Open Veterinary Journal, (2025), Vol. 15(2): 847-862
ISSN: 2226-4485 (Print)
ISSN: 2218-6050 (Online)

Research Article
DOI: *10.5455/OVJ.2025.v15.i2.34*

Submitted: 05/11/2024 Accepted: 21/01/2025 Published: 28/02/2025

The role of veterinary drug use in driving antimicrobial resistance of *Staphylococcus aureus* isolates in smallholder swine farms in Central Vietnam

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ABSTRACT
Background: *Staphylococcus aureus* is a well-known opportunistic pathogen widely present in humans and food-producing animals. The emergence of antimicrobial resistance (AMR) in *S. aureus* represents a major challenge to animal and public health. Poor biosecurity practices and the misuse and overuse of veterinary drugs in farming settings may apply environmental pressure, which favors the selection of AMR bacteria.
Aim: This study aimed to describe veterinary drug usage (VDU), prevalence of AMR phenotypes, and associations among *S. aureus* isolates from swine of smallholder farms in Central Vietnam.
Methods: A cross-sectional survey was conducted to collect VDU data from smallholder swine farms. A total of 155 nasal swab samples were collected and used for isolating *S. aureus*. The AMR of *S. aureus* strains was tested using the disk diffusion method.
Results: Approximately 56.8%, 71.6%, 36.1%, and 69.7% of farmers used vaccines, disinfectants, and antimicrobials (AMs) for prevention and treatment, respectively. Of the 155 nasal swab samples, 99 (63.9%) were positive for *S. aureus*. Resistance was most commonly observed against oxacillin (59.6%), cefotaxime (59.6%), and linezolid (53.5%). Positive associations were found between the use of vaccines and resistance to oxytetracycline (OR = 3.28, p = 0.01) and povidone usage and resistance to meropenem (OR = 9.35, p = 0.03). Almost all positive associations were observed between the use of AMs (for both prevention and treatment) and AMR in *S. aureus*. Negative associations were found between resistance to oxytetracycline and the use of gentamicin, linezolid, streptomycin, and norfloxacin.
Conclusion: The present study highlights information on VDU, prevalence, AMR, and their associations with *S. aureus* isolated from a smallholder swine farm in Central Vietnam. These findings are expected to aid in developing countermeasures against AMR against swine production in Vietnam.
Keywords: Antimicrobial, Disinfectant, Resistance, *Staphylococcus aureus*, Swine, Vaccine.

Introduction

Staphylococcus aureus is a leading cause of infectious diseases in humans and animals. This Gram-positive, non-spore-forming, non-motile, catalase-positive bacterium is commonly found on the skin, hair, nose, and respiratory tract of humans and animals (Kluytmans *et al.*, 1997; Graber *et al.*, 2013). Among staphylococci, *S. aureus* is the most invasive species and an etiological agent of diverse human and animal maladies, including skin infections, abscesses, food poisoning, toxic shock syndrome, septicemia, and pneumonia (DeLeo and Chambers, 2009; Woodford and Livermore, 2009). Additionally, *S. aureus* is one of the most prominent causes of hospital-, community-, and livestock-acquired bacterial infections worldwide (Song *et al.*, 2011; Tong *et al.*, 2015), which underscores the importance of determining the Antimicrobial resistance (AMR) of strains from humans and animals.

AMR is a serious and growing threat to global health. Evidence indicates that antimicrobial use (AMU) in livestock is a major driver of increased AMR and multidrug resistance (MDR) (Magouras *et al.*, 2017; Collignon & Beggs, 2019). In many countries, AMs are extensively used to promote growth and prevent or treat infections in livestock (Magouras *et al.*, 2017; Collignon and Beggs, 2019), particularly in low- and middle-income countries (Lam *et al.*, 2019). This practice carries potential risks to human health that must be addressed (Van Boeckel *et al.*, 2017). In the swine industry, AMU has promoted the resistance of both commensal and pathogenic bacteria (Holmer *et al.*, 2019; Zhang *et al.*, 2019). On farms, AMU

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leads to an increase in AMR bacteria, which can be transmitted directly to humans through contact or meat consumption or indirectly through environmental pathways (Silbergeld *et al.*, 2008; Wee *et al.*, 2020).

More than four decades ago, Swann *et al.* (1969) discussed the association between AMU in livestock and the emergence of AMR in animals. Since then, many studies have described the association between AMU and AMR (Asai *et al.*, 2005; Chantziaras *et al.*, 2014; Jibril *et al.*, 2021). In Vietnam, high levels of AMR in foodborne pathogens isolated from swine, poultry, cattle, and meat, such as *Salmonella* spp., *Campylobacter* spp., *E. coli*, and *S. aureus*, have been reported (Vo *et al.*, 2012; Nguyen *et al.*, 2016a; Nghiem *et al.*, 2017; Huynh and Ly, 2018; Vu *et al.*, 2020; Tuat *et al.*, 2021). Farmers can buy and use AMs to prevent and treat infections that are available over the counter without a prescription. Some studies have reported the overuse of AMs in swine and poultry farming, although the quantities of AMs used are unknown (Pham *et al.*, 2013; Nguyen *et al.*, 2016b; Nhung *et al.*, 2016). However, these studies did not evaluate the association between AMU and AMR, and the validity of the AMU data was not confirmed by direct observations on farms.

Vietnam has the fifth-highest swine production in the world. Swine production is an important economic activity in Vietnam, with most swine farmers being smallholders in rural areas. AMU in swine production is a risk factor for increased AMR. However, there is limited information on the use of AMs, vaccines, disinfectants, and AMR profiles and their association with the abundance of *S. aureus*. This study describes the use of AMs, vaccines, and disinfectants in smallholder swine farms in Quang Ngai and Thua Thien Hue provinces in Central Vietnam. The prevalence and AMR profiles of *S. aureus* strains in swine from the farms were analyzed. The associations between AMU, vaccines, disinfectants, and AMR in the isolated *S. aureus* strains were also investigated. These results provide a first glimpse into the use of AMs, vaccines, and disinfectants in smallholder swine farms in Central Vietnam, as well as the prevalence and epidemiology of AMR in *S. aureus*. This information will be useful for the clinical control of infectious diseases caused by *S. aureus* and for the development of policies and clinical practice guidelines to reduce AMR in swine production.

Materials and Methods

Experiment and information collection

A cross-sectional survey of the use of AMs, vaccines, and disinfectants in smallholder swine farms (scale 2–20 swine) was conducted in two provinces in Central Vietnam from February 2022 to September 2023. A total of 155 smallholder swine farmers were randomly selected from Thua Thien Hue (HUE, n = 69) and Quang Ngai (QN, n = 86) provinces. Questionnaires were compiled after a test survey and subsequent adjustment and were used for direct interviews with farmers, animal health workers, and veterinarians. Information on veterinary drug usage, antimicrobial components, and active ingredients available on the farm was tracked and collected through labels found on remedy packs or jars left around animal housing or at a local veterinary pharmacy. To ensure the confidentiality of all remedy use information, the names and addresses of all householders were kept secure by encoding the addresses at the time of the survey.

Sample collection and S. aureus identification

In the cross-sectional survey carried out in parallel with the current study, 155 nasal swab samples were collected from swine (anorexia, fever, dermatitis, dyspnea, pneumonia, arthritis) or without clinical signs on the same swine farms (these farms were surveyed). Each sample was placed on Baird-Parker agar (Himedia Laboratories, Mumbai, India) supplemented with 5% (v/v) egg yolk tellurite emulsion and 6.5% (w/v) NaCl and incubated at 37°C for 18–24 hours. *Staphylococcus aureus* grows as black, shiny colonies with fine white rims surrounded by a clear zone. The colonies identified as *S. aureus* were confirmed by a positive coagulase result (Lin *et al.*, 2009). In addition, each strain was confirmed to be *S. aureus* by polymerase chain reaction testing for the presence of *the S. aureus*-specific *nuc* gene (Brakstad *et al.*, 1992).

Antimicrobial susceptibility testing

Susceptibility testing was performed on the isolated *S. aureus* strains (one strain per sample) using the disk diffusion method. The test was performed in accordance with the Clinical and Laboratory Standards Institute (CLSI, 2020) protocol. The common AMs used to prevent and treat infectious disease in livestock were chosen for the antimicrobial susceptibility tests, including ampicillin (10 µg, AMP), oxacillin (1 µg, OX), meropenem (10 µg, MEM), cephalexin (30 µg, CFL), cefotaxime (30 µg, CTX), enrofloxacin (5 µg, ENR), oxytetracycline (30 µg, OTX), doxycycline (30 µg, DOX), streptomycin (10 µg, STR), and linezolid (30 µg, LNZ) (Oxoid Ltd., Hampshire, UK). The inoculum was prepared from cultures in Brain Heart Infusion (BHI) broth incubated for 4–6 hours before adjusting the turbidity to 0.5 on the McFarland scale (DensiCHEK™ Plus, ALT, San Diego, USA). One hundred microliters of the bacterial suspension was spread on Mueller–Hinton agar (MHA, Merck KGaA, Darmstadt, Germany). The appropriate antimicrobial-impregnated disks were placed on the agar surface, and the plates were incubated at 37°C for 24 hours. Thereafter, the zones of inhibition were measured, and the antimicrobial susceptibility of the strains was determined using interpretative standards for *Staphylococcus* species (Eurl, 2018; CLSI, 2020). Strains with phenotypic resistance to two or more antimicrobial agents were defined as multiple-AMR strains.

Data analysis

The data were entered into a Microsoft Excel 2016 (Microsoft Corporation, Redmond, WA, USA) spreadsheet for descriptive statistical analysis and then exported to IBM SPSS statistic 18.0 (IBM, Armonk, NY, USA) for inferential analysis. The one-way analysis of variance and Student's unpaired *t* test were used to test for significance between the prevalence of *S. aureus*, AMR, and categorical variables (location, with or without clinical signs; use and non-use veterinary drugs). The associations between AM, vaccine, and disinfectant use and the AMR phenotype were calculated using chi-square and Fisher's exact tests. Statistically significant associations are shown as ORs with 95% CIs. An association was considered significant when the *p*-value was less than 0.05.

Results

Identification vaccination, disinfectant, and antimicrobial use on farms

The results of veterinary drug use for swine health management are presented in Table 1. Approximately 56.8% (88/155), 71.6% (111/155), 36.1% (56/155), and 69.7% (108/155) of the farmers reported using vaccines, disinfectants, AMs for prevention and AMs for treatment, respectively. The vaccination program aimed to control six common diseases in swine, including classical swine fever, pasteurellosis, salmonellosis, *E. coli*, porcine reproductive and respiratory syndrome (PRRS), and FMD. The most commonly used vaccines were trivalent (67.0%), *E. coli* (22.7%), and PRRS (19.3%). The rates of farms in Quang Ngai (QN) using trivalent (29/29, 100%) and *E. coli* (18/29, 62.1%) vaccines were significantly higher than those in Thua Thien Hue (HUE) ($p < 0.05$). Differences in the rates of farms using disinfectants: calcium hydroxide powder, Bencocide, iodine, Povidine, glutaraldehyde, and Vime-Protex) were observed. The usage rate of calcium hydroxide powder (36.9%, 41/111) was the highest, followed by iodine (31.5%, 35/111) and Povidine (17.7%, 19/111). A significant difference ($p < 0.05$) in the usage rates of calcium hydroxide powder and iodine between QN and HUE was observed (Table 1). The AM use for prevention was reported in 36.1% of the farms, with the most common AMs being AMP (46.4%), followed by AMX (41.1%), CL (39.3%), and DOX (17.9%). Moreover, the AM use for treatment occurred in 69.7% (108/155) of the farms. Of the 18 AMs used across the six classes, ENR (41.7%) was the most common AM used for treatment, followed by PEN (35.2%), AMX (34.3%), OTC, and CL (32.4% each), and DOX (31.5%).

Prevalence of S. aureus isolates from swine

A total of 155 swine nasal swab samples were collected, of which 99 (63.9%) tested positive for *Staphylococcus aureus* (Fig. 1). The results revealed that the isolation rate of *S. aureus* varied significantly by region and presence of clinical signs (*p* 0.05). The prevalence of *S. aureus* in samples taken from HUE (56/69, 81.2%) than in QN (43/86, 50.0%) ($p < 0.0001$). The prevalence of *S. aureus* was higher in samples with clinical signs (66/75, 88.0%) than in those without clinical signs (33/80, 41.3%) ($p < 0.001$).

Antimicrobial resistance

Of the 99 *S. aureus* strains isolated from 155 samples, 56 were from HUE and 43 were from QN. Among all strains tested, resistance levels were as follows: OX and CTX (59.6% each), LNZ (53.5%), OTC (44.4%), AMP and DOX (42.4% each), CFL (35.4%), ENR (28.3%), STR (24.2%), and MEM (16.2%). The strains from QN showed a higher prevalence of resistance to OX (81.4% *vs.* 42.9%), AMP (53.5% *vs.* 33.9%), ENR (44.2% *vs.* 16.1%), and STR (51.2% *vs.* 3.6%) than the strains from HUE ($p < 0.05$) (Table 2). Furthermore, strains from swine without clinical signs showed significantly higher resistance to STR (36.4% *vs.* 18.2%) than those from swine with clinical signs. MDR was observed in 81.8% of the strains; notably, five strains from QN (two strains from swine with and three strains from swine without clinical signs) were resistant to 10 AMs (Table 3).

Effects of veterinary drug use on antimicrobial resistance in S. aureus strains

The effects of veterinary drug use on AMR in *S. aureus* are presented in Table 4. There was a higher prevalence of resistance to MEM (29.7% *vs.* 8.1%), ENR (40.5% *vs.* 21.0%), and STR (43.2% *vs.* 12.9%) in strains from farms that did not use vaccines ($p < 0.05$). Strains from farms that used disinfectants showed a higher prevalence of resistance to OTC (53.2% *vs.* 13.6%) and a lower prevalence of resistance to STR (18.2% *vs.* 45.5%) ($p < 0.05$). Furthermore, strains from farms where AMs were used preventatively showed a higher prevalence of resistance to all AMs except STR ($p < 0.05$) than strains from farms where AMs were not used. *Staphylococcus aureus* strains from farms that used AMs for treatment had a higher prevalence of resistance to CFL (42.0% *vs.* 20.0%), MEM (21.7% *vs.* 3.3%), CTX (66.7% *vs.* 43.3%), ENR (34.8% *vs.* 13.3%), DOX (52.2% *vs.* 20.0%), and LNZ (63.8% *vs.* 30.0%) than those from farms where AMs were not used ($p < 0.05$).

The statistical analyses revealed significant associations between the use of veterinary drugs on swine farms and the prevalence of AMR in *S. aureus* (Table 5). A significant positive association was found between vaccination in swine farms and resistance to OTC (OR = 3.28, $p = 0.01$) in *S. aureus*. Specifically, the use of trivalent, *E. coli*, PRRS, and FMD vaccines was strongly associated with resistance to OTC (OR = 2.44, $p = 0.04$); AMP (OR = 4.91, $p = 0.03$), MEM (OR = 4.94, $p = 0.02$), and STR (OR = 3.83, $p = 0.04$); OTC (OR = 3.75, $p = 0.04$); and DOX (OR = 9.33, $p = 0.02$), respectively. For disinfectant use, Povidine had a significant positive association with MEM resistance (OR = 9.35, $p = 0.03$). In contrast, the use of calcium hydroxide powder was

Table 1. Use of veterinary drugs in swine farms.

Questions	Thua Thien Hue (*n* = 69)		Quang Ngai (*n* = 86)		OR (CI 95%)	*p-value*	Total (*n* = 155)	
	No.	(%)	No.	(%)			No.	(%)
Did you vaccinate the swine?[*]								
Yes	59	85.5	29	33.7	0.09 (0.04–0.19)	< 0.00	88	56.8
No	10	14.5	57	66.3			67	43.2
If yes, which vaccine did you use?								
Trivalent (vaccine against classical swine fever, pasteurellosis, and salmonellosis)[1]	30	50.8	29	100.0	NA	< 0.00	59	67.0
E. coli	2	3.4	18	62.1	46.64 (9.44–230.33)	< 0.001	20	22.7
Porcine reproductive and respiratory Syndrome vaccine	12	20.3	5	17.2	0.82 (0.26–2.58)	0.78	17	19.3
Foot and mouth disease vaccine	4	6.8	6	20.7	3.59 (0.93–13.91)	0.07	10	11.4
Bivalent (vaccine against classical swine fever and pasteurellosis)	2	3.4	0	-		NA	2	2.3
Others	0	-	4	13.8		NA	4	4.5
Unknown	21	35.6	0	-		NA	21	23.9
Did you use a disinfectant during swine production?								
Yes	64	92.8	47	54.7	0.09 (0.03–0.26)	< 0.00	111	71.6
No	5	7.2	39	45.3			44	28.4
If yes, which disinfectant did you use?								
Calcium hydroxide powder	29	45.3	12	25.5	0.41 (0.18–0.94)	0.046	41	36.9
Benzalkonium and glutaraldehyde (Trade name: Bencocide)	19	29.7	16	34.0	1.22 (0.54–2.74)	0.68	35	31.5
Iodine	1	1.6	18	38.3	39.1 (4.98–307.16)	< 0.001	19	17.1
Alkyldimethylbenzyl ammonium chloride and 1-5-pentanedial (Trade name: Vime-Protex)	10	15.6	0	-		NA	10	9.0
Glutaraldehyde	7	10.9	1	2.1	0.18 (0.02–1.49)	0.13	8	7.2
Povidone	2	3.1	4	8.5	2.88 (0.51–16.45)	0.39	6	5.4
Others	11	17.2	0	-		NA	11	9.9
Did you use AM to prevent disease in swine?								
Yes	23	33.3	33	38.4	1.25 (0.64–2.42)	0.52	56	36.1
No	46	66.7	53	61.6			99	63.0
If yes, which antimicrobial was used by you?								
Ampicillin (AMP)	1	4.3	25	75.8	68.75 (7.96–593.98)	< 0.0001	26	46.4
Amoxicillin (AMX)	7	30.4	16	48.5	2.15 (0.70–6.60)	0.27	23	41.1
Gentamicin (GEN)	0	-	6	18.2		NA	6	10.7
Streptomycin (STR)	2	8.7	7	21.2	2.83 (0.53–15.07)	0.28	9	16.1
Tiamulin (TI)	7	30.4	0	-		NA	7	12.5
Tetracycline (TET)	0	-	5	15.2		NA	5	8.9
Doxycycline (DOX)	5	21.7	5	15.2	0.64 (0.16–2.54)	0.73	10	17.9
Colistin (CL)	0	-	22	66.7		NA	22	39.3
Others	2	8.7	3	9.1	1.05 (0.16–6.84)	> 0.05	5	8.9
Unknown	16	69.6	0	-		NA	16	28.6

Questions	Thua Thien Hue (n = 69)		Quang Ngai (n = 86)		OR (CI 95%)	p-value	Total (n = 155)	
	No.	(%)	No.	(%)			No.	(%)
Did you use AM for swine disease treatment?								
Yes	41	59.4	67	77.9	2.41 (1.20–4.85)	0.02	108	69.7
No	28	40.6	19	22.1			47	30.3
If yes, which antimicrobial was used by you?								
Ampicillin (AMP)	5	12.2	20	29.9	3.06 (1.05–8.95)	0.05	25	23.1
Amoxicillin (AMX)	8	19.5	29	43.3	3.15 (1.27–7.83)	0.01	37	34.3
Penicillin (PEN)	10	24.4	29	41.8	2.23 (0.94–5.27)	0.09	39	35.2
Enrofloxacin (ENR)	12	29.3	33	49.3	2.35 (1.03–5.36)	0.04	45	41.7
Norfloxacin (NOR)	3	7.3	26	38.8	8.03 (2.25–28.72)	< 0.001	29	26.9
Streptomycin (STR)	3	7.3	27	40.3	8.55 (2.39–30.53)	< 0.001	30	27.8
Gentamicin (GEN)	3	7.3	22	32.8	6.19 (1.72–22.30)	0.004	25	23.1
Tylosin (TYL)	0	-	5	7.5		NA	5	4.6
Tetracycline (TET)	13	31.7	19	28.4	0.85 (0.37–1.99)	0.83	32	29.6
Oxytetracycline (OTC)	13	31.7	22	32.8	1.05 (0.46–2.42)	> 0.05	35	32.4
Doxycycline (DOX)	7	17.1	27	40.3	3.28 (1.27–8.47)	0.02	34	31.5
Colistin (CL)	11	26.8	24	35.8	1.52 (0.65–3.57)	0.33	35	32.4
Florfenicol (FLO)	10	24.4	20	29.9	1.32 (0.54–3.19)	0.66	30	1.32
Thiamphenicol (TAP)	0	-	8	11.9		NA	8	7.4
Lincomycin (L)	3	7.3	19	28.4	5.01 (1.38–18.21)	0.01	22	20.4
Others	0	-	18	42.9		NA	18	22.8
Unknown	23	56.1	0	-		NA	23	21.3

[1]Vaccination: During the surveying, swine were vaccinated. NA: no analysis

significantly negatively associated with resistance to CFL (OR = 0.28, p = 0.02), ENR (OR = 0.31, p = 0.05), and STR (OR = 0.16, p = 0.01). Regarding the use of AMs for prevention, significant positive associations were found with resistance to AMP (OR = 3.72, p = 0.003), OX (OR = 3.87, p = 0.0006), CFL (OR = 3.04, p = 0.02), MEM (OR = 3.46, p = 0.03), CTX (OR = 3.11, p = 0.02), ENR (OR = 3.94, p = 0.003), OTC (OR = 4.72, p < 0.0001), DOX (OR = 2.56, p = 0.04), and LNZ (OR = 4.60, p = 0.001). Significant positive associations were also observed between the use of AMX, AMP, CL, and STR for the prevention and resistance to several AMs (e.g., AMX and AMP; AMP and AMP; CL and ENR; STR and CTX). The overall use of AMs for treatment was significantly positively associated with resistance to CFL, MEM, CTX, ENR, DOX, and LNZ in *S. aureus* strains. Most associations between AM use for treatment and AMR in *S. aureus* were positive, except for the associations between resistance to OTC and the use of GEN, LNZ, STR, and NOR, which were negative.

Discussion

In the context of both reducing AMR and preventing the spread of epidemic diseases, prioritizing preventive veterinary management strategies is crucial for the sustainability of animal health (Renault *et al.*, 2021). Previous studies indicate that improving biosecurity on livestock farms is particularly vital in combating AMR, as it can help reduce AMU and curb the dissemination and persistence of resistant microbes within farms (Davies and Wales, 2019; Kruse *et al.*, 2020; Dhaka *et al.*, 2023). Among the various parameters of biosecurity, the role of cleaning, disinfection, and vaccination measures has been highlighted in various studies (Martelli *et al.*, 2017; De Lorenzi *et al.*, 2020; Kruse *et al.*, 2020; Dhaka *et al.*, 2023). In Vietnam, swine farm biosecurity measures vary because of non-standardized procedures or regulations (Duong *et al.*, 2019; Ngo *et al.*, 2020). Moreover, data on the level of implementation of biosecurity measures on small swine farms in Vietnam are limited (Auplish *et al.*, 2024). In the present study, the prevalence of farms using vaccines (56.8%) and disinfectants (71.6%) was higher than that of AMU for prevention (36.1%). Swine production has been facing challenges in recent years, including high animal feed prices and unpredictable epidemics, such as ASF, PRRS, and FMD, causing significant losses to small farms (Zhang & Kono, 2012; Le *et al.*, 2019; Nguyen *et al.*, 2021). Therefore,

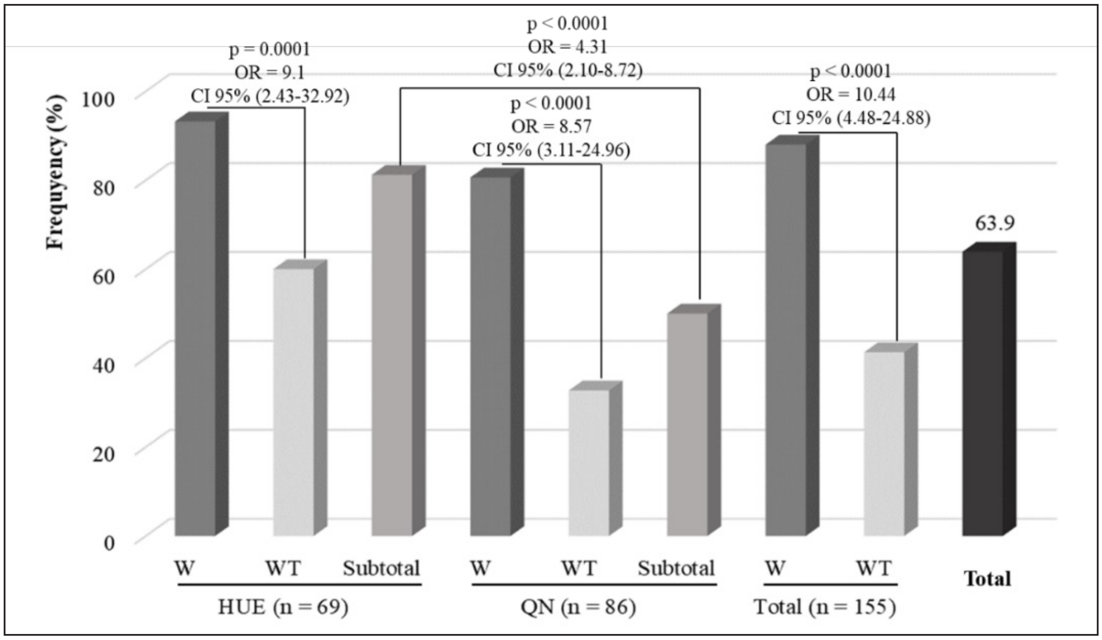

Fig. 1. Prevalence of *S. aureus* isolates from swine in Thua Thien Hue and Quang Ngai Provinces, Vietnam.

W: with clinical (anorexia, fever, dermatitis, dyspnea, pneumonia, arthritis); WT: without clinical; HUE: Thua Thien Hue province; QN: Quang Ngai province.

Table 2. Prevalence of antimicrobial resistance to *S. aureus* strains.

AM class	AM agents*	Province		Clinical sign		Total (n = 99)
		Thua Thien Hue (n = 56)	Quang Ngai (n = 43)	With (n = 33)	Without (n = 66)	
ß-lactam	AMP	33.9[a]	53.5[b]	39.4	48.5	42.4
	OX	42.9[a]	81.4[b]	56.1	66.7	59.6
Cephalosporin	CFL	37.5	32.6	36.4	33.3	35.4
	MEM	0.0	37.2	13.6	21.2	16.2
	CTX	55.4	65.1	60.6	57.6	59.6
Aminoglycosides	STR	3.6[a]	51.2[b]	18.2[c]	36.4[d]	24.2
Fluoroquinolone	ENR	16.1[a]	44.2[b]	28.8	27.3	28.3
Tetracyclines	OTC	55.4[a]	30.2[b]	45.5	42.4	44.4
	DOX	42.9	41.9	40.9	45.5	42.4
Oxazolidinone	LNZ	50.0	58.1	54.5	51.5	53.5

[a, b] Signification difference (p-value < 0.05) in the resistance rates of the Thua Thien Hue and Quang Ngai provinces, [c, d] Signification difference (p-value < 0.05) in the resistance rates of the patients with and without clinical signs. *Ampicillin (10 µg, AMP), oxacillin (1 µg, OX), meropenem (10 µg, MEM), cephalexin (30 µg, CFL), cefotaxime (30 µg, CTX), enrofloxacin (5 µg, ENR), oxytetracycline (30 µg, OTC), doxycycline (30 µg, DOX), streptomycin (10 µg, STR), linezolid (30 µg, LNZ).

household livestock farms have applied various biosecurity measures to limit the impact of epidemics (Ngo *et al.*, 2020). Moreover, some vaccines, such as those for salmonellosis, swine fever, and pasteurellosis, are included in the mandatory vaccination program according to veterinary law (National Assembly of the Socialist Republic of Vietnam, 2018). The rate of households using AMs to prevent diseases was lower than that reported in some previous studies (Pham *et al.*, 2013; Duong and Nguyen, 2015; Nhung *et al.*, 2016). Since 2020, the veterinary law has introduced a list of prohibited AMs added to feed for disease prevention (National Assembly of the Socialist Republic of Vietnam, 2018). Among AMUs (in both

Table 3. Prevalence of multidrug resistance in *S. aureus* strains.

No. of AM agents	Thua Thien Hue (*n* = 56)		Quang Ngai (*n* = 43)		Total (*n* = 99)	
	No. strain	Cumulative rate (%)	No. strain	Cumulative rate (%)	No. strain	Cumulative rate (%)
0	7	100.0	4	100.0	11	100.0
1	7	87.5	0	90.7	7	88.9
2	8	75.0	3	90.7	11	81.8
3	8	60.7	10	83.7	18	70.7
4	8	46.4	4	60.5	12	52.5
5	6	32.1	5	51.2	11	40.4
6	6	21.4	5	39.5	11	29.3
7	4	10.7	3	27.9	7	18.2
8	2	3.6	1	20.9	3	11.1
9	0	0.0	3	18.6	3	8.1
10	0	0.0	5	11.6	5	5.1

prevention and treatment), AMP, AMX, PEN, CL, GEN, and ENR were commonly used by the farmers, as reported in other studies (Pham *et al.*, 2013; Duong and Nguyen, 2015; Nhung *et al.*, 2016). These include AMs considered critically important to human health, such as PEN, CL, and GEN (Collignon *et al.*, 2016). The B-lactams were the AMs of choice because they are long-acting, cheap, and have a broad spectrum (Bush and Bradford, 2016). Overreliance on these AMs can promote the development of AMR bacteria, potentially limiting their future effectiveness, especially when the drugs are underdosed in both prevention and treatment. This study observed a high prevalence of farms using CL for both prevention (39.3%) and treatment (32.4%). Previous studies have reported that CL is a popular veterinary drug used not only to treat infections but also as a growth promoter and protective agent (Duong and Nguyen, 2015; Rhouma *et al.*, 2016; Luu *et al.*, 2021). However, CL is considered a last-resort drug for treating drug-resistant bacterial infections (Wand *et al.*, 2017).

The present study found an estimated prevalence of *S. aureus* of 63.9% in swine farms. Studies conducted by Linhares *et al.* (2015) and Sun *et al.* (2015) reported a higher prevalence of *S. aureus* isolated from swine farms (77.0% and 91.1%, respectively) than that reported in the present study. The prevalence of *S. aureus* strains similar to those found in this study (63.6% and 68.6%) (Nobre *et al.*, 2021; Sineke *et al.*, 2021) or even lower (36.2%) (Zehra *et al.*, 2017). *Staphylococcus aureus* can be endemic in swine populations, and its relative prevalence varies geographically and probably temporally (Espinosa-Gongora *et al.*, 2014). A study in Bac Ninh province, North Vietnam, found a lower prevalence of *S. aureus* strains in nasal swab samples of swine (13/80, 16.25%) (Vu *et al.*, 2020) than observed in this study. In the present study, a significant difference in the prevalence of *S. aureus* strains was observed between QN (43/86, 50.0%) and HUE (56/69, 81.2%), with a *p*-value 0.05.

The emergence of AMR in *S. aureus* represents a major challenge to animal and public health. Poor biosecurity practices and the use, misuse, and overuse of veterinary drugs in farming settings may apply environmental pressure, which favors the selection of AMR bacteria (Vestergaard *et al.*, 2019; Urban-Chmiel *et al.*, 2022). *S. aureus* is the most commonly identified AMR pathogen worldwide (Foster, 2017). It is resistant to almost all β-lactams and other major AM classes, such as fluoroquinolones (Monaco *et al.*, 2017; Kumar *et al.*, 2020). In this study, high resistance rates were obtained for OX, CTX (each 59.6%), and LNZ (53.5%), corroborating the findings of other studies (Nguyen *et al.*, 2014; Guo *et al.*, 2018; Lekagul *et al.*, 2019; Vu *et al.*, 2020). These AMs are frequently used in swine farming to treat diseases, and the capacity of *S. aureus* to acquire resistance to these drugs has already been demonstrated (Duong and Nguyen, 2015; Nhung *et al.*, 2016; Luu *et al.*, 2021). In addition, high frequencies of strains resistant to OTC (44.4%), AMP, DOX (each 42.4%), and CFL (35.4%) were also observed, corroborating the results of other studies (Nhung *et al.*, 2016; Vu *et al.*, 2020; Sineke *et al.*, 2021). These results are worrisome because these AMs belong to classes with the highest priority among those critically important for human medicine and should be used prudently in both humans and animals (Collignon *et al.*, 2016). MDR *S. aureus* strains from swine may play an important role in spreading AMR strains and ARGs among animals, humans with direct animal contact, or even pork consumers, thereby impacting the treatment of possible infections. In this study, MDR, defined as the resistance to two or more AMs, was found in 81 (81.8%) S. *aureus* strains. This was

Table 4. Effects of veterinary drug usage on antimicrobial resistance in *S. aureus* strains (n = 99).

AM	Vaccinated Number (%)		Disinfection used No. (%)		AM prevention No. (%)		AM treatment No. (%)	
	No (n = 37)	Yes (n = 62)	No (n = 22)	Yes (n = 77)	No (n = 62)	Yes (n = 37)	No (n = 30)	Yes (n = 69)
AMP	13 (35.1)	29 (46.8)	8 (36.4)	34 (44.2)	19 (30.6)[a]	23 (62.2)[b]	12 (40.0)	30 (43.5)
OX	25 (67.6)	34 (54.8)	15 (68.2)	44 (57.1)	30 (48.4)[a]	29 (78.4)[b]	14 (46.7)	45 (65.2)
CFL	13 (35.1)	22 (35.5)	6 (27.3)	29 (37.7)	16 (25.8)[a]	19 (51.4)[b]	6 (20.0)[a]	29 (42.0)[b]
MEM	11 (29.7)[a]	5 (8.1)[b]	6 (27.3)	10 (13.0)	6 (9.7)[a]	10 (27.0)[b]	1 (3.3)[a]	15 (21.7)[b]
CTX	20 (54.1)	39 (62.9)	13 (59.1)	46 (59.7)	31 (50.0)[a]	28 (75.7)[b]	13 (43.3)[a]	46 (66.7)[b]
ENR	15 (40.5)[a]	13 (21.0)[b]	8 (36.4)	20 (26.0)	11 (17.7)[a]	17 (45.9)[b]	4 (13.3)[a]	24 (34.8)[b]
OTC	10 (27.0)[a]	34 (54.8)[b]	3 (13.6)[a]	41 (53.2)[b]	19 (30.6)[a]	25 (67.6)[b]	12 (40.0)	32 (46.4)
DOX	17 (45.9)	25 (40.3)	10 (45.5)	32 (41.6)	21 (33.9)[a]	21 (56.8)[b]	6 (20.0)[a]	36 (52.2)[b]
STR	16 (43.2)[a]	8 (12.9)[b]	10 (45.5)[a]	14 (18.2)[b]	12 (19.4)	12 (32.4)	4 (13.3)	20 (29.0)
LNZ	20 (54.1)	33 (53.5)	10 (45.5)	43 (55.8)	25 (40.3)[a]	28 (75.7)[b]	9 (30.0)[a]	44 (63.8)[b]

[a, b] Significant difference in the resistance frequency between householders using veterinary drugs and those not.

observed mainly on farms that used a wide variety of AMs for purposes other than treatment. Many strains showed resistance to up to 10 AMs. As in other reports, AMs are commonly used on swine farms, with usage frequency varying according to the geographic region (Foster, 2017; Abreu *et al.*, 2019; Adesoji *et al.*, 2019). Most of the farms where MDR *S. aureus* was isolated carried out disinfection of pens, used at least three AMs, and used AMs for purposes other than treatment. The broader use of AMs is expected to be associated with greater MDR colonization in swine. The use of disinfectants and downtime are biosecurity practices adopted to reduce the introduction and dissemination of infectious agents among animals. Nevertheless, disinfectant resistance may contribute to the selection of MDR bacteria, especially when the responsible genes are co-located with ARGs in mobile genetic elements (Davies & Wales, 2019; Maertens *et al.*, 2019; Bischofberger *et al.*, 2020). The high MDR rate highlights the need for AM stewardship to ensure prudent AMU in animal production, as it may have serious consequences for human and environmental health.

Vaccination is a highly effective and valuable tool for fighting AMR. However, the present study found a significantly lower rate of *S. aureus* strain resistance to MEM (8.1%), ENR (21.0%), and STR (12.9%) in the vaccinated group compared with the non-vaccinated group (29.7%, 40.5%, and 43.2%, respectively). Moreover, a negative association between vaccination and AMR in *S. aureus* strains [resistance to MEM (OR = 0.21; p = 0.006), ENR (OR = 0.39, p = 0.04), and STR (OR = 0.2, p = 0.001)] was observed (Table 4). The association between vaccination and AMU/AMR has been reported (Bak and Rathkjen, 2009; Kruse *et al.*, 2016; Temtem *et al.*, 2016; Peiponen *et al.*, 2018; Buchy *et al.*, 2020; Costanzo and Roviello, 2023). Bak and Rathkjen (2009) found significantly lower AMU in the group vaccinated against *Lawsonia intracellularis* (LAW) than in the non-vaccinated group. However, Peiponen *et al.* (2018) found only a slightly, but not statistically significant, lower AMU in the group vaccinated against LAW. The associations between vaccination and AMU have also been studied at the population level, with varying results. A cross-sectional study by Temtem *et al.* (2016) found that herds vaccinated against Porcine Circovirus Type 2 (PCV2), *Mycoplasma hyopneumoniae* (MYC), and/or LAW had significantly higher AMU in weaners than herds not vaccinated against any of these infections. Similarly, Postma *et al.* (2016) found that the use of vaccines against higher numbers of pathogens was associated with a higher AMU in swine from birth to slaughter. Kruse *et al.* (2016) reported that initiating vaccination against PCV2, MYC, *Actinobacillus pleuropneumoniae*, PRRS, and LAW had no effect on the change in AMU in weaners and finishers. Obolski *et al.* (2018) found that vaccination can result in a rapid increase in the frequency of preexisting resistant variants of non-vaccine serotypes due to the removal of competition from vaccine serotypes. Similarly, the results of this study show that among the vaccines used (Table 1), none is used to prevent diseases related to *S. aureus* infection. Finally, vaccination is a potential weapon against AMR. However, while AMU remains at high levels, we need to understand and act to avoid increasing AMR in non-vaccine serotypes, as outlined by this study and others.

Recent studies have evaluated the association between AMR and decreased susceptibility to disinfectants in bacteria isolated from livestock and the environment (Herruzo *et al.*, 2015; Wieland *et al.*, 2017; Basiry *et al.*, 2022). In the present study, the positive association between disinfectant use and resistance to OTC (OR =

Table 5. Association between vaccination, disinfectant use, and antimicrobial resistance in *S. aureus*.

Veterinary drug	Characteristics of strains					Agreement between veterinary drug use and AMR (n = 99)		
	n-St	AM	n-SR	NR/U	NU/R	OR	95%CI	p value
Vaccination	62	MEM	16	57	11	0.21	0.07–0.66	0.006
		ENR	28	49	15	0.39	0.16–0.95	0.04
		OTC	44	28	10	3.28	1.36–7.91	0.01
		STR	24	54	16	0.20	0.07–0.52	0.001
Trivalent	38	OTC	44	16	22	2.44	1.06–5.59	0.04
E. coli	12	AMP	42	3	33	4.91	1.24–19.45	0.03
		MEM	16	7	11	4.94	1.33–18.30	0.02
		STR	24	6	18	3.83	1.10–13.31	0.04
PRRS	14	OTC	44	4	34	3.75	1.09–12.93	0.04
FMD	7	DOX	42	1	36	9.33	1.08–80.77	0.02
Disinfectant	77	OTC	44	36	3	7.21	1.97–26.40	0.01
		STR	24	63	10	0.27	0.10–0.74	0.01
Povidine	5	MEM	16	2	13	9.35	1.42–61.41	0.03
Calcium hydroxide powder	29	CFL	35	24	30	0.28	0.10–0.81	0.02
		ENR	28	25	24	0.31	0.10–0.98	0.05
		STR	24	27	22	0.16	0.04–0.74	0.01
AMU for prevention	37	AMP	42	14	19	3.72	1.58–8.75	0.003
		OX	59	8	30	3.87	1.53–9.78	0.006
		CFL	35	18	16	3.04	1.28–7.17	0.02
		MEM	16	27	6	3.46	1.14–10.50	0.03
		CTX	59	9	31	3.11	1.26–7.66	0.02
		ENR	28	20	11	3.94	1.57–9.87	0.003
		OTC	44	12	19	4.72	1.97–11.31	< 0.001
		DOX	42	16	21	2.56	1.11–5.92	0.04
		LNZ	53	9	25	4.60	1.86–11.39	0.001
AMX	20	AMP	42	7	29	3.20	1.15–8.94	0.03
		OX	59	2	41	8.34	1.81–38.37	0.002
		MEM	16	11	7	8.42	2.60–27.22	< 0.001
		CTX	59	4	43	3.35	1.03–10.92	0.04
		ENR	28	8	16	5.91	2.07–16.87	0.001
		OTC	44	7	31	2.88	1.03–8.01	0.046
		STR	24	9	13	6.21	2.14–17.96	0.001
		LNZ	53	5	38	3.24	1.07–9.77	0.04
AMP	12	AMP	42	1	31	19.87	2.45–161.24	< 0.001
		MEM	16	4	8	19.75	4.85–80.36	< 0.001
		ENR	28	4	20	6.70	1.83–24.58	0.004
		OTC	44	3	35	4.46	1.13–17.63	0.03
		ETR	24	4	16	8.87	2.38–33.13	0.001
		LNZ	53	1	42	11.79	1.46–95.27	0.005
CL	12	MEM	16	6	10	7.70	2.08–28.52	0.004
		ENR	28	5	21	4.40	1.26–15.33	0.02

(Continued)

Veterinary drug	Characteristics of strains					Agreement between veterinary drug use and AMR (n = 99)		
	n-St	AM	n-SR	NR/U	NU/R	OR	95%CI	p value
		STR	24	4	16	8.88	2.38–33.13	0.001
STR	7	CTX	35	2	30	5.16	1.00–28.19	0.05
		MEM	16	2	11	18.41	3.18–106.64	0.001
		STR	28	1	22	19.09	2.18–167.29	0.002
AMU for treatment	69	CFL	35	40	6	2.90	1.05–8.00	0.04
		MEM	16	54	1	8.06	1.01–64.09	0.03
		CTX	59	23	13	2.62	1.09–6.30	0.04
		ENR	28	45	4	3.47	1.08–11.10	0.05
		DOX	42	33	6	4.36	1.59–12.00	0.004
		LNZ	53	25	9	4.11	1.63–10.33	0.002
GEN	22	MEM	16	14	8	4.93	1.58–15.35	0.007
		ENR	28	10	16	4.58	1.68–12.48	0.003
		OTC	44	18	40	0.21	0.06–0.66	0.007
		STR	24	8	10	11.73	3.93–35.00	< 0.001
LNZ	22	MEM	16	13	7	6.92	2.19–21.90	0.001
		ENR	28	10	16	4.58	1.68–12.48	0.003
		OTC	44	18	40	0.21	0.06–0.66	0.007
		STR	24	8	10	11.73	3.93–35.00	< 0.001
STR	25	MEM	16	15	6	7.56	2.38–24.01	0.001
		ENR	28	12	15	4.26	1.62–11.22	0.004
		OTC	44	19	38	0.30	0.11–0.83	0.02
		STR	24	9	8	14.66	4.89–43.97	< 0.001
ENR	32	MEM	16	23	7	3.35	1.12–10.06	0.04
		ENR	28	15	11	5.77	2.23–14.90	< 0.001
FLO	25	MEM	16	17	8	3.88	1.27–11.85	0.02
		ENR	28	9	12	9.19	3.30–25.58	< 0.001
		DOX	42	9	26	3.28	1.27–8.45	0.02
		STR	24	15	14	2.86	1.06–7.68	0.05
AMX	35	AMP	42	15	22	2.55	1.09–5.93	0.04
		OX	59	4	28	9.96	3.15–31.55	< 0.001
		MEM	16	23	4	13.03	1.50–113.27	0.007
		ENR	28	18	11	4.55	1.80–11.51	0.001
		DOX	42	13	20	3.72	1.57–8.85	0.003
		STR	24	19	8	5.90	2.18–15.95	< 0.001
CL	31	OX	59	8	36	2.56	1.00–6.51	0.05
		ENR	28	17	14	3.18	1.27–7.97	0.02
		DOX	42	12	23	3.10	1.28–7.47	0.02
		STR	24	18	11	3.74	1.43–9.79	0.01
		LNZ	53	7	29	4.61	1.75–12.16	0.002
NOR	21	MEM	16	12	7	7.61	2.38–24.31	0.001
		ENR	28	6	13	12.50	4.09–38.25	< 0.001

(Continued)

Veterinary drug	Characteristics of strains					Agreement between veterinary drug use and AMR (n = 99)		
	n-St	AM	n-SR	NR/U	NU/R	OR	95%CI	p value
		OTC	44	16	39	0.31	0.10–0.94	0.047
		STR	24	9	12	7.33	2.54–21.18	< 0.001
DOX	25	AMP	42	8	25	4.17	1.58–10.97	0.004
		OX	59	5	39	3.59	1.22–10.58	0.02
		MEM	16	17	8	3.88	1.27–11.85	0.02
		ENR	28	11	14	5.46	2.04–14.54	0.001
		DOX	42	7	24	5.36	1.97–14.56	0.001
		STR	24	13	12	4.77	1.76–12.95	0.003
		LNZ	53	7	35	2.87	1.07–7.67	0.04
OTC	24	OTC	44	7	27	4.32	1.59–11.72	0.00
PEN	35	AMP	42	15	22	2.54	1.09–5.93	0.03
		OX	59	7	31	4.26	1.63–11.15	0.003
		MEM	16	25	6	3.87	1.27–11.80	0.02
		CTX	59	9	33	2.71	1.10—6.69	0.03
		ENR	28	19	12	3.65	1.46–9.11	0.006
		STR	24	19	8	5.90	2.18–15.95	< 0.001
TET	29	AMP	42	12	25	2.55	1.05–6.19	0.045
		ENR	28	16	15	2.98	1.18–7.54	0.03
AMP	24	AMP	42	5	23	8.59	2.86–25.83	< 0.001
		OX	59	3	38	6.82	1.87–24.80	0.002
		MEM	16	15	7	5.83	1.87—18.13	0.003
		ENR	28	11	15	4.73	1.77–12.62	0.002
		STR	24	11	11	6.88	2.46–19.20	< 0.001
		LNZ	53	6	35	3.43	1.23–9.60	0.02

n-St: number of strains from householders using veterinary drugs; n-SR: number of strains expressing the phenotype resistant to the indicated antimicrobial agents; NR/U: Number of the strains expressing phenotype nonresistant (NR) in households using veterinary drugs (U); R/NU: number of strains expressing phenotype-resistant (R) but not used by householders (NU); Only the results for the AMR phenotype that displayed an association with the use of veterinary drugs at a p-value 0.05 are shown.

7.21, p = 0.01), as well as between the use of Povidine and resistance to MEM (OR = 9.35, p = 0.03), was also investigated. Previous studies have discussed cross-resistance mechanisms between AMs and disinfectants, (de Carvalho *et al.*, 2020; Pereira *et al.*, 2021), mostly related to general resistance responses, changes in membrane permeability (Pereira *et al.*, 2021), efflux pumps (Nguyen *et al.*, 2015; Blanco *et al.*, 2016), and the structural effects of biofilms. In this regard, it is not surprising that these mechanisms cause cross-resistance because they all decrease the accessibility of disinfectants and AMs to bacterial cells. These results indicate that the cross-resistance between disinfectant resistance and AMR mechanisms is the result of general microbial adaptation to a hostile environment. Although many countries have banned the use of AMs in livestock farming (Official Journal of the European Union, 2006; FDA, 2015; The Ministry of Agriculture and Rural Development, 2020), this policy will likely increase the use of disinfectants to ensure biosecurity. However, the use of disinfectants also risks increasing resistance to disinfectants and AMR, as discussed in this study and in previous studies.

Antimicrobial use is generally accepted as the main driver of AMR, and the relationship between AMU and AMR in animals is, therefore, a topic of considerable interest (Holmer *et al.*, 2019; Jibril *et al.*, 2021; Sali *et al.*, 2021). Our investigation revealed significant associations between AMU (in both prevention and treatment) and the presence of certain AMR phenotypes. The AMR phenotype is common among *E. coli* indicators isolated from swine in the United States (Spronk *et al.*, 2023) and European countries (EFSA, 2021). Similar to the findings of Kobayashi *et al.* (2023), the results of this study showed that AMU was associated with resistance not only to AMs belonging to the same AM class (AMX and AMP; GEN and STR) but also to AMs from other classes (AMX and ENR; FLO and DOX). Resistance genes occurring in the same mobile genetic elements and gene cassettes (Birkegård *et al.*, 2017; Partridge *et al.*, 2018) may explain the observed AMR phenotypes and should be addressed in more detail in future investigations. However, not all associations between AMU and AMR phenotypes in this study could be explained. For example, the use of LNZ, STR, and NOR (as treatment) was negatively associated with the presence of the OTC phenotype. In other studies, both corresponding and divergent associations between AMU and AMR, including direct and implicit resistance selection mechanisms, have been reported (Callens *et al.*, 2015; Makita *et al.*, 2016). Makita *et al.* (2016) suggested that these issues were due to natural, cross- or co-selection based on analyses of AMR in *E. coli* isolates from swine and AMU.

Conclusion

Smallholder swine farmers in the two provinces used several essential veterinary drugs (including disinfectants, vaccines, and AMs) on their farms for prevention and treatment. The *S. aureus* isolates from swine included those from healthy swine that threatened public and animal health. Resistance to some AMs in S. *aureus* isolates was associated with the use of vaccines, disinfectants, and corresponding AMs, implying that increasing the use of such AMs would increase resistance. These results should help establish countermeasures against AMR in *S aureus* in smallholder swine farms in Central Vietnam. The findings provide support only for analyses conducted at a single time point: on-farm veterinary drug usage is associated with on-farm AMR. Other complex multifactorial relationships may contribute to the selection of AMR bacteria, which we hope to investigate further in future studies.

Acknowledgment

The authors would like to thank Mr. Hoang Dinh Quoc, who helped us with sampling. We also thank the farmers in Quang Ngai and Hue provinces, who participated in the interviews, provided honest information, and allowed sampling from their pigs.

Conflict of interest

The authors declare that they have no conflicts of interest regarding any financial, personal, or other relationships with individuals or organizations related to the material discussed in this manuscript.

Funding

This work was supported by a Hue University-level research project (No. DHH2023-02-176. The authors are grateful to the president of Hue University for allowing them to conduct this study.

Authors' contributions

All authors contributed to the study's conception and design. Nguyen Van Chao developed the original hypotheses, designed the experiments, and collaborated in interpreting the results. Ho Thi Dung, Bui Thi Hien, and Vu Thi Thanh Tam collected the data for this study, conducted the statistical analyses, and collaborated in the interpretation of the results. Ho Thi Dung, Vu Thi Thanh Tam, Phan Thi Hang, and Bui Thi Hien collaborated in interpreting the results and finalized the manuscript. All authors have read and approved the finalized manuscript.

Data availability

Data supporting the findings of this study are available from the corresponding author under the Project funding, upon reasonable request.

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