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Antimicrobial Resistance in *Stenotrophomonas* spp.

YANG WANG,[1] TAO HE,[2] ZHANGQI SHEN,[1] and CONGMING WU[1]

[1]Beijing Advanced Innovation Center for Food Nutrition and Human Health, College of Veterinary Medicine, China Agricultural University, Beijing, 100193, China; [2]Jiangsu Key Laboratory of Food Quality and Safety—State Key Laboratory Cultivation Base of MOST, Institute of Food Safety, Jiangsu Academy of Agricultural Sciences, Nanjing 210014, China

ABSTRACT Bacteria of the genus *Stenotrophomonas* are found throughout the environment, in close association with soil, sewage, and plants. *Stenotrophomonas maltophilia*, the first member of this genus, is the predominant species, observed in soil, water, plants, animals, and humans. It is also an opportunistic pathogen associated with the increased number of infections in both humans and animals in recent years. In this article, we summarize all *Stenotrophomonas* species (mainly *S. maltophilia*) isolated from animals and food products of animal origin and further distinguish all isolates based on antimicrobial susceptibility and resistance phenotypes. The various mechanisms of both intrinsic and acquired antimicrobial resistance, which were mainly identified in *S. maltophilia* isolates of nosocomial infections, have been classified as follows: multidrug efflux pumps; resistance to β-lactams, aminoglycosides, quinolones, trimethoprim-sulfamethoxazole, and phenicols; and alteration of lipopolysaccharide and two-component regulatory systems. The dissemination, coselection, and persistence of resistance determinants among *S. maltophilia* isolates have also been elaborated.

INTRODUCTION

The genus *Stenotrophomonas* comprises 16 characterized species (Table 1), and 13 validated species are included in the List of Prokaryotic names with Standing in Nomenclature (1). The first *Stenotrophomonas* species —*Stenotrophomonas maltophilia*—was isolated in 1943 from human pleural fluid. It was classified as *Bacterium bookeri* and subsequently renamed *Pseudomonas maltophilia*/*Xanthomonas maltophilia* (1, 2). Another 12 *Stenotrophomonas* species were first identified residing in soil, sewage, or plants. Of the remaining three species, *Stenotrophomonas* sp. D-1 and *Stenotrophomonas koreensis* were first isolated from deer fur and animal compost, respectively, and *Stenotrophomonas africana* was initially isolated from a sample of cerebrospinal fluid from a human immunodeficiency virus seropositive Rwandan refugee with primary meningoencephalitis (3). *S. maltophilia* is the most widely distributed bacterium of the *Stenotrophomonas* spp. in the environment and is isolated from soil, water, plants, animals, and humans. Moreover, the number of nosocomial infections caused by this opportunistic pathogen is increasing (4). Therefore, various studies of *Stenotrophomonas* in both animals and humans focus on the emergence, infections, treatment, and antimicrobial resistance of *S. maltophilia* as an opportunistic pathogen (4, 5). The main purpose of this article is to describe the antimicrobial resistance of *S. maltophilia* isolated from animals.

The earliest study of *S. maltophilia* reported its isolation from sources associated with rabbits, raw milk, and frozen fish in 1961 (6). It is the predominant bacterial species in swine and chicken feces (7), as well as in composted swine manure (8). *S. maltophilia* isolates have been found to coexist with influenza virus in the

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Correspondence: Yang Wang, wangyang@cau.edu.cn

TABLE 1 Characterization of *Stenotrophomonas* species

Species	Year of first identification/ designation	Host when first identified	Characterization	Countries/ continents	Ref.
S. maltophilia	1943	Human	*S. maltophilia*, a new bacterial genus for *X. maltophilia*, is first identified from a specimen of pleural fluid	England/Europe	99
S. africana	1997	Human	Opportunistic pathogen from cerebrospinal fluid	Rwanda/Africa	3
S. nitritireducens	2000	Ammonia-supplied biofilters	It reduced nitrite, but not nitrate, without production of nitrogen	Germany/Europe	100
S. sp. D-1	2002	Animal (deer fur)	A keratin-degrading bacterium isolated from soil containing deer fur; 16S rDNA revealed it has only 90.6% homology with *S. nitritireducens*	Japan/Asia	101
S. acidaminiphila	2002	Upflow anaerobic sludge blanket (UASB) reactor	A strictly aerobic, mesophilic bacterium isolated from UASB reactor treating a petrochemical wastewater	Burkina Faso/Africa	102
S. rhizophila	2002	Environment (plant)	Plant-associated bacterium with antifungal properties	Germany/Europe	103
S. dokdonensis	2006	Environment (soil)	The levels of 16S rDNA sequence similarity between *S. dokdonensis* and the type strains of *Stenotrophomonas* species ranged from 95.5 to 97.5%	Korea/Asia	104
S. koreensis	2006	Environment (animal compost)	A Gram-negative, rod-shaped, non-spore-forming bacterium was isolated from compost near Daejeon city	Korea/Asia	105
S. humi	2007	Environment (soil)	The nitrate-reducing bacterium was isolated from soil	Belgium/Europe	106
S. terrae	2007	Environment (soil)	The nitrate-reducing bacterium was isolated from soil	Belgium/Europe	106
S. chelatiphaga	2009	Environment (sewage)	An EDTA-utilizing gammaproteobacterial strain was isolated from municipal sewage sludge	Russia/Europe	107
S. ginsengisoli	2010	Environment (soil)	A Gram-negative, non-spore-forming, rod-shaped bacterium was isolated from soil from a ginseng field	Korea/Asia	108
S. daejeonensis	2011	Environment (sewage)	Comparative 16S rDNA analysis showed it was related most closely to *S. acidaminiphila* (97.9% similarity)	Korea/Asia	109
S. pavanii	2011	Environment (plant)	A Gram-negative, rod-shaped, non-spore-forming, and nitrogen-fixing bacterium was isolated from stems of a Brazilian sugar cane variety	Brazil/South America	110
S. tumulicola	2015	Environment (spot and gels)	A major contaminant of the stone chamber interior in blackish moldy spots and viscous gels (biofilms) collected from both tumuli	Japan/Asia	111
S. sp. DDT-1	2016	Environment (contaminated soil)	A novel bacterium capable of utilizing 1,1,1-trichloro-2,2-bis (p-chlorophenyl)ethane (DDT) as the sole carbon and energy source.	China/Asia	112

oral, nasal, and tracheal tissues of pigs and horses (9, 10). *S. maltophilia* is a predominant bacterial species in raw milk, milk processing plants, and milk products such as cheese (11–13) and is likely a constituent of the normal microflora of the mouth and cloacae of squirrels and captive healthy snakes (14, 15). In aquaculture, *Stenotrophomonas* spp. are predominant members of bacterial communities found in the internal organs of cultured snow crabs (*Chionoecetes*) (16) and are commonly isolated from cultured yellowtail (17), shrimp (18), and samples taken from salmon farms (19, 20).

Although *Stenotrophomonas* spp. are less frequently considered as primary pathogens, *S. maltophilia* is the major cause of the bacteriospermia in porcine or bovine semen in the United States and United Kingdom (21–23), as well as the infection of *Xenopus laevis* oocytes (24). It was also found to be associated with an outbreak of lymphadenitis in Omani goats (25) and causes fleece rot in sheep (26). Closely related *S. maltophilia* strains were isolated from an outbreak of bovine mastitis (27), which may be explained by the higher adhesion of these isolates to bovine mammary gland epithelial cells (28). *S. maltophilia* was identified as a cause of pyogranulomatous hepatitis in a female buffalo (*Bubalus bubalis*) in a herd in Serres, Greece (29), as well as the cause of necrosis and friability of the nictitating membrane of the giant panda (*Ailuropoda melanoleuca*) (30). It is also associated with chronic respiratory disease among horses, dogs, and cats (31, 32), as well as septicemia in pigs and crocodiles (33, 34). Moreover, the DNA of *S. maltophilia* is identified most frequently in the knee joints of dogs with inflammatory arthritis (35).

ANTIMICROBIAL SUSCEPTIBILITY

The susceptibility testing methods for *S. maltophilia* include disk diffusion, agar/broth dilution, commercially available microdilution strips, and microtiter panels (Table 2). Although the Clinical Laboratory Standards Institute (CLSI) has not defined breakpoints for *S. maltophilia* isolated from animals, the breakpoints for human isolates of *S. maltophilia* for sulfamethoxazole/trimethoprim (SXT), minocycline, levofloxacin, ticarcillin-clavulanic acid, ceftazidime, and chloramphenicol have been commonly adopted (36). The breakpoints for *Enterobacteriaceae* and *Pseudomonas* spp. are also frequently employed to interpret the susceptibility data for *S. maltophilia* (29, 32). Other breakpoints, such as those specified by the National Reference Laboratory for Antibiotics (National Institute of Public Health, Prague, Czech Republic) and the Antibiogram Committee of the French Microbiology Society, have also been used (13, 15).

Available data are limited for the antimicrobial susceptibility of *S. maltophilia*, because it is not considered as a major pathogen in animals. However, *S. maltophilia* isolates from animals are resistant to numerous antimicrobials that are commonly used in human and veterinary medicine, including β-lactams (penicillins and cephalosporins), aminoglycosides, macrolides, and tetracyclines (except minocyline) (Table 2). In contrast, they are often susceptible to fluoroquinolones, polymyxins (mainly including polymyxin B and polymyxin E [colistin]), and SXT. The antibiotic resistance of *S. maltophilia* varies among different animal species. For example, one isolate from swine in China showed high resistance to most antimicrobials, including fluoroquinolones, polymyxins, and SXT (33), whereas isolates from Omani goats were susceptible to all tested antimicrobials except β-lactams (25). Despite its intrinsic resistance to β-lactams, the resistance rates of *S. maltophilia* isolates from captive snakes to these antimicrobials range from 36.2 to 95.7% (15, 37). Moreover, antimicrobial resistance varies with the incubation temperature and time. For instance, the MICs at 37°C and 30°C (after 24 h or 48 h) of 24 antibiotics were determined (microdilution method) for *S. maltophilia* isolates from captive snakes, but resistance rates increased when the strains were incubated at 30°C or for 48 h (37). However, SXT and levofloxacin were the most effective drugs at both temperatures. In addition, the *S. maltophilia* isolates from animal products also exhibit a multidrug-resistant (MDR) phenotype. For example, *S. maltophilia* was the most frequently isolated species among a large collection of Gram-negative bacteria isolated from milk and cheese in France. These *S. maltophilia* isolates showed high resistance rates to β-lactams, chloramphenicol, and tetracycline (13), representing a potential risk to food safety and public health.

MOLECULAR MECHANISMS OF ANTIMICROBIAL RESISTANCE

S. maltophilia employs an array of mechanisms that singularly or collectively, intrinsic or acquired contribute to antimicrobial resistance (Table 3). The following subsections provide detailed descriptions of the major mechanisms.

Multidrug Efflux Pumps

The genome of *S. maltophilia* encodes multidrug efflux pumps, which contribute to intrinsic or acquired

TABLE 2 Antimicrobial resistance of *S. maltophilia* isolated from animals and animal products

Origin	Year of identification	Country	Strain no.	Standards and methods of susceptibility testing[a]	β-Lactams (penicillins, cephalosporins, carbapenems)	Macrolides
Swine semen	2000	USA	6	NCCLS M31-A, 1999; disk diffusion	AMP (100)	ERY (100) and TIL (100)
Omani goats	2003	Oman	15	NCCLS M2-A4, 1992; disk diffusion	PEN, AMP, AMC, and TIC (100) CAZ, CTX, and CEP (100)	ERY (0)
Salmon farm	2003	Chile	1	NCCLS M7-A5, 1998; agar dilution		
Yellowtail (*Seriola quinqueradiata*)	2005	Japan	6	Sensi-Disks (Showa, Tokyo, Japan); disk diffusion	AMP (100)CTX and CAZ (100)	
13-lined ground squirrel	2007	USA	1	*Clinical Microbiology Procedures Handbook*; broth microdilution	AMP and AMX (R)	
Captive snakes[c]	2007	Czech Republic	47	NCCLS M2-A8, 2003; breakpoints from National Reference Laboratory for Antibiotics (National Institute of Public Health, Prague, Czech Republic); broth microdilution	AMP (87.2), ATM (89.4), CAZ (68.1), CFP (63.8), CFZ (95.7), CPS (51.1), CTX (85.1), CXM (95.7), FEP (80.9), FOX (95.7), MEM (74.5), PIP (48.3), SAM (68.1), TZP (36.2)	
Horse, cat, dog, and python	2009	Germany	7	Automated susceptibility test strips ATB PSE 5 and ATB VET strips (BioMérieux); microdilution	TIC, PIP, IPM, and CAZ (100)	
Giant panda	2010	USA	1	Unknown	AMC, AMP, CAZ, CTX, CEF, and CEP (R)	AZI (R)
Captive snakes	2010	Czech Republic	45	CLSI M100-S19, 2009; broth microdilution	CAZ (44.4)	
Buffalo (*Bubalus bubalis*)	2010	Greece	1	CLSI M100-S15, 2005; breakpoints of *Pseudomonas* spp. used; broth microdilution	TIC and PIP (R)CAZ and IPM (R)	
Horse	2010	Denmark	7	CLSI M100-S13, 2003; broth microdilution	PEN, AMP, and AMC (100)CF, CPD, and IPM (100)	ERY (100)
Oocytes of *Xenopus laevis*	2011	USA	5	Unknown; disk diffusion	AMX, AMC, and TIC (100), CZ, CF, CTX, CPD, CEF, CXM, and CN (100) CRO (80), CAZ and IPM (0)	
Milk and Cheese	2012	France	3	Antibiogram Committee of the French Microbiology Society (CA-SFM), 2008/2009; disk diffusion	AM, PIP, AMX, AMC, TIM, CTX, and CAZ (100)IPM (66.7)	
Pig	2012	China	7	Unknown; disk diffusion	AMP, AMX, and novobiocin (100) CTX and CAZ (100)	
Bovine mastitis	2012	Japan	13	CLSI M31-A3 (2008) and M100-S21 (2011); commercially prepared microtiter panel (Opt Panel MP) and disk diffusion	MOX (0), CAZ (92.3)	
Pig	2015	China	1	CLSI VET01-A4 (2013) and M100-S24 (2014); broth microdilution	AMP, AMC, CEF, CAZ, and MEM (R)	ERY and AZI (R)

[a]For more than one strain, the resistance rate was calculated, and the susceptibility results were interpreted as resistant/intermediate/susceptible (R/I/S) for single strains. CLSI breakpoints were only available for *S. maltophilia* from humans for SXT, MIN, LEV, TIM, CAZ, SXT, and CHL determined using disk diffusion or dilution method For other antimicrobials, the breakpoints for *Enterobacteriaceae* or *Pseudomonas* spp. were used to interpret the susceptibility results for *S. maltophilia*.

[b]PEN, penicillin G; AMP, ampicillin; AMX, amoxicillin; PIP, piperacillin; TIC, ticarcillin; TIM, ticarcillin/clavulanic acid; AMC, amoxycillin/clavulanic acid; SAM, ampicillin/sulbactam; TZP, piperacillin/tazobactam; CAZ, ceftazidime; CTX, cefotaxime; CEF, ceftiofur; CEP, cephalothin; CFZ, cefazolin; CFP, cefoperazone; CN, cephalexin; CRO, ceftriaxone; CPS, cefoperazone/sulbactam; CF, cephalothin; CXM, cefuroxime; FEP, cefepime; FOX, cefoxitin; CPD, cefpodoxime; CZ, cefazolin; MOX, moxalactam; IPM, imipenem; MEM, meropenem; ERY, erythromycin; TIL, tilmicosin; AZI, azithromycin; CHL, chloramphenicol; FFC, florfenicol; GEN, gentamic KAN, kanamycin; AMK, amikacin; SPT, spectinomycin; STR, streptomycin; NEO, neomycin; TOB, tobramycin; TET, tetracycline; DOX, doxycycline; OTC, oxytetracycli MIN, minocycline; CIP, ciprofloxacin; LVX, levofloxacin; OFX, ofloxacin; ENO, enrofloxacin; MAR, marbofloxacin; DIF, difloxacin; OFX, ofloxacin; OBX, orbifloxacin; CL, colistin; CLI, clindamycin; VAN, vancomycin; S3, sulfonamides; SMX, sulfamethoxazole; TMP, trimethoprim; SXT, trimethoprim-sulfamethoxazole.

[c]Resistance rates varied with incubation temperature (30°C or 37°C) and time (24 h or 48 h). Susceptibility data presented here were determined when isolates were incubated at 37°C for 24 h.

Antimicrobial agents used for susceptibility testing (resistance rates, %)[b]							
Phenicols	Aminoglycosides	Tetracyclines	Fluoroquinolones	Polymyxins	Lincosamides/ glycopeptides	Sulfonamides	Ref.
	GEN and SPT (100)	OTC (100)		CL (0)		Triple sulfa (100)	21
CHL (0)	KAN, GEN, and AMK (0)	TET (0)	ENO (0)			SXT (0)	25
		OTC (R), DOX (R), MIN (S)					19
							17
CHL (R)	GEN and SPT (R)	TET (R)					14, 113
CHL (61.7)	AMK (31.9), GEN (25.5), TOB (57.4)	TET (89.4)	LVX (0), OFX (2.1), CIP (42.6)	CL (21.3)		SXT (2.1)	15
CHL (28.6)	AMK (42.9), GEN (71.4), TOB (57.1)	TET (100)	CIP and ENO (0)	CL (0)		SXT (14.3)	31
CHL (S)	GEN, NEO, and TOB (R)	DOX (S) OTC and TET (R)	CIP and ENO (S)	CL (R)	CLI and VAN (R)	SXT (I)	30
CHL (28.9)			LVX (0)			SMX (2.2)	37
CHL (S)	AMK, GEN, and TOB (R)	TET (R)	CIP and ENO (S)	CL (S)		SXT (S)	(29)
	GEN and AMK (100)	TET (0)	MAR and ENO (0)			SXT (0)	32
CHL (100)	GEN and TOB (100) AMK (0)	TET (100)	CIP (0)DIF, ENO, OFX, and OBX (100) MAR (80)				24
CHL (100)		TET (100)					13
	GEN and STR (100)					S3 and TMP (100)	10
CHL (7.7)			CIP (7.7)ENO (0)			SXT (15.4)	27
CHL and FFC (R)	GEN, STR, and SPT (R)	TET and DOX (R)	ENO (R), LVX (I), CIP (R)	CL (R)		SMX and SXT (R)	33

TABLE 3 Molecular mechanisms of antimicrobial resistance of *S. maltophilia*[a]

Resistance mechanisms and related genes	Products	Antibiotic resistance phenotype	Intrinsic/ acquired resistance	Gene location	Ref.
Multidrug efflux pumps					
smrA	ABC-type efflux pump	Fluoroquinolones, tetracycline, doxorubicin	NK/yes	C	38
fuaABC	ABC-type efflux pump	Fusaric acid	Yes/no	C	41
macABCsm	ABC-type efflux pump	Macrolides, aminoglycosides, polymyxins	Yes/NK	C	39
emrCABsm	MFS-type efflux pump	Nalidixic acid, erythromycin	No/yes	C	40
mfsA	MFS-type efflux pump	Aminoglycosides, cephalosporins, fluorpquinolones, erythromycin, rifampicin, tetracycline, chloramphenicol	Yes/NK	C	50
smeABC	RND-type efflux pump	β-lactams, aminoglycosides and quinolones	No/yes	C	42
smeDEF	RND-type efflux pump	Quinolones, tetracyclines, macrolides, chloramphenicol, novobiocin, SXT	Yes/yes	C	43, 53
smeVWX	RND-type efflux pump	Chloramphenicol, quinolones, tetracyclines	No/yes	C	44
smeIJK	RND-type efflux pump	Aminoglycosides, tetracyclines, fluorpquinolones, leucomycin	Yes/yes	C	46, 55
smeYZ	RND-type efflux pump	Aminoglycosides, SXT	Yes/yes	C	45, 46, 54
smeOP-TolC$_{Sm}$	RND-type efflux pump	Nalidixic acid, doxycycline, aminoglycosides, macrolides	Yes/no	C	47
β-lactamases					
bla$_{L1}$	Metallo-β-lactamase	β-Lactams except monobactams	Yes/yes	C or P	56, 97
bla$_{L2}$	Cephalosporinase	Penicillins and cephalosporins	Yes/yes	C	57, 97
bla$_{TEM-2}$, *bla*$_{TEM-116}$, *bla*$_{TEM-127}$, *bla*$_{CTX-M-1}$, *bla*$_{SHV-1}$ and *bla*$_{CTX-M-15}$	β-lactamase	Penicillins and/or cephalosporins	No/yes	P	62–65
bla$_{NDM-1}$	Metallo-β-lactamase	β-Lactams except monobactams	No/yes	C	66
Aminoglycoside-inactivating enzymes					
aac(6')-Iz	Aminoglycoside acetyltransferase	Amikacin, netilmicin, sisomicin, tobramycin	Yes/no	C	67
aph(3')-IIc	Aminoglycoside phosphotransferase	Kanamycin, neomycin, butirosin, paromomycin	Yes/no	C	68
aac(6')-Iak	Aminoglycoside acetyltransferase	Amikacin, arbekacin, dibekacin, isepamicin, kanamycin, neomycin, netilmicin, sisomicin, tobramycin	Yes/no	C	69
aac(6')-Iam	Aminoglycoside acetyltransferase	NK	NK	C	45
Qnr family					
Sm*qnr*	Pentapeptide repeat proteins	Low-level quinolone resistance	Yes/no	C	76–78
SXT resistance					
sul1 and *sul2*	Folate reductase enzyme	Trimethoprim/sulfamethoxazole	No/yes	C or P	82–84
dfrA1, *dfrA5*, *dfrA12*, *dfrA17*, and *dfrA27*	Dihydrofolate reductase enzyme	Trimethoprim/sulfamethoxazole	No/yes	C or P	85
Phenicol exporters					
floR	MFS exporter protein	Chloramphenicol, florfenicol	No/yes	P	83
floRv	MFS exporter protein	Chloramphenicol, florfenicol	No/yes	GI in C	33
cmlA	MFS exporter protein	Chloramphenicol	No/yes	I-integron	90
Lipopolysaccharide					
spgM	Phosphoglucomutase	Polymyxin B/E, nalidixic acid, gentamicin	Yes/NK	C	92
phoPQ	Two-component regulatory system	Polymyxin B, chloramphenicol, ampicillin, aminoglycosides	Yes/yes	C	96

[a]NK, not known.

antibiotic resistance, as follows: ATP-binding cassette (ABC)-type (SmrA, FuaABC, and MacABCsm), major facilitator superfamily (MFS)-type (EmrCABsm, MsfA), and eight predicted resistance nodulation cell division (RND)-type efflux systems with SmeABC, SmeDEF, SmeVWX, SmeIJK, SmeYZ, and SmeOP-TolCSm characterized (38–47) and SmeMN and SmeGH uncharacterized (45). Most of the efflux pumps are superficially quiescent or expressed at low levels (39, 42, 44), and their overexpression is associated with reduced antibiotic susceptibility. Acquired resistance may be due to mutations in regulatory genes of these efflux systems (43, 46, 48).

SmrA, the first ABC-type efflux pump identified in *S. maltophilia*, confers acquired resistance to fluoroquinolones, tetracycline, doxorubicin, and multiple dyes (38). FuaABC, a fusaric acid (5-butylpicolinic acid, a mycotoxin) efflux pump, which is classified as a member of a subfamily of the ABC-type family, is induced by fusaric acid and contributes to fusaric acid resistance when overexpressed (41). The MacABCsm efflux pump confers intrinsic resistance to aminoglycosides, macrolides, and polymyxins and contributes to oxidative and envelope stress tolerance as well as biofilm formation (39). The MFS-type pump EmrCABsm is involved in the extrusion of hydrophobic compounds, including the antibiotics nalidixic acid and erythromycin, as well as the uncoupling agents carbonyl cyanide 3-chlorophenylhydrazone, and tetrachlorosalicylanilide (40). A novel MFS efflux pump (MfsA) with 14 transmembrane domains plays an important role in mediating resistance to paraquat (49), as well as to antibiotics such as aminoglycosides (kanamycin, streptomycin, and neomycin), cephalosporins (cefazolin and cefalexin), fluoroquinolones (ciprofloxacin, norfloxacin, levofloxacin, and ofloxacin), the macrolide erythromycin, rifampicin, tetracycline, and chloramphenicol (50).

SmeABC is involved in acquired, but not intrinsic, resistance to β-lactams, aminoglycosides, and quinolones. The deletion of *smeC* (encoding a porin) affects susceptibility to certain antibiotics, suggesting the relationship of porin to other unidentified efflux pumps (42). SmeDEF is involved in intrinsic and acquired (in the condition of overexpression) resistance to quinolones, tetracyclines, macrolides, chloramphenicol, novobiocin, and SXT, as well as acquired resistance to triclosan (51–53). SmeVWX mediates acquired resistance to chloramphenicol, quinolones, and tetracyclines and when overexpressed, increases susceptibility to aminoglycosides (44). SmeYZ mediates intrinsic resistance to aminoglycosides and SXT (45, 54), while SmeIJK is involved in intrinsic reduced susceptibility to gentamicin, amikacin, tetracycline, minocycline, ciprofloxacin, and leucomycin (45, 55). SmeIJK also mediated acquired resistance to levofloxacin, when overexpressed alone or in coordinate hyperproduction with SmeYZ (46). The activity of the SmeOP-TolCSm efflux pump is associated with the decreases in susceptibility to nalidixic acid, doxycycline, aminoglycosides (amikacin and gentamicin), and macrolides (erythromycin and leucomycin), as well as several nonantibiotic compounds including carbonyl cyanide 3-chlorophenylhydrazone, crystal violet, sodium dodecyl sulfate, and tetrachlorosalicylanilide (47).

Resistance to β-Lactam Antibiotics

The *S. maltophilia* genome encodes the inducible β-lactamases L1 and L2. L1 is a class B Zn^{2+}-dependent metallo-β-lactamase with substrate preference for penicillins, cephalosporins, and carbapenems, except for monobactams; and L2 is a class A clavulanic acid-sensitive cephalosporinase that hydrolyzes penicillins, cephalosporins, and monobactams (56, 57). The expression of L1 and L2 is simultaneously regulated by AmpR, a transcriptional regulator encoded by *ampR*, located upstream of bla_{L2}, which acts as a weak repressor or activator of the bla_{L2} in the presence or absence of β-lactam antibiotics, respectively (58). The induction of β-lactamases is inhibited by the deletion of the *ampN-ampG* operon, which encodes a permease transporter (59). The hyperproduction of L1/L2 β-lactamases occurs when the transcription of *mrcA* or $ampD_I$ (encoding penicillin-binding protein 1a [PBP1a] and a cytoplasmic *N*-acetyl-muramyl-L-alanine amidase [$AmpD_I$], respectively) is inhibited (60, 61). In addition, the β-lactamases TEM-2, TEM-116, TEM-127, CTX-M-1, SHV-1, and CTX-M-15 and the globally disseminated metallo-β-lactamase NDM-1 are present in human clinical and environmental isolates of *S. maltophilia* (62–66), suggesting that this pathogen may serve as a reservoir for mobile genes that encode β-lactamases.

Resistance to Aminoglycosides

The mechanisms employed by *S. maltophilia* that mediate resistance to aminoglycosides primarily involve aminoglycoside-modifying enzymes and multidrug efflux pumps. These enzymes include the aminoglycoside acetyltransferase AAC(6′)-Iz (67) and the aminoglycoside phosphotransferase APH(3′)-IIc (68), both of which confer low-level resistance to aminoglycosides, with the exception of gentamicin. The novel aminoglycoside acetyltransferase AAC(6′)-Iak, which exhibits 86.3%

amino acid identity to AAC(6′)-Iz, is expressed by an MDR *S. maltophilia* strain isolated from Nepal and acetylates amikacin, arbekacin, dibekacin, isepamicin, kanamycin, neomycin, netilmicin, sisomicin, and tobramycin, but not apramycin, gentamicin, or lividomycin (69). Moreover, AAC(6′)-Iam [84.3% amino acid sequence identity to AAC(6′)-Iak], was detected in a clinical isolate of *S. maltophilia* (45). However, the resistance phenotype conferred by this enzyme is unknown. In addition, the efflux pumps SmeABC, SmeYZ, SmeOP-TolCsm, and MacABCsm are associated with aminoglycoside resistance (Table 3).

Resistance to Quinolones

Mutations in the quinolone-resistance-determining region of genes encoding topoisomerases (*gyrA*, *gyrB*, *parC*, and *parE*) are associated with the major mechanism of quinolone resistance employed by bacteria (70). So far, mutations have not been detected in the quinolone-resistance-determining region of *gyrA* of *S. maltophilia* (71, 72). Amino acid residue substitutions are present in the quinolone-resistance-determining region-encoding regions of *gyrB*, *parC*, and *parE* of clinical isolates of *S. maltophilia* that cause bacteremia; however, these alterations have not been directly associated with quinolone resistance (73). The specific mechanisms associated with the quinolone resistance of *S. maltophilia* are mediated by both the efflux pumps and the chromosomal *qnr* gene (Sm*qnr*) that protects gyrase and topoisomerase IV from quinolones (74). Sm*qnr* and its functional 12 variants belong to the *qnr* family (75) and contribute to low-level intrinsic quinolone resistance (76–78). Genes that encode efflux pumps that mediate quinolone resistance are as follows: *smeDEF*, *smeIJK*, *smeABC*, and *smeVWX* (Table 3). The most prevalent cause of quinolone resistance in *S. maltophilia* is the overproduction of multidrug efflux pumps, among which the SmeDEF plays the most important role (79). Furthermore, overexpression of *smeVWX* in clinical isolates of *S. maltophilia* is associated with high-level resistance to quinolones (80).

Resistance to Trimethoprim-Sulfamethoxazole

The resistance of Gram-negative bacteria to sulfonamides is mainly conferred by the acquisition of either *sul1* or *sul2*, encoding dihydropteroate synthases (81). The *sul1* gene carried by class 1 integrons and *sul2*, which is linked to insertion sequence common region (ISCR) elements, was identified in SXT-resistant *S. maltophilia* isolates (82–84). The resistance of *S. maltophilia* to trimethoprim is mainly conferred by the dihydrofolate reductase *dfr* genes. For instance, the *dfrA* variant genes (*dfrA1*, *dfrA5*, *dfrA12*, *dfrA17*, and *dfrA27*), which are located within class 1 integrons as part of various resistance gene cassettes, are associated with high-level trimethoprim resistance in *S. maltophilia* isolates. Both types of *sul* and *dfr* genes can occur together in high-level SXT-resistant isolates (85, 86). Moreover, the efflux pumps SmeDEF, TolCsm, and SmeYZ are associated with SXT resistance (54, 87, 88).

Resistance to Phenicols

The main phenicol resistance determinant in *S. maltophilia* is *floR*, which encodes an exporter protein of the MFS family that mediates resistance to chloramphenicol and florfenicol (83). Florfenicol is extensively used in livestock to prevent or cure bacterial infections (89). In addition, the MFS exporter gene *cmlA1* and chloramphenicol acetyltransferase genes *catB2* and *catB8*, which separately reside in a gene cassette of class 1 integrons, confer resistance to chloramphenicol in *S. maltophilia* (82, 85, 90). Reports of the prevalence of *floR* in *S. maltophilia* are rare. One report that investigated an international collection of 55 clinical isolates of *S. maltophilia* found that four strains harbored *floR* (83). The novel variant *floRv* was detected in one porcine *S. maltophilia* isolate in China. The *floRv* gene encodes an exporter protein of 404 amino acids, which is 84.1 to 91.8% identical to FloR sequences deposited in GenBank. This FloR variant mediates resistance to chloramphenicol and florfenicol (33).

Alteration of Lipopolysaccharide and Two-Component Regulatory Systems

As in other Gram-negative bacteria, lipopolysaccharide (LPS) is an important structural component of the outer membrane of *S. maltophilia* and forms an effective barrier to exogenous compounds (91). The *spgM* gene encodes a phosphoglucomutase that is associated with LPS biosynthesis in *S. maltophilia* (92). Mutants lacking *spgM*, which produce less LPS compared with the SpgM$^+$ strain, synthesize shorter *O*-polysaccharide chains and exhibit modest increases in susceptibility to polymyxin B, colistin, nalidixic acid, and gentamicin but increased resistance to vancomycin (92). The mobile colistin resistance gene *mcr-1*, which encodes a phosphoethanolamine transferase, couples phosphoethanolamine to the lipid A domain of the LPS component of the outer membrane of Gram-negative bacteria, and negates the efficacy of polymixins (93), has not been detected in *Stenotrophomonas* spp. The two-component regulatory

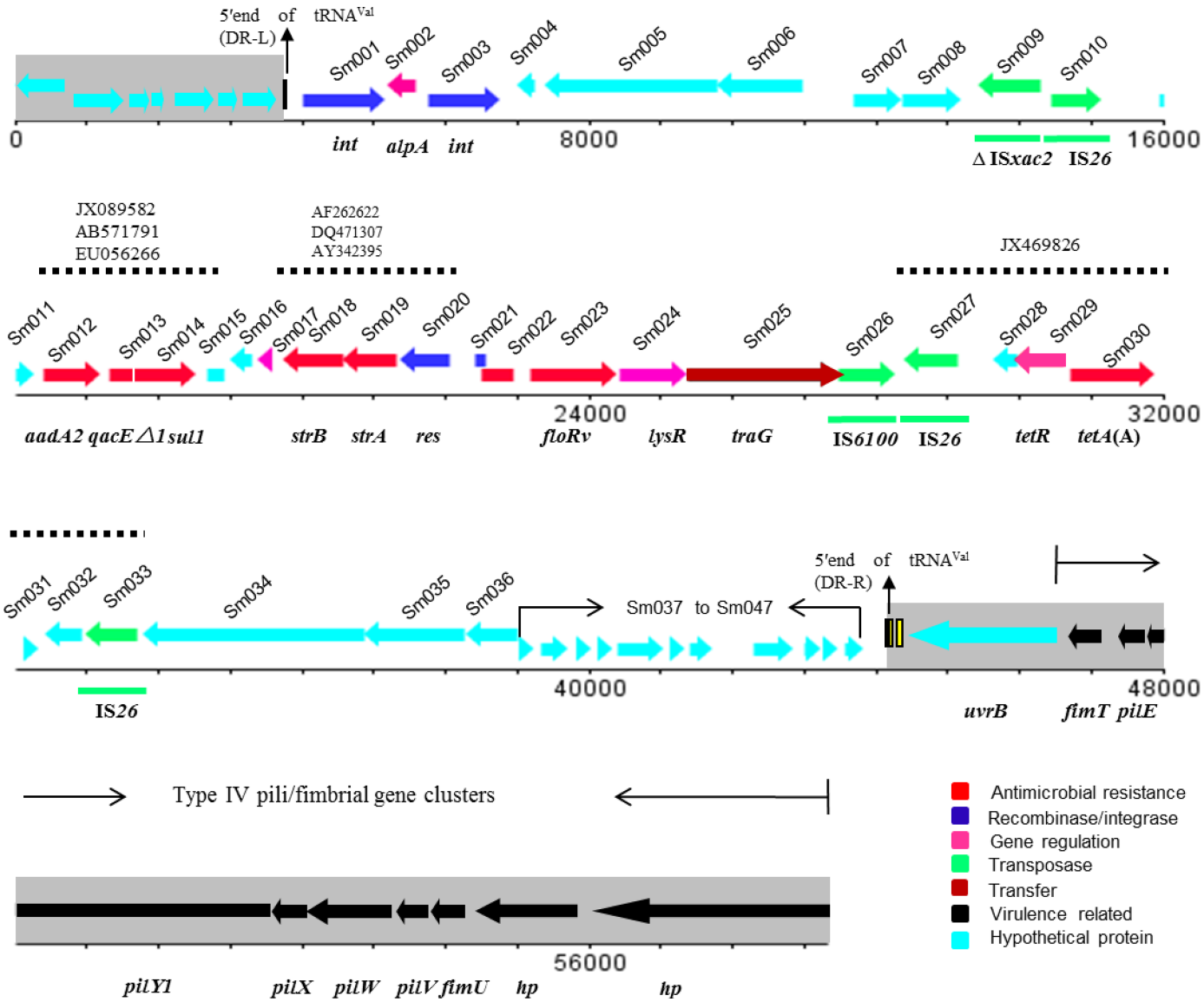

FIGURE 1 Linear representation of the complete GI and its flanking regions in *S. maltophilia* GZP-Sm1. The regions in gray represent the flanking regions of the GI when inserted into the bacterial chromosome. The arrows indicate the directions of gene transcription, and truncated genes are indicated by rectangles without arrowheads. Genes are depicted in different colors, and the regions of particular relevance (≥95% nucleotide sequence identity) are indicated by the dotted lines (33).

system PhoPQ is involved in the resistance of numerous Gram-negative bacteria, including *S. maltophilia*, to cationic antimicrobial polypeptides, i.e., polymyxin B (94–96). Mutation of *S. maltophilia* PhoP increases susceptibility to polymyxin B, chloramphenicol, ampicillin, gentamicin, kanamycin, streptomycin, and spectinomycin (96). Moreover, downregulation of the SmeZ efflux transporter expressed by a PhoP mutant contributes to increased drug susceptibility, particularly to aminoglycosides (96).

DISSEMINATION, COSELECTION, AND PERSISTANCE OF RESISTANCE DETERMINANTS

As described above, the reduced susceptibility of *S. maltophilia* to most antibiotics can be attributed to intrinsic and acquired resistance. The proteins mediating intrinsic resistance of *S. maltophilia* include chromosomally encoded multidrug efflux pumps, antibiotic-inactivating enzymes (L1/L2 β-lactamases and aminoglycoside-inactivating enzymes), and the chromosomally encoded

Qnr pentapeptide repeat proteins (74), which are present in most, if not all, strains of *S. maltophilia*, suggesting they did not arise during the recent evolution of resistance caused by antibiotic therapy. In addition, *S. maltophilia* can acquire mechanisms to increase its resistance through horizontal gene transfer via integrons, transposons, plasmids, and genomic islands (GIs). The *sul1* gene is always associated with the class 1 integron in *S. maltophilia*, indicating the role of the latter in the acquisition and dissemination of *sul1* within this species (82–86, 90). The *qacEΔ1* gene, which encodes resistance to quaternary amines, coexists with *sul1* at the 3′-termini of class 1 integrons (83, 85, 90). The gene cassettes, which comprise the variable regions of integrons, integrate different combinations of drug-resistance genes donated by other Gram-negative bacteria, including those encoding resistance to aminoglycosides [*aacA4*, *aacA7*, *aadA1*, *aadA2*, *aadA4*, *aadA5*, *aadB*, *aac(6′)-II*, *aac(6′)-Ib*, *aac(3′)-Ia*, and *ant(3″)-Ia*], trimethoprim (*dfrA1*, *dfrA5*, *dfrA12*, *dfrA17* and *dfrA27*), β-lactams ($bla_{\text{CARB-8}}$), rifampicin (*arr-3*), and chloramphenicol (*catB2*, *catB8*, *cmlA1*) (82, 85, 90).

ISCR elements are frequently associated with antimicrobial resistance genes and are always linked to *sul2* in *S. maltophilia*. For example, seven *sul2*-positive *S. maltophilia* isolates harbor ISCR elements (five ISCR2 and two ISCR3 elements) on a plasmid (83). Moreover, *sul2* and *floR* are linked to ISCR2 in all *sul2*-positive *S. maltophilia* isolates. Constitutively expressed $bla_{\text{TEM-2}}$ resides within a novel Tn*1*/Tn*3*-type transposon in the genome of *S. maltophilia* isolate J675Ia (65). The transposon could mobilize $bla_{\text{TEM-2}}$ onto the broad host-range conjugative plasmid R388, which is then transferred to *E. coli*.

The genes encoding β-lactamases L1 and L2 are invariably chromosomal and reside on an approximately 200-kb plasmid present in 10 clinical isolates of *S. maltophilia* (97). However, the sequences of the L1 and L2 genes diverge from that of the published strain IID 1275, indicating that the presence of β-lactamase genes on a plasmid may lead to their relatively quick evolution (97).

A literature search identified only a single report of an MDR GI in the *S. maltophilia* isolate GZP-Sm1 in China (33). GZP-Sm1 was isolated from swine with septicemia, and susceptibility testing revealed that the isolate was resistant to most antimicrobials employed in human and veterinary clinical practice (33). Whole-genome sequencing identified a GI of 40,226 bp, which contains an MDR region (19,364 bp) and is flanked by IS*26* in opposite orientations (Fig. 1). Furthermore, six resistance genes exist in this region, including *floRv* (phenicol resistance), *tet*(A)-*tetR* (tetracycline resistance), *strA*/*strB* (streptomycin resistance), *sul1* (sulfonamide resistance), and *aadA2* (streptomycin/spectinomycin resistance). The MDR region comprises several segments with sequence similarity to plasmids or chromosomal sequences of other Gram-negative bacteria. For example, the *aadA2* cassette and the 3′-CS region (*qacEΔ1*-*sul1*-Δ*orf5*), which form part of an integron structure identified in this GI, occur in diverse bacterial species such as *Salmonella* spp., *Pseudomonas* spp., and *E. coli*. The 4,766-bp segment of Δ*sul*-*floRv*-*lysR*-*traG* is 86.3% identical to the corresponding region of plasmid pAB (accession no. HQ917128) detected in a clinical isolate of *Acinetobacter baumannii* from Chile. The composite transposon comprising IS*26*-*tet*(A)-*tetR*-IS*26* flanked by a direct repeat of GC is 95.1% identical to the corresponding region of the plasmid pB12 from uncultivable bacteria (accession no. JX469826). Inverse PCR showed that the GI could be excised from the chromosome by recombination between the direct repeats to generate a circular extrachromosomal form (Fig. 1). The emerging resistance of *S. maltophilia* to numerous antimicrobials raises the concern that the presence of resistance genes in the novel MDR GI drastically limit therapeutic options and may enhance their coselection when antimicrobials are administered.

S. maltophilia could acquire antibiotic resistance from Gram-positive bacteria. For example, a gene cluster involved in resistance to antibiotics and heavy metals was detected in a clinical isolate of *S. maltophilia* (98). These genes encode a macrolide phosphotransferase (*mphBM*) and a cadmium efflux determinant (*cadA*), as well as its transcriptional regulator (*cadC*), encoding its cognate transcriptional regulator. The *cadC*-*cadA* region is flanked by a truncated IS*257* sequence and a region coding for a *bin3* invertase. The sequences of these genetic elements are highly similar to those of *Staphylococcus aureus*, indicating their Gram-positive origin.

CONCLUSION

S. maltophilia is the most widely distributed environmental species among *Stenotrophomonas*, and it is also an opportunistic pathogen associated with the increased number of infections in both humans and animals. *S. maltophilia* isolates from animals are resistant to most antimicrobials used in both human and veterinary medicine, which compromise the design of optimal therapeutic strategies in clinical chemotherapy. The antimicrobial resistances in *S. maltophilia* are conferred not only by intrinsic mechanisms, but also by

multiple acquired resistance mechanisms, which are commonly associated with mobile genetic elements such as integrons, transposons, and plasmids. Moreover, for the first time, the transmission mechanism conferred by MDRGI was identified in a porcine *S. maltophilia* isolate. Therefore, continued surveillance of MDR *S. maltophilia* from animals is warranted for not only optimizing treatment of infections caused by this bacterium, but also tackling the transmission of antimicrobial resistance from animals to humans by either food-chain or environmental routes.

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