Alenizi, 2014; Thompson and Brown, 2017; Rasmi et al., 2022).

Herein, we provide a summary of ARGs and BRGs in *S. aureus* and on whole-genome sequence (WGS)-based methods for the surveillance of such resistances. An overview of novel strategies to control *S. aureus* biofilm and contamination in food and food-contact surfaces is also provided. Moreover, we discuss the possibility of the *S. aureus* complex-related species emerging as new antimicrobial-resistant pathogens of the food chain.

Antimicrobial resistance genes in *S. aureus*

Glycopeptide antibiotics

Glycopeptide antibiotics, such as vancomycin and teicoplanin, bind with high affinity to the dipeptide D-Ala4-D-Ala5 of lipid II that forms complexes with peptidoglycan precursors, inhibiting cell wall synthesis (Loll and Axelsen, 2000). There are two different types of glycopeptide resistance described in *S. aureus*. Genetic bases of the intermediate vancomycin (glycopeptide)-resistant (VISA/GISA) *S. aureus* strains, which result in an increased cell wall thickness, involve stepwise mutations in genes encoding molecules mainly implicated in cell wall biosynthesis and its regulation (McGuinness et al., 2017). The high vancomycin resistance mechanism is based, as in other microorganisms, on the presence of *van* genes, located on mobile elements that encode for enzymes that replace D-ala-D-ala with a low-affinity depsipeptide, D-alanyl-D-lactate (D-ala-D-lac) (Bugg et al., 1991). The first high-level vancomycin-resistant *S. aureus* (VRSA) strain carrying *van*A operon was isolated in 2002 (Chang et al., 2003). This high-level vancomycin-resistant *S. aureus* isolate harbored a 57.9-kilobase multiresistance conjugative plasmid (pLW1043) from *Enterococcus faecalis*, within which it was integrated into the Tn*1546*, encoding the vancomycin resistance gene cluster (Weigel et al., 2003). A genetic study by Bakthavatchalam et al. (2018) in methicillin-resistant *S. aureus* (MRSA) with reduced teicoplanin susceptibility identified mutations in the *tca*A and *tca*B genes of the *tca*RAB operon as determinants of teicoplanin resistance. The *tca*RAB operon was identified by Brandenberger et al. (2000); insertional inactivation of *tcaA* or deletion of the entire operon increased teicoplanin resistance in *S. aureus* in a strain-dependent way, and, in the methicillin-resistant strain COL, it was coupled with a remarkable decrease in methicillin resistance.

Tetracycline

Tetracycline resistance is determined by two different mechanisms: the action of efflux pumps, encoded by *tet*K and *tet*L genes that are plasmid-located, and ribosomal protection by elongation factor-like proteins, encoded by *tet*(O)/*tet*(M) genes, typically chromosomally located on conjugative transposons such as Tn*916* and Tn*1545* (Jensen and Lyon, 2009). *Tet*K is located on the small pT181 plasmid, which has also been found integrated within the SCC*mec*III cassette of MRSA strains (Jensen and Lyon, 2009). TetO/M binds to the EF-G binding site on the ribosome, thus dislodging tetracycline from the ribosome (Burdett, 1996; Trieber and Taylor, 2002). Resistance can also be determined by mutations causing the increased expression of chromosomally encoded efflux pumps, such as Tet38 (Truong-Bolduc et al., 2022).

Chloramphenicol

Chloramphenicol acetyltransferase (CAT) is an inducible detoxifying enzyme that inactivates by acetylation of chloramphenicol, which inhibits protein biosynthesis by binding with the peptidyltransferase center at the 50S ribosomal subunit of 70S ribosomes (Schlünzen et al., 2001; Schwarz et al., 2004). *cat* genes, alone or in combination with streptomycin resistance (Gillespie and Skurray, 1988; Schwarz and Grölz-Krug, 1991), are carried by RC plasmids, of which pC221, pC223, pUB112, and pC194 have been characterized (Horinouchi and Weisblum, 1982; Brückner and Matzura, 1985; Projan et al., 1985; Schwarz et al., 2004; Smith and Thomas, 2004). In addition, the 23S rRNA methyltransferase gene *cfr* was shown to confer resistance to chloramphenicol, as well as efflux systems, inactivation by phosphotransferases, mutations of the target site, permeability barriers, and the presence of the non-enzymatic inducible

chloramphenicol resistance determinant (*clm*A) carried on the transposon Tn*1696* (Bissonnette et al., 1991; Stokes and Hall, 1991).

Aminoglycosides

Aminoglycoside resistance in *S. aureus* is conferred by the action of aminoglycoside-modifying enzymes (AMEs) (aminoglycoside phosphotransferase, acetyltransferases, and nucleotidyl-transferase) (Ardic et al., 2006). Streptomycin is an aminoglycoside antibiotic that irreversibly binds to the 16S rRNA and S12 protein within the bacterial 30S ribosomal subunit (Demirci et al., 2013). While high-level streptomycin resistance in clinical *S. aureus* is associated with a chromosomal mutation affecting ribosome affinity (Lacey and Chopra, 1972), low-level resistance is associated with the streptomycin adenylyltransferase-encoding *str* gene, which is plasmid-located (Projan et al., 1988). The kanamycin resistance plasmid was first isolated and characterized in 1974 by Stiffler et al. (1974). This plasmid carries the Tn*4001* transposon, which also mediates resistance to gentamicin and tobramycin (Lyon et al., 1984). Resistance is achieved by the action of a bifunctional protein with aminoglycoside acetyltransferase [AAC(6′)] and aminoglycoside phosphotransferase [APH(2″)] activities encoded by *aac*A-*aph*D (Rouch et al., 1987). Additionally, *aad*D (also referred to as *ant*(6) or *ant*(6)Ia) and *aph*A-3 code for an aminoglycoside adenyltransferase and a phosphotransferase, respectively, involved in neomycin and kanamycin resistance. These genes are, respectively, carried by the Tn*5405* transposon and the plasmid pUB110, whose integration was mediated by IS257 (Byrne et al., 1991; Derbise et al., 1996). The transposon Tn*5405* also carries *aad*E and *sar*4, which code for a streptomycin adenylyltransferase and the streptothricin acetyltransferase, respectively, involved in antibiotic resistance.

Fluoroquinolone

Fluoroquinolone resistance in *S. aureus* is due to mutations in the *gyr*A, *gyr*B, and *par*C genes, causing the synthesis of proteins with reduced susceptibility to this class of antibiotics (Lowry, 2003). Resistance can also be ascribable to the overexpression of fluoroquinolone efflux pumps encoded by *nor*A, *nor*B, *nor*C, *sdr*M, and other major facilitator superfamilies (MFSs) (Tanaka et al., 2000; Ding et al., 2008).

Macrolides

The target of macrolides (such as erythromycin), common also to lincosamides and streptogramin B, is the V domain of the 23S rRNA of the subunit 50S. Resistance is thus achieved by four types of mechanisms: 1) the action of rRNA methyltransferases (coded by *erm* genes), which modify an adenine residue of the 23S rRNA, reducing the affinity with the antibiotic (Roberts et al., 1999); 2) antibiotic resistance ATP-binding cassette subfamily F proteins, encoded by *msr* genes that protect the ribosomal site, displacing the antibiotic from the target (Feßler et al., 2018); 3) MFS membrane transporters, encoded by *mef* genes, involved in macrolide efflux (Feßler et al., 2018); and 4) enzymatic inactivation by macrolide phosphotransferase or macrolide esterase, encoded by *mph*(C) or *ere*(A) and *ere*(B) genes, respectively (Feßler et al., 2018). Many of these genes can be transferred across strains, species, and even genera since they are located on mobile elements such as plasmids, transposons, or genomic islands (Schwendener et al., 2020).

Beta-lactams

Beta-lactam antibiotics, such as penicillin and methicillin, impair the synthesis of the bacterial cell wall by targeting enzymes involved in the synthesis of peptidoglycans (transpeptidases, carboxypeptidases, and transglycosylases) (Zeng and Lin, 2013). Several mechanisms are associated with beta-lactam resistance, including the synthesis of additional penicillin-binding proteins (PBP2a), the synthesis of beta-lactamases, and, rarely reported a mutation in the PBP coding genes, which reduce their affinity to antibiotics. *S. aureus* beta-lactamases are synthesized by the *bla*Z gene, which is usually located within the *bla*I–*bla*R1–*bla*Z operon in plasmids and transposons, comprising the regulatory gene coding for the DNA binding protein BlaI and the gene coding for the signal transducer BlaR1 (Hao et al., 2012). PBP2a proteins, expressed by MRSA, are low-affinity transpeptidases conferring resistance to almost all *ß*-lactams, including methicillin, cefoxitin, and oxacillin. They are synthesized by *mec*A within the *mec* gene complex (*mec*A, *mec*RI, and *mec*I) located in the staphylococcal chromosomal cassette *mec* (SCC*mec*) (Hanssen and Sollid, 2006). SCC*mec* are transferable genomic islands, classified into main types according to the combination of the *ccr* chromosomal recombinase gene complex (*ccr*A, *ccr*B, and *ccr*C) and *mec* genes harbored. To date, 14 major types of SCC*mec* have been described and sequenced (Mlynarczyk-Bonikowska et al., 2022). SCC*mec* can additionally harbor genes conferring resistance to other groups of antibiotics, such as macrolides, aminoglycosides, tetracyclines, lincosamides, and streptogramin B (Hiramatsu et al., 2001; Hanssen and Sollid, 2006; Liu et al., 2016). For additional genes involved in specific resistance to less relevant antibiotics from a clinical and epidemiological perspective, please refer to other available exhaustive reviews on this topic (Foster, 2017; Mlynarczyk-Bonikowska et al., 2022).

Overview of antimicrobial resistance in *S. aureus* from RTE food and food-contact surfaces

The presence of antimicrobial-resistant *S. aureus* is being constantly reported in RTE food of different categories, such as meat-based products, seafood, fruits and vegetables, egg- and milk-derived food, bakery and confectionery products, and mixed RTE food made with a variety of ingredients, as well as from food-contact surfaces in food facility environment (Table 1), the latter representing sources of cross-contamination for food, other utensils or surfaces, and humans, especially employed in the food industry (Di Ciccio et al., 2015; Ho et al., 2015; Plaza-Rodríguez et al., 2019). In particular, considering all the tested isolates and the most frequently investigated antimicrobials in the recently reported studies (Table 1), *S. aureus* shows relatively high rates of resistance toward beta-lactams [penicillin (80.7%); ampicillin (27.1%); oxacillin (25%) and cefoxitin (31.4%)]; macrolides [azithromycin (49.5%) and erythromycin (33.6%)]; folate pathway inhibitors [trimethoprim/sulfamethoxazole (48.7%)]; tetracyclines [tetracycline (39.5%)]; lincosamides [clindamycin (38.1%)]; and aminoglycosides [gentamicin (21%)], while slightly lower resistance is observed for fluoroquinolones, including ciprofloxacin (12.9%) and levofloxacin (12.3%). Although the detection of ARGs is not systematically addressed, to date, several genes

TABLE 1 Recently reported *S. aureus* in ready-to-eat food and food-contact surfaces, and related antimicrobial resistance.

Source	No. of *S. aureus* (prevalence %)	Tested antimicrobials	Resistance (no. of *S. aureus* out of the total)	Antimicrobial resistance genes	Reference
RTE meat products					
Meat products	31 (2.0%)	CIP, CLI, ERY, FOX, GEN, LEV, LNZ, MXF, OXA, PEN, RIF, SXT, SYN, TET, TGC, and VAN	CIP (4/31); CLI (11/31); CLIin (7/31); ERY (14/31); FOX (1/31); GEN (2/31); LEV (3/31); MXF (3/31); OXA (1/31); PEN (27/31); RIF (1/31), SXT (2/31); and TET (8/31)	*blaZ*, *erm*[a], and *tet*[b]	Lin et al. (2019)
Meat sandwiches (beef burger and hot dog)	190 (83.1%)	AMK, AMP, CEP, CIP, CTX, DOX, ERY, GEN, KAN, NAL, OXA, PEN, SXT, TET, and VAN	AMK (11/190), AMP (29/190), CEP (93/190), CIP (29/190), CTX (172/190), DOX (75/190), ERY (61/190), GEN (43/190), KAN (190/190), NAL (183/190), OXA (43/190), PEN (140/190), SXT (151/190), TET (119/190), and VAN (4/190)	*mec*A	Mahros et al. (2021)
Chicken- and pork-based street-food	5 (15.1%)	AMC, AMP, CAZ, CHL, CIP, CLI, CRO, ERY, FA, GEN, NAL, NIT, OFX, OXA, PEN, STR, SXT, and VAN	FA (3/5), OFX (1/5), and TET (1/5)	NR	Manguiat and Fang (2013)
Hamburgers, chicken nuggets, and salami	14 (6.8%)	AMK, AZM, CHL, CIP, CLI, DOX, ERY, GEN, LEV, PEN, RIF, SXT, and TET	AMK (4/14), AZM (7/14), CHL (5/14), CIP (8/14), CLI (7/14), DOX (4/14), ERY (9/14), GEN (10/14), LEV (7/14), PEN (13/14), RIF (4/14), SXT (8/14), and TET (13/14)	*blaZ*, *aac*A-D, *msr*A, *erm*A, *tet*(K), *tet*(M), *gyr*A, *grl*A, *lin*A, *dfr*A, *cat*1, and *rpo*B	Mesbah et al. (2021)
RTE seafood					
Prawn fritters	1 (NR)	AMC, AMK, AMP, AZM, CHL, CIP, CRO, FOX, GEN, NOR, PEN, SXT, and TET	AMC (1/1), AMP (1/1), AZM (1/1), CRO (1/1), FOX (1/1), and PEN (1/1)	*mec*A	Aung et al. (2017a)
Raw tuna and salmon (sashimi)	163 (73%)	CIP, ERY, FOX, OXA, PEN, TET, and VAN	CIP (4/163), ERY (21/163), FOX (64/163), OXA (64/163), PEN (131/163), TET (18/163), and VAN (2/163)	*mec*A	Carvalho et al. (2020)
Fish and seafood products	3 (3.1%)	AMK, AMP, CAZ, CHL, CIP, CPD, CTX, DOX, ERY; FOX, GEN, IPM, KAN, LEV, LNZ, MEM, MIN, NOR, PEN, RIF, SXT, TEC, TET, and VAN	AMP (2/3), KAN (1/3), and PEN (2/3)	Absence of *mec*A	Harada et al. (2018)
Raw salmon with soured rice (sushi)	51 (9.4%)	AMP, CEP, CHL, CIP, CLI, CXM, ERY, FOX, GEN, KAN, LNZ, OXA, PEN, RIF, RL, TET, and TMP	AMP (16/51), CLI (3/51), ERY (21/51), KAN (14/51), PEN (26/51), RL (3/51), and TET (11/51)	*blaZ*, *erm*(C), and *tet*(K)	Li et al. (2019)
RTE fruits and vegetables					
Sliced onion	1 (NR)	AMC, AMK, AMP, AZM, CHL, CIP, CRO, FOX, GEN, NOR, PEN, SXT, and TET	AMC (1/1), AMP (1/1), AZM (1/1), CRO (1/1), FOX (1/1), and PEN (1/1)	*mec*A	Aung et al. (2017a)
Salads	16 (29.6%)	CIP, FA, FOX, GEN, NOR, OFX, OXA, PEN, SXT, and TOB	CIP (9/16), FA (15/16), FOX (15/16), GEN (1/16), OFX (3/16), OXA (16/16), PEN (16/16), SXT (1/16), and TOB (8/16)	Absence of *mec*A	Touimi et al. (2020)
Lightly pickled vegetables	6 (6.3%)	AMK, AMP, CAZ, CHL, CIP, CPD, CTX, DOX, ERY; FOX, GEN, IPM, KAN, LEV, LNZ, MEM, MIN, NOR, PEN, RIF, SXT, TEC, TET, and VAN	AMP (2/6) and PEN (2/6)	Absence of *mec*A	Harada et al. (2018)
Fruits and vegetables	9 (1.8%)	CIP, CLI, ERY, FOX, GEN, LEV, LNZ, MXF, OXA, PEN, RIF, SXT, SYN, TET, TGC, and VAN	CIP (1/9); CLI (3/9); ERY (3/9); GEN (1/9); LEV (1/9); MXF (1/9), PEN (8/9); SXT (2/9); and TET (1/9)	*blaZ*, *erm*[a], and *tet*[b]	Lin et al. (2019)
Grilled mushrooms	15 (30%)	AMK, AZM, CHL, CIP, CLI, DOX, ERY, GEN, LEV, PEN, RIF, SXT, and TET	AMK (5/15), AZM (6/15), CHL (5/15), CIP (7/15), CLI (5/15), DOX (3/15), ERY (7/15), GEN (11/15), LEV (5/15), PEN (13/15), RIF (5/15), SXT (7/15), and TET (13/15)	*blaZ*, *aac*A-D, *msr*A, *erm*A, *tet*(K), *tet*(M), *gyr*A, *grl*A, *lin*A, *dfr*A, *cat*1, and *rpo*B	Mesbah et al. (2021)

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TABLE 1 (*Continued*) Recently reported *S. aureus* in ready-to-eat food and food-contact surfaces, and related antimicrobial resistance.

Source	No. of *S. aureus* (prevalence %)	Tested antimicrobials	Resistance (no. of *S. aureus* out of the total)	Antimicrobial resistance genes	Reference
Egg- and milk-derived RTE food					
Fried egg	1 (NR)	AMC, AMK, AMP, AZM, CHL, CIP, CRO, FOX, GEN, NOR, PEN, SXT, and TET	AMC (1/1), AMP (1/1), AZM (1/1), CRO (1/1), FOX (1/1), and PEN (1/1)	*mec*A	Aung et al. (2017a)
Dairy products	6 (2.0%)	CIP, CLI, ERY, FOX, GEN, LEV, LNZ, MXF, OXA, PEN, RIF, SXT, SYN, TET, TGC, and VAN	CIP (2/6); CLI (6/6); CLIin (3/6); ERY (6/6); GEN (3/6); PEN (6/6); and SXT (2/6)	*bla*Z, *erm*[a], and *tet*[b]	Lin et al. (2019)
Bakery and confectionery RTE products					
Handmade sweets	12 (12%)	AMP, CEP, CHL, CIP, CLI, ERY, FOX, GEN, PEN, SSS, TET, and VAN	AMP (8/12), CEP (1/12), ERY (1/12), GEN (1/12)[c], PEN (8/12), SSS (1/12), and TET (4/12)	NR	Kroning et al. (2016)
Pastries	2 (8.3%)	CIP, FA, FOX, GEN, NOR, OFX, OXA, PEN, SXT, and TOB	FOX (2/2), OXA (2/2), and PEN (2/2)	Absence of *mec*A	Benjelloun Touimi et al. (2020)
Desserts	7 (8.0%)	AMK, AMP, CAZ, CHL, CIP, CPD, CTX, DOX, ERY; FOX, GEN, IPM, KAN, LEV, LNZ, MEM, MIN, NOR, PEN, RIF, SXT, TEC, TET, and VAN	AMP (2/7), CAZ (1/7), CPD (2/7), CTX (1/7), ERY (1/7), FOX (1/7), KAN (1/7), and PEN (1/7)	*mec*A	Harada et al. (2018)
Desserts	8 (2.0%)	CIP, CLI, ERY, FOX, GEN, LEV, LNZ, MXF, OXA, PEN, RIF, SXT, SYN, TET, TGC, and VAN	CLI (2/8); ERY (2/8); FOX (2/8); GEN (1/8); OXA (2/8), PEN (8/8); and TET (3/8)	*bla*Z, *erm*[a], and *tet*[b]	Lin et al. (2019)
Various or mixed RTE food					
Hot meals	2 (1.3%)	CIP, FA, FOX, GEN, NOR, OFX, OXA, PEN, SXT, and TOB	FA (2/2), FOX (2/2), OXA (2/2), PEN (2/2), and TOB (2/2)	*mec*A	Touimi et al. (2020)
Milk and meat products	16 (6.7%)	AMP, CLI, ERY, GEN, MET, NOV, and VAN	AMP (16/16), CLI (11/16), ERY (12/16), GEN (4/16), MET (15/16), and VAN (7/16)	NR	Lakhanpal et al. (2019)
Meat and meat products, cereal products, fruits, and vegetables	127 (NR)	AZM, CLI, ERY, GEN, LEV, LNZ, MXF, PEN, RIF, SXT, TET, and VAN	AZM (66/127), CLI (70/127), ERY (75/127), GEN (8/127), LEV (4/127), PEN (116/127), SXT (39/127), and TET (54/127)	*mec*A, *acc(6′)/aph(2″)*, *aph(3′)-III*, *ant(4′,4″)*, *erm*B, *erm*C, and *msr*A	Luo et al. (2018)
Chicken meat-based salad (salad Olivieh), falafel, and corn with sauces (Mexican corn)	35 (21.9%)	AMK, AZM, CHL, CIP, CLI, DOX, ERY, GEN, LEV, PEN, RIF, SXT, and TET	AMK (14/35), AZM (14/35), CHL (8/35), CIP (17/35), CLI (12/35), DOX (10/35), ERY (18/35), GEN (26/35), LEV (12/35), PEN (29/35), RIF (8/35), SXT (18/35), and TET (29/35)	*bla*Z, *aac*A-D, *msr*A, *erm*A, *tet*(K), *tet*(M), *gyr*A, *grl*A, *lin*A, *dfr*A, *cat*1, and *rpo*B	Mesbah et al. (2021)
Meat-, vegetable-, cereal-, milk- and egg-based food and pastries	12 (23.2%)	CLI, ERY, FA, FOS, FOX, GEN, KAN, L, LNZ, NIT, OFX, OXA, PEN, PRI, RIF, SXT, TEC, TET, TOB, and VAN	ERY (1/12), FOX (1/12), KAN (2/12), L (1/12), OFX (1/12), OXA (1/12), PEN (10/12), and TET (2/12)	*mec*A, *bla*Z, *gyr*A, *erm*B, *lmr*S, *tet*(L), *tet*(38), *aph*(3′)-IIIa, and *ant*(6)-I	Mekhloufi et al. (2021); Fanelli et al. (2022)
Food-contact surfaces					
Gloves	2 (NR)	AMC, AMK, AMP, AZM, CHL, CIP, CRO, FOX, GEN, NOR, PEN, SXT, and TET	AMC (2/2), AMP (2/2), CRO (2/2), FOX (2/2), and PEN (2/2)	*mec*A	Aung et al. (2017a)
Chopping machine, knives, weighing machine, sink, recipient, stainless steel worktops, and cutting boards	80 (33.6)	CIP, FA, FOX, GEN, NOR, OFX, OXA, PEN, SXT, and TOB	CIP (10/80), FA (80/80), FOX (50/80), GEN (36/80), NOR (10/80), OFX (32/80), OXA (80/80), PEN (80/80), SXT (73/80), and TOB (45/80)	Absence of *mec*A	Touimi et al. (2020)

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TABLE 1 (*Continued*) Recently reported *S. aureus* in ready-to-eat food and food-contact surfaces, and related antimicrobial resistance.

Source	No. of *S. aureus* (prevalence %)	Tested antimicrobials	Resistance (no. of *S. aureus* out of the total)	Antimicrobial resistance genes	Reference
Food establishment surfaces and environment	49 (NR)	CIP, CLI, ERY, FOX, GEN, and SXT	CLIin (3/49), ERY (3/49), and FOX (2/49)	*erm*B, *erm*C, *erm*A, and *mec*A	Machado et al. (2020)

AMC, amoxicillin/clavulanic acid; AMK, amikacin; AMP, ampicillin; AMS, ampicillin/sulbactam; AMX, amoxicillin; AZM, azithromycin; CAZ, ceftazidime; CEC, cefaclor; CEP, cephalothin; CFZ, cefazolin; CHL, chloramphenicol; CIP, ciprofloxacin; CLA, clarithromycin; CLI, clindamycin; CLIin, inducible clindamycin resistance; CPD, cefpodoxime; CPM, cefepime; CRO, ceftriaxone; CTX, cefotaxime; CXM, cefuroxime; DAP, daptomycin; DOX, doxycycline; ERY, erythromycin; ETP, ertapenem; FA, fusidic acid; FOS, fosfomycin; FOX, cefoxitin; GEN, gentamicin; IPM, imipenem; KAN, kanamycin; L, lincomycin; LEV, levofloxacin; LNZ, linezolid; MEM, meropenem; MET, methicillin; MIN, minocycline; MUP, mupirocin; MXF, moxifloxacin; NAL, nalidixic acid; NIT, nitrofurantoin; NOR, norfloxacin; NOV, novobiocin; OFX, ofloxacin; OXA, oxacillin; PEN, penicillin; PIP, piperacillin; PRI, pristinamycin; PTZ, piperacillin/tazobactam, RIF, rifampicin; RL, sulfamethoxazole; SSS, sulfonamides; STR, streptomycin; SXT, trimethoprim/sulfamethoxazole; SYN, quinupristin/dalfopristin; TEC, teicoplanin; TEL, telithromycin; TET, tetracycline; TGC, tigecycline; TMP, trimethoprim; TOB, tobramycin; VAN, vancomycin; NR, not reported (when specified in "antimicrobial resistance genes" column means that the detection of antimicrobial resistance genes is not addressed in the cited reference);
[a]indicates *erm*A and/or *erm*C;
[b]indicates *tet*(L), *tet*(M), and/or *tet*(K);
[c]reported as intermediate resistant.

have been identified in RTE food- and contact surface-derived *S. aureus* (Table 1) that present a risk for the spreading of antimicrobial resistance in both foodborne and human bacterial communities. Studies are mainly focused on the detection of the *mec*A gene (Table 1) since MRSA, able to resist methicillin, oxacillin, cefoxitin, and almost all the other beta-lactam antibiotics, has emerged as a growing public health issue since the 1990s (Oniciuc et al., 2017). Vancomycin has been selected as the main drug to treat serious infections caused by MRSA (Mahros et al., 2021); thus, the emerging occurrence of vancomycin-resistant *S. aureus* (VRSA) in food, including RTE food (Mahros et al., 2021; Table 1), is alarming and raises concern related to their overall spread. Therefore, although the rates of vancomycin resistance are relatively quite low (2.2%) in the recently published studies (Table 1), the detection of VRSA deserves significant attention, and systematic surveillance may allow a deeper understanding of the health burden that VRSA, beyond MRSA, might pose to consumers.

Biocide resistance genes (BRGs) in *S. aureus*

In *S. aureus*, resistance to commonly used disinfectants is mediated by efflux pumps generally encoded by plasmid-borne genes (Vijayakumar and Sandle, 2019).

Qac genes encode efflux pumps capable of expelling many quaternary ammonium compounds (QACs), such as benzalkonium chloride and cetrimide, from bacterial cells (Wassenaar et al., 2015). The first study on this efflux system was performed by assaying the ethidium bromide efflux (Johnston and Dyke, 1969); the gene involved was identified on a plasmid in 1989 and thus named *ebr* by Sasatsu et al. (1989).

The *qac*A gene is located on the psK1 plasmid (Rouch et al., 1990) and codes for the production of a transmembrane efflux protein of the major facilitator superfamily named QacA (Tennent et al., 1989). *qac*A requires the activity of a transcriptional regulator coded by *qac*R (Peters et al., 2009). The *qac*B gene was sequenced from the plasmid psK23 in 1996 (Paulsen et al., 1996) and found to share a high degree of homology with *qac*A; its sequence differs from that of *qac*A in only seven nucleotides, resulting in changes in six amino acid positions. Despite this genetic similarity, *qac*B has a different substrate specificity, recognizing monovalent organic cations due to the presence of an uncharged residue, alanine, instead of aspartic acid as found in QacA (Paulsen et al., 1996). The *qac*C gene was first sequenced from the plasmid pSK89 (Littlejohn et al., 1991) but then isolated from other *S. aureus* plasmids and reported with alternative names, such as *smr* (staphylococcal multidrug resistance) or *qac*D (Grinius et al., 1992; Grinius and Goldberg, 1994). The *smr* gene has been detected on large conjugative multiresistance plasmids (Lyon and Skurray, 1987; Evans and Dyke, 1988) and on small non-conjugative plasmids (<3 kb; Emslie et al., 1986; Leelaporn et al., 1994). This transporter functions as a homodimer and does not require any transcriptional regulator. While QacA and QacB proteins are members of the MFS, QacC belongs to the small multidrug resistance (SMR) protein family.

The intact *qac*E gene was only recently detected in *S. aureus*, isolated from a clinical setting (Sarwar et al., 2022). QuaE is a four-transmembrane segment SMR protein and has a partially active deletion derivative (Paulsen et al., 1993). The *qac*J gene was detected from a newly discovered RC plasmid (pNVH01) and then identified in several equine isolates of *S. aureus* (Bjorland et al., 2003); the *qac*H gene was identified on pST94 in food industry staphylococcal isolates by Heir et al. (1999), but not yet reported in *S. aureus*.

Transfer and co-selection of ARGs and BRGs

Horizontal gene transfer is considered one of the major factors responsible for the spread of antimicrobial resistance (AMR) in bacterial species (Sun et al., 2019; von Wintersdorff et al., 2016).

ARGs are mainly located in mobile genetic elements (MGEs), which, in *Staphylococcus*, can be classified into genomic islands, transposons, phages, plasmids, integrative conjugative elements (Sansevere and Robinson, 2017), integrons, and staphylococcal chromosomal cassettes (SCCs) (Lindsay, 2010; Alibayov et al., 2014). Approximately 15%–20% of the *S. aureus* genome is composed of MGEs, whose diversity confers the genome's high variability (Chambers and DeLeo, 2009; McCarthy et al., 2014).

Although bacteriophages rarely carry ARGs, they play pivotal roles in the mobility of ARGs in *S. aureus* (Deghorain and Van Melderen, 2012; Xia and Wolz, 2014). *S. aureus* pathogenicity islands (SaPIs), which use helper phages for replication and dissemination or remain integrated into the bacterial chromosome (Penadés and Christie, 2015), can harbor ARGs such as *aad*, *erm*A, fosfomycin resistance genes, or multidrug exporters (Novick et al., 2010).

Transfer of MGEs mainly occurs during colonization of human or animal hosts, as evidenced by epidemiological studies (Knight et al., 2012; Lindsay et al., 2012; Stanczak-Mrozek et al., 2015), or during biofilm formation (Savage et al., 2013).

ARGs carried on *S. aureus* MGE and mechanisms of gene transfer were recently reviewed by Haaber et al. (2017).

Plasmid-carrying ARGs can be transferred between distantly related bacteria (Dahlberg et al., 1998), even between Gram-positive and Gram-negative bacteria, and this raises further concern in relation to the spread of resistance (Courvalin, 1994). An example of this was reported by Bes et al. (2021), who recently demonstrated the *in vitro* conjugative transfer of the plasmid p_8N_qac carrying the *qac*A gene from *S. aureus* to *E. coli*, highlighting how this issue is also associated with the dissemination of resistance to common sanitizers.

The role of biocides in the spread of AMR is controversial and argued. Some AMR and biocide resistance mechanisms may share a common mechanism based on the action of efflux pumps, changes in the permeability, and biofilm formation; MGEs carrying biocide resistance genes can also harbor some ARG, as in the case of *qac*E (Pal et al., 2015); furthermore, the exposure to biocides can induce the expression of efflux pumps involved in AMR (Paul et al., 2019).

In 2009, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR, 2009) established that the use or misuse of certain active substances in biocidal products in various settings may contribute to increasing the opportunities for co-selection both in humans and in the environment across taxonomic groups and different types of biocides. Indeed, the co-selection potential has been discussed in several papers (Jones and Joshi, 2021) and contexts: in farms (reviewed by Davies and Wales, 2019), in clinical practice (Russell, 2002), and in community environments (Chen et al., 2021).

A focused analysis by Pal et al. (2015) clarifies that the *Staphylococcus* genus is one of the bacterial groups in which the higher proportion of plasmids hosted (approximately 20%) tended to carry both BRGs and ARGs on the same plasmid. Plasmids with co-selection potential tend to be conjugative and more often carry toxin–antitoxin systems, which have a role in stabilizing plasmids in their hosts by killing daughter cells that do not inherit the plasmids (Gerdes et al., 1986). Results of this study, however, suggest that plasmids provide limited opportunities for biocides and metals to promote the horizontal transfer of antibiotic resistance through co-selection (Gullberg et al., 2014), whereas wide possibilities exist for indirect selection via chromosomal biocide/metal resistance genes.

Some studies demonstrated that the use of biocides can produce selective pressure on *S. aureus*. Ciusa et al. (2012) demonstrated that the biocide triclosan produces a selective pressure on *S. aureus*, identifying novel resistance mechanisms with high potential for horizontal gene transfer linked to the presence of a mutated *fab* gene, coding for the NADH-dependent trans-2-enoyl-acyl carrier protein reductase, or an additional sh-fabI allele, derived from *S. haemolyticus*.

Hardy et al. (2018) demonstrated that the increased use of antiseptics (chlorhexidine and octenidine) was associated with reduced susceptibility in clinical isolates of *S. aureus*. Biocide susceptibility did not correlate with the carriage of *qac* efflux pump genes, but mutations within the NorA or NorB efflux pumps, associated with chlorhexidine export, were suggested to exert an important mechanism of biocide tolerance. Htun et al. (2019) demonstrated a positive association between *qac*A/B carriage and chlorhexidine/octenidine exposure. Chlorhexidine exposure was associated with reduced chlorhexidine susceptibility (MIC >4 mg/L), and carriage of *qac*A/B or *qac*C was associated with reduced chlorhexidine susceptibility. Neither octenidine exposure nor carriage of *qac*A/B or *qac*C genes was associated with reduced susceptibility to octenidine; on the contrary, isolates exposed to octenidine were four times less likely to have reduced susceptibility to octenidine than unexposed isolates.

Concerning food production, the report of the Joint FAO and WHO Expert Meeting on foodborne antimicrobial resistance held in Rome (FAO and WHO, 2019) declared that "insufficient evidence is available to identify biocide use in food production as a driver of AMR. However, the identified association between biocide tolerance and resistance to one or more classes of antimicrobials underscores the need for increased awareness and prudent use of these products".

AMR has several routes to enter the food chain: selective pressure by overuse and misuse of antimicrobials in farms and exposure to biocides or cationic compounds used as disinfectants, antiseptics, preservatives, supplements for livestock, and crop protectants. With the emergence of AMR, food may play an underestimated role as a reservoir and hotspot in the spread of resistance.

WGS-based surveillance of AMR in *S. aureus*

Many studies reported the WGS-based prediction of *S. aureus* AMR in food (Zhang F. et al., 2022; Fanelli et al., 2022; Li et al., 2022; Sri Prabakusuma et al., 2022; Wu et al., 2022). Resistance prediction databases, such as CARD, MEGARes, and AMRFinder, generally rely on BLASTn analysis and require significant computational resources and time (Gordon et al., 2014; Babiker et al., 2019). Depending on the tools used, the accuracy of these methods can vary significantly (Mason et al., 2018) and relies on the quality of the available database (Hendriksen et al., 2019); furthermore, studies on the concordance between phenotypic assessment and genomic prediction provided discordant results (Mason et al., 2018; Babiker et al., 2019). In 2022, Wang et al. (2022) created a novel *S. aureus* prediction model based on the analysis of antimicrobial-resistant phenotypes of training isolates and k-mer calculation, combined with machine learning algorithms, to predict the resistome of *S. aureus*.

Nowadays, automated pipelines have also been introduced in clinical environments to detect transmission chains and subtypes and monitor outbreaks of *S. aureus*, providing fast and cost-effective surveillance of MRSA (Leopold et al., 2014; Dymond et al., 2020; Slott Jensen et al., 2020).

These novel typing methods are based on WGS sequencing data and are defined as core genome multi-locus sequence typing (cgMLST) and target 1,861 *S. aureus* core loci (https://www.cgmlst.org/ncs/schema/141106/https://www.cgmlst.org/ncs/schema/141106/) (Leopold et al., 2014). cgMLST pipelines have been implemented within many bioinformatics software, such as BioNumerics (bioMérieux SA, Sint-Martens-Latem, Belgium), SeqSphere+ (Ridom, Germany), PHYLOViZ (http://www.phyloviz.net/), Galaxy@Sciensano (http://galaxy.sciensano.be/), and chewBBACA (Silva et al., 2018).

Since the development of the *S. aureus* cgMLST scheme (Leopold et al., 2014), a few dozen papers have been published on the cgMLST for epidemiological study. The majority of these are associated with CA-MRSA or MSSA outbreaks (Park et al., 2017; Madigan et al., 2018; Cheng et al., 2019; Cho et al., 2020; Slingerland et al., 2020).

Konstantinovski et al. (2021) used this method to monitor the transmission of oxacillin-resistant SA in hospital environments, while Kinnevey et al. (2021) studied the transmission of MRSA in healthcare workers, patients, and environments in non-outbreak settings. Zhu et al. (2021), by performing cgMLST analysis to map the transmission of CA-MRSA in households, revealed that the home environment was an important MRSA reservoir. Slott Jensen (2020) evaluated the transmission of livestock-associated MRSA CC398 in hospitals by calculating the cost of the intervention to stop the transmission and demonstrated the utility of cgMLST for the surveillance of transmission of LA-MRSA in hospitals.

Effelsberg et al. (2019), by analyzing the LA-MRSA CC398 in pigsty fieldworkers, traced the origin of the Western German LA-MRSA CC398 back to the 1990s. This clone diversified into farm-specific genotypes, which stayed relatively consistent over time. Loncaric et al. (2019) investigated the diversity of Australian MRSA from companion animals, highlighting the predominance of the ST398 lineage and the presence of new clones.

Other studies on animals are those carried out by i) Scholtzek et al. (2019), which characterized equine SA isolates, exhibiting reduced oxacillin susceptibility, ii) Leijon et al. (2021) and Ndahetuye et al. (2021) on SA associated with bovine clinical mastitis, iii) Kaiser-Thom et al. (2022) on SA isolated from horses with equine pastern dermatitis, and iv) Ozawa et al. (2022) on MRSA isolated from pigs in Japan.

Only three cgMLST studies have so far been reported on food. Tegegne et al. (2021) characterized 34 livestock-associated MRSA *spa* Type t899 strains belonging to different sequence types isolated from humans, animals, and a few food items, of which 20 belonged to ST398, 13 to ST9, and one to ST4034; all t899 isolates harbored the mecA gene on a SCC*mec*IVa (2B) element, except for two, which presented either the SCC*mec*V element or an undefined cassette. The SNP-based phylogeny analysis was consistent with the core genome multilocus sequence typing (cgMLST) analysis, with *S. aureus* isolates clustering apart based on STs. Phiri et al. (2022) investigated the prevalence and diversity of SA in the dairy value chain in Zambia, with a focus on raw milk. cgMLST performed on 93 isolates indicated transmission of strains along the dairy chain in Zambia with possible persistence in the chain over time. cgMLST also revealed a very close relatedness between some isolates from milkers, raw milk, or milk buckets, confirming a possible transmission between the milker and milk chain and clearly supporting the hypothesis of a direct or indirect transfer of human-derived *S. aureus* to cows, raw milk, or the surface of milk-handling equipment. The predominant *spa* type varied depending on the province, underlining the local characteristics of the traditional Zambian dairy chain. Mikhaylova et al. (2022) evaluated the genomic relatedness of 35 SA isolated from RTE food in Russia. The isolates belonged to 15 different MLST-based types, with the predominant ones belonging to clonal complex 22. The authors, examining the isolates belonging to the same/single strain based on cgMLST analysis, identified the differences in their accessory genomes, marking their dynamics and plasticity. A total of 14 samples (40%) carried at least one enterotoxin gene; additionally, a major portion of the isolates harboring the *tsst*1 gene were MRSA. cgMLST-based approaches have been demonstrated to provide high-resolution typing and be efficient and cost-effective in the surveillance of SA transmission in different environments, including clinical settings, animals, and food.

In 2022, Lagos et al. (2022) performed a comparative analysis between cgMLS- and SNP-based methods, using two cgMLST schemes and two SNP pipelines. The authors concluded that, independently from the approach used, an estimated genomic variation rate of 2.0–5.8 genetic events per year (without recombination) is a general guideline to be used for surveillance and outbreak investigation at clinical laboratories. The authors also highlighted the importance of selecting a reference genome with a well-defined core genome closely related to the sequences analyzed in order to avoid bias that can influence the subsequent analysis, such as the detection of genetic events.

Eradication of AMR infections is challenged by the existence of asymptomatic colonization (MacKinnon and Allen, 2000; Smith et al., 2004), and time is an essential factor for the success of intervention measures against the spread of AMR, especially in healthcare-associated infections (Bootsma et al., 2006). While WGS data production has become increasingly fast and accurate, limitations occurred when all the data produced had to be analyzed and interpreted. In this scenario, the need to develop user-friendly bioinformatics platforms, which allow the management and interrogation of data for workers that do not have bioinformatics expertise, remains pivotal.

S. aureus biofilm and novel strategies to control contamination in the food sector

Biofilm is a bacterial community embedded in a self-produced matrix made of extracellular polymeric substances (EPSs). The main constituents of EPSs are polysaccharide intercellular adhesin or poly-N-acetylglucosamine, as well as proteins, lipids, RNA, and extracellular DNA (Forson et al., 2020). Biofilm formation is controlled by the quorum sensing system that confers the ability to sense the bacterial cell density and respond to environmental stimuli through a cell-to-cell communication using small diffusible chemical signaling molecules called autoinducers (Peng et al., 2022). In *Staphylococcus*, quorum sensing is regulated by the accessory gene regulator (*agr*) system (Le and Otto, 2015).

S. aureus biofilm may form on food and food facility equipment, facilitating the persistence of bacterial cells, including antimicrobial-resistant forms, on such surfaces and the possibility that they could cross-contaminate other materials and food. This increases the

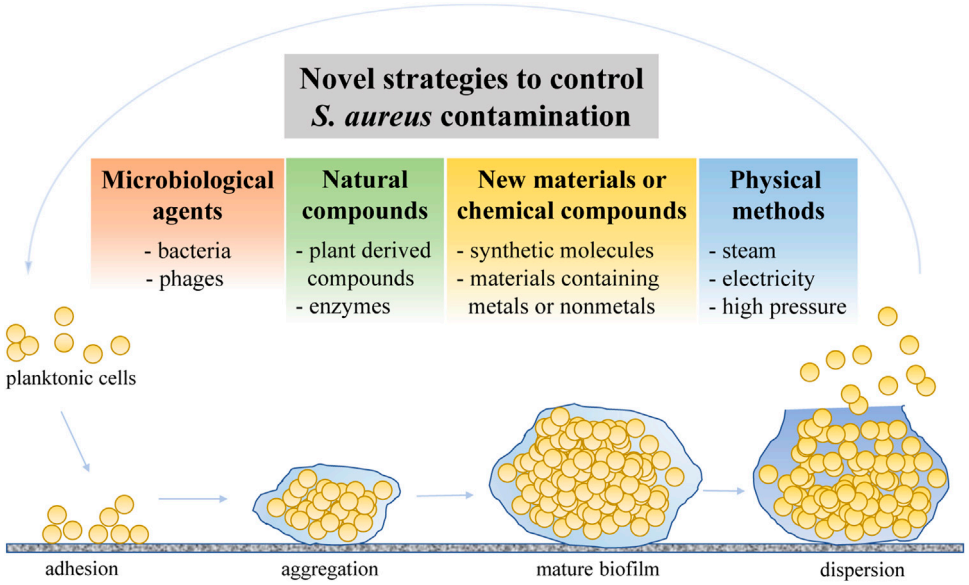

FIGURE 1
Summary of novel strategies proposed to control *S. aureus* contamination.

spreading of *S. aureus* and the possible consequent onset of *S. aureus*-related diseases. Moreover, biofilm protects cells against adverse environmental conditions such as nutrient limitation, change in temperature, and dehydration (Idrees et al., 2021); therefore, cells living in biofilm exhibit a greater resistance than their planktonic form (Liu et al., 2019).

Stainless steel, glass, polystyrene, and polyvinyl chloride (PVC) are commonly used materials in food facilities and, although not unequivocally demonstrated (da Silva Meira et al., 2012; Pagedar et al., 2010; Cha et al., 2019; Lee et al., 2015), surfaces with high free energy, such as those made of stainless steel and glass, exhibit greater hydrophilicity, which may allow a better bacterial attachment, which easily leads to biofilm formation (Lee et al., 2015; Cha et al., 2019).

Traditionally, various cleaning agents and biocides such as quaternary ammonium compounds, sodium hypochlorite (NaClO) and other chlorine-based compounds, sodium hydroxide (NaOH), nitric acid (HNO_3), anionic acids, and iodophors (Martin et al., 2016) are used in the food sector for surface decontamination. However, beyond the issue related to the onset of the genetic resistance to the utilized biocides (Butucel et al., 2022), their effectiveness is actually hampered by the reduced penetrability of these agents toward biofilm due to its peculiar structure that protects the embedded cells (Idrees et al., 2021).

It has been shown that a commercial chlorine-based sanitizer applied on stainless steel (type 304, no. 4 finish) for 1 min at room temperature, when compared with distilled water able to reduce *S. aureus* biofilm cells by 0–2 Log colony-forming units (CFU), decreased *S. aureus* biofilm cells approximately by only 1–3 Log CFU (starting from an *S. aureus* biofilm cell density of approximately 3–6 Log CFU/10 cm^2) (Lee et al., 2015). Martin et al. (2016) assessed the efficacy of a cleaning protocol employing sodium hypochlorite in cheese-producing dairy plants. Although a certain efficacy was observed in removing adhered *S. aureus* cells from stainless steel and polypropylene surfaces at a temperature of 5°C, the protocol was ineffective in removing the *S. aureus* cells at the cheese-making temperature of 35°C, which is probably due to the higher number of cells adhering at this higher temperature (1.95–4.98 versus 5.15–6.58 Log CFU/cm^2 at 5°C and 35°C, respectively) (Martin et al., 2016), suggesting that traditional cleaning protocols should be revised in order to control *S. aureus* more effectively. Considering this, researchers are driven to seek novel strategies to address the issue related to *S. aureus* contamination and its spread in the food sector (Figure 1; Table 2).

Strategies using microbiological agents

Lactic acid bacteria may produce molecules with antibacterial and antibiofilm activities so that cell-free supernatants (CFSs) may be effective against *S. aureus*. In particular, it has been demonstrated that CFSs of *Lactobacillus acidophilus* LA5 and *Lactobacillus casei* 431 possess antibacterial activity, being able to inhibit *S. aureus* growth, as determined by the agar-well diffusion test, and reduce 2-day-old biofilms grown on polystyrene and glass surfaces by 45%–70%, depending on the CFS concentrations used (40%–100%) (Koohestani et al., 2018).

Specific bacterial molecules have also been evaluated for their activity against *S. aureus*. Surfactin produced by *Bacillus subtilis* has been proposed as a potential coating agent for contact surfaces to prevent *S. aureus* biofilm formation (Liu et al., 2019). In particular, this environmentally friendly low-toxicity biosurfactant inhibited *S. aureus* growth, showing a minimum-inhibitory concentration (MIC) of 32 μg/mL and a minimum bactericidal concentration (MBC) of 128 μg/mL. Moreover, likely due to its effect on the *S. aureus* quorum sensing system and the ability to downregulate the *ica*A and *ica*D gene expression, impairing the biofilm polysaccharide production, this molecule decreased the formation of *S. aureus*

TABLE 2 Novel strategies to control *S. aureus* contamination in the food sector.

Employed strategy	Anti-biofilm/anti-*S. aureus* agent or compound	Activity	Reference
Microbiological agents	*Lactobacillus* (*L.*) *acidophilus* LA5 and *L. casei* 431 cell-free supernatants (CFSs) at different concentrations (40%–100%)	*L. acidophilus* LA5 and *L. casei* 431 CSFs (100%) resulted in inhibition zones of 50.26 and 37.06 mm, respectively, against *S. aureus* ATCC 25923, and ca. 45%–70% reduction (used at concentrations of 40% to 100%) of 2-day-old biofilms grown on polystyrene and glass surfaces	Koohestani et al. (2018)
	Surfactin produced by *Bacillus subtilis* at concentrations of 8 to 128 μg/mL	Surfactin showed a MIC of 32 μg/mL and an MBC of 128 μg/mL against *S. aureus* ATCC 65389; 40 to >80% reduction of biofilm formation (at concentrations of 8 to 128 μg/mL), and <10 to 90% mature biofilm removal on glass, polystyrene, and stainless-steel (at a concentration of 0.05% to 0.1% after 1 to 4 h of treatment)	Liu et al. (2019)
	Bacteriophage of the family *Myoviridae* (vB_SauM_CP9) in combination with 1% thyme (*Thymus vulgaris*) essential oil	87.22% reduction of multidrug-resistant *S. aureus* (*S. aureus* ATCC 25923 and nine strains from chicken products) concentration on chicken fillets (after 120-min treatment)	Abdallah et al. (2021)
	Endolysin LysCSA13 (50 nM–1000 nM)	82%–84% and 92%–88% reduction of *S. aureus* RN4200 and CCARM 3090 biofilm on stainless-steel and glass, respectively	Cha et al. (2019)
Natural compounds	Essential oils of manuka leaves (*L. scoparium* J. R. et G. Forst) (MIC: 0.012%–0.024% v/v), thymus (*T. vulgaris L.*) (MIC: 0.024% v/v), cinnamon bark (*C. zeylanicum* L.), (MIC: 0.049%–0.098% v/v) and bergamot (*C. bergamia* Risso) (MIC: ≥0.781% v/v)	Growth inhibition of three milk-derived biofilm-producing *S. aureus* strains (including MRSA) and two biofilm-producing reference *S. aureus* strains (ATCC 35556 and ATCC 12600)	Pedonese et al. (2017)
	Quinic acid (0.3125–1.25 mg/mL)	55%–70% *S. aureus* ATCC 29213 biofilm reduction, decreased adhesion to fibrinogen, metabolic activity and viability, and adhesion to stainless steel	Bai et al. (2019)
	Moringa oleifera seed oil extract (MOSO)	MOSO at 0.5% and 1% showed inhibitory and bactericidal activity, respectively, against *S. aureus* biofilms on polystyrene surfaces. MOSO at 1% reduced 2.38 log CFU/cm^2 of *S. aureus* biofilms formed on the PVC (polyvinyl chloride) surface	de Oliveira et al. (2021)
	Eleutherine americana bulb crude extract	1 mg of the extract reduced *S. aureus* ATCC 25923 by 5 log	Ifesan et al. (2009)
	α-Amylase, amyloglucosidase, cellulase R-10, DNase I, and proteinase K	100 mg/mL of *a*-amylase reduced by 38%–83% biofilm formation by *S. aureus* strains	Kim et al. (2019a)
New food-contact materials or new chemical compounds	Synthetic compound LMM6 (1,3,4-oxadiazole)	LMM6 (0.48 to 62.5 μg/mL) reduced the concentration of *S. aureus* by 4 log CFU, the preformed biofilm by 1 log CFU per cm^2, and 60% of biofilm biomass	Dante Formagio et al. (2022)
	Copper (Cu)-bearing 304 type stainless steel (304CuSS)	Reduction of *S. aureus* ATCC 25923 biofilm after 2, 4, and 7 days of exposure at 37°C (*S. aureus* adhered cells ranged from 3.28 to 4.39 log CFU/mL) compared to traditional 304 type stainless steel (*S. aureus* adhered cells ranged from 6.93 to 7.91 log CFU/mL)	Nan et al. (2015)
	Molybdenum disulfide surfaces with different particle size	28.5% reduction of *S. aureus* biofilm	Amin et al. (2020)
	Silver (Ag-NPs) and zinc oxide (ZnO-NPs) nanoparticle-containing polyester surfaces (400 ppm–850 ppm)	400 ppm of Ag-NPs and a combination of 850 ppm of Ag-NPS and 400 ppm of ZnO-NPs reduced *S. aureus* biofilm by 3.84 and 4.11 log CFU/cm^2, respectively	Fontecha-Umaña et al. (2020)
	Selenium (Se)-coated paper towels	89% inhibition of the growth of *S. aureus* ATCC 25923 after 24, 48, and 72 h compared to Se-uncoated paper towels	Wang and Webster (2013); Wang et al. (2015)
Physical methods	Superheated steam (SHS) at 150 °C for 10–15 s at a nozzle-surface distance of 7 cm	Reduction below the detection limit of a three-strain (ATCC 25923, ATCC 27213, and ATCC 29213) 5-day-old *S. aureus* biofilm grown on types 4 and 2B	Kim et al. (2019b)

(Continued on following page)

TABLE 2 (*Continued*) Novel strategies to control *S. aureus* contamination in the food sector.

Employed strategy	Anti-biofilm/anti-*S. aureus* agent or compound	Activity	Reference
		finish 304 stainless steel (10 s treatment), high-density polyethylene and polypropylene (15 s treatment)	
	High-voltage prick electrostatic field (HVPEF) (10, 11, 12, or 13 kV for 15 or 30 min)	*S. aureus* NCTC 8325-4 contamination on salmon, griskin, cheese, and sausage (ca. 10^5 CFU/cm^2) reduced between 46% and 56% (HVPEF at 10 kV for 15 min) and 98% and 99% (HVPEF at 13 kV for 30 min)	Qi et al. (2021)
	High-voltage prick electrostatic field (HVPEF) (9, 10, 11, and 12 kV for 90 min; 13 kV for 15, 30, 45, 60, 75, and 90 min)	24-h (ca. 7 log CFU/cm^2)- and 48-h (ca. 6 log CFU/cm^2)-old *S. aureus* NCTC 8325–4 biofilms on polystyrene were reduced between ca. 0.5 (13 kV for 15 min) and 2.5–3 log CFU/cm^2 (13 kV for 90 min), while 24-h (ca. 6.5 log CFU/cm^2)-old *S. aureus* NCTC 8325–4 biofilms on polypropylene, stainless steel, and glass were reduced between ca. 0.1-0.9 (13 kV for 15 min) and 2.5-3 (13 kV for 90 min) log CFU/cm^2. *S. aureus* NCTC 8325–4 biofilm formation in static growing conditions was significantly ($p < 0.001$) and increasingly reduced by HVPEF applied at 11 to 13 kV for 90 min or at 13 kV for 60 to 90 min	Qi et al. (2022)
	Acidic electrolyzed water (AEW) (pH 2.5–3.5) and basic electrolyzed water (BEW) (pH 10.8–11.6) generated from 0.1% NaCl solution	AEW reduced S. *aureus* ATCC 6538 biofilm viability by ca. 80% (pH 3.5)–95% (pH 2.5) and BEW reduced S. *aureus* ATCC 6538 biofilm biomass by ca. 42% (pH 10.8)–78% (pH 11.6) after 2 min treatment at 37°C	Sun et al. (2012)
	Ultra-high-pressure homogenization (UHPH) at 40,000-pound square inch (PSI) (for one–three cycles)	1.56 log CFU/mL (after one cycle) and 2.91 log CFU/mL (after three cycles) reduction of five chicken-derived *S. aureus* mixed planktonic cells (initial concentration ca. 10^{7-8} CFU/mL); 0.95 log CFU/mL (after three cycles) reduction of five chicken-derived *S. aureus* mixed-biofilm detached-cells (initial concentration ca. 10^{7-8} CFU/mL)	Zhang et al. (2021)

MIC, minimum inhibitory concentration; MBC, minimum bactericidal concentration.

biofilm by 40 to >80% and decreased the formation of mature biofilm on glass, polystyrene, and stainless-steel surfaces by < 10 to 90%, depending on surfactin concentrations and duration of treatment (Liu et al., 2019).

Strategies employing viruses have also been evaluated against *S. aureus*. When used on poultry products in combination with 1% thyme essential oil, a bacteriophage of the family *Myoviridae* (vB_SauM_CP9) able to resist different food processing stress factors (such as pH and temperature changes), showed lytic activity on several multidrug-resistant *S. aureus* strains resistant to several antibiotics, including methicillin, nalidixic acid, sulfamethoxazole, amoxicillin, doxycycline, cefotaxime, erythromycin, norfloxacin, gentamicin, and ciprofloxacin. Thus, it was recommended for application in the food sector by spraying or via packaging materials (Abdallah et al., 2021). A phage-encoded endolysin (LysCSA13) from an *S. aureus*-specific bacteriophage (CSA13) showed activity against *S. aureus* biofilm and planktonic cells, including MRSA, when applied on polystyrene, glass, and stainless-steel surfaces, demonstrating its potential use in food facility environments (Cha et al., 2019).

Strategies using natural compounds

Recent studies have indicated that various natural compounds not only inhibit biofilm formation but also eradicate mature biofilm produced by several bacterial species, including *S. aureus* (Mastoor et al., 2022). Essential oils are mixtures of secondary metabolites obtained from plants, which can exert an antimicrobial activity directly when used in food products and in active food packaging, or indirectly when used as sanitizing or antibiofilm agents on food- and other contact surfaces (Pedonese et al., 2017). In particular, it has been found that manuka leaf (*Leptospermum scoparium* J. R. et G. Forst), thymus (*Thymus vulgaris* L.), and cinnamon bark (*Cinnamomum zeylanicum* L.) essential oils may have a better growth inhibition activity against foodborne MRSA and foodborne biofilm-producing *S. aureus* strains than bergamot (*Citrus bergamia* Risso) essential oils, likely due to the presence of terpene (carvacrol, leptospermone, p-cymene, thymol, trans-Calamenene, and *ß*-caryophyllene) and non-terpene ((E)-cinnamaldehyde) derivatives as major compounds, being therefore proposed as food additives, food packaging constituents, and possible surface sanitizers in the food sector (Pedonese et al., 2017).

In addition, organic acids extracted from plants may have good inhibitory activities against foodborne pathogens. Quinic acid, widely spread in plants, has been shown to inhibit biofilm formation, mainly decreasing the initial *S. aureus* adhesion, as well as reducing the metabolic activity and the viability of the *S. aureus* biofilm cells (Bai et al., 2019). Moreover, a certain

ability to reduce established *S. aureus* cells adhered to stainless steel has been demonstrated. Those results suggested that quinic acid can be used in food facilities as an antibiofilm agent, especially for preventing surface biofilm formation (Bai et al., 2019).

Among plant extracts, environmentally friendly molecules can be extracted using green technologies in order to reduce the impact of pollution derived from the widespread usage of traditional chemical sanitizers. *Moringa oleifera* seed oil extracted using pressurized *n*-propane instead of toxic solvents (*n*-hexane, ethanol, and DMSO) could be used in the food sector, providing an option for a safe and efficient large-scale producible antibiofilm agent (de Oliveira et al., 2021). Probably due to its high percentage of fatty acids (especially oleic acid, behenic acid, and palmitic acid), *Moringa oleifera* seed oil extract showed activity against *S. aureus* biofilm, being able to inhibit its formation or eliminate the formed biofilm, depending on its concentration (0.25, 0.5, and 1%) and contact time (10, 20, 40, and 60 min), on polystyrene or PVC (de Oliveira et al., 2021). In addition, the bulb extract from the plant *Eleutherine americana* Merr., which is commonly used in Thai cuisine and in folk medicine, has been suggested as a potential natural preservative to be used in food against *S. aureus*, due to the ability of the ethanol crude extract (0.25 mg/mL–4 mg/mL) to reduce the concentration of foodborne *S. aureus* by approximately 3–6 log cfu/mL, depending on the strain tested (Ifesan et al., 2009).

Enzymes, derived mainly from animals, fungi, or bacteria, may also represent a promising technology to be used in food facilities. It was found that 1 U/100 μL of *a*-amylase, cellulase R-10 and DNase I, and 1 milli-Anson unit/100 μL of proteinase K could have a certain inhibitory effect on the formation or exert a certain degradative effect on the formed *S. aureus* biofilm on polystyrene, while amyloglucosidase showed only an inhibitory effect on biofilm formation (Kim M. J. et al., 2019). However, it should be noted that the work by Kim M. J. et al. (2019) reported a strong strain-dependent effect and, in one case, also a paradox effect occurred since the enzymatic treatment (α-amylase, amyloglucosidase, cellulase, and proteinase K) enhanced the biofilm formation by *S. aureus* ATCC 12600 (Kim M. J. et al., 2019).

Strategies using new food-contact materials or new chemical compounds

Apart from microbiological agents and natural substances, new chemical compounds and new food-contact materials are exploitable to control *S. aureus* contamination. Recently, a new derivative belonging to the oxadiazole class, i.e., the synthetic 1,3,4-oxadiazole compound LMM6, previously reported for its fungicidal activity against *Candida albicans* (Faria et al., 2021), has been described to inhibit both bacterial growth in liquid culture and biofilm formation, as well as reduce the biomass of the already formed biofilm, probably interfering with the exopolysaccharide matrix, leading to biofilm disruption. Therefore, it was proposed as an innovative synthetic molecule to be used also in combination with other sanitizers or methods for *S. aureus* control (Dante Formagio et al., 2022).

In addition, novel food-contact surfaces may be used in food facilities. In particular, a novel type of stainless steel containing copper (304CuSS) has been shown to have an antibacterial ability against *S. aureus* when compared to traditional stainless steel, reducing the formation of biofilm even after a 7-day-long exposure to *S. aureus* (Nan et al., 2015). Such activity is likely due to the presence of saturated Cu-rich precipitates that continuously release Cu^{2+} ions that bind to EPS and bacterial proteins, thus altering their properties (Nan et al., 2015). Molybdenum disulfide (MoS_2) surfaces, although depending on the size and concentration of the constitutive MoS_2 particles, were demonstrated to reduce *S. aureus* retention and biofilm formation, as well as having no cytotoxic activity on eukaryotic cells (renal human cells HK-2), therefore being potentially safe for consumers and exploitable in the food sector (Amin et al., 2020). Additionally, silver (Ag-NPs) and zinc oxide (ZnO-NPs) nanoparticles can be incorporated into a polymer matrix (polyester) and then exploited as an antimicrobial food-contact surface due to the release and migration of biocidal ions (Fontecha-Umaña et al., 2020). Ag-NPs showed better antimicrobial activity against *S. aureus* at all the tested concentrations (400 ppm–850 ppm), but the usage in combination with ZnO-NPs (400 ppm) resulted in a synergistic action which further increased the antimicrobial efficacy (Fontecha-Umaña et al., 2020). Chemical elements could also be added to other disposable materials. For instance, bacterial growth can occur on paper products, such as wrappings and towels used in the food sector, that, therefore, may represent sources of *S. aureus* contamination during food packaging, surface cleaning, or hand drying (Wang and Webster, 2013; Wang et al., 2015). Considering this, paper towels coated with selenium (Se) nanoparticles were shown to be able to inhibit the growth of *S. aureus* by 89% when compared to Se-uncoated paper towels (Wang and Webster, 2013; Wang et al., 2015). The ability to adsorb large amounts of proteins is probably one of the mechanisms by which the Se-coated paper towels inhibited bacterial growth, and they were proposed as a promising selenium-based antibacterial strategy that may prevent bacterial spreading in the food sector (Wang and Webster, 2013; Wang et al., 2015).

Strategies using physical methods

Steam has been evaluated for its anti-*S. aureus* activity. In particular, the so-called superheated steam (SHS) able to reach 150 °C, above the saturation temperature, is more effective than saturated steam (SS) at 100 °C (Kim S. H. et al., 2019). SHS reduced, below the detection limit, multi-strain 5-day-old *S. aureus* biofilms, grown on stainless steel, polypropylene, and high-density polyethylene, in 10 (stainless steel) to 15 (polypropylene and high-density polyethylene) seconds (Kim S. H. et al., 2019). It resulted in a time-saving and non-polluting technology, as it does not employ any chemical compound, and it has the potential to be used in the food sector.

On the other hand, low-temperature sterilization techniques are gaining increasing attention for being able to preserve materials sensitive to high temperatures. Electric field techniques are being considered and, contrary to ultraviolet light (UV) sterilization, they prevent radiation damage (Qi et al., 2022). Recently, the high-voltage prick electrostatic field (HVPEF), which has a simpler generation system than that of the previously investigated pulsed electric field (PEF) (Khan et al., 2016; Guo et al., 2018; Wang et al., 2018), has been evaluated against *S. aureus* present on surfaces and on food (Qi et al., 2021; Qi et al., 2022). HVPEF showed activity against *S. aureus* contamination on cheese, sausage, salmon, and griskin, and the mortality rate increased with the increase of the

electric voltage (10–13 kV) and treatment time (15–30 min), reducing the *S. aureus* contamination up to 98%–99% (Qi et al., 2021). HVPEF was also effective against *S. aureus* in the biofilm form (Qi et al., 2022). In particular, it reduced 24- and 48-h-old biofilms established on different surfaces, mainly by killing the embedded bacteria. In addition, it was able to inhibit the *S. aureus* biofilm formation, likely due to its direct effect on the planktonic cells, together with the ability to reduce the release of the key components of EPS and regulate the expression of biofilm formation-related genes (*icaA, ebh, cidA, sarA, icaR,* and *sigB*) (Qi et al., 2022).

Electricity could also be employed in another way. It can be used to produce electrolyzed water (EW), which is a low-cost and environmentally friendly product obtained by electrolyzing water containing NaCl or other salts (e.g., $NaNO_3$) (Sun et al., 2012). It has been shown that the EW acidic fraction (i.e., acidic electrolyzed water, AEW) had a bactericidal effect on the *S. aureus* cells present in biofilm, while the EW basic fraction (i.e., basic electrolyzed water, BEW) had the ability to directly remove biofilm biomass formed on polystyrene (Sun et al., 2012), indicating that AEW and BEW could be applied as a bactericidal and removing agent against *S. aureus* biofilm (Sun et al., 2012).

High pressure is being explored as a means for *S. aureus* decontamination. In particular, it has been shown that ultra-high-pressure homogenization (UHPH) may have the ability to decrease the number of *S. aureus* planktonic cells that may contaminate liquid food, but such technology showed poor effectiveness in reducing the number of *S. aureus* cells detached from the biofilm that may form within pipes and that may demonstrate a higher resistance to pressure (Zhang et al., 2021).

Overall, many methods have been investigated to prevent or control *S. aureus* contamination in food and on food-contact surfaces. The use of natural substances draws much attention, along with the possibility of employing new chemical compounds and new materials, as well as applying physical methods in innovative ways. It must be emphasized that these methods could be considered at an early stage of implementation because there is a substantial lack of practical application in the food establishments to verify (i) their *in situ* effectiveness, (ii) the economic viability for the food company, (iii) the ability to preserve the organoleptic characteristics of the wide variety of food products that can potentially be treated, and (iv) the absence of short- and long-term undesirable effects on the consumers. Nevertheless, the investigation of these new technologies represents a crucial area to be explored in order to address not only the issue related to chemical residues in food and the environmental impact but also to overcome the known mechanisms of genetic resistance that *S. aureus*, and bacteria in general, may exhibit to traditional biocides. Such novel technologies are paving the way to improve the safety of food products, preventing contamination by *S. aureus*, including its antimicrobial-resistant forms, and the onset of *S. aureus*- related diseases.

Staphylococcus aureus complex-related species: new antimicrobial-resistant pathogens of the food chain?

Few novel species are closely phenotypically and genotypically related to *S. aureus*, being part of the so-called *Staphylococcus aureus* complex. In 2015, this complex was conceived to include *S. aureus* and the two novel species *Staphylococcus argenteus* and *Staphylococcus schweitzeri* (Tong et al., 2015). Very recently, *Staphylococcus singaporensis* (Chew et al., 2021) and *Staphylococcus roterodami* (Schutte et al., 2021) were added to this complex, although, due to phylogenetic analyses, the classification into these two latter species seems questionable (Monecke et al., 2022). However, to date, the *Staphylococcus aureus* complex comprises *S. aureus* as well as *S. argenteus*, *S. schweitzeri*, *S. singaporensis*, and *S. roterodami*. With the exception of *S. schweitzeri*, the other three novel species (i.e., *S. argenteus, S. singaporensis*, and *S. roterodami*) are all associated to human infections (Becker et al., 2019; Chew et al., 2021; Schutte et al., 2021), highlighting that similar to *S. aureus*, they may act as pathogenic bacteria. Nevertheless, *S. schweitzeri* was found to have virulence abilities comparable to those of *S. aureus*, i.e., similar cellular invasion, pro-inflammatory cellular activation, and intracellular cytotoxicity, as well as higher extracellular cytotoxicity (Grossmann et al., 2021). It could also escape from phagolysosomes, coagulate plasma, and form biofilm; therefore Grossmann et al. (2021) warned that it may become an emerging pathogen in the near future. Considering the possibility that the *S. aureus* complex-related species may act as pathogens, the onset of antimicrobial resistance is a critical issue since it may hinder recovery if a pathological condition occurs. Interestingly, however, *S. schweitzeri* seems to be antimicrobial-susceptible to all the tested antibiotics (Table 3), while *S. roterodami* and *S. singaporensis* strains were found to be resistant or intermediate resistant to some antibiotics (Table 3). It should be noticed that *S. roterodami* and *S. singaporensis* were, so far, isolated from humans, fruit bats (*Eidolon helvum*), and a captive bird (diamond firetail finch, *Stagonopleura guttata*) in the few studies available to date (Chew et al., 2021; Schutte et al., 2021; Monecke et al., 2022). *S. schweitzeri* was reported in Africa, isolated from fruit bats (*Rousettus aegyptiacus*; *Eidolon helvum*) (Held et al., 2017; Olatimehin et al., 2018), non-human primates (Schaumburg et al., 2015; Tong et al., 2015), and surfaces of fomites (currency note and computer keyboard) (Shittu et al., 2020), while the transmission to humans appeared to be occasional (Schaumburg et al., 2015). Although, to the best of our knowledge, the presence of *S. roterodami*, *S. singaporensis*, and *S. schweitzeri* has not been reported so far in food, most likely due to lack of relevant targeted studies, it should be pointed out that bats and monkeys are food sources in some areas of Africa (Schaumburg et al., 2015; Held et al., 2017). Therefore, bushmeat could actually be a possible source of contamination and spreading of such novel species, deserving investigation in the near future. Conversely, *S. argenteus*, known for its ability to cause various pathological conditions in humans (e.g., sepsis, joint infection, endocarditis, and lymphadenitis) (Chantratita et al., 2016; Jiang et al., 2018; Ohnishi et al., 2018; Hirai et al., 2022) and animals (e.g., abscess, wound infection, and bovine mastitis) (Indrawattana et al., 2019; Pumipuntu et al., 2019; Meijer et al., 2022), is being reported from food, and it is increasingly recognized as an emerging foodborne pathogen (Shi and Zhang, 2018; Fusco et al., 2020), being able to cause staphylococcal food poisoning due to the production of enterotoxins, as assessed in three outbreaks reported so far in Japan (Suzuki et al., 2017; Wakabayashi et al.,

TABLE 3 ***S. aureus*** **complex-related species (*S. argenteus, S. schweitzeri, S. singaporensis*, and *S. roterodami*): sources and reported antimicrobial resistance.**

Sources	Samples	No. of isolates (prevalence %)	Tested antimicrobials	Resistance (no. of isolates out of the total)	Antimicrobial resistance genes	Reference
			S. argenteus			
RTE food	Delicatessen food containing eggplant, minced meat, and cheese (from food poisoning outbreak)	1 (NR)	NR	NR	NR	Suzuki et al. (2017)
	Boxed-lunch food (from food poisoning outbreak)	13 (100%)	AMK, CHL, CIP, DOX, ERY, FOX, GEN, KAN, LEV, LNZ, MIN, NOR, PEN, RIF, SXT, TEC, TET, and VAN	GEN (13/13) and KAN (13/13)	NR	Wakabayashi et al. (2018)
	Chicken, cold vegetable dish, fried rice, roast chicken, roast duck, and roast pork	16 (NR)	AMC, AMK, AMP, CAZ, CHL, CIP, CLI, CPM, ERY, FA, FOX, GEN, KAN, LNZ, NIT, NOR, PEN, RIF, STR, SXT, SYN, TEC, TEL, and TET	AMC (1/16), AMK (1/16), AMP (16/16), CHL (2/16), CLI (2/16), ERY (3/16), FA (3/16), GEN (3/16), KAN (3/16), PEN (16/16), STR (1/16), TEL (3/16), and TET (10/16)	NR	Wu et al. (2020)
Food	Pork	1 (NR)	NR	NR	NR	Zhang et al. (2016)
	Pork	NR	NR	NR	NR	Zhang et al. (2018)
	Aquatic products (crucian, cuttlefish, freshwater fish, sea-fish, shrimp, sleeve-fish, and white pomfret); edible mushrooms (*Pleurotus eryngii*); pasteurized milk; quick-frozen meat (beef, chicken, and dumpling); raw meat (beef, chicken, duck, mutton, pork, and sausage); vegetables (tomato)	98 (2%)	AMC, AMK, AMP, CAZ, CHL, CIP, CLI, CPM, ERY, FA, FOX, GEN, KAN, LNZ, NIT, NOR, PEN, RIF, STR, SXT, SYN, TEC, TEL, and TET	AMC (5/98), AMK (5/98), AMP (78/98), CHL (9/98), CIP (2/98), CLI (6/98), ERY (6/98), FA (19/98), GEN (4/98), KAN (29/98), NIT (2/98), NOR (3/98), PEN (80/98), STR (10/98), SYN (2/98), TEC (2/98), TEL (11/98), and TET (68/98)	NR	Wu et al. (2020)
	Chicken	21 (13.9%)	CHL, CIP, CLI, DOX, ERY, FOX, GEN, LEV, LNZ, MIN, MXF, PEN, RIF, SXT, TEC, and TET	DOX (1/21), PEN (2/21), and TET (1/21)	NR	Wakabayashi et al. (2022)
Contact surfaces	Cooking utensils (from food poisoning outbreaks)	6 (54.5%)[a]	AMK, CHL, CIP, DOX, ERY, FOX, GEN, KAN, LEV, LNZ, MIN, NOR, PEN, RIF, SXT, TEC, TET, and VAN	GEN (1/6)[a] and KAN (1/6)[a]	NR	Wakabayashi et al. (2018)
Food handlers	Nasal swab	5 (0.9%)	CLI, ERY, FOX, GEN, LEV, OXA, and VAN	All susceptible (2/2)[b]	NR	Aung et al. (2017b)
	Feces (collected after food poisoning outbreaks)	2 (28.6%)[a]	AMK, CHL, CIP, DOX, ERY, FOX, GEN, KAN, LEV, LNZ, MIN, NOR, PEN, RIF, SXT, TEC, TET, and VAN	GEN (1/2)[a] and KAN (1/2)[a]	NR	Wakabayashi et al. (2018)
			S. schweitzeri			
Animals	Non-human primates	24 (26.6%)	CLI, ERY, FOX, PEN, RIF, SXT, and TET	All susceptible (24/24)	NR	Schaumburg et al. (2015)
	Fruit bat (*Rousettus aegyptiacus*) pharyngeal swabs	2 (4%)	LNZ, SXT, TET, aminoglycosides, beta-lactams, glycopeptides, and quinolones	All susceptible (2/2)	NR	Held et al. (2017)
	Straw-colored fruit bat (*Eidolon helvum*) feces	11 (NR)		All susceptible (11/11)	NR	Olatimehin et al. (2018)

(Continued on following page)

TABLE 3 (*Continued*) *S. aureus* complex-related species (*S. argenteus, S. schweitzeri, S. singaporensis*, and *S. roterodami*): sources and reported antimicrobial resistance.

Sources	Samples	No. of isolates (prevalence %)	Tested antimicrobials	Resistance (no. of isolates out of the total)	Antimicrobial resistance genes	Reference
			CLI, DAP, ERY, FOS, GEN, LEV, LNZ, OXA, PEN, RIF, SXT, TET, and glycopeptides			
Fomites	Currency note and computer keyboard	2 (0.8%)	AMC, AMP, AMS, AMX, AZM, CEC, CFZ, CLA, CLI, CRO, CXM, DAP, ERY, ETP, FA, FOS, GEN, IPM, LEV, LNZ, MEM, MUP, OXA, PEN, PIP, PTZ, RIF, SXT, TEC, TET, TGC, and VAN	All susceptible (2/2)	Absence of *mec*A	Shittu et al. (2020)
S. singaporensis						
Humans	Clinical specimens	6[c] (NR)	CIP, CLI, ERY, FA, GEN, LNZ, MIN, MUP, NIT, OXA, PEN, SXT, SYN, TEC, and VAN	GEN (1/6)[d]	*aac(6′)-aph(2″)*, *aad*D; absence of *mec*A, *mec*C, and *bla*Z	Chew et al. (2021)
S. roterodami						
Animals and humans	Straw-colored fruit bat (*Eidolon helvum*) feces; diamond firetail finch (*Stagonopleura guttata*) pulmonary sample; human foot wound	4[c] (NR)	CIP, CLI, ERY, FA, FOS, FOX, GEN, LEV, LNZ, MUP, MXF, NIT, OXA, PEN, RIF, SXT, TEC, TET, TOB, and VAN	CIP (2/4)[e,f], LEV (2/4)[e,f], MUP (2/4)[e,f], PEN (1/4), RIF (2/4)[e,f], and TET (1/4)	*aad*K, *bla*Z/I/R, *grl*A, *gyr*A, *par*E (=*grl*B), *tet*(M); absence of *mec*A, and *mec*C	Monecke et al. (2022)

AMC, amoxicillin/clavulanic acid; AMK, amikacin; AMP, ampicillin; AMS, ampicillin/sulbactam; AMX, amoxicillin; AZM, azithromycin; CAZ, ceftazidime; CEC, cefaclor; CFZ, cefazolin; CHL, chloramphenicol; CIP, ciprofloxacin; CLA, clarithromycin; CLI, clindamycin; CPM, cefepime; CRO, ceftriaxone; CXM, cefuroxime; DAP, daptomycin; DOX, doxycycline; ERY, erythromycin; ETP, ertapenem; FA, fusidic acid; FOS, fosfomycin; FOX, cefoxitin; GEN, gentamicin; IPM, imipenem; KAN, kanamycin; LEV, levofloxacin; LNZ, linezolid; MEM, meropenem; MIN, minocycline; MUP, mupirocin; MXF, moxifloxacin; NIT, nitrofurantoin; NOR, norfloxacin; OXA, oxacillin; PEN, penicillin; PIP: piperacillin; PTZ: piperacillin/tazobactam; RIF: rifampicin; STR: streptomycin; SXT: trimethoprim/sulfamethoxazole; SYN: quinupristin/dalfopristin; TEC, teicoplanin; TEL, telithromycin; TET, tetracycline; TGC, tigecycline; TOB, tobramycin; VAN, vancomycin; NR, not reported (when specified in "antimicrobial resistance genes" column means that the detection of antimicrobial resistance genes is not addressed in the cited reference);

[a]data are expressed considering the two reported food poisoning outbreaks (Wakabayashi et al., 2018);

[b]antimicrobial susceptibility testing results were reported for two out of the five *S. argenteus* isolates (Aung M. S. et al., 2017).

[c]including *S. singaporensis* DSM111408^T (isolated from human cholecystostomy specimen);

[d]*S. singaporensis* DSM111408^T resulted susceptible to all the tested antimicrobials by Chew et al. (2021), while it resulted as intermediate resistant to CIP, LEV, MUP, and RIF by Monecke et al. (2022);

[e]including *S. roterodami* DSM111914^T (isolated from human foot wound);

[f]reported as intermediate resistant.

2018). Although the actual prevalence and distribution of *S. argenteus* in food products and food-related environments is still unclear (Shi and Zhang, 2018), *S. argenteus* has been recently reported from different food sources, including RTE food, comprising those involved in food poisoning, as well as contact surfaces of kitchen utensils and specimens from food handlers (Table 3). These isolates also demonstrated resistance to several antimicrobials (Table 3), therefore highlighting the possibility that food and contact surfaces may represent sources of *S. argenteus* and that the problem of antimicrobial resistance should not be overlooked for this emerging pathogenic bacterium. Nevertheless, to the best of our knowledge, the resistance to critical antimicrobials such as penicillinase-stable penicillins (e.g., methicillin, oxacillin, and cefoxitin) and vancomycin has not been reported so far in isolates from food and food-related environments, although methicillin-resistant *S. argenteus* strains are being found among clinical isolates (Giske et al., 2019; Witteveen et al., 2022), sharing this antimicrobial resistance feature with the related species *S. aureus*. Foodborne *S. argenteus* isolates were able to form a biofilm, showing weak-to-strong biofilm production as assessed on polystyrene (Wu et al., 2020), that, therefore, may allow survival in hostile conditions and the persistence of *S. argenteus* in food and food facility environments. Considering this, strategies to control *S. argenteus* in the food sector should be contemplated and implemented, and next to methods employing classical biocides, novel methods may represent a thriving sector to be explored as being conducted for *S. aureus*. The first attempt was made by evaluating a *Lactobacillus plantarum*-derived bacteriocin (*LSB1*) that inhibited the growth of *S. argenteus* planktonic cells and inhibited the biofilm formation up to 80% (Zhang Y. M. et al., 2022), being a candidate to be used as antibacterial agent or natural food preservative for *S. argenteus* control.

The novel species of the *S. aureus* complex may therefore represent an emerging issue for public health, also involving the food sector. The constant development and improvement of methods for their accurate identification, such as those based on mass spectrometry (MS) and polymerase chain reaction (PCR) (Zhang et al., 2016; Schuster et al., 2017; Chen et al., 2018), will help define their actual prevalence in food and food-related environments and understand if they represent ecological niches for these microorganisms. Although first genome

sequences of strains belonging to these novel species have been deposited in publicly available databases (Chew et al., 2021; Goswami et al., 2021; Grossmann et al., 2021; Monecke et al., 2022), investigations on their antimicrobial resistance genes are lacking (Table 3), deserving future attention. These studies will help understand the antimicrobial resistance potential of these species and evaluate their role in the context of public health and the spreading of antibiotic resistance, allowing us to gain further knowledge on their overall virulence and pathogenic traits.

Conclusion

S. aureus is a pathogenic microorganism that can contaminate both food-contact surfaces and food, including RTE products whose consumption may pose a direct risk to consumer health. Different antimicrobial as well as biocide resistance genes are responsible for i) resistance to antibiotic treatments if infections occur and ii) resistance to sanitizers during cleaning procedures, which facilitates *S. aureus* persistence on surfaces, especially in the biofilm form. WGS-based analyses, mainly based on the development of resistance prediction pipelines and genome-based typing, represent valuable tools to understand the actual arsenal of resistance genes and allow the epidemiological surveillance of *S. aureus*, aimed at deeply understanding the public health burden represented by this antimicrobial-resistant pathogenic bacterium. Novel strategies for S. *aureus* decontamination, employing natural substances, new chemical compounds, or innovative physical methods, represent a new exploration area that may overcome the drawbacks derived from traditional ineffective sanitizing protocols and need to be implemented in the food sector to prevent the spreading of *S. aureus*, including its antimicrobial-resistant forms, in both food and food-related environment. Novel phenotypically and genotypically related species belonging to the *S. aureus* complex (*S. argenteus*, *S. schweitzeri*, *S. singaporensis*, and *S. roterodami*) may represent emerging antimicrobial-resistant foodborne pathogens, whose prevalence in RTE food and role in threatening consumers' health needs to be defined, requiring targeted studies and the development of methods for their simple, fast, and accurate identification.

Author contributions

VF conceived the work. DC and FF wrote the first draft of the manuscript. VF revised the overall manuscript and is responsible for the overall review quality control. All authors contributed to the manuscript revision, and read and approved the submitted manuscript.

Funding

This review was prepared within the project PE13 "One Health Basic and Translational Research Actions Addressing Unmet Needs on Emerging Infectious Diseases" funded by the Italian National Recovery and Resilience Plan (PNRR).

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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