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History, Structure, Epidemiology and Molecular Typing of *Staphylococcal Cassette Chromosomes Mec* (Sccmec) involved in Multiple Resistances to Beta-Lactams in the Genus Staphylococcus: an Overview

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Abstract

Staphylococcal cassette chromosomes mec (SCCmec) are chromosomal mobile genetic determinants that confer to the Staphylococcus strain hosting a multi-resistance to antibiotics and metallic trace elements. The objective of this study was to review the literature on the history, structure, epidemiology and characterization techniques of SCCmec. Data were collected from articles in scientific journals through Google scholar and PubMed engines. In 1999, was characterized the first SCCmec type on genome of S. aureus N315. A type of SCCmec is characterized by the complex type ccr and the class complex mec. The first classification took place in 2001. Today, there are 15 recognized SCCmec types. SCCmec type IV is the most disseminated and predominates on the continents. The application of PCR and Illimina or MinION sequencing have revolutionized SCCmec typing, which is one of the main methods of epidemiological surveillance of methicillin resistance Staphylococcus aureus. MRSA are the most threatening bacteria in the hospital environment and cause enormous problems in community settings and in animal health. SCCmec typing is a very effective means of characterizing the genetic determinants of resistance in MRSA. Popularization of SCCmec typing through their applications in routines and accessibility to improve epidemiological monitoring of MRSA.

Keywords: Antibiotics; Methicillin Resistance; Staphylococcus; SCCmec; Typing

Introduction

Staphylococci are ubiquitous bacteria that represent one of the major threats in bacterial infections in both human and animal health [1-3]. The species *Staphylococcus aureus* (*S. aureus*) is the second cause of bacterial human pathologies after *Escherichia coli* [4,5]. In addition to their high prevalence across investigations around the world, *Staphylococcus aureus* has been closely linked to the history of control and epidemiology of bacterial resistance to antibiotics. In this effect, the first antibiotic (Penicillin G) was discovered in the 1940s, the deductions of which began following the accidental contamination by *Penicillium notatum* on a culture of *S. aureus* carried out by Sir Alexander Fleming Scottish biologist on September 3, 1928 [5]. But the first bacterial resistance to Penicillin G was officially reported in 1942 in a strain of *S. aureus* which showed sensitivities to penicillinase produced by *Penicillium notatum* [6]. Thus a molecule of semi-synthesized antibiotic <<methicillin>> insensitive to the action of penicillinase was set up in 1959

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to remedy this phenomenon of resistance. But, immediately after a year and a few months (in 1961) in England, the first bacterial resistance to methicillin was reported in a strain of *S. aureus* [7]. Methicillin-resistant (MRSA) strains of *S. aureus* are also resistant to almost all beta-lactams [8]. Indeed, resistance to methicillin in *Staphylococcus aureus* is caused by the modification of penicillin-binding proteins (PLP) possessing an enzymatic activity (trans-peptidases, carboxypeptidases or glycosyltransferases) involved in the synthesis of the bacterial wall and possessing an affinity for beta-lactams [10,11]. These modified PLPs bear the name of PLP2a, which has very little affinity with beta-lactams. The work performed allowed the complete sequencing of the genetic determinant of PLP2a (the *mec* gene). Today, there are 4 types (A, B, C, and D) of known guy genes. Among these 4 types of *mec* gene, 3 types of the 4 (A, B and C) have been characterized in *S. aureus* and type D has been reported in *Macrococcus caseolyticus* [11]. The mec genes in *S. aureus* are mostly chromosomal and integrate into the bacterial genome to express themselves through the coordinated action of a mobile genetic complex called *staphylococcal cassette chromosome mec* (SCCmec) with a molecular weight ranging from 21 to 67 kb [12]. A staphylococcal cassette chromosome would be the genetic unit for the transfer and expression of virulence and/or resistance genes in the genus Staphylococcus [14,15]. SCCmec types confer resistance to Staphylococcus strains against beta-lactam residues [15]. It was in 1999 that the first SCCmec was described in the strain of *S. aureus* N315 but it was in 2001 that their classification was initiated [10]. After the description of the first SCCmecs in patients in hospital settings, subsequent investigations reported that MRSA carriers of SCCmecs were equipped with genes on their SCCmecs that allowed them to adapt and proliferate also in community settings and in animals. Epidemiologically, a diversity of SCCmec has been reported in strains of *S. aureus* in Europe, America, Africa and Asia (Table 2) [17,18]. The proliferation of SCCmecs and their roles in multi-antibiotic resistance in MRSA have become public health issues being addressed by top global health officials. Thus, an international structure in charge of the follow-up in the world of SCCmec called <<the International Working Group on the Classification of *Staphylococcal Cassette Chromosome Elements*>> (IWG-SCC) was created. Since 2009, the IWG-SCC has shown the guidelines to follow for the nomenclature of types and subtypes of SCCmec [18]. Today, the IWG-SCC has registered 15 types of SCCmec, of which the last SCCmec was type XV (7A) and was characterized in strain NV_1 by [19]. This study aims to conduct an overview through retrospective data from official publications on *Staphylococcal Cassette Chromosome mec* implicated in multi-resistance to beta-lactams in *Staphylococcus*. Specifically to: (i) provide information on the history and structuring of SCCmec types (ii) detail on the structural functioning and epidemiology of SCCmec (iii) list the application of technology for the characterization of molecular weight of SCCmec.

Methodology

Relevant documents on the subject were searched on websites through Google scholar and Pub Med. The documentation lasted between September 2021 to February 2022. The expressions and keywords that were used during this documentary research were only related to the specific objectives. These words and expressions concerned "the work of Sir Alexander Fleming" for the discovery of the first antibiotic, "definition and history and resistance to methicillin", "expression of the *mecA* gene and the resistance of MRSA to the metallic traces elements and other families of antibiotics other than beta-lactams" for the operation of the SCCmec cassette, "definition and types of *Staphylococcal cassette chromosome mec*" for a general view of SCCmec and "the prevalence of MRSA and SCCmec in continents and by country" of which for 87 countries were surveyed and more than half were excluded with reasons listed in Figure 1.

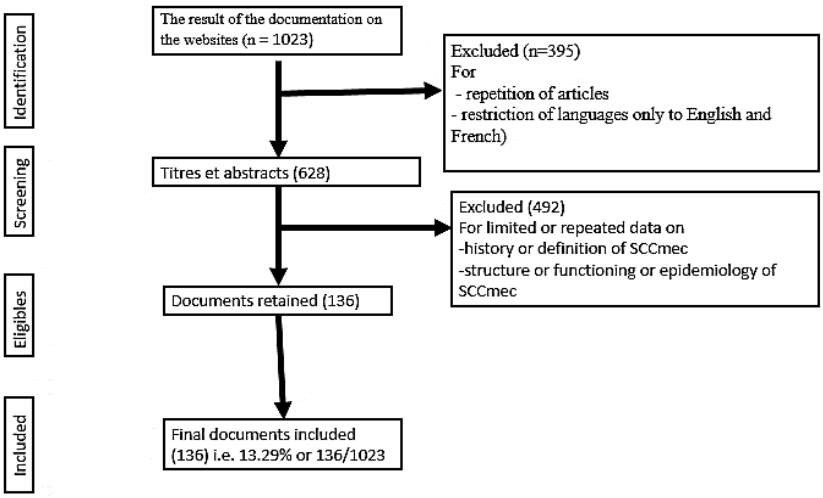

Figure 1: Illustration of the documentary inclusion and exclusion process.

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Table 1: Types of *Staphylococcal cassette chromosome mec* (SCCmec).

Types SCCmec	Complex mec	complex mec organization	Complex ccr	Genes ccr	reference of the strain	Origin of the strain	Countries	Accession N° Genbank	Reference
I	Class B	IS1272-ΔmecR1-mecA-IS431	Type 1	ccrA1 and ccrB1	NCTC 10442	Human	England	AB033763	[10]
II	Class A	mecI-mecR1-mecA-IS431	Type 2	ccrA2 and ccrB2	N315	Human	Japan	D86934	[10]
III	Class A	mecI-mecR1-mecA-IS431	Type 3	ccrA3 and ccrB3	85/2082	Human	News Zealand	AB037671	[10]
IV	Class B	IS1272-ΔmecR1-mecA-IS431	Type 2	ccrA2 and ccrB2	JCSC1986	Human	USA	AB063172	[23]
V	Class C2	IS431-mecA-ΔmecR1-IS431	Type 5	ccC1	JCSC3624	Human	Australia	AB121219	[24]
VI	Class B	IS1272-ΔmecR1-mecA-IS431	Type 4	ccrA4 and ccrB4	HDE288	Human	Portugal	AF411935	[26]
VII	Class C1	IS431-mecA-ΔmecR1-IS431	Type 5	ccrC1	JCSC6082	Human	Sweden	AB373032	[27]
VIII	Class A	mecI-mecR1-mecA-IS431	Type 4	ccrA4 and ccrB4	C10682	Human	Canada	FJ390057	[29]
IX	Class C2	IS431-mecA-ΔmecR1-IS431	Type 1	ccrA1 and ccrB1	JCSC943	Human	Denmark	AB505628	[30]
X	Class C1.2	IS431-mecA-ΔmecR1-IS431	Type 7	ccrA1 and ccrB6	JCSC945	Human	Denmark	AB505630	[30]
XI	Class E	blaZ-mecA-mecR1-mecI	Type 8	ccrA1 and ccrB3	IGA251	Cattle et Human	Denmark	FR821779.1	[31]
XII	Class C2	ΔIS431-mecA-ΔmecR1-IS431	Type 9	ccrC2	BAO1611	Cattle	China	KR187111	[33]
XIII	Class A	IS431-mecI-mecR1-mecA-IS43	Type 9	ccrC2	ST152	Human	Denmark	MG674089	[34]
XIV	Class A	IS431-mecI-mecR1-mecA-IS43	Type 5	ccrC1	SC792	Human	Japan	LC440647	[35]
XV	Class A	mecI-mecR1- mecA-IS431	Type 7	ccrA1 and ccrB6	NV_1	Food	China	-	[19]

Results and Discussionz

History of Drug Resistance and Early Descriptions of Sccmec Types

Methicillin was the first semi-synthesized antibiotic developed in 1959 for the treatment of infections with penicillinase-producing strains of *S. aureus*. Its routine use in hospitals had very short success, because in 1961 the first methicillin-resistant strain was reported in England [7]. After this hard blow on the fight against bacterial resistance to antibiotics, epidemiological investigations on the surveillance of MRSA and the determination of the genetic supports responsible for this resistance. But it was in 1980 that the first chromosomal fragment (DNA) responsible for resistance to methicillin was reported in the Japanese MRSA strain N315. This genetic determinant with a molecular weight of approximately 30 kb was named *mecDNA*. Following this discovery, the *mecA* gene was detected on *mecDNA* and was sequenced in a clone of the same Japanese strain. In the same decade 1980-1990 reasoning led to believe that *S. aureus* susceptible to methicillin (SASM) and MRSA formed two different bacterial species. But it has been demonstrated in a study based on 23s-RNA ribotyping of community MRSA strains (collected in Tokyo in 1959), MRSA and SASM strains from 19 hospitals in Japan (collected 1982 and 1983 entries), and MRSA strains from the Malaya hospital center (collected between 1987 and 1989) that MRSA and SASM form the same bacterial species [20]. Indeed, the SASM chromosome would simply be a support for the insertion of the *mecA* gene for possible acquisition of resistance to methicillin [20]. During 1990-1995, it was reported that the functioning of the *mecA* gene depended on the state of expression of another gene placed upstream of the *mecA* gene; it is the regulatory gene of the *mecA* gene named *mecI*. This brings the genetic determinant of methicillin resistance back to a *mecI-mecR1-mecA* complex. However, it has been reported that on the *mecDNA* of some SARMs, the mecI gene is absent and it is substituted by an IS1272 insertion sequence. Thus, the classification of *mecDNAs* in MRSA was based solely on the differences of the genes that make up the mec complex. Elsewhere, the complete sequencing of the genome of the Japanese strain N315 (isolated in 1982) by Kuroda et al., (2001) and compared with the chromosomal fragment (at position 1274-1933) of the MRSA strain NCTC 8325, made it possible to bring more information on the *mecDNA* determinant [21]. This study reported that beyond *mecDNA*,

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Table 2: MR-CoNs (coagulase-negative methicillin-resistant *Staphylococcus*), MRSA (methicillin-resistant *Staphylococcus aureus*).

		Year	Origines	Epecies of Staphylococcus MR	Strains MR (n)	Prevalence (%) SCCmec type												Reference
						I	II	III	IV	V	VI	VII	VIII	IX	X	XI	XII	
	South africa	2020	Human	SARM	2019	0.1	0.6	28.2	6.4	0.1	-	-	-		-	-	-	[88]
		2019	Human	SARM	484	0.2	9	49	28	0.6	0.6	-	-	-	-	-	-	[89]
	Egypt	2021	Human	SARM	72	-	-	57	15	11	-	-	-	-	-	-	-	[90]
		2021	Human	SARM	24	-	8.3	-	75	8.3	-	-	-	-	-	-	-	
	Rwanda	2018	Human	SARM	46	52.2	-	2.6	15.4	-	-	-	-	-	-	-	-	[91]
Africa	Nigeria	2021	Goat	SARM	20	-	-	-	-	10	-	10	-	-	-	-	-	[92]
		2014	Human	MR-CoNs	53	7.54	-	-	17	-	-	-	-	-	-	-	-	[93]
		2020	Human	SARM	34	-	-	2.9	2.9	94.2	-	-	-	-	-	-	-	[94]
	Alegria	2021	Human	SARM	40	-	2.5	72.5	20	2.5	-	-	-	-	-	-	-	[61]
	Ghana	2015	Human	SARM	30	13.33	3.33	3.33	53.33	23.33	-	-	-	-	-	-	-	[62]
	Tunisia	2019	Beef, manure et human	MR-CoNs	11	9.09	27.27	-	18.18	9.09	-	9.09	-	-	-	-	-	[95]
		2020	Livestock et humain	SARM	5	-	-	-	40	40	-	-	-	-	-	20	-	[96]
	England	2020	Milk	MR-CoNs et SARM	18	5.55	-	33.33	22.22	-	-	-	-	-	-	11.11	-	[97]
		2018	Human	MR-CoNs	68	11.76	6	2	7	19	-	-	2	-	-	-	-	[98]
		2019	Dog	MR-CoNs	19	-	-	78.94	15.78	-	-	-	-	-	-	-	-	[99]
	Italia	2019	Pig	SARM	219	-	-	-	5.02	94.97	-	-	-	-	-	-	-	[100]
		2018	Human	SARM et MR-CoNs	27	-	11.11	--	55.55	29.62	-	3.7	-	-	-	-	-	[59]
	Portugal	2021	Hospitals wastewaters	SARM	28	-	3.57	-	96.42	-	-	-	-	-	-	-	-	[101]
	Hungary	2022	Hedgehog wilds	SARM	2	-	-	-	50	-	-	-	-	-	-	50	-	[51]
Europe	Spain	2021	Human	SARM	20	-	5	-	85	-	-	-	-	-	-	-	-	[102]
	Germany	2021	Human	SARM	19	-	-	-	100	-	-	-	-	-	-	-	-	[64]
		2019	Dogs	MR-CoNs	97	-	-	60.82	21.65	15.46	-	-	-	-	-	-	-	[103]
	Turkey	2021	Human	SARM	30	3.33	16.66	60	13.33	6.66	-	-	-	-	-	-	-	[104]
		2019	Foods	SARM	108	-	-	8.33	63.88	9.25	-	-	-	-	-	-	-	[105]
	China	2019	Human	SARM	76	1.31	3.94	7.89	63.15	11.84	-	-	-	-	-	-	-	[106]
		2018	Human	SARM	64	-	-	28.1	68.8	-	-	-	-	-	-	-	-	[107]
		2021	Human	SARM	345	7.5	10.1	38.3	34.8	8.4	-	-	-	-	-	0.9	-	[108]
	Iran	2021	Human	SARM	111	15.31	1.18	-	12.61	14.14	-	-	-	-	-	-	-	[109]
Asia		2021	Human	SARM	61	16.3	22.9	36	21.3	16.3	-	-	-	-	-	-	-	[110]
		2021	Environnement and Human	SARM	63	-	23.08	7.93	1.58	33.33	3.17	20	3.17	-	-	-	4.76	[15]
	India	2021	Human	SARM	233	7	3	27	13	42	-	-	-	-	-	-	-	[111]
		2021	Fish	SARM	23	-	-	-	17.39	-	-	-	-	-	-	-	-	[112]
	Japan	2021	Place and materials medicals	SARM et MR-CoNs	62	24.19	12.9	-	14.51	48.38	-	-	-	-	-	-	-	[113]
		2021	Human	SARM	277	-	61.7	-	30.8	-	-	-	-	-	-	-	-	[48]
		2020	Human	SARM	120	-	17	-	83	-	-	-	-	-	-	-	-	[114]
	Saudi arabia	2020	Hospital's staff	SARM	17	-	-	-	52.94	29.41	-	-	-	-	-	-	-	[115]
		2021	Hospital's staff	SARM	41	24.4	-	34.1	36.6	-	-	-	-	-	-	-	-	[116]
	Brazil	2021	Human	SARM	15	20	13.33	-	66.66	-	-	-	-	-	-	-	-	[117]

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		2021	Hospital's staff	SARM	245	75	-	12.5	4.16	8.33	-	-	-	-	-	-	-	[118]
		2020	Human	SARM	51	-	84.31	-	5.88	-	-	-	-	-	-	-	-	[119]
	Mexico	2018	Foods	MR-CoNs	11	-	-	-	45,45	-	-	-	-	-	-	-	-	[120]
America		2020	Human	SARM	107	3	97	-	-	-	-	-	-	-	-	-	-	[121]
	Canada	2019	Chicken	SARM	15	-	-	-	33.33	66.66	-	-	-	-	-	-	-	[122]
	Venezuela	2020	Human	SARM	55	62.5	-	12.5	25	-	-	-	-	-	-	-	-	[123]
	Argentina	2021	Human	SARM	190	-	-	-	99.5	-	-	-	-	-	-	-	-	[67]
	Peru	2021	Human	SARM	115	79.2	-	1.9	7.5	-	-	-	-	-	-	-	-	[124]
	Colombia	2021	Human	SARM	37	-	-	-	81.1	18.9	-	-	-	-	-	-	-	[125]
Oceania	Australia	2019	Human	SARM	25	-	-	4	48	48	-	-	-	-	-	-	-	[126]
		2019	Human	SARM	10	-	-	-	100	-	-	-	-	-	-	-	-	[127]
		2018	Human	SARM	347	-	-	-	99.13	0.29	-	-	-	-	-	-	-	[128]

there are other genes on the mec chromosome that may contribute to the determinism of methicillin resistance. Thus, all of this large DNA fragment weighing approximately 52 kb where a mec complex carrying the mecA gene is located is called Staphylococcal cassette chromosome mec (SCCmec). A year after the description of the first SCCmec, Katayama et al., (2000) reported that on the SCCmec fragment of the S. aureus strain N315, there is a set of genes forming a complex <<the chromosomal recombinase (ccrA/B) cassette>> other than the nearby mec complex, which is responsible for the recombination of the various genes on SCCmec [22]. The diversity of the nucleotide sequences of this new complex made it possible to set up the first bases of the classification of SCCmec. This classification takes into account, on the one hand, the type of the ccr complex and, on the other hand, the class of the mec complex. In this effect, Ito et *al*. (2001) reported in strains NCTC 10442, N315 and 85/2082 three types of SCCmec respectively classified as SCCmec type I, SCCmec type II and SCCmec type III. Thus, SCCmec type I harbors the mec class B complex whose gene sequence is "IS1272-ΔmecR1-mecA-IS431" and the type 1 ccr complex (with the ccrA1 and ccrB1 genes) (table 1). SCCmec type II and type III were all positive for the mec class A complex and showed homology differences on the nucleotide sequences of their ccr complex. The ccr type 2 (ccrA2/B2) and ccr type 3 (ccrA3/B3) complexes have been identified respectively in SCCmec type II and SCCmec type III [10]. As for SCCmec type IV, it was immediately described in the work of [23]. It was following hybridization techniques with the nucleotide sequences of the first three types of SCCmec that Ma's team found perfect homology with the sequences of the mec class B complex and rates of 96.2 and 98.2 % homology to the ccrA2 and ccrB2 genes respectively [23]. In another investigation, Ito et al., (2004) described a new class of the mec complex in a WIS-encoded community-acquired MRSA strain (WBG8318). This class of the mec complex is characterized by the appearance on the mec complex sequence of a new copy of the IS431 insertion gene to the left of the mecA gene; this was called the *mec* class C2 complex, the gene structure which is IS431-*mecA*-Δ*mecR1*-IS431 [24]. The nucleotide sequence of the ccr complex of this SCCmec presented a great difference of homology with the other types of the ccr complex already known. This new complex thus sequenced was noted ccr type 5 complex carrying the ccrC1 gene [24]. The new SCCmec cassette carrying the *mec* class C2 complex and the ccr type 5 complex has been recognized by IWG-SCC and classified as SCCmec type V. The determination of the structure of the SCCmec type VI has gone through many twists and turns before being finalized in 2006 with the publication of the work of Chongtrakool et al., (2006) on a new classification of SCCmec [25]. Indeed, Oliveira et *al*. (2001) had characterized the ccr type 4 complex (with the ccrA4 and ccrB4 genes) and the *mec* class B complex in the strain *S. aureus* HDE288 [26]. The structure of this SCCmec (ccrA/B4 and *mec* class B complex) was considered until 2005 as a new variant of SCCmec type IV before being accepted by IWG-SCC as a different SCCmec [25]. In 2008, other levels of knowledge on new genetic sequences of SCCmec in MRSA were reached. Indeed, the *mec* class C1 complex which had been described in *Staphylococcus haemolyticus* (SH621) by Katayama et *al*. (2001) was also characterized on the SCCmec of the MRSA strain JCSC6082 in 2008 in Sweden [27]. One of the important differences between the class C1 and class C2 *mecs* complexes would be the orientation of the IS431 insertion gene located downstream of the *mecA* gene. On the gene sequences of the two complexes, the *mecA* genes are oriented in opposite directions. In the same survey Berglund et *al*. (2008) salso reported the ccr type 5 complex on the same SCCmec that had been described in SCCmec type V. This ccr type 5 complex was almost identical (99.9%) to the ccr complex of the SCCmercure strain 85/2082 [27-29]. Finally the structure of the SCCmec of MRSA JCSC6082 described by Berglund et *al*. (2008), is recognized as a new type of SCCmec and classified as SCCmec type VII. In the same year, the work of Zhang et *al*. (2009) reported in a Canadian strain C10682 a new type of SCCmec structured by a combination of the mec class A complex and the ccr type 4 complex. For this purpose,

the two complexes had been reported separately on other SCCmecs, but this was the first time both were worn by the same SCCmec [29]. This characterized SCCmec was therefore recognized as SCCmec type VIII. The genes of the *mec* class A complex of SCCmec type VIII showed 100% genetic homology to those of the *mec* class A complex of SCCmec type II in strain N315. As for its ccrA4 and ccrB4 genes of its ccr complex, they showed homologies of 89.6% and 94.5% respectively to those of SCCmec type VI of the strain HDE288. Furthermore Li et *al*. (2011) carried out screening surveys for SCCmec in *Staphylococcus* strains isolated from participants of the 19th International Swine Veterinary Conference in Denmark in 2006. During this study, Li et *al*. (2011) characterized two other types of SCCmec in two strains of MRSA encoded JCSC6943 and JCSC6945 respectively isolated from a Thai participant and a Canadian participant [30]. The first SARM JCSC6943 carries in its genetic heritage a SCCmec harboring on the one hand a ccr type 1 complex which carries the ccrA1 and ccrB1 genes and on the other hand a *mec* class C2 complex. This new combination of the ccr type 1 complex and the *mec* class C2 complex on the same SCCmec is identified by IWG-SCC as SCCmec type IX. However, the second SARM JCSC6945 had a SCCmec that carried a ccr type 7 complex having ccrA1 and ccrB6 genes and its mec complex was identified as class C1.2. This *mec* complex is distinct from those of the other class C1 *mecs* complexes, by its weight (6422 bp) unlike that of SCCmec type VII (7212 bp) and the direction of orientation of its genes opposite to those of SCCmec type VII and SCCmec type I. The SCCmec of MRSA JCSC945 has been recognized in this sense as SCCmec type X [30]. The same year, as part of the epidemiological surveillance of MRSA strains in cattle and humans in Denmark, García-Álvarez et *al*. (2011) reported a *mecA* gene (in a MRSA strain IGA251 called mec AIGA251) having a homology of 70% of the *mecA* genes previously described [31]. In addition, the team reported a class (E) of the mec complex described for the first time in a strain of *Staphylococcus*, but it should be noted that this complex had been described on a plasmid pMCCL2 of a strain of *Macrococcus caseolyticus* JSCS5402 by [32]. This *mec* complex is characterized by the gene sequence "*mecI-mecR1-mecA-blaZ*" and is designated by the class E *mec* complex[13,31]. The ccrA1 and ccrB3 genes were characterized on the ccr complex carried by the SCCmec of the same MRSA IGA251 strain. This ccr complex is thus called type 8. The SARM IGA251 strain however harbors a SCCmec different from the previous SCCmecs described and was identified by IWG-SCC as being SCCmec type XI. In 2015, another variant of the ccrC complex was reported by Wu et al., (2015) in a strain of MRSA (MRSA-BAO1611) isolated from cow's milk in the Chinese North-West zone. This complex carried a particular ccrC2 gene having nucleotide homologies of 62.6% to 69.4% with those of the ccr1 genes already reported in SCCmec types V and VII [33]. Thus, the ccr complex carrying this ccrC2 gene was classified as a ccr type 9 complex. This strain harbored a SCCmec which, in addition to ccr type 9, also possesses the mec class C2 complex. This new combination of the ccr type 9 and mec class C2 complexes on the same SCCmec has been recognized as a new SCCmec and has been classified as SCCmec type XII by IWG-SCC. In the same dynamism of epidemiological studies of MRSA, Baig et *al.* (2018) in Denmark reported in a clone of MRSA-ST152, a SCCmec harboring the ccr type 9 complex and the mec class A complex. This was also new to IWG-SCC and was identified as SCCmec type XIII. The ccrC2 gene of this type 9 ccr complex reported by Baig et *al.* (2018) had nucleotide homologies of 68.5% to 70.2% of the sequences of the ccC1 genes identified on SCCmec V and VII [34]. The *mecA* complex hosted by this SCCmec presented a gene sequence IS431-*mecI-mecR1-mecA*-IS43. A new type of SCCmec (type XIV) was reported by Urushibara et *al*. (2020) in one of their publications in two strains of MRSA (SC640 and SC792) in Hokkaido in Japan [35]. This SCCmec presented a combination of mec class A complex and ccr type 5 complex. If these complexes had already been described in other types of SCCmec, such as mec class A complex in SCCmec types II, III and VIII or the complex ccr type 5 in SCCmec types V and VII, this DNA fragment harbors a new combination of these complexes, described for the first time. In addition, this DNA also carried an SCC-like harboring two gene clusters including Arginine Catabolic Mobile Element (ACME-arc) and Sespermine/spermine-N1-acetyltransferase (speG). The ACME and speG genes give strains resistance to certain hostile environmental factors such as acidity (from ACME-arc), polyamine toxicity (from speG) [35,36]. Sabat et *al*. (2021) reported a new class of the mec complex on a variant of SCCmec type IV hosted by an *S. epidermidis* strain IVUMCG335 in the Netherlands. Indeed, on this new *mec* class B4 complex, a plasmid pUB110 is inserted into the structure of the *mec* class B complex of SCCmec type IV. Thus, the new *mec* complex has the following structure IS431-*ΔmecR1-mecA*-IS431-pUB110-IS431-ΨIS1272 contrary to the previously described structure IS1272-△*mecR1-mecA*-IS431 [37]. However, it is not a new type of SCCmec according to the IWG-SCC, but a subtype of SCCmec type IV. Until 2020, the IWG-SCC has registered 14 types of SCCmec whose classification is based on the combination of 5 classes of mec complex (A, B, C1, C2 and E) and 8 types of ccr complex. In January 2022, Wang et *al*. (2022) in China in their publication reported a new type of SCCmec. This is SCCmec XV with a class A *mec* complex (*mecI-mecR1-mecA*-IS431) and a type 7 ccr complex (A1B6) [19]. Figure 2 illustrates a few years marking the history of meticillin resistance in *S. aureus* and the first characterizations of SCCmec types.

Structure and Nomenclature of *Staphylococcal Cassette Chromosome mec* (SCCmec)

The management of *Staphylococcus* is ubiquitous and its different species manage to adapt to the different, often

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very difficult conditions of the environments they colonize [9]. This adaptability of these strains has found first in-depth explanations with the complete sequencing of the genome of the strain *S. aureus* N315 (Figure 3) by [21]. Indeed, the *Staphylococcus* genome in general is made up of two distinct functional domains. Most of their genome contains the genes that ensure the bacteria's vital functions. The second part of the genome is made up of accessory and mobile genetic elements such as plasmids, transposons, prophages or islands of pathogenesis carrying most of the genes associated with virulence factors and antibiotic resistance [17,18,38]. In this part, this study will focus on the description of the SCCmec and these constituents. SCCmec is part of the mobile genetic elements that confer resistance to *Staphylococcus* against beta-lactams following the pressure of beta-lactams. Each SCCmec is characterized by two complexes, the *mec* complex and the ccr complex. A SCCmec has three joining sequences (J1, J2 and J3) complementary to their structures, which delimit the regions occupied by the two complexes (Figure 3).

The mec Complex

The mec complex includes the mec gene (A or C) of approximately 2.1 kb, regulatory genes (*mecI* encodes a transcriptional repressor of mecA and *mecR1* encodes the

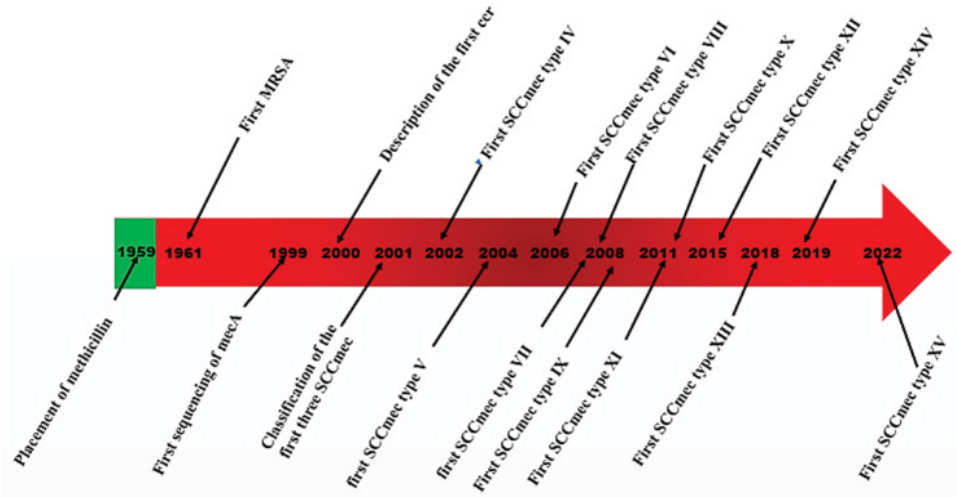

Figure 2: Illustration of the history of methicillin-resistance in Staphylococcus through some investigations.

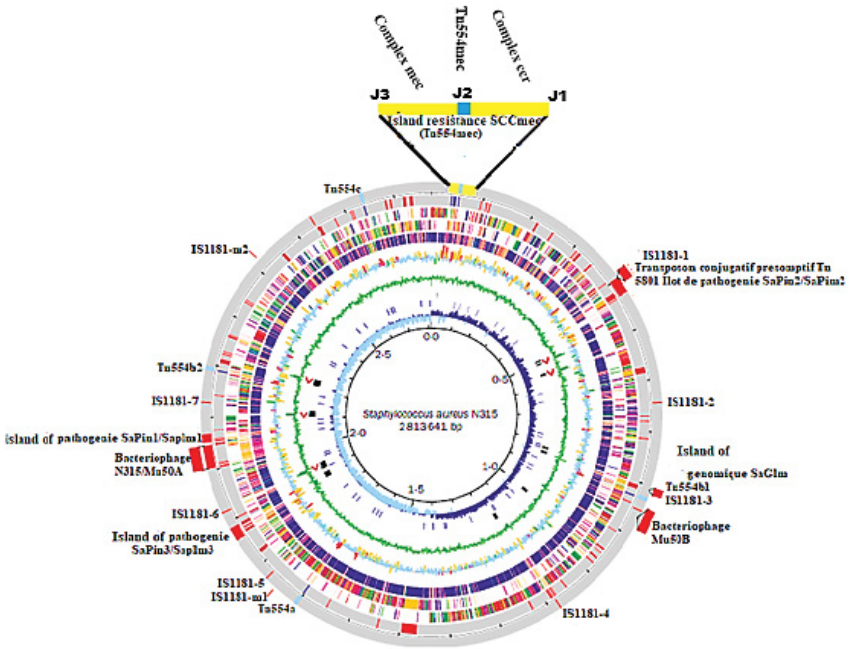

Figure 3: Illustration of the *S. aureus* N315 genome, with the SCCmec resistance island in large character (adapted from [21]).

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MecR1 protein) and insertion sequences (IS431 or IS1272) [28]. The *MecR1* protein detects the presence of beta-lactams by to its extracellular domain. Once the antibiotic binds, there is activation of the intracellular domain which acquires protease activity and degrades the repressor *MecI*, thus promoting the expression of *mecA*. These regulatory genes can be intact or truncated, mutations occurring in these regulatory genes can affect the level of methicillin resistance. In bacteria, there are 4 types of *mec* gene including *mecA*, *mecB*, *mecC* and *mecD*. These 4 *mec* genes share between 60 and 70% nucleotide sequence homology and can also be subdivided into allotypes which share between 70 and 95% sequence homology between them (Figure 4). Indeed, a mec gene is classified as a new type or a new allotype, if it has respectively nucleotide similarity rates between 60 and 70% or between 70% and 95% to the others. Thus, the identity of the mec gene combined with those of the regulatory genes and insertion sequences carried by the DNA of the mec complex, make it possible to determine the class of the mec complex. The IWG-SCC currently recognizes five mec complex classes (from A to E) in staphylococci.

The Recombinase Gene Complex (ccr)

Recombinases are responsible for the recombinaison and mobility of the genes on cassette. The recombinases gene complex consists of either a pair of genes, ccrA and ccrB combined, or a single ccrC gene [39]. Five types of SCCmec including types V, VII, XII, XIII and XIV which harbor the ccrC gene in their ccr complex. The other ten carry the ccrA and ccrB gene pair (Table 1). Figure 5 illustrates the classification of ccr complexes recognized by IWG-SCC. The classification of ccr complexes is based on the homology rates of their nucleotide sequences. Two ccr complexes would be classified in two types of ccr complex, if the rate of their nucleotide homologies is less than or equal to 50%. However, if this rate is strictly between 50-85%, the two complexes are said to be of different allotype. And the ccr complexes are classified in the same allotype if the homology rate of their sequences is greater than or equal to 85%. As for the function of the ccr complex, the genes of the ccr complex code for a recombinase of integration or excision of the gene sequences of the SCCmec [40]. The integrating role of recombinases is similar to that of bacteriophage integrases. In addition, the ccr complex also has the ability to cleave DNA to allow the exchange of gene fragments and recombinations between the two attachment sites [41]. There are other gene fragments also carried by the SCCmecs, which accompany the ccr complex in the different functions. This is the case of inverted repeated sequences (or inverted repeats) which have a role of excising but do not allow integration.

Junction Regions

Each SCCmec has in its structure three zones which delimit the positions of the two complexes. These areas are today called junction regions (J) numbered J1, J2 and J3. On the front panel these regions bore the designations LC (for J1) located between the extreme right and the ccr complex, CM (for J2) positioned between the ccr complex and the mec complex and IR (for J3) between the mec complex and the far left of the SCCmec structure [18]. The junctions harbor certain accessory elements such as plasmids (pUB110) or transposons (Tn554) or other genes which confer resistance to other antibiotics. In the classification of SCCmec, the components of junctions serve to distinguish allotypes of a type of SCCmec [41,42].

SCCmec Nomenclature

SCCmecs are identified into different types of SCCmecs based on the class of the mec complex and the type of ccr complex they harbor. Indeed, a type of SCCmec is named by two radicals in brackets, the first of which is designated by an Arabic numeral corresponding to the type of the ccr complex and the second is in uppercase alphabet letter which corresponds to the complex. Figure 6 illustrates a representation of SCCmec type I. The IWG-SCC has recognized and classified between 2000 and 2020, 14 types of SCCmec. It was not until January 2022 that the fifteenth type of SCCmec was identified with the work of [19]. This

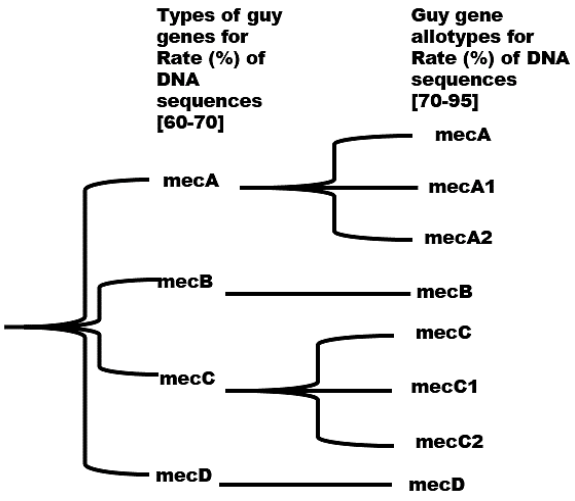

Figure 4: Illustration of the *mec* gene classification system.

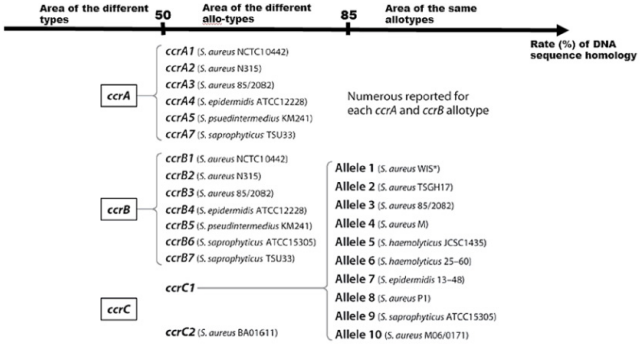

Figure 5: Illustration of ccr gene classification (adapted from [41]).

Citation: Ouédraogo Ganamé Abasse, Kaboré Boukaré1, Cissé Hama, Zongo Oumarou, Ouédraogo Sidabéwindin Henri, Bassolé Imael Henri Nestor, Traoré Yves, Tchoumbougnang François, Savadogo Aly. History, Structure, Epidemiology and Molecular Typing of *Staphylococcal Cassette Chromosomes Mec* (Sccmec) involved in Multiple Resistances to Beta-Lactams in the Genus Staphylococcus: an Overview. Archives of Clinical and Biomedical Research 6 (2022): 781-799.

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sets the total at fifteen types of SCCmec.

SCCmec Type I or (1B): This SCCmec was first described in 2021 in the strain of *S. aureus* NCTC10442 (Genbank number AB033763) isolated since 1961 in England. It is one of the genetic carriers conferring resistance to beta-lactams, predominant in commensal MRSA (HA-MRSA) [43]. SCCmec type I harbors the class B *mec* complex with the ccr type 1 complex carrying the ccrA1 and ccrB1 genes (Figure 7). Its IA allotype relates to its J3 junction region, the plasmid pUB110. In SARM-NCTC10442, the SCCmec is 34359 nucleotides long. In general, a variety of accessory elements are incorporated into the structure of the SCCme type I, which contribute to its operation. These include 41 coded DNA sequences (CDS) with 36 ORFs (Open Reading Frames), 2 mobile sequences and repeated regions. In one of their investigations, Lakhundi and Zhang (2018) oriented these last departures and others on the structure of the SCCmec type I; upstream of the ccr complex (one repeated region and 17 CDS), at the level of the ccr complex (the two ccrA1 and ccrB1 genes and 7 CDS), on the *mec* complex (the *mecR1* and *mecA* genes, 2 mobile elements, 2 repeated regions and 10 CDS), downstream of the mec complex (a repeated region

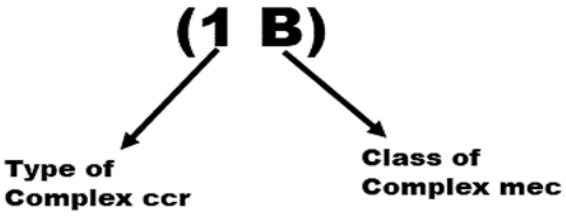

Figure 6: Illustration of the SCCmec type I nomenclature model.

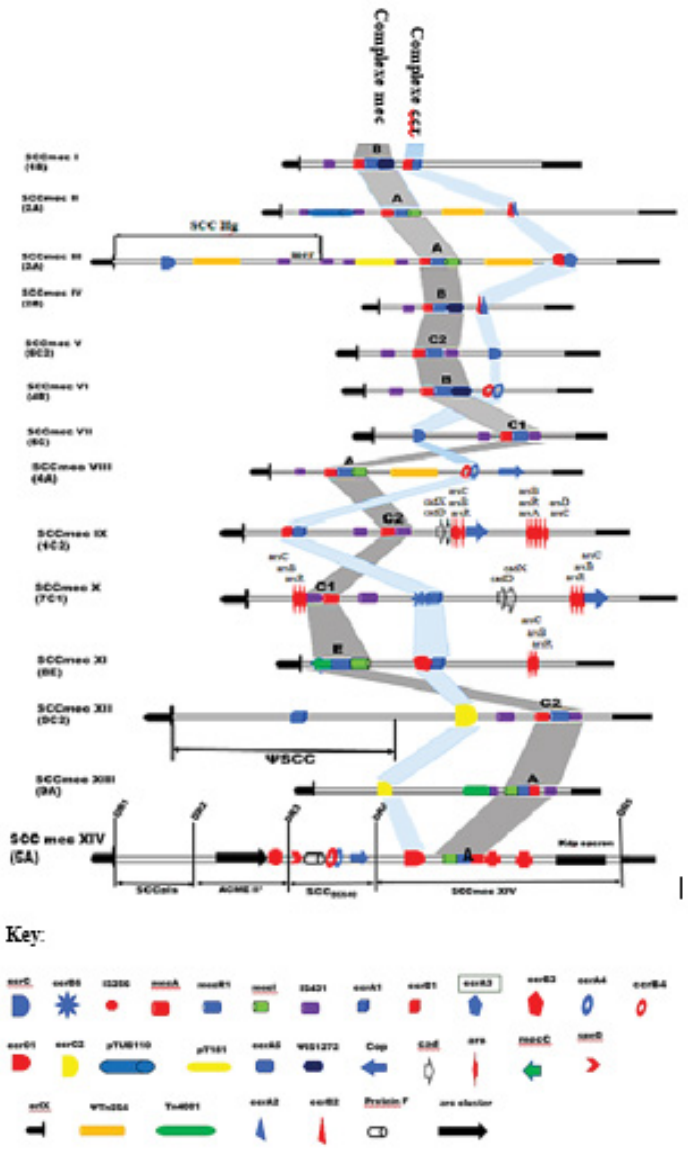

Figure 7: Illustration of the different SCCmec structures.

Citation: Ouédraogo Ganamé Abasse, Kaboré Boukaré1, Cissé Hama, Zongo Oumarou, Ouédraogo Sidabéwindin Henri, Bassolé Imael Henri Nestor, Traoré Yves, Tchoumbougnang François, Savadogo Aly. History, Structure, Epidemiology and Molecular Typing of *Staphylococcal Cassette Chromosomes Mec* (Sccmec) involved in Multiple Resistances to Beta-Lactams in the Genus Staphylococcus: an Overview. Archives of Clinical and Biomedical Research 6 (2022): 781-799.

and 3 CDS) and the ORFs sequences in the ends [41]. The functions of most of these ORFs remain unknown, however, exceptionally, CEO10 is the ORF which codes for the polypeptide plasmid-sequence surface protein (PLs) and two other ORFs on PLs, code for the glycerophosphoryl diester phosphodiesterase and the putative transposase.

SCCmec Type II or (2A): It has a large size of approximately 53017 nucleotides and is frequent in commensal strains. SCCmec II is characterized by this combination of the class A *mec* complex and the type 2 ccr complex on its structure (Figure 7). It also hosts several other fragments including 4 repeated regions, 3 mobile elements and 51 CDS. Thus, upstream of the ccr complex (a repeated region and 15 CDS), at the level of the ccr complex (the ccrA2 and ccrB2 genes and 16 CDS), between the two complexes (a mobile element and 12 CDS), at the level of the mec complex (the *mecA*, *mecR1*, *mecI* and IS431 genes and 5 CDS) and at the downstream end of the *mec* complex (one mobile element, 2 repeat regions and 8 CDS). This cassette also has other remarkable elements such as at the J3 junction, the copy of the Staphylococcal plasmid pUB110 and an ORF (pre) coding for the recombination enzyme for pUB110. In addition, on the J1 junction there is a regulatory gene kdp or between the complexes there is a transposon Tn554 involved in resistance to streptomycin and erythromycin. Investigations have reported a diversity of SCCmec type II subtypes, including SCCmec types IIA, IIB, IIC, IID or IIE. However, the first SCCmec II was described in 1999 in Japan in MRSA strain N315 (with Genbank accession number D86934) [44].

SCCmec Type III or (3A): it is a very large cassette with 66891 nucleotides and it is among the most characterized SCCmec in commensal MRSA. SCCmec III harbors the class A *mec* complex and the type 3 ccr complex (Figure 7). SCCmec III carries 10 repeat regions, 6 elements and 97 CDS (with 22 CDS of unknown function). These structures are located upstream of the ccr complex (a repeated region and 2 CDS), on the ccr complex (the ccrA3 and ccrB3 genes and 11 CDS), between the complexes (a mobile element and 18 CDS), on the mec complex (the *mecA*, *mecR1*, *mecI* and IS431 genes, a mobile element, 2 repeat regions and 9 CDS) and downstream of the mec complex (4 mobile elements, 7 repeat regions and 52 CDS) [10]. On the J3 junction there is a transposon Tn554 which carries genes encoding resistance to erythromycin and a copy of the plasmid pUB181 harboring genes encoding resistance to tetracycline and mercury. The J2 junction carries a transposon ΨTn554 coding for cadmium resistance determinants. The first SCCmec III was identified in 2001 in the MRSA strain 85/2082 which had been isolated in 1985. Today several subtypes of SCCmec have been identified, including SCCmec subtypes IIIA, IIIB, IIIC, IIID and IIIE [45].

SCCmec Type IV or (2B): It was described for the first time in 2002 following the work of Ma et *al*. (2002) in the United States of America. During this investigation, two subtypes of SCCmec IV (SCCmec IVa and SCCmec IVb) were characterized respectively in MRSA JCSC1986 (Genbank accession number AB063173) and MRSA JCSC1978 (Genbank accession number ABO63172). SCCmec IV are characterized by the combination of the class B mec complex and the type 2 ccr complex (Figure 7). Subtype IVa harbors two mobile elements, 4 repeat regions and 22 CDS (of which 17 CDS have unknown functions). These structures are distributed upstream of the ccr complex (one repeated region and 4 CDS), on the ccr complex (the ccrA2 and ccrB2 genes and 6 CDS), on the mec complex (the *mecA*, IS1272 and *mecR1* genes, 2 mobile elements, 2 repeat regions and 5 CDS) and downstream of the *mec* complex (one repeat region and 3 CDS). This subtype is approximately 24244 nucleotides in size. As for subtype IVb, it has a small size of 20916. SCCmec IV is the type of SCCmec that has more variants including subtypes IVa, IVb, IVc, IVd, IVe, IVf, IVg, IVh, IVi, IVj, IVk, IVl, IVm, IVn and Ivo.

SCCmec Type V or (5C): It has a size of 27638 nucleotides and its high prevalence have been reported in community-acquired MRSA. SCCmec V is characterized by the combination of the *mec* class C complex and the ccr type 5 complex (with the ccrC1 gene) [24]. It relates to its structure 6 repeated regions, 2 mobile elements and 23 CDS (of which 15 CDS have unclarified functions). These different elements are located upstream of the *mec* complex (a repeated region and a CDS), at the level of the *mec* complex (the *mecA*, *mecRI* and IS431 genes, 2 mobile elements and 4 repeated regions), between the complexes (2 CDS), on the ccr complex (the ccrC1 genes and 6 CDS) and downstream of the ccr complex (one repeat region and 7 CDS). SCCmec V was first identified in 2004 in MRSA strain JCSC3624 and has no antibiotic resistance gene other than the *mecA* gene. SCCmec type V has very few subtypes including Va and Vb variants [47].

SCCmec Type VI or (4B): This type of cassette is characterized by a combination of the class B mec complex (IS1272-△*mecR1*-*mecA*-IS431) and the ccr type 4 complex (Figure 7). The structure of its ccr complex has a composition almost identical to that of the ccr complex type 3. The region downstream of its ccr complex has a 99% similarity with that of SCCmec type I. SCCmec VI has been described for the first in 2001 following the work of Oliveira et *al*. (2001) in the MRSA strain HDE288 (Genbank accession number AF411935). SCCmec VI had been identified as a variant of SCCmec IV and subsequently redefined in 2006 as SCCmec VI by the IWG-SCC [26].

SCCmec Type VII or (5C1): it has a size of approximately 26753 nucleotides and is more characterized in community-

acquired MRSA strains. SCCmec type VII is characterized by the combination of the class C1 *mec* complex and the type 5 ccr complex (Figure 7). Its structure also contains 2 repeat regions and 29 CDS (with 16 CDS having unclear functions). Along its structure present upstream of the ccr complex (a repeated region and 3 CDS), on the complex (the ccrC1 gene and 6 CDS), between the complexes (8 CDS), on the *mec* complex (the IS431 gene sequences -*mecA*-△*mecR1*-IS431 and 4 CDS) and downstream of the *mec* complex (one repeat region and 5 CDS). It also carries three Tnp genes, two of which code for the IS431 transposase enzyme and the other codes for the IS12960D transposase B protein. SCCmec was first described in 2008 in MRSA strain JCSC6082 (Genbank accession number AB373032). Very few subtypes of SCCmec VII have been characterized. However, SCCmec VIIa and VIIb subtypes have been demonstrated in several infestations [35,48].

SCCmec Type VIII or (4A): It is a medium-sized cassette of about 32184 nucleotides and its highest prevalence is in MRSA acquired from animals and food (LA-acquired) [49,50]. SCCmec VIII is characterized by a combination of the class A mec complex and the type 4 ccr complex (Figure 7). Its structure also carries 6 repeated regions, a mobile element and 36 CDS (with 14 CDS with unknown functions). These last elements are distributed upstream of the mec complex (2 repeated regions and 2 CDS), on the mec complex (the sequence *mecI-mecR1-mecA*-IS431, a mobile element, 2 repeated regions and 6 CDS), between the complexes (19 CDS), on the ccr complex (the ccrA4 and ccrB4 genes) and downstream of the ccr complex (2 repeat regions and 5 CDS). Its J1 junction carries 5 ORFs including a code for a putative membrane protein and a truncated ccr gene. The J2 junction hosts 7 ORFs including *ermA* which codes for rRNA adenine N-6-methyltransferase, *aad9* which codes for streptomycin 3'-adenyltransferase, *tmpA* which codes for transposase A, *tmpB* expressing for transposase B, *tmpC* for transposase C the other two ORFs are mobile elements of transposon Tn554. SCCmec VIII was first described in 2008 in the MRSA C10682 strain isolated in 2003 in Canada. Reported SCCmec VIII subtypes are VIIIa, VIIIb, and VIIIc [50].

SCCmec Type IX or (1C1): it is 43675 nucleotides long and is characterized by a combination of class C2 *mec* complex and the type 1 ccr complex (Figure 7). Other most remarkable elements reported on its structure, 6 repeated regions, 2 mobile elements and 42 CDS (with 22 ORFs with unknown functions). The gene sequences on the SCCmec IX are distributed upstream of the ccr complex (a repeated region and 3 CDS), on the ccr complex (the ccrA1 and ccrB1 genes and 6 CDS), between the complexes (5 CDS), on the mec complex (the sequence IS431-*mecA*-△*mecR1*-IS431, 2 mobile elements, 4 repeat regions and 5 CDS) and downstream of the *mec* complex (one repeat region and 20 CDS). Its J1 junction presents several resistance genes to metallic trace elements. This is the case of the *CadD* and *CadX* genes which encode the cadmium-binding protein and the cadmium variant-resistant protein respectively. The *copB* gene on J1 codes for copper-transporting ATPase which mediates copper detoxification. The J1 junction also harbors genes for arsenic resistance including *ArsR*, *ArsA*, *ArsB*, *ArsC* and *ArsD* which code respectively for the enzymes, arsenical resistance operon repressor, arsenical pump-driving ATPase, arsenical pump-membrane protein, arsenical reductase and arsenical resistance operon trans-acting. The SCCmec IX cassette was first identified in 2011 in Denmark in MRSA strain JCSC6943 (Genbank accession number AB505628).

SCCmec Type X or (7C1): This is a large cassette of approximately 50803 nucleotides, identified by the combination of the class C1 *mec* complex and the type 7 ccr complex (Figure 7). It also harbors 6 repeat regions, 2 mobile elements, 54 CDS (with 33 CDS having unclear functions) and several metal trace element resistance genes [42]. The SCCmec X is structured; upstream of its *mec* complex (one repeat region and 6 CDS), on the mec complex (the sequence IS431-*mecA*-△*mecR1*-IS431, 2 mobile elements, 4 repeat regions and 5 CDS), between the complexes (4 CDS), on the ccr complex (the ccrA1 and ccrB6 genes and 5 CDS) and downstream of the ccr complex (one repeat region and 30 CDS). On the J1 junction, it harbors the insert sequence ISSha1, an arsRBC operon for the expression of the arsB, arsC and arsR genes encoding arsenic detoxification. The same Junction carries the copB and cadD/X genes encoding resistance to copper and cadmium respectively. Its J3 junction also carries the arsB, arsC and arsR genes for the same arsenic detoxification functions. It was first characterized in 2011 in Denmark in MRSA strain JCSC945 (Genbank accession number AB505630) (Table 1).

SCCmec Type XI or (8E): it has a weight of 29.4 kb and is identified by the combination of the *mec* E complex and the ccr type 8 complex (Figure 7). SCCmec XI has a gene sequence *mecA* gene (*blaZ-mecA-mecR1-mecI*) with 69% nucleotide homology to other *mecA* genes. Its J1 and J2 junctions host ORF sequences that code for membrane export proteins and lipases [41]. The J1 junction also carries arsenic resistance genes. The SCCmec XI cassette was first characterized in 2011 in the MRSA clone CC130 (LGA251). This MRSA was isolated in 2007 in Denmark. SCCmec XI is a particularly common cassette in MRSA circulating in Europe and its incidence is more of animal origin [51].

SCCmec Type XII or (9C2): This is a cassette weighing approximately 25 kb located between DR2 (repeated sequence 2 or direct repeats 2) and DR3 of the mec DNA fragment. In total, the SCCmec XII cassette carries 31 ORFs (from the 31st ORF to the 62nd of the *mec* DNA fragment) [33]. It is characterized by the combination of the class C2 *mec* complex and the type 9 ccr complex (Figure 7). The *mec*

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complex (located between 44th ORF and 50th ORF) carries the Δ*mvaS*, *ugpQ*, *maoC*, *mecA* and Δ*mecR1* genes and at the ends, insert sequences ΔIS431-1 and ΔIS431-2. The *mec* DNA carrying the SCCmec XII cassette is characterized on its structure by another cassette located between DR1 and DR2 called pseudo-SCC. This pseudo-SCC has a weight of 24.3 kb with 30 ORFs along its length and carries the ccrA1 genes which would appear to be a semi-complex *mec* type 1. Studies have reported on the structure of SCCmec XII several other antibiotic resistance genes. Than *mecA* including, *blaZ* (coding for beta-lactamases), *aadA*, *aadE* and *aacA-aphD* (resistance to Aminoglycosides), *lnuB* (resistance to macrolide/lincosamide/streptogramin), *tetL* (resistance to tetracyclines), *dha1* and *fexA* (resistance to phenicols) [52]. MRSA harboring SCCmec XII are generally of animal origin. The first characterization of the SCCmec XII cassette was in 2015 in the MRSA strain BAO1611 (Genbank number KR187111) isolated from cow's milk [33].

SCCmec Type XIII or (9A): It has a weight of 32.3 kb and is characterized by a combination of the class A *mec* complex and the type 9 ccr complex (Figure 7). The SCCmec XIII cassette harbors on its J2 junction a transposon Tn4001 which carries the *aac*(6')-*aph*(2") resistance genes to gentamycin. It also carries the plasmid *pSaa*619 which harbors the *blaZ* gene coding for resistance to beta-lactams. The SCCmec cassette was first described in 2018 in the MRSA strain ST152 isolated in Denmark [34].

SCCmec Type XIV or (5A): This is a cassette weighing approximately 41 kb and characterized by the class A *mec* complex and the type 5 ccr complex (Figure 7). It is potted between DR4 and DR5 of a chromosomal fragment having three pseudo cassettes [35]. The first pseudo cassette located between DR1 and DR2 has a weight of 12kb and carries a pseudo-SCC lacking with genes that code for the plasmin-sensitive protein (ΨSCCpls). The second pseudo-cassette has a weight of 14 kb, located between DR2 and DR3 and hosts an arc cluster (ACMEII') which codes for the resistance to the acidity of the medium. The third pseudo cassette has a weight of 14 kb, located between DR3 and DR4, it carries the *speG* gene which codes for resistance to the effects of polyamines, the *copA* gene which codes for the copper-transforming ATPase protein (for resistance to copper), the protein F gene (teichoic acid bio-synthesis protein) and the ccr type 4 complex genes (ccrA4-/B4). The SCCmec XIV cassette was characterized for the first time in 2020 in the MRSA strain SC792 in Japan.

Some Epidemiological Data on SCCmec

Staphylococcal Cassettes Chromosomes *mec* are highly diverse mobile genetic carriers (Figure 7) that confer multi-resistance staphylococcal beta-lactams [53,54]. These bacterial gene pools are public health concerns with very little new data on global distribution. Nevertheless, some representative investigations allow insights into the distribution and prevalence of SCCmec types on the continents [55]. In this part, the review is limited to recent data reported in publications found in official journals. In Africa, certain types of SCCmec (table 2) have been identified in the *Staphylococcus* genus predominated by *Staphylococcus aureus* species isolated from humans as well as from animals or environmental samples [56-58]. The distribution of SCCmec types is not uniform, however we can see the presence of SCCmec type III and type IV with high prevalence in the different areas of the African continent (Figure 8). Sekyere and Mensah (2019) made the same findings during their investigation of the literature on the molecular epidemiology and mechanism of antibiotic resistance in *Enterococcus* spp., *Staphylococcus* spp. and *Streptococcus* spp. in Africa. They reported a predominance of strains harboring SCCmec IV (747/4437) followed by SCCmec III (305/4437), SCCmec II (163/4437), SCCmec V (135/4437) and SCCmec I (79/4437). The proliferation and dissemination of SCCmec would be favored by the easy acquisition mechanisms (transformation,

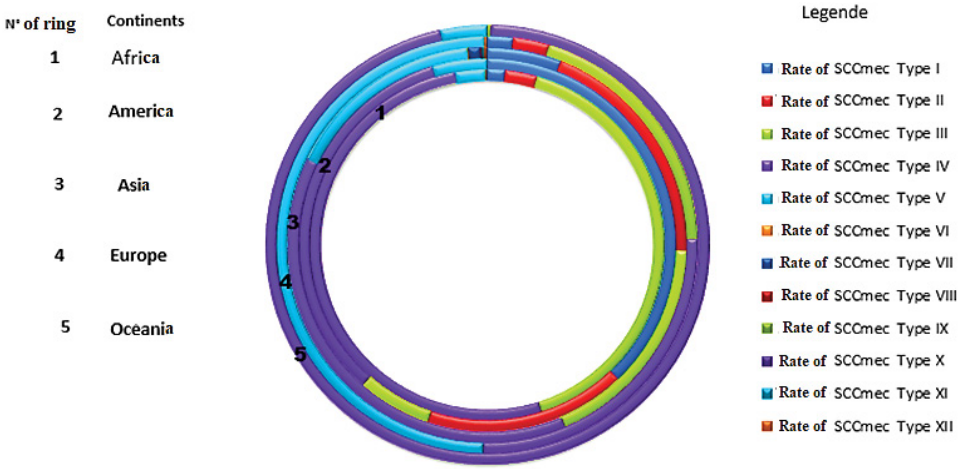

Figure 8: Illustration of the rates of SCCmec types on the different continents.

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transition and conjugation) of these cassettes between strains of the genus *Staphylococcus* on the one hand and on the other hand by the ability of these strains to resist environmental factors [16,53,59]. Indeed, the *Staphylococcal Cassettes Chromosome* (SCC) can carry other genes such as the mer gene, the ACME gene or the *speG* gene in addition to the *mecA* gene, whose expressions would allow *Staphylococcus* carriers to resist high levels of mercury (*mer* gene) acidity (*ACME* gene), polyamine toxicity (*speG* gene) [40,59,60]. Others investigations in Africa have reported Staphylococcus strains harboring both SCCmec type III or type IV with SCCmer [61] or with the ACME gene [62]. In Europe, *Staphylococcus* harboring SCCmec IV have the greatest distribution in the different countries (Table 2) and SCCmec IVa and IVc subtypes have been the most reported [63-65]. This predominance was confirmed during an investigation of Bartels et *al*. (2020) in Northern Europe on 466 MRSA from Denmark (354), France (10), Norway (24), Sweden (27) and England (51)[66]. They reported that 94% of the 466 MRSA harbored SCCmec and 100% of these SCCmec were type IVa. As in Africa or Europe, in the rest of the world *Staphylococcus* carrying SCCmec IV predominates (Figure 8) in human or animal infections and food contamination or healthcare activity surfaces. On the other continents, several authors have come to the conclusion of the predominance of *Staphylococcus* harboring various subtypes of SCCmec IV and by the high frequency of cohabitation of SCCmec IV and the *ACME*, *speG* and *mer* genes on their *mecDNA* [41,67 -70].

Application of Technology for the Characterization of SCCmec

Methicillin-resistant *Staphylococcus*, especially MRSA, are the strains that undoubtedly represent the greatest threats in the fight against bacterial multi-resistance to antibiotics in hospitals [71]. This threat also affects the community and veterinary sectors. To this end, their management is generally very complex due to confusion in practice about the type of MRSA that causes the infection or contamination. However, molecular typing techniques for MRSA have been proposed and over time, rapid and effective screening models have been put in place, all of which contribute to knowledge of the molecular epidemiology and evolution of MRSA [72,73]. Among these techniques, MLST (multi locus sequence type), *spa* typing (protein A sequence) and SCCmec typing are the most used for determining the types and subtypes of MRSA [8,74]. For typing efficiency, very often techniques are combined. In this part, the study will stop on the SCCmec typing. SCCmec typing is a technique that consists of determining types and subtypes of the SCCmec genetic determinants, which carry the *mecA* gene and other genes for resistance to antibiotics and metallic trace elements (Figure 8), carried by MRSA. The first SCCmec typing techniques were methods of hybridization of *mecA* gene and Tn554 transposon probes based on restriction enzyme digestion with *ClaI* genomic DNA. This technique has been used since 1988, for the identification of repeated DNA elements (characterized by insert elements) of the genome of the Bordetella pertussis strain, well before the first nomenclatures of SCCmec cassettes [75]. It was first used to characterize *mecDNA* fragments with the work of [76]. Today, improved methods with digestive restriction enzymes combined with PCR (polymerase chain reaction) are applied to SCCmec typings [77-79]. This is the case of the SCCmec typing method based on PCR amplification of the ccrB genes (of the ccr complex) with RFLP (restriction fragment length polymorphism) or the case of the ME-AFLP method. After the 2000s, methods solely based on multiplex PCR were applied to SCCmec typings. This technology uses a set of multiple primer pairs to simultaneously amplify multiple DNA targets in a single PCR reaction, rather than a single primer pair to amplify a single DNA target. Thus, in 2002 the multiplex PCR technique was applied for the first time to characterize types I to IV of SCCmec [80]. Subsequently, it was used for the characterization of SCCmec types and subtypes. Thus, in 2007 several methodologies of the multiplex PCR technique were used by Kondo et *al*. (2007) for the characterization of SCCmec type I to V with their variants. In recent years, it is the technique that seems to predominate in research centers, for the characterization of types and subtypes of SCCmec [15,77,81-83]. In addition to the two previous SCCmec typing methods, real-time PCR was the third method applied since 2004 with the work performed by Francois et al., (2004) in Switzerland [84]. Real-time PCR is based on the detection and quantification of a fluorescent contribution whose emission is directly proportional to the quantity of amplicons generated during the PCR reaction. Initially, this technique had very little success in SCCmec typing, because the first tests were not considered innovative to the knowledge already acquired [78]. Later, with the use of padlock probes, it gave great success to the application by real time PCR in SCCmec typing thanks to its diagnostic efficiency of trace elements on regions of the *mecA*, ccrB and ccrC genes [85]. This technology has been used to characterize the types and subtypes of SCCmec in several investigations [61,86,87]. In the last decade, new sequencing technologies (*Illimina* or *MinION*) are used in the determination of SCCmec types and subtypes. The principle of *Illimina* sequencing is based first on the amplification of DNA fragments of 100 to 500 bp coupled to regions complementary to the oligonucleotides of the plate, and then sequenced using a fluorescent emitter with lengths specific to the types of nucleotides. Baig et *al*. (2018) have combined these two technologies to describe for the first time the SCCmec type XIII.

Conclusions

The *staphylococcal cassette chromosome* mec are mobile genetic carriers harboring genes for resistance to

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antibiotics and metallic trace elements and virulence genes. They are present in Staphylococcus and are characterized by the mec and ccr complex genes. Until January 2022, fifteen types of SCCmec numbered from I to XV, have been described with their subtypes. Epidemiological studies have reported the existence of multi-resistant Staphylococcus carrying SCCmec on all continents. The global spread of SCCmec is predominated by SCCmec type IV. During the last three decades, technological methods have made the characterization of SCCmec types rapid and increasingly precise, presenting SCCmec typing as one of the best options for monitoring the epidemiology and managing Staphylococcus Methicillin-resistant.

Author Contributions

Conceptualization, Ouédraogo G. Abasse, Savadogo Aly and Tchoumbougnang François; methodology, Ouédraogo G. Abasse; software, Ouédraogo G. Abasse; validation, Ouédraogo S. Henri and Kaboré Boukaré; formal analysis, Ouédraogo G. Abasse and Kaboré Boukaré; resources, Ouédraogo G. Abasse; writing review and editing, Ouédraogo G. Abasse, Cissé Hama, Zongo Oumarou; visualization, Cissé Hama, Bassolé I. H. Nestor; supervision, Bassolé I. H. Nestor, Tchoumbougnang François, Savadogo Aly; project administration, University Joseph KI-ZERBO and University of Douala; funding acquisition, AFRIDI.

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Conflicts of Interest

The authors declare no conflict of interest.

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