



## Diversity of methicillin-resistant *Staphylococcus aureus* CC22-MRSA-IV from Saudi Arabia and the Gulf region



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### SUMMARY

**Objectives:** CC22-MRSA-IV, UK-EMRSA-15/Barnim EMRSA, is a common and pandemic strain of methicillin-resistant *Staphylococcus aureus* (MRSA) that has been found mainly in Western Europe, but also in other parts of the world including some Gulf countries. One suspected case of an infection with this strain in a patient who was admitted to the surgical unit in Riyadh, Kingdom of Saudi Arabia (KSA) was investigated in order to check whether this strain has reached KSA.

**Methods:** Besides the index isolate, 46 additional isolates of CC22-MRSA-IV from patients from KSA, Abu Dhabi, Kuwait, and Germany (patients with a history of travel in the Middle East), were characterized by microarray hybridization.

**Results:** The study revealed a regional presence of as many as six distinct 'strains' of CC22-MRSA-IV that could be distinguished based on carriage of SCCmec IV subtypes and virulence factors. No true UK-EMRSA-15/Barnim EMRSA was identified in Riyadh; all suspected isolates from Riyadh were assigned to other, albeit related strains. However, this strain was identified in Abu Dhabi and Kuwait.

**Conclusions:** CC22-MRSA-IV from KSA could be linked to other epidemic strains from the Middle East and possibly India, rather than to the Western European UK-EMRSA-15/Barnim EMRSA. High-resolution typing methods, including SCCmec subtyping, might help to differentiate related epidemic strains and to monitor routes of transmission.

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## 1. Introduction

Epidemic methicillin-resistant *Staphylococcus aureus* (EMRSA)-15 (CC22-MRSA-IV) was first identified in the UK in the early 1990s and has become the most prevalent hospital-acquired strain of methicillin-resistant *Staphylococcus aureus* (MRSA) in the UK.<sup>1,2</sup>

This pandemic MRSA strain has also been reported from many other regions of the world, including Ireland, Germany (where it is called 'Barnim EMRSA' after the county in which it was first found), Denmark, Belgium, Spain, Portugal, Malta, Sweden, Singapore, Australia, New Zealand, Qatar, and Kuwait.<sup>1,3–21</sup> CC22-MRSA-IV that differ in harbouring *tst1* (encoding toxic shock toxin) have been reported from the Gaza Strip, Jordan, the United Arab Emirates (UAE), the Kingdom of Saudi Arabia (KSA), Kuwait, the USA, and Italy.<sup>11,20,22–26</sup> Furthermore, CC22-MRSA-IV harbouring the genes encoding the Pantone–Valentine leukocidin (PVL) have

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frequently been observed in the Middle East,<sup>5,11,27</sup> Iran,<sup>28</sup> and India,<sup>29–31</sup> and also in sporadic cases<sup>32</sup> and localized outbreaks<sup>33</sup> in other regions, such as Western Europe.

In this report, the characteristics of CC22-MRSA-IV causing an infection in a patient who presented to the surgical unit of King Khalid University Hospital (KKUH) in Riyadh, KSA, are presented. Furthermore, the molecular typing of CC22-MRSA-IV isolated in the Arabian Gulf region and from patients from Germany with a history of previous travel to the Middle East is discussed.

## 2. Materials and methods

### 2.1. Case history

A middle-aged male patient presented to the surgical unit of KKUH with a history of intermittent fever and peri-umbilical pain, with an associated peri-umbilical discharge of 2-week duration. The patient gave a history of travel to Egypt (including healthcare exposure) and of two previous surgical interventions at different hospitals during the last few years. The first one was a gastric bypass procedure; the second one an abdominal herniorrhaphy with mesh implant. He received antibiotics, but neither details of the antibiotic therapy nor information on the laboratory investigations were available. There was no history of any chronic illness apart from the presenting complaints. No family members were documented to have recurrent skin or soft tissue infections.

On admission, the patient had stable vital signs. Physical examination revealed an anterior abdominal wall scar running from the xiphoid process to the umbilicus and a discharging wound in the umbilical area. There was associated tenderness in the para-umbilical and left hypogastric areas. Investigations carried out at presentation included an abdominal computed tomography scan, which was significant for thickening of the anterior abdominal wall with minimal subcutaneous collection. A culture of the wound swab collected at presentation yielded a mixed growth of *Klebsiella pneumoniae*, which was sensitive to all tested antibiotics, and MRSA, which was resistant to penicillin, ampicillin, and imipenem but susceptible to gentamicin, ciprofloxacin, erythromycin, rifampicin, trimethoprim/sulfamethoxazole, tetracycline, and vancomycin. The patient underwent wound debridement with partial mesh removal and drainage a day after presentation, and the postoperative period was uneventful. He was discharged 3 days after presentation on a combination of clindamycin (450 mg, 8-hourly) and ciprofloxacin (750 mg, 12-hourly). At the 2-week follow-up visit, the patient's wound had healed completely.

### 2.2. Additional isolates

Additional isolates were included for comparison. All had previously been identified as CC22-MRSA-IV using the StaphyType DNA microarray (see below). These included isolates with hybridization profiles consistent with UK-EMRSA-15/Barnim EMRSA, as well as some randomly selected PVL- or *tst1*-positive CC22-MRSA-IV strains. These isolates originated from Riyadh (KSA; five isolates sampled in 2014 and 13 sampled in 2010/11), Abu Dhabi (UAE; *n* = 16 sampled in 2009/10), and Kuwait (*n* = 6; 2013), as well as from Germany. The German isolates included some local UK-EMRSA-15/Barnim EMRSA isolates (*n* = 4; 2015/16) and some PVL- or *tst1*-positive CC22-MRSA-IV from patients with a history of recent travel in the Middle East (*n* = 3; 2014–2016).

### 2.3. Array procedures

Molecular characterization of the MRSA isolate from the index case was performed as part of a wider study in which archived MRSA isolates from KKUH were characterized using the StaphyType

DNA microarray (Alere Technologies GmbH, Jena, Germany). Probes, primers, and procedures have been described previously in detail,<sup>11,34</sup> and protocols are provided by the manufacturer.

Additional probes and primers were used in order to discern SCCmec subtypes and CC22 strains (Table 1). Amplification and hybridization protocols were identical to those described previously.<sup>11,34</sup>

## 3. Results

The recovered isolate harboured the accessory gene regulator (*agrI*) and capsular genes type 5 (*cap5*), as well as genes for collagen adhesin (*cna*), *Staphylococcus aureus* surface protein G (*sasG*), and the *egc* cluster. This was in accordance with previously characterized CC22 isolates and strains.<sup>11,34</sup> Furthermore, it harboured *mecA* as part of an SCCmec IV element. It lacked the genes encoding fibronectin-binding protein B (*fnbB*), exfoliative toxin (*etA*, *etB*, and *etD*), toxic shock toxin (*tst*), and PVL, as well as the arginine catabolic mobile element (ACME). Based on this profile, the isolate was preliminarily regarded as CC22-MRSA-IV, UK-EMRSA-15/Barnim EMRSA. Staphylokinase (*sak*), chemotaxis-inhibiting protein (*chp*), and *Staphylococcus* complement inhibitor (*scn*) genes were present, and enterotoxin C and L genes (*sec* and *sel*) were absent.

SCCmec subtyping using new probes revealed that this isolate differed in SCCmec subtype from Western European UK-EMRSA-15/Barnim EMRSA isolates (that harbour SCCmec IV h/j) in the carriage of an SCCmec element of subtype IVa. The hybridization pattern of the actual isolate (Table 2) matched the computed/predicted pattern for the sequence of strain CMFT503, GenBank HF569113.1, yielding signals for *mecA*, *ugpQ*, delta *mecR1*, *mvaS*, *cstB-SCC2*, *Q931B7*, *ccrA/B-2*, and 'SCCterm 1' (an intergenic region between *orfX* and the first codons of the SCC element that is alternative to *dcs*).

Based on this observation, a convenience sample of 46 additional isolates was selected and subtyped for comparison (see Materials and methods). When focusing on SCCmec IV subtypes as well as on the carriage of PVL and *tst1* genes, these 46 isolates could be categorized into six distinct variants, or strains. Details are shown in Table 2. All Saudi isolates differed from the Western European UK-EMRSA-15/Barnim EMRSA CC22-MRSA-IV h/j. However, this strain was identified in Abu Dhabi (UAE) and Kuwait.

## 4. Discussion

The changing epidemiology of MRSA necessitates the continuous surveillance of patients. Well-documented hospital and community strains of MRSA in Saudi Arabia include ST239-MRSA-III, ST80-MRSA-IVc, and ST30-MRSA-IV.<sup>27</sup>

In this report, the characteristics of a CC22-MRSA-IV (CC22-IV) isolate from a patient in Saudi Arabia are presented; this isolate was similar but not identical to the widely distributed UK-EMRSA-15/Barnim EMRSA. On investigating this case and other similar isolates from KSA and other regions, several different strains (or very distinct variants) of CC22-IV could be distinguished based on SCCmec IV subtypes and the carriage of clinically important toxin genes.

These included UK-EMRSA-15/Barnim EMRSA as described from Western Europe (see Introduction). These isolates have SCCmec IV h/j elements and do not carry *tst1* or PVL genes, but frequently harbour enterotoxin C and L genes (*sec* and *sel*). Usually they are phenotypically resistant to ciprofloxacin, often also to erythromycin and clindamycin (mediated by *erm(C)*). Other resistance properties, however, are rather rare. This strain is also susceptible to weak lysis by phage 75.<sup>1</sup>

**Table 1**  
Markers used for subtyping of CC22-MRSA-IV

Gene	Gene product/function	Probe(s)	Primer(s)
<i>agr</i> groups I–IV, capsule type 5 and 8	<i>agr</i> - and capsule-specific probes ( <i>agr</i> I and capsule type 8 alleles present in CC22)	11,34	11,34
<i>mecA</i>	Modified penicillin binding protein (PBP2a) causing oxacillin/methicillin resistance and thus defining MRSA	11,34	11,34
<i>ccrA/B-2</i>	Cassette chromosome recombinase A allele found in SCC <i>mec</i> II and IV elements	11,34	11,34
<i>mvaS</i> -SCC	Truncated 3-hydroxy-3-methylglutaryl CoA synthase, variably present in SCC <i>mec</i> I, II, IV, V	BA000033.2 [37280:37304] and BA000033.2 [37432:37460]	BA000033.2 [37307:37326:r] and BA000033.2 [37488:37510:r]
<i>cstB</i> - <i>scc2</i> (IVa)	CsoR-like sulfur transferase-regulated genes B/ metallo-beta-lactamase superfamily protein (truncated); present in SCC <i>mec</i> X, variably present in SCC <i>mec</i> I and IV; marker for IVa	CP000046.1 [54284:54313:r] and CP000046.1 [53882:53910:r]	CP000029.1 [2492569:2492590:r] and CP000046.1 [53836:53854]
B2Y834	Abortive phage resistance protein used for identification of SCC <i>mec</i> IV A, G, c and SCC <i>mec</i> MRSZAH47	AE015929.1 [51095:51119]	AE015929.1 [51124:51144:r]
B6VQU0	Putative protein used for identification of SCC <i>mec</i> IVh/j	AB425824.1 [20412:20443]	AB425824.1 [20498:20525:r]
Q93IB71	LytTR domain DNA-binding regulator present in some SCC <i>mec</i> III elements and in IVa from CMFT503 GenBank HF569113.1	FN433596.1 [434532:434550]	FN433596.1 [68041:68058]
Q9XB68-dcs	Located at the terminus of SCC <i>mec</i> directly next to <i>orfX</i> , comprises the downstream constant segment ( <i>dcs</i> ) that includes a copy of the SCC direct repeat DR_SCC (AGAAGCTTATCATAAGTAA)	11,34	11,34
SCC <i>mec</i> Terminus 1	SCC integration site alternate to <i>dcs</i>	GU235983.1 [568:594]	FN433596.1 [67354:67380:r]
SCC <i>mec</i> Terminus 5	SCC integration site alternate to <i>dcs</i>	AB425427.1 [754:779]	AB425427.1 [800:824:r]
<i>erm</i> (C)	rRNA adenine N-6-methyltransferase	11,34	11,34
<i>aacA</i> - <i>aphD</i>	macrolide–lincosamide–streptogramin B resistance protein	11,34	11,34
	Bifunctional enzyme Aac/Aph, 6'-aminoglycoside N-acetyltransferase/2''-aminoglycoside phosphotransferase; gentamicin and tobramycin resistance	11,34	11,34
<i>aadD</i>	Aminoglycoside adenylyltransferase, tobramycin resistance	11,34	11,34
<i>dfrA</i>	Dihydrofolate reductase, mediates trimethoprim resistance	11,34	11,34
<i>lukF/S</i> -PV	Panton–Valentine leukocidin	11,34	11,34
<i>tst1</i>	Toxic shock syndrome toxin	11,34	11,34
<i>sec+sel</i>	Enterotoxins C and L	11,34	11,34
<i>egc</i> cluster	Enterotoxin gene cluster (comprising <i>seg</i> , <i>sei sem</i> , <i>sen</i> , <i>seo</i> , <i>seu</i> )	11,34	11,34
<i>sak</i> , <i>chp</i> , <i>scn</i>	Staphylokinase, chemotaxis-inhibiting protein, staphyl. complement inhibitor	11,34	11,34
<i>eta</i> , <i>etb</i> , <i>etd</i>	Exfoliative toxins	11,34	11,34
ACME	Arginine catabolic mobile element	11,34	11,34
<i>fnbB</i>	Fibronectin binding protein B, variably detected in CC22 because it is in some strains fused with <i>fnbA</i>	11,34	11,34
<i>cna</i> , <i>sasG</i>	Collagen adhesin; <i>Staphylococcus aureus</i> surface protein G (present in CC22)	11,34	11,34

Although some were superficially similar, not a single one of the 18 KSA isolates characterized herein could be assigned to UK-EMRSA-15/Barnim EMRSA, mainly because of the carriage of other SCC*mec* IV subtypes. Some isolates from Kuwait and Abu Dhabi matched this strain. Furthermore, two additional isolates from Abu Dhabi had an SCC*mec* IV variant element that has apparently not yet been described or sequenced.

Another related epidemic strain – ST22-MRSA-IVa – is usually reported to carry *tst1* as well as SCC*mec* IVa. It is probably widely distributed in the Middle East and the Mediterranean, and is sometimes dubbed the ‘Gaza epidemic strain’.<sup>11,20,22–25,27</sup> Study isolates that could be assigned to this strain originated from KSA, Abu Dhabi, and Kuwait, or were isolated in Germany from patients with a history of travel to the Middle East.

There were also *tst1*-negative isolates with SCC*mec* IVa elements. Previously observed UK-EMRSA-15/Barnim EMRSA-like isolates from KSA have belonged to this category,<sup>27</sup> as well as the

isolate from the case described herein. It can be assumed that they might rather be *tst1* deletion mutants of the Middle Eastern ‘Gaza epidemic strain’ than derived from imported European UK-EMRSA-15/Barnim EMRSA.

Furthermore, three *tst1*-negative isolates (one each from KSA, Abu Dhabi, and Kuwait) were found to carry SCC*mec* IV b/d/i elements.

Finally, there were a number of PVL-positive CC22-IV. All characterized isolates of PVL-positive CC22-MRSA-IV had SCC*mec* IVc elements, ruling out the possibility that they directly evolved from UK-EMRSA-15/Barnim EMRSA by acquisition of a PVL phage. This strain also appears to be present in India (with two recent genome sequences being virtually identical to the isolates tested herein: <http://www.ncbi.nlm.nih.gov/bioproject/PRJDB1743> and <http://www.ncbi.nlm.nih.gov/bioproject/PRJDB2070>). This suggests an epidemiological link to the Arabian Gulf, as previously also assumed for other MRSA.<sup>35</sup>

**Table 2**  
CC22-MRSA-IV strains and isolates

Isolates	CC22-MRSA-IV with SCCmec IVa	UK-EMRSA-15/Barnim EMRSA with SCCmec IV h/j	CC22-MRSA-IV with unknown SCCmec IV h/j variant	<i>tst1</i> -positive 'Gaza epidemic strain' with SCCmec IVa	CC22-MRSA-IV with SCCmec IV b/d/i	PVL-positive CC22-MRSA-IV with SCCmec IVc
	Index case from the case report and 3 others from Riyadh (2010/11)	7 isolates from Abu Dhabi (2009/10), 2 from Kuwait (2013), and, for comparison, 4 from Dresden (locals; 2015/16)	2 from Abu Dhabi (2009/10)	2 isolates from Abu Dhabi (2009/10), 2 from Kuwait (2013), 2 from Riyadh (2014), 4 from Riyadh (2010/11), 2 from Dresden (with travel history; 2016)	1 from Riyadh (2014), 1 from Abu Dhabi (2009/10), 1 from Kuwait (2013)	4 from Abu Dhabi (2009/10), 1 from Kuwait (2013), 1 from Riyadh (2014), 6 from Riyadh (2010/11), 1 from Dresden (with travel history; 2014)
<i>mecA</i>	Positive	Positive	Positive	Positive	Positive	Positive
<i>ccrA/B-2</i>	Positive	Positive	Positive	Positive	Positive	Positive
<i>mvaS</i> -SCC	Positive	Positive	Positive	Positive	Positive	Negative
<i>cstB</i> - <i>scs2</i> (IVa)	Positive	Negative	Positive	Positive	Negative	Negative
B2Y834 (IVc)	Negative	Negative	Negative	Negative	Negative	Positive
B6VQU0 (IV h/,j)	Negative	Positive	Positive	Negative	Negative	Negative
Q931B71	Positive	Negative	Negative	Positive	Negative	Negative
Q9XB68-dcs	Negative	Positive	Negative	Negative	Positive	Positive
SCCmec Terminus 1	Positive	Negative	Negative	Positive	Negative	Negative
SCCmec Terminus 5	Negative	Negative	Positive	Negative	Negative	Negative
<i>erm</i> (C)	Negative	Variable	Negative	Variable	Variable	Variable
<i>aacA</i> - <i>aphD</i>	Negative	Negative	Negative	Negative	Negative	Positive
<i>aadD</i>	Negative	Negative	Negative	Negative	Negative	Variable
<i>dfrA</i>	Negative	Negative	Negative	Negative	Negative	Variable
<i>lukF</i> /S-PV	Negative	Negative	Negative	Negative	Negative	Positive
<i>tst1</i>	Negative	Negative	Negative	Positive	Negative	Negative
<i>sec</i> + <i>sel</i>	Negative	Variable	Negative	Negative	Positive	Negative
<i>egc</i> cluster	Positive	Positive	Positive	Positive	Positive	Positive
<i>fnbB</i>	Negative	Negative	Negative	Negative	Variable	Variable

In conclusion, 'true' UK-EMRSA-15/Barnim EMRSA was not identified from KSA, with all tested CC22-MRSA-IV differing either in toxin carriage and/or in SCCmec subtype. UK-EMRSA-15/Barnim-like strains from KSA might have evolved independently from other Middle Eastern CC22-MRSA-IV (by loss of *tst1*) or directly from methicillin-sensitive *S. aureus*, by acquisition of SCCmec IV b/d/i.

Due to the small number of isolates characterized herein, it is not possible to state that UK-EMRSA-15/Barnim EMRSA does not exist in KSA at all, or whether it is just less common than the other CC22-MRSA-IV strains.

UK-EMRSA-15/Barnim EMRSA was found in other countries in the region. The higher prevalence of this strain in Kuwait and the UAE than in KSA could possibly be attributed to the higher number of European expatriates and tourists in Kuwait and the UAE.

One might also wonder what makes CC22-MRSA-IV so successful an entity that at least six different CC22-MRSA-IV strains co-exist in the Arabian Gulf region.

The isolation and characterization of these isolates underscores the diversity of CC22 MRSA strains based on SCCmec subtyping, as well as the potential of SCCmec subtyping for molecular epidemiology. It also calls for continued surveillance and screening, including the application of highly sensitive molecular methods for the characterization of isolates.

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**Ethical approval:** MRSA typing (research project E-15-1406) at King Khalid University Hospital, Riyadh, Kingdom of Saudi Arabia, was reviewed and approved by the Institutional Review Board. Any identifying information on the index case has been omitted. The patient gave consent for the publication of this anonymized report. The other parts of this study deal with molecular typing/epidemiological surveillance based on archived isolates without accompanying patient-related information, for which no ethical approval was required.

**Conflict of interest:** Ralf Ehrlich and Stefan Monecke are employees of Alere Technologies, the company that manufactures the microarrays used in this study. The arrays used herein are (or will be developed to be) a marketed product.

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