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Current Opinion in Microbiology

Global epidemiology of community-associated methicillin resistant *Staphylococcus aureus* (CA-MRSA)

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During the 1990s, various reports of community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) infections appeared in the literature, caused by novel strains genetically distinct from traditional healthcare-associated MRSA (HA-MRSA). Numerous lineages of CA-MRSA have since emerged on every continent, several of which have spread internationally, most notably USA300. CA-MRSA strains are increasingly implicated in nosocomial infections, and may eventually displace HA-MRSA strains in hospitals. Consequently, distinctions based on clinical epidemiology and susceptibility are becoming less relevant, arguing in favor of genotypic definitions. We review the current molecular epidemiology of CA-MRSA with respect to genetic diversity, global distribution, and factors related to its emergence and spread.

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Current Opinion in Microbiology 2012, **15**:588–595

This review comes from a themed issue on **Antimicrobials**

Edited by **Didier Mazel** and **Shahriar Mobashery**

For a complete overview see the Issue and the Editorial

Available online 5th October 2012

1369-5274/$ – see front matter,

http://dx.doi.org/10.1016/j.mib.2012.08.003

Introduction

Methicillin resistance in staphylococci is associated with acquisition of a large transmissible element known as staphylococcal cassette chromosome *mec* (SCC*mec*), an event that occurred in *Staphylococcus aureus* prior to the isolation of the first methicillin-resistant *S. aureus* (MRSA) strain in 1961 [1]. For most of the half-century following this watershed event, MRSA was considered to be a nosocomial pathogen, with a limited number of clonal backgrounds causing serious infections in individuals with healthcare-associated risk factors [2]. During the 1990s, however, reports of *de novo* community-associated MRSA (CA-MRSA) infections among healthy individuals began to appear in the literature, and were soon shown to be associated with genetically distinct lineages of MRSA, apparently unrelated to existing healthcare-associated MRSA (HA-MRSA) strains [3]. Soon thereafter, numerous lineages of CA-MRSA emerged on every continent [4••,5••,6••]. CA-MRSA strains are increasingly implicated in nosocomial infections [7], and mathematical models predict that they will ultimately displace traditional HA-MRSA strains in healthcare settings [8,9]. Moreover, antimicrobial resistance is steadily increasing in certain lineages [10], which are likewise implicated in a widening spectrum of invasive disease [4••,11]. Consequently, traditional distinctions between HA-MRSA and CA-MRSA based on clinical epidemiology and susceptibility are becoming increasingly less relevant [4••,12], leading some authors to argue in favor of genotypic-based definitions for CA-MRSA [13•]. Given the multiplicity of CA-MRSA strains which continue to emerge, this review will focus on the current molecular epidemiology of CA-MRSA.

Molecular typing of *Staphylococcus aureus*

An understanding of molecular typing methods for *S. aureus* is necessary to appreciate the nomenclature currently used to describe distinct clonal groups. At the present time, there are four primary methods in use internationally, including pulsed-field gel electrophoresis (PFGE), multilocus sequence typing (MLST), *spa* typing, and SCC*mec* typing for MRSA [14,15]. The first two methods have been developed for numerous bacterial and fungal species, while the latter two are specific to staphylococci. PFGE is a classic 'fingerprinting' method which compares banding patterns from whole-genome macrorestriction digests, and is considered the gold standard for outbreak investigations involving closely-related strains [14]. Although highly discriminating, inter-laboratory comparisons and data portability are limited, such that similar strains may reflect national or regional nomenclature (Table 1). The PFGE database in the United States, for example, classifies major *S. aureus* clones as USA100, USA200, USA300, and so on, whereas other international designations include EMRSA (United Kingdom), WA (Western Australia), and CMRSA (Canada).

By contrast, MLST is a sequence-based typing method characterized by universal nomenclature, with an unambiguously curated database [14]. The *S. aureus* MLST scheme is based on 7 'housekeeping' genes (*arcC*, *aroE*, *glpF*, *gmk*, *pta*, *tpiA*, *yqiL*) distributed throughout the genome, fragments of which are sequenced and submitted to the *S. aureus* MLST database for identification (http://saureus.mlst.net). Known variants of each gene are thereby assigned allelic numbers, which are then concatenated to form unique allelic profiles referred to as 'sequence types' (Table 1). Related sequence types (ST) may be visualized readily using the program eBURST

Table 1

Genotypic characteristics of CA-MRSA lineages

ST	*arcC*	*aroE*	*glpF*	*gmk*	*pta*	*tpiA*	*yqiL*	*spa* type (Ridom)	*spa* type (eGenomics)	*spa* repeat pattern (eGenomics)	SCC*mec* type	Regional clones
1	1	1	1	1	1	1	1	t128	131	UJJFKBPE	IV	USA400, CMRSA7, WA-1
5	1	4	1	4	12	1	10	t002	2	TJMBMDMGMK	I, II, IV, V, VI	Geraldine, Pediatric
6	12	4	1	4	12	1	3	t207	*unk*	YHGFMBQBLOO	IV	
8	3	3	1	1	4	4	3	t008	1	YHGFMBQBLO	IV, V, VI	USA300, CMRSA10, WA-12
22	7	6	1	5	8	8	6	t005	113	TJEJNCMOMOKR	IV, V	
30	2	2	2	2	6	3	2	t019	19	XKAKAOMQ	IV, V	SWP, OSPC, WSPP, USA1100
45	10	14	8	6	10	3	2	t015	73	XKAKBEMBKB	IV, V, VI	
59	19	23	15	2	19	20	15	t216	17	ZDMDMNKB	IV, V	USA1000, Taiwan
72	1	4	1	8	4	4	3	t148	193	UJGFGMDMGGM	IV, V	USA700
75	36	3	43	34	39	52	49	*unk*	*unk*	Q2NMMMLMMJML	IV, V	WA-8, WA-79
78	22	1	14	23	12	53	31	t2815	*unk*	UEBBPB	IV	
80	1	3	1	14	11	51	10	t044	70	UJGBBPB	IV	European CA-MRSA
88	22	1	14	23	12	4	31	t186	9	UGFMEEBBPB	IV, V, VI	
91	1	26	28	18	18	54	50	t375	416	Y2EJCMBPB	II, IV, V	
93	6	64	44	2	43	55	51	t202	1143	YMJMMKKO	IV, V	Queensland
97	3	1	1	1	1	5	3	t267	105	UJGFMBBBPB	IV, V	
121	6	5	6	2	7	14	5	t159	312	I2Z2EGMMJH2M	V	
152	46	75	49	44	13	68	60	t355	207	UJ2GMKKPNSG	V	Balkan
377	46	75	49	50	13	68	60	t355	207	UJ2GMKKPNSG	V	Balkan
398	3	35	19	2	20	26	39	t011	*unk*	XKAOBQO	IV, V	LA-MRSA, ST398
772	1	1	1	1	22	1	1	t345	692	TJEFMBBPB	V	Bengal Bay, WA-60

Molecular characteristics of CA-MRSA strains listed in Table 2 and Figure 1. From left-to-right: (a) multilocus sequence typing (MLST) data, including sequence type and allele numbers for the 7 MLST housekeeping genes (*arcC-aroE-glpF-gmk-pta-tpiA-yqiL*); (b) representative *spa* type (Ridom and eGenomics) and *spa* repeat pattern (eGenomics), with 24-bp VNTR *spa* repeats denoted by letters; (c) SCC*mec* types known to be associated with each clonal lineage; (d) known regional clone names associated with a particular CA-MRSA lineage. ST, sequence type; *spa*, staphylococcal protein A; SCC*mec*, staphylococcal cassette chromosome *mec*; CMRSA, Canadian epidemic MRSA; WA, Western Australia; SWP, South West Pacific; OSPC, Oceanic Southwest Pacific; WSPP, Western Samoan Phage Pattern; LA-MRSA, livestock-associated MRSA; *unk*, unknown *spa* types or repeat patterns.

(http://eburst.mlst.net), which groups together STs that share at least 5/7 alleles into 'clonal complexes' that highlight the underlying population structure of the species (Figure 1).

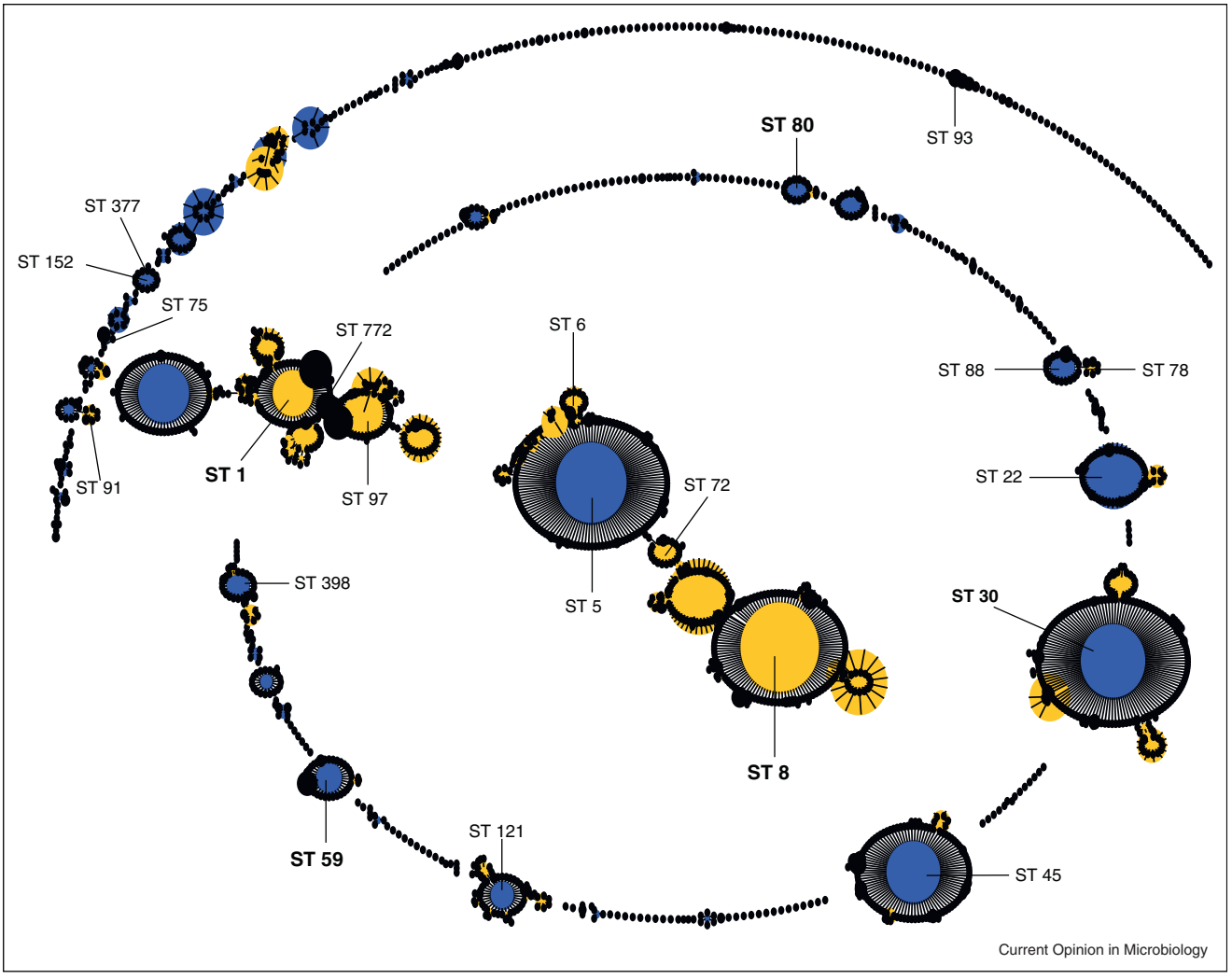
Spa typing is another sequence-based technique which targets the polymorphic variable-number tandem repeat (VNTR) region of staphylococcal protein A (*spa*). The *spa* repeats are typically 24 bp in length, with presumptive duplications, deletions, and rearrangements contributing to the identification of more than 10 000 unique patterns known as '*spa* types' [14]. Insofar as the technique is straightforward and cost-effective, it is noteworthy that the clonal background predicted by *spa* typing usually agrees with that of MLST, and can therefore be used to infer clonal complexes (CC). As with MLST, *spa* typing data is unambiguous and portable, but it should be noted that there are two nomenclature systems in use (see Table 1): eGenomics (http://www.egenomics.com) and Ridom (http://spaserver.ridom.de).

Whereas PFGE, MLST, and *spa* typing describe the genetic background of *S. aureus*, SCC*mec* typing classifies distinct allotypes of the horizontally acquired SCC*mec* elements present in MRSA strains [1,14]. Eleven SCC*mec* types have been described thus far (http://www.sccmec.org), with traditional HA-MRSA clones characterized by possession of types I, II, and III, while CA-MRSA strains typically feature smaller type IV and V elements [1,15]. Contemporary conventions for MRSA nomenclature rely on the juxtaposition of MLST sequence type (or clonal complex) and SCC*mec* type (e.g. ST5-II, ST8-IV) [1], with additional resolution provided by other molecular methods such as *spa* typing (Table 1). SCC*mec* subtyping can provide additional information, often discriminating between distinct lineages within a given clonal background, as in the case of the North American (ST8-IVa) and Latin American (ST8-IVc) lineages of USA300 [16•]. This approach, while not always exhaustive or unambiguous, allows for a universal short-hand to catalog the regional and historic clone names which appear frequently in the literature.

Origins and emergence of CA-MRSA

In 1999, following a report describing four pediatric fatalities in the midwestern United States, CA-MRSA was

Figure 1



Multilocus sequence types of the CA-MRSA lineages described in the Tables and text, depicting the wide range of genetic heterogeneity; the five primary lineages (ST1, ST8, ST30, ST59, ST80) are denoted in large font. The figure represents the population structure of the *Staphylococcus aureus* multilocus sequence typing (MLST) database (http://saureus.mlst.net) as of May 2012, depicted graphically by eBURST v.3 (http://eburst.mlst.net). Each circle represents an individual sequence type (ST), defined by concatenated allele numbers for the seven MLST genes (*arcC-aroE-glpF-gmk-pta-tpiA-yqiL*). Circle size indicates the frequency of a particular ST within the database, and may reflect researcher bias rather than clinical or epidemiologic significance. The eBURST algorithm draws a line between all sequence types which share 6/7 alleles (single locus variants, SLV), and groups together sequence types which share at least 5/7 alleles (double locus variants, DLV) into clusters referred to as clonal complexes (CC). Blue circles within CCs represent 'founders', defined as the ST with the greatest number of SLVs, and typically represent the most prevalent ST within a CC. The name of the CC is derived from the name of the ST, for example, ST8 is the founder of CC8. Yellow circles denote 'subgroup founders' within a given CC. Several CCs which were previously depicted separately have recently become subgroup founders of other CCs, potentially confounding existing nomenclature. For example, CC8 now appears to be a subgroup of CC5, but given the degree of genetic divergence, it would be impractical to refer to CC8 lineages as 'CC5'. In light of recent hybridization data highlighting genetic differences between 'subgroups' classified within the same CC [23], the authors recommend that all subgroups be referred to as individual CCs in order to avoid confusion in the literature.

recognized as a distinct clinical entity [17]. Before that, putative CA-MRSA cases were associated with intravenous drug users in Detroit, Michigan, and aboriginal populations in Western Australia [5••,17]. Both the Australian (WA-1) and the U.S. (MW2) strains were subsequently classified as MLST clonal complex (CC) 1. Beginning in 2000, further outbreaks of CA-MRSA infections were reported among athletes and prisoners in the U.S., which were subsequently associated with a different lineage (CC8), and dubbed 'USA300' [5••,11]. The latter quickly eclipsed MW2 (USA400), becoming the primary cause of skin and soft tissue infections (SSTI) in the U.S., and greatly increasing the burden of community MRSA carriage and transmission [18]. During the same period, genetically distinct CA-MRSA lineages were reported from numerous countries, with some lineages exhibiting

Table 2

CA-MRSA lineages reported in the literature as of May 2012

ST	SCC*mec*	Country
ST1	IV	Abu Dhabi, Australia, Brazil, Canada, China, Denmark, Egypt, Finland, France, Germany, Greece, Ireland, Italy, Japan, Pakistan, Romania, Samoa, Singapore, South Korea, Switzerland, United Kingdom, United States
ST5	I	France, Iceland, South Africa
	II	Iceland, Japan
	IV	Algeria, Argentina, Australia, Austria, Azores, Canary Islands, China, France, Germany, Iceland, Italy, Morocco, Samoa, Senegal, Spain, Switzerland, United Kingdom
	V	Australia, Cameroon, Egypt, Japan, Nigeria
	VI	Azores, Spain
ST6	IV	Japan, Malaysia
ST8	IV	Abu Dhabi, Argentina, Australia, Austria, Belgium, Brazil, Bulgaria, Cameroon, Canada, Canary Islands, China, Colombia, Costa Rica, Cuba, Czech Republic, Denmark, Ecuador, Finland, France, French Polynesia, Gabon, Germany, Greece, Hong Kong, Iceland, India, Iraq, Ireland, Israel, Italy, Japan, Madagascar, Mexico, Netherlands, New Zealand, Nigeria, Norway, Pakistan, Peru, Poland, Portugal, Romania, Russia, Samoa, South Korea, Spain, Sweden, Switzerland, Trinidad & Tobago, United Kingdom, United States, Uruguay, Venezuela
	V	Germany, Nigeria
	VI	Portugal
ST22	IV	Australia, Azores, Canary Islands, Germany, India, Ireland, Japan, Netherland, Singapore, United Kingdom
	V	Germany
ST30	IV	Abu Dhabi, Australia, Austria, Brazil, Canary Islands, China, Czech Republic, Denmark, Egypt, Finland, France, French Polynesia, Germany, Hong Kong, Ireland, Italy, Japan, Kuwait, Latvia, Malaysia, Netherlands, New Zealand, Pakistan, Peru, Philippines, Poland, Romania, Russia, Samoa, Singapore, South Korea, Spain, Sweden, Switzerland, Taiwan, Turkey, United Kingdom, United States, Uruguay
	V	China, Madagascar
ST45	IV	Australia, Azores, Belgium, Germany, Hong Kong
	V	Australia, China, Hong Kong
	VI	Switzerland
ST59	IV	Australia, China, Denmark, Finland, Germany, Hong Kong, Netherlands, Singapore, Sweden, Taiwan, United Kingdom, United States, Vietnam
	V	Australia, China, Germany, Hong Kong, Japan, Poland, Singapore, Sweden, Taiwan, United Kingdom, United States, Vietnam
ST72	IV	Abu Dhabi, Czech Republic, Germany, Portugal, South Korea, Sweden, United States
	V	United States
ST75	IV	Australia
ST78	IV	Australia
ST80	IV	Abu Dhabi, Algeria, Australia, Austria, Belgium, Bulgaria, Croatia, Czech Republic, Denmark, Egypt, Finland, France, Germany, Greece, Ireland, Israel, Italy, Jordan, Kuwait, Lebanon, Libya, Malta, Netherlands, Norway, Poland, Portugal, Romania, Singapore, Slovenia, Spain, Sweden, Switzerland, Tunisia, United Kingdom
ST88	IV	Abu Dhabi, Angola, Cameroon, China, Gabon, Italy, Japan, Madagascar, Mali, Netherlands, Niger, Nigeria, Portugal, Senegal, Spain, Sweden, United Kingdom
	V	China, Italy, Madagascar, Sweden
ST91	II	Japan
	IV	Japan
	V	Japan
ST93	IV	Australia, Czech Republic, Finland, Italy, Netherlands, Samoa, United Kingdom
ST97	IV	Abu Dhabi, Canary Islands, Denmark, Germany, Netherlands
	V	Egypt, Kuwait, United Kingdom
ST121	V	Australia, Cambodia
ST152	V	Austria, Canary Islands, Denmark, Germany, Kosovo, Macedonia, Slovenia, Sweden, Switzerland
ST377	V	Australia, France, Greece, Netherlands, Switzerland
ST398	II	Hong Kong
	IV	Austria, Belgium, China, Denmark, Germany, Hong Kong, Italy, Netherlands
	V	Austria, Belgium, Canada, China, Denmark, Germany, Hong Kong, Italy, Netherlands, Norway, Portugal, Spain, Sweden, United States
	NT	Belgium, Denmark, Germany, Netherlands
ST772	IV	India
	V	Abu Dhabi, Australia, Bangladesh, Finland, Germany, Hong Kong, India, Ireland, Italy, Japan, Netherlands, United Kingdom

Data were gathered from numerous publications, and are not necessarily included within the references. Each clone is denoted by a specific ST and SCC*mec* type, as described in the text; SCC*mec* subtypes are not indicated. LA-MRSA strain ST398 is included as it is sometimes referred to as CA-MRSA in the literature. ST, sequence type; SCC*mec*, staphylococcal cassette chromosome *mec*; I, SCC*mec* type I; II, SCC*mec* type II; IV, SCC*mec* type IV; V, SCC*mec* type V; VI, SCC*mec* type VI; NT, non-typable SCC*mec* element.

restricted geographic ranges, and others characterized by international epidemicity [19] (Table 2).

Various theories have been proposed to account for the rapid emergence of global CA-MRSA clones within the last two decades. Some have suggested a link with the worldwide increase in fluoroquinolone use [5••], while others theorize that CA-MRSA exploited vacant colonization niches following global immunization efforts against *Streptococcus pneumoniae* [5••]. The close epidemiologic association with Panton-Valentine leukocidin (PVL) has likewise generated significant debate regarding its potential role in the origin and dissemination of CA-MRSA [20]. Others argue that the appearance of novel SCC*mec* elements led to successive epidemic 'waves' of MRSA evolution, with the appearance of SCC*mec* type IV during the late 1980s presumably driving the simultaneous emergence of multiple CA-MRSA lineages [3,6••]. However, given the recent emergence of livestock-associated MRSA (LA-MRSA) strains such as ST398 [21], it is likely that no single explanation can suffice, and that 'MRSA' represents a continuously emergent phenomenon driven by multifactorial interactions between the classic triad of host, pathogen, and environment.

Molecular epidemiology of CA-MRSA

Currently, worldwide reports of CA-MRSA are associated with >20 distinct genetic lineages (Figure 1, Tables 1 and 2), five of which are globally predominant, including ST1-IV (WA-1, USA400), ST8-IV (USA300), ST30-IV (South West Pacific clone), ST59-V (Taiwan clone), and ST80-IV (European clone) [5••,6••,22•]. Among the latter, ST8-IV and ST30-IV may be considered pandemic, as they have been isolated repeatedly from every continent [6••,23••]. ST8-IV is primarily associated with the global spread of USA300, discussed separately in the following section. ST30-IV, commonly referred to as the South West Pacific clone (SWP), was previously considered a descendant of the pandemic phage-type 80/81 penicillin-resistant *S. aureus* strain, but appears to have diverged from a common CC30 ancestor along with HA-MRSA strain EMRSA-16 [24]. It is currently one of the primary CA-MRSA strains in Australia, Asia and South America, as well as Europe and the Middle East, and while it often causes serious infections, it is generally susceptible to more antibiotics than other CA-MRSA strains [3,4••,6••].

CA-MRSA is generally less prevalent in Europe than it is in the U.S. [22•], and is characterized by considerable genetic heterogeneity [25,26], in contrast to the predominant spread of USA300 in North America. The so-called 'European CA-MRSA' clone ST80-IV nevertheless stands out by virtue of having been isolated in nearly every European country sampled to date [4••,23••,25,26••,27]. It was initially reported in 2003 in Greece, the country with the highest CA-MRSA incidence in Europe, where it is responsible for the majority of both CA-MRSA and HA-MRSA infections [4••,25]. Although it has been identified in Danish isolates dating back to 1993, it appears to have originated in North Africa or the Middle East, given that it is the predominant community and nosocomial MRSA strain in these regions, and that initial European reports of ST80 were associated with North African immigrants [28].

ST59-IV and ST59-V comprise the most common CA-MRSA strains in Taiwan, China, and several other Asian countries, but are also found in Europe, Australia, and the United States, where it is known as USA1000 [23••]. It appears that ST59-IV (USA1000) may be restricted primarily to the U.S., whereas ST59-V (Taiwan clone) is widespread in Asia and Australia [23••]. By contrast, ST1-IV is primarily associated with Native American communities in Alaska and the midwestern regions of the U.S. (USA400) and Canada (CMRSA-7) [29], and with aboriginal communities in Western Australia (WA-1) [30]. Whereas the North American ST1-IV strains invariably harbor PVL, the Australian strains are nearly always PVL-negative [30]. USA400 appears to be more virulent than USA300 [6••], but is rarely isolated in the U.S. outside of the aforementioned regions. In recent years, ST772-V (Bengal Bay clone), a single locus variant of ST1 (differing by a single MLST allele), has emerged as a virulent and unusually resistant CA-MRSA strain in Bangladesh and India [31], and is increasingly reported in the U.K. and Europe [23••,32].

Aside from the major lineages described above, several other CA-MRSA clones are worth mentioning (Tables 1 and 2). These include ST72-IV (USA700), the primary CA-MRSA strain in South Korea [33]; ST88-IV (or ST88-V), frequently found in Africa and Asia [34]; ST93-IV (Queensland clone), currently the primary CA-MRSA strain in Australia, but rarely isolated elsewhere [35]; ST97-V, originally of animal origin but recently described among CA-MRSA infections in the U.K. [36]; and ST152-V and ST377-V, single locus variants which occur frequently as PVL+ methicillin-susceptible *S. aureus* (MSSA) in Africa [23••], but which have been associated with CA-MRSA infections in the Balkans and central Europe [4••,23••,27]. Also noteworthy is ST75-IV, an early-branching lineage considered a potential subspecies of *S. aureus*, and restricted to remote aboriginal communities in Australia [37•]. Lastly, various lineages typically associated with HA-MRSA, such as ST22-IV (EMRSA-15), are also increasingly associated with CA-MRSA infections [22•,23••]. Notable examples include ST5-IV, the primary CA-MRSA clone in Argentina [38], and ST5-I, the so-called 'Geraldine' clone, which harbors the gene coding for toxic shock syndrome toxin (TSST-1) [39].

USA300

Most reports of CA-MRSA involve USA300, currently the most prevalent MRSA strain in the U.S., and the only

CA-MRSA strain thus far which appears to pose a global epidemic threat [16•,40•]. The earliest known cases of USA300 were associated with a collegiate football team in Pennsylvania, followed by several outbreaks among prisoners in Mississippi and Los Angeles [11], and some authors speculate that the prevalence of incarceration in the U.S. may be amplifying the epidemic spread of USA300 [22•,41]. Associated primarily with particular risk groups including military personnel, prisoners, athletes, intravenous drug users, the homeless, urban populations, and men who have sex with men [11], it has nevertheless become the primary cause of SSTI among the general population [18].

The heightened transmissibility of USA300 has been associated with carriage of the arginine catabolic mobile element (ACME) [42], previously considered to be a unique marker for this lineage [16•,36]. Unlike traditional HA-MRSA strains, it appears to preferentially colonize extranasal sites including the rectum [43,44], while environmental transmission via fomites has also been implicated [44,45]. It is increasingly described as a cause of serious invasive disease, including community-acquired pneumonia, endocarditis, and necrotizing fasciitis [16•,40•,42], and is progressively becoming endemic in nosocomial settings, displacing ST5-II as the primary cause of bloodstream infection in parts of the U.S. [46]. Worrisomely, it appears to be steadily acquiring greater antibiotic resistance [10], and 'multidrug-resistant' USA300 strains harboring conjugative plasmids conferring high-level mupirocin resistance have been reported in high frequencies in San Francisco [47], Chicago [48], and New York City (authors' unpublished observations).

Reports of USA300 outside of the U.S. have increased greatly since its discovery [16•]. Originally described among high-risk groups in Vancouver, it is currently the primary CA-MRSA strain in Canada (CMRSA-10) [29], and is increasingly reported in Europe, Japan and Australia [16•,26••]. Both community and nosocomial infections with USA300-like strains were reported in Colombia beginning in 2006, and subsequently described in neighboring countries [49]. Interestingly, this strain, recently dubbed 'USA300-LV' (Latin American variant), appears to be a separate lineage which may be distinguished from the North American strain (USA300-0114) by various molecular features including SCC*mec* subtype (IVc) and absence of ACME, and appears to be circulating in South America, Europe, and Australia [16•,49].

Panton-Valentine leukocidin (PVL)

The potential role of the bacteriophage-encoded PVL toxin in CA-MRSA pathogenesis remains a matter of significant controversy, as reviewed extensively elsewhere [5••,6••,20]. The epidemiologic association between PVL and CA-MRSA is nevertheless striking [19], insofar as it is harbored by nearly every major CA-MRSA lineage [27], but found infrequently (<5%) in HA-MRSA and MSSA [3,20]. It is also conspicuously absent from certain CA-MRSA lineages such as WA-1 (ST1-IV) [3,23••], and its utility as a marker for CA-MRSA is diminishing as new PVL negative clones are described, although in the U.K. surveillance is routinely performed for 'PVL-MRSA' [50]. The underlying reasons behind the worldwide emergence of PVL+ CA-MRSA lineages during the past decade remain an open question. Given that the pandemic phage-type 80/81 strain from the 1950s was PVL+ [24], it is tempting to speculate that PVL phages were 'seeded' globally during this period, with distinct PVL+ MSSA lineages subsequently acquiring SCC*mec* IV or V elements [51]. Recent studies suggest that several distinct PVL phages circulate within international CA-MRSA lineages [52•], and that PVL phage transmission is an ongoing process. Given the evolutionary dynamics of SCC*mec* transmission, and the existence of numerous PVL+ MSSA lineages worldwide [51], it is likely that additional PVL+ CA-MRSA lineages will emerge in the future.

Conclusion

The simultaneous global emergence of genetically divergent CA-MRSA strains rivals the earlier spread of intercontinental HA-MRSA lineages, and highlights the evolutionary versatility of MRSA as a pathogen no longer limited to healthcare environments [2,3]. A recent study suggests that higher levels of methicillin resistance in HA-MRSA strains may suppress expression of virulence factors, thereby limiting their ability to compete with CA-MRSA strains in community settings [53•]. Moreover, recent mathematical models predict that CA-MRSA strains harboring smaller SCC*mec* elements will eventually displace traditional HA-MRSA strains in hospitals, with significant clinical and public health implications [8,9]. Indeed, a growing body of evidence suggests that other CA-MRSA lineages besides USA300 are increasingly responsible for healthcare-associated infections [7]. Finally, the recent phenomenon of LA-MRSA, characterized primarily by the international emergence of ST398, highlights the existence of additional reservoirs of MRSA strains which may become established in both community and nosocomial settings [21]. Taken together, such developments may be viewed as a dynamic landscape of continuously emerging 'waves' of MRSA evolution [2], with definitions such as HA-, CA-, and LA-MRSA having transient significance at best.

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- •• of outstanding interest

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