**Microorganisms**

**Review**

Human *mecC*-Carrying MRSA: Clinical Implications and Risk Factors

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**Abstract:** A new methicillin resistance gene, named *mecC*, was first described in 2011 in both humans and animals. Since then, this gene has been detected in different production and free-living animals and as an agent causing infections in some humans. The possible impact that these isolates can have in clinical settings remains unknown. The current available information about *mecC*-carrying methicillin resistant *S. aureus* (MRSA) isolates obtained from human samples was analyzed in order to establish its possible clinical implications as well as to determine the infection types associated with this resistance mechanism, the characteristics of these *mecC*-carrying isolates, their possible relation with animals and the presence of other risk factors. Until now, most human *mecC*-MRSA infections have been reported in Europe and *mecC*-MRSA isolates have been identified belonging to a small number of clonal complexes. Although the prevalence of *mecC*-MRSA human infections is very low and isolates usually contain few resistance (except for beta-lactams) and virulence genes, first isolates harboring important virulence genes or that are resistant to non-beta lactams have already been described. Moreover, severe and even fatal human infection cases have been detected. *mecC*-carrying MRSA should be taken into consideration in hospital, veterinary and food safety laboratories and in prevention strategies in order to avoid possible emerging health problems.

**Keywords:** *Staphylococcus aureus*; methicillin resistance; human infection; CC130

1. Introduction

*Staphylococcus aureus* is an opportunistic pathogen that causes high morbidity and mortality. This microorganism is able to cause diverse diseases that range from having a relatively minor impact, such as a skin infection, to serious and life-threatening episodes, such as endocarditis, pneumonia or sepsis. The impact of *S. aureus* is enhanced by its great capacity to develop and acquire resistance to various antimicrobial agents. Among the antibiotic resistance of *S. aureus*, methicillin resistance mediated by the *mecA* gene is highly relevant as this mechanism provides this bacterium resistance to almost all beta-lactam antibiotics, seriously limiting therapeutic options [1,2]. Recently, the World Health Organization (WHO) outlined the greatest threats in terms of antimicrobial resistance and methicillin-resistant *S. aureus* (MRSA) was classified as a high-priority microorganism. For many years, MRSA infections were only reported in hospitals, with it being considered to be a nosocomial pathogen (hospital-associated MRSA or HA-MRSA). In the 1990s, community-associated MRSA (CA-MRSA) cases in healthy humans without any connection to healthcare settings started to be described and, nowadays, the distinction between CA-MRSA and HA-MRSA seems to be disappearing [3,4].

For the last two decades, a third epidemiological group known as livestock-associated MRSA (LA-MRSA) has been described. *S. aureus* has been considered to be an important zoonotic agent with...
a great capacity to cause infections in different animal species and in humans. Various studies have suggested that there is a high specificity of the different genetic lineages of S. aureus for the host [5]. However, many cases of clones related to animals have been detected and have caused infections in humans [6,7]. Presently, different clonal lineages associated with LA-MRSA have been described and, among these, the clonal complex (CC) CC398 stands out (Table S1). CC398 is related to production animals, mainly pigs, and has been detected worldwide [8]. Infection cases have been identified in humans, both in contact and without contact with animals [9–11]. In addition to CC398, there are other clonal complexes associated with animals such as CC5 in birds, CC9 in pigs, CC97 in cattle or CC133 in small ruminants [12–15].

Remarkably, a new methicillin resistance gene (mecA_LGA251, which shares only 70% similarity to mecA (Figure S1)) was first described in 2011 in both humans and animals [16,17]. Initially these strains were associated with dairy cows and these animals were considered to be a possible reservoir [16]. Since then, this gene has been detected in different production and free-living animals and as an agent causing infection in some humans [8,18]. This new gene was named mecC since mecB had previously been described in macrococci, but not in staphylococcal species [19]. Worryingly, mecB has been recently identified in S. aureus and future studies should determine the potential risk that this entails [20]. In the case of MRSA isolates carrying the mecC gene (mecC-MRSA isolates), these isolates have already been identified as belonging to diverse clonal lineages such as CC130, CC49, sequence type (ST) 151, ST425, CC599 or CC1943 and in very different hosts, including its detection in environmental samples [8,21–23]. There are different theories about the origin of the mecC gene and the possible impact that these isolates can have in clinical settings. In this review, the objective was to describe current knowledge about mecC detection in humans and its possible clinical implications, as well as to determine the infection types associated with this resistance mechanism, the characteristics of these mecC-carrying isolates, their possible relationship with animals and the presence of other risk factors.

2. Detection of mecC-MRSA Isolates in Humans
2.1. Human Studies Related to mecC-MRSA

Although the mecC gene was initially discovered in an isolate from bulk milk in England, the first human mecC-MRSA isolates were also identified in that same study [16]. These human isolates were obtained from patients of the United Kingdom and Denmark. Moreover, in a publication from the same year, two human MRSA isolates carrying this new resistance gene were independently identified in Ireland [17].

Since then, several retrospective and prospective studies using human S. aureus isolates/samples were carried out in order to search for mecC-MRSA isolates (Tables 1 and 2) [16,18,24–74]. Most of these studies were performed in European countries (Tables 1 and 2), and the UK and Denmark were the countries in which the highest levels of mecC-MRSA isolates were detected [16,24,25,39,41].
Table 1. Human studies related to meC-MRSA isolates in which prevalence can be estimated

| Reference | Country | Sampling Date | Prevalence: meC Positive Isolates/S. aureus or Methicillin Resistant S. aureus (MRSA) (%) | Type of Sample/Infection (Number of Isolates) | Clonal Complex: Sequence Type \(^1\) (Number of Isolates) | IEC \(^3\) (Number of Isolates) | Non-beta lactam Resistance (Number of Isolates) \(^4\) | Possible Relationship with Animals |
|-----------|---------|---------------|-------------------------------------------------------------------------------------|-----------------------------------------------|------------------------------------------------|---------------------------------|---------------------------------|---------------------------------|
| [18,24]   | Denmark | 1960–2011     | 112 (0.21%)/53746 MRSA                                                              | Wound (37), skin (26), blood (8), post-operative wound (5), urine (4), eye/ear (2), impetigo (2), unknown (28) Screen swab (10), Skin and soft tissue infections (7), nose (5), wound (5), blood (4), skin (4), nose/mouth (2), ear (1), eye/ear (1), finger (1), fluid (1), hand (1), PEG site (1), sputum (1), toe (1), unknown (6) | CC130 (98)/CC2361 (14): ST2173, ST2174 | Negative (2) Q (NOR) (1), S (111) | Most were from rural areas (106): 4 with contact with animals |
| [16]      | United Kingdom (UK) and Denmark | 1975–2011   | 51 (0.04%)/approximately 120500 S. aureus                                          | -                                             | CC130: ST130 (18), ST1245 (3), ST1764 (3), ST1945 (3), ST1526 (1), ST1944 (1), nfd (17)/CC1943: ST1943 (1), ST1946 (1)/CC425: ST425 (3) | - | S (51) | - |
| [25]      | Denmark | 1975–011      | 127/- in routine testing 12 (5.91%)/203 MRSA                                         | -                                             | CC130 (107): ST130, ST1245, ST1526, ST1945/CC1943 (14); ST1943, ST1946, ST2173, ST2174/CC425 (6): ST425 | - | - | - |
| [26]      | Ireland | 2000–2012     | 1 (1.14%)/88 MRSA                                                                  | -                                             | CC130 (1) | Negative (1) Q (NOR) (1) | Patient lived on a Farm |
| [27]      | Germany  | 2000–2016     | 2 (0.16%)/1277 MRSA                                                                | -                                             | CC130 (2) | - | - | - |
| [28]      | Austria  | 2002–2012     | 1 (0.31%)/327 MRSA                                                                 | -                                             | CC130 (1) | - | - | - |
| [29]      | Belgium  | 2003–2012     | 9 (0.18%)/4869 S. aureus                                                           | Screen swab (4), urine (2), wound (2), sputum (1) | CC130 (4)/CC49 (3)/CC1943 (2) | - | S (9) | Most were from a rural area with a high density of cattle farms |
| [30,31]   | Germany and The Netherlands | 2004–2011  | 16/-                                                                                   | nasal swab (11), wound (2), joint aspirate (1), mouth swab (1), sputum (1) | CC130 (14)/CC1943: ST2361 (1)/CC599: ST599 (1) | Negative (16) | S (1) | - |
| [32]      | Germany  | 2004–2005 | 2010–2011                             | 2 (0.06%)/3207 MRSA                                                               | Screen swab (1), sputum (1) | - | - | - |
| [33]      | Germany  | 2006–2011     | 11 (0.09%)/12691 MRSA                                                              | Wound (8), dermatitis (1), nasal swab (1), nosocomial pneumonia (1) | CC130 (11) | Negative (11) Q [CIP (1), MFL (1)] (2), S (9) | Veterinarian (1) |
| [34,35]   | UK       | 2006–2012     | 2/-                                                                                   | Screen swab (2)                               | CC130 (2) | - | - | - |
| [36]      | Slovenia  | 2006–2013    | 6 (1.52%)/395 MRSA                                                                  | Wound (4), Screen swab (2)                  | CC130: ST130 (6) | Negative (6) | S (6) | Most were from rural areas |
| [37]      | Spain    | 2008–2013     | 2 (0.04%)/5505 S. aureus                                                           | Joint fluid (1), wound (1)                  | CC130: ST1945 (2) | - | S (2) | - |
| [38]      | Austria  | 2009–2013     | 6 (2%)/301 S. aureus                                                               | blood (2), screen swab (2), wound (2)       | CC130: ST130 (3), new SLV (1)/CC599: ST599 (2) | - | S (6) | Contact with pet rabbit (1), unknown (5) |
Table 1. Cont.

| Reference | Country | Sampling Date | Prevalence: mecC Positive Isolates/S. aureus or Methicillin Resistant S. aureus (MRSA) (%) | Type of Sample/Infection (Number of Isolates) | Clonal Complex: Sequence Type 1 (Number of Isolates) | IEC 2 (Number of Isolates) | Non-beta lactam Resistance (Number of Isolates) 3 | Possible Relationship with Animals |
|-----------|---------|----------------|-----------------------------------------------------------------------------------------------|-----------------------------------------------|---------------------------------------------------|-------------------------------|-----------------------------------|----------------------------------|
| [39]      | Denmark | 2010-2011      | 6 (6.32%)/95 MRSA                                                                           | -                                             | CC130: ST130 (2), ST1245 (4), ST2573 (1), ST2574 (1)/CC425: ST425 (1) | -                             | -                                 | -                               |
| [40]      | England | 2011-2012      | 9 (0.45%)/2010 MRSA                                                                          | Screen swab (6), wound (2), leg ulcer (1)     | CC130: ST1245 (6), ST130 (2), ST1945 (1), ST2574 (1)/CC425: ST425 (1)/CC1943: ST1943 (1) | Negative (1)/type E (1) | L (CLI) (1): M (ERY) (1), S (8) | -                               |
| [41]      | UK      | 2012-2013      | 12 (0.53%)/2282 MRSA                                                                         | Screen swab (9), SSTI (3)                    | CC130: ST130 (2), ST1245 (4), ST2573 (1), ST2574 (1)/CC425: ST425 (1) | -                             | -                                 | -                               |
| [42]      | England | 2015          | 1 (0.08%)/1242 MRSA                                                                          | Screen swab (1)                              | CC130: ST130 (1)                                      | Negative (1)                  | S (1)                             | -                               |
| [43]      | England | 2018-2019      | 1 (0.7%)/142 S. aureus                                                                      | -                                             | -                                                 | -                             | -                                 | -                               |
| [44]      | Germany, UK, Belgium | - | 80/-                                                                                     | -                                             | -                                                 | -                             | -                                 | -                               |

1 Case reports were also analyzed in some other studies but, in this table, only results from prevalence studies are included. 2 CC, clonal complex; ST, sequence type; 3 IEC, immune evasion cluster; 4 L, resistant to lincomasides (CLI, clindamycin); M, resistant to macrolides (ERY, erythromycin); Q, resistant to fluoroquinolones (CIP, ciprofloxacin, MFL, moxifloxacin, NOR, norfloxacin); S, susceptible to all non-beta lactam agents tested. UK, United Kingdom.
Table 2. Studies performed on humans, in which mecC-MRSA isolates were sought but not detected.

| Reference | Country       | Sampling Date | Type of Samples | Number of Samples or (S. aureus or MRSA) Isolates |
|-----------|---------------|---------------|-----------------|--------------------------------------------------|
| [45]      | Switzerland   | 2005–2012     | Clinical/screening | 1695 S. aureus isolates                           |
| [46]      | Ghana         | 2007–2012     | Clinical         | 9834 blood samples                                |
| [47]      | Turkey        | 2007–2014     | Clinical         | 1700 S. aureus isolates                           |
| [48]      | Belgium       | 2009–2011     | Screening        | 149 farmers and family members (41 MRSA isolates) |
| [49]      | Hungary       | 2009–2011     | Screening        | 878 children                                      |
| [50]      | United States | 2009–2011     | Clinical/screening | 364 S. aureus isolates (102 MRSA isolates)       |
| [51]      | Ireland       | 2011          | Screening        | 64 residents                                      |
| [52]      | UK            | 2011          | Screening        | 307 cattle veterinarians                          |
| [53]      | Jordan        | 2011–2012     | Screening        | 716 humans (56 MRSA isolates)                    |
| [54]      | Germany       | 2011–2013     | Screening        | 1878 non-hospitalized adults                      |
| [55]      | Belgium       | 2012–2013     | Clinical         | 510 cystic fibrosis patients                      |
| [56]      | Greece        | 2012–2013     | Screening        | 18 veterinary personnel                           |
| [57]      | The Netherlands| 2012–2013    | Clinical/screening | 13,387 samples                                   |
| [58]      | UK            | 2012–2013     | Clinical         | 500 S. aureus isolates                            |
| [59]      | Egypt         | 2013          | Clinical/screening | 1300 dental patients                             |
| [60]      | Taiwan        | 2013–2014     | Clinical/screening | 3717 S. aureus isolates                          |
| [61]      | Turkey        | 2013–2014     | Screening        | 7 MRSA isolates                                   |
| [62]      | Turkey        | 2013–2016     | Clinical/screening | 494 MRSA isolates                                |
| [63]      | Spain         | 2014          | Screening        | 15 humans in contact with animals                 |
| [64]      | Poland        | 2014–2016     | Screening        | 953 students (only one MRSA isolate)              |
| [65]      | Germany       | 2015          | Clinical         | 140 Gram-positive isolates                        |
| [66]      | UK            | 2015          | Clinical         | 520 S. aureus isolates                            |
| [67]      | United States | 2015          | Screening        | 479 patients                                      |
| [68]      | India         | 2015–2017     | Screening        | 32 animal handlers                                |
| [69]      | Spain         | 2016          | Clinical/screening | 45 non-beta-lactam susceptible MRSA isolates   |
| [70]      | Greece        | 2016–2017     | Screening        | 68 farmers                                       |
| [71]      | Denmark       | 2017          | Screening        | 16 workers at wildlife rehabilitation centres     |
| [72]      | Italy         | 2017–2018     | Clinical/screening | 102 MRSA isolates                               |
| [73]      | Egypt         | -             | Screening        | 223 health care personnel                         |
| [74]      | Madagascar    | -             | Screening        | 1548 students and healthcare workers              |

1 Screening: isolates obtained in epidemiological studies for colonization detection.
Unfortunately, the design of these studies was very different, which complicates any comparison of the data obtained. Importantly, the criteria chosen for the selection of the initial isolates/samples varied significantly. While all S. aureus isolates were collected in some studies [29,38,45], only MRSA isolates were included in others [24,26–28,32,33,36,41,42]. Moreover, several studies were more restrictive and only used isolates that showed characteristics suspected of carrying the mecC gene such as spa types associated with mecC-positive clonal lineages previously described, mecA-negative MRSA isolates, isolates with antimicrobial susceptibility suspected to be mecC-positive or pvl-negative MRSA isolates [25,26,37,69] (Table S1). In any case, the mecC-MRSA human prevalence detected in most of the studies was very low. Several studies did not identify any mecC-positive S. aureus among included human isolates/samples (Table 2) [45–74]. In studies in which this gene was detected (Table 1), the prevalence identified, considering the total number of isolates/samples included, was < 1% in most of the cases [24,27–29,32,33,37,40–43], similar to that identified in the first study in which mecC was discovered (approximately 0.04%) [16]. In a few studies, the prevalence was > 1% but, in all of these, only a small number of initial isolates (<400 isolates) was used; this may be the reason for the high prevalence value obtained (up to 6.3%) [25,26,36,38,39]. Recently, a meta-analysis of the prevalence of mecC-MRSA, based on previously published results, estimated the prevalence of mecC-MRSA in the human subgroup at 0.004% (95% CI = 0.002–0.007), and the prevalence in the animal subgroup to be 0.098% (95% CI = 0.033–0.174) [75].

2.2. mecC-MRSA Human Case Reports

A total of 61 human case reports associated with mecC-MRSA isolates has been described (Table 3) [17,36,37,45,76–81]. Although mecC-positive isolates have been identified in Asia, Europe, and Oceania [21,82,83] in different hosts, all human case reports were described in European countries (Table 3). This was to be expected considering that the majority of the papers in which mecC-MRSA has been detected in both animals and humans, as well as in environmental samples, have been focused on countries on this continent [8,21–23].

In 4 of the 61 human case reports, mecC-MRSA was only identified in screen swabs (for colonization detection), with it not being related to the cause of the patient’s admission [36,37,45], and the clinical information was not indicated in another two case reports [17]. In the remaining 56 studies, mecC-MRSA isolates were related to (number of cases): skin and wound infections (47 cases) [37,76,79,81], joint and bone infections (3 cases) [37,77,78], respiratory infections (2 cases) [76] and bacteremia (2 cases) [37,80]. Taking into consideration the type of samples in which mecC-positive isolates have been detected in humans (Tables 1–4), most mecC human cases were implicated in skin or wound infections. However, the detection of mecC-MRSA isolates in other types of samples such as blood, sputum or urine is remarkable (Table 4). Pertinently, some serious infections have been described, such as severe bone infections [78], nosocomial pneumonia [33] and bacteremia [16,24,80], in some cases ending with the death of the patient [37].
Table 3. Human mecC MRSA case reports.

| Reference | Country | Sampling Date | Number of Described Case Reports | Year-Old Patient | Type of Sample/Infection | Clonal Complex: Sequence Type | IEC | Non-Beta Lactam Resistance | Possible Relationship with Animals |
|-----------|---------|---------------|---------------------------------|------------------|--------------------------|-----------------------------|-----|--------------------------|----------------------------------|
| [76]      | Sweden  | 2005–2014     | 45                              | Median age (range) 60 (2–86) | Wound, sputum, nasopharynx | CC130/CC2361                | -   | L-M (1 isolate), S (44 isolates) | Most were from a rural area: farmer (1), patients lived on farms (4) |
| [77]      | France  | 2007          | 1                               | 67                | Fluid of lesion heel     | CC130: ST1945                | -   | -                        | No epidemiological data were available except for one patient who did not have any contact with animals |
| [37]      | Spain   | 2008–2013     | 7                               | 3, 50, 63, 64, 76, 80, 85 | Blood, joint fluid, nasal screen swab, urine, wound | CC130: ST130, ST1945         | -   | S                        | Patient lived in rural area with high density of livestock animals |
| [78]      | France  | 2010          | 1                               | 48                | Blood, ear fluid, retrosternal abscess | CC130                      | Negative | S (but detection of tet efflux) | Contact with a cow |
| [17]      | Ireland | 2010          | 2                               | 64, 85            | -                        | CC130: ST130, ST1764         | Negative | -                        | Patient lived in rural area with high density of livestock animals |
| [45]      | Switzerland | 2011     | 1                               | 59                | Groin, nose, and throat screen swab | CC130: ST130                | -   | -                        | Patient lived on a farm and had contact with pigs, cats and dogs |
| [79]      | Spain   | 2012          | 1                               | 46                | Skin lesion swab         | CC130                      | -   | S                        | Contact with livestock |
| [36]      | Slovenia | 2013         | 1                               | 86                | Nose and skin screen swabs | CC130: ST130                | Negative | S                        | Patient lived on a farm and had contact with pigs, cats and dogs |
| [80]      | Spain   | 2013          | 1                               | 76                | Blood                    | CC130: ST1945                | -   | S                        | No contact with livestock |
| [81]      | Spain   | 2013–2014     | 1                               | 34                | Superficial skin lesion swab | CC130: ST130                | Negative | S                        | Contact with livestock animals |

1 Prevalence studies were also included in some papers but, in this table, only case report results are present. 2 Screen swab: sample for colonization detection. 3 CC, clonal complex; ST, sequence type; 4 IEC, immune evasion cluster. 5 L, resistant to lincosamides; M, resistant to macrolides; S, susceptible to all non-beta lactam agents tested.
Table 4. Type of sample/infection in which mecC-MRSA isolates have been identified among human patients.

| Type of Sample/Infection                                      | Number of Isolates \(^2\) | References                                                                 |
|--------------------------------------------------------------|----------------------------|----------------------------------------------------------------------------|
| Screen swab \(^1\)                                          | 54                         | [16,29–34,36,38,40–42,45,76]                                               |
| Skin lesion/dermatitis/impetigo wound/post-operative wound/ | 158                        | 16,24,29,30,33,36-38,40,41,79,81                                           |
| and soft tissue infections                                   |                            |                                                                            |
| Blood                                                        | 16                         | [16,24,37,38,80]                                                            |
| Urine                                                        | 7                          | [24,29,37]                                                                  |
| Nosocomial pneumonia/sputum/Tracheal aspirate                | 7                          | [29,30,32,33,76]                                                            |
| Nose                                                         | 5                          | [16]                                                                       |
| Eye/ear                                                      | 3                          | [16,24]                                                                     |
| Fluid of heel/joint fluid                                    | 3                          | [30,37,77]                                                                  |
| Mouth/Nose                                                   | 2                          | [16]                                                                       |
| Ear                                                          | 1                          | [16]                                                                       |
| Finger                                                       | 1                          | [16]                                                                       |
| Fluid                                                        | 1                          | [16]                                                                       |
| Hand                                                         | 1                          | [16]                                                                       |
| Percutaneous endoscopic gastrostomy site                    | 1                          | [16]                                                                       |
| Retrosternal abscess                                         | 1                          | [78]                                                                       |
| Toe                                                          | 1                          | [16]                                                                       |
| Unknown                                                      | 34                         | [16,24]                                                                     |

\(^1\) In screen swab: all samples in which was clearly indicated that they did not cause infection were included. However, in several studies it was not indicated whether samples were screen samples or if these samples were taken in infection sites. \(^2\) In human case reports, only one isolate from the most representative infection sample was considered.

3. Risk Factors for mecC-MRSA Infection

3.1. Contact with Animals

Since the first description of the mecC gene, contact with animals has been considered to be a risk factor for mecC-MRSA infection or carriage for several reasons [16,17]. This gene was identified in isolates belonging to CC130, and this clonal complex was predominantly detected among methicillin-susceptible *S. aureus* (MSSA) isolates from bovine sources [17]. Moreover, the discovery of this gene in isolates obtained from dairy cows suggested that these animals might provide a reservoir of this resistance mechanism [16]. Thereby, in some of the studies carried out since then, information about the possible contact of patients with animals was indicated (Tables 1 and 3). Many studies found out that most of the patients lived in rural areas or areas with a high density of farms [18,24,26,29,36,76,79]. In this sense, four studies indicated patient contact with livestock or farm animals [18,24,76,78,81], two referred to only contact with pets [38,45], two patients had no contact with animals and the authors did not have a plausible explanation for the detection of these isolates [37,80], one patient was a veterinarian [33], and in several studies this information was not indicated [16,17,27,30,31,41,77]. Interestingly, mecC-MRSA transmission between animals and humans was demonstrated in two human infection cases by whole genome sequencing. Specific clusters including isolates from each human infection case and their own livestock were detected. Thus, human and animal isolates from the same farm only differed by a small number of SNPs [18]. These findings highlight the role of livestock as a potential reservoir for mecC-MRSA.

3.2. mecC-MRSA Carriage in Humans

*S. aureus* shows a great capacity to colonize the skin and nares of hosts, being able to last over time and cause opportunistic infections [84,85]. mecC-MRSA isolates were identified as commensals in several prevalence and case report studies (see screen swab in Tables 1–4). At least 54 mecC-MRSA
positive isolates were obtained from screen swabs, mainly from the nose, but also from throat and groin sites. Moreover, isolates obtained from other types of samples could also be considered as commensals, as in one human case report in Spain in which the isolate recovered from the urine of one patient was considered as a colonizer since the patient did not present urinary symptoms [37].

*mecC*-MRSA isolates implicated in both colonization and infection were obtained from the same patient in some studies [18,37]. Indeed, one patient with bacteremia due to a *mecC*-MRSA isolate also presented nasal colonization by the same *mecC*-MRSA isolate (with the same genetic characteristics) [18]. These results corroborated the importance of colonization being the previous step, which enables isolates causing severe disease. Interestingly, in another bacteremia case in which the patient died, a household transmission between grandfather and grandson was detected, with the grandson being colonized by the same isolate [37]. Nevertheless, in other studies, *mecC*-MRSA isolates were not identified as colonizers from patients with *mecC* infections [81], and it has been suggested that *mecC*-MRSA isolates might be worse colonizers and less contagious in humans than *mecA*-MRSA isolates [76]. In the study carried out in Sweden, only two out of the patient’s 27 family members were positive for *mecC*-MRSA isolates and the median time for *mecC* carriage was 21 days [76].

3.3. Patient Age

Most of the patients described in case reports (Table 3) were middle-aged or elderly [17,36,37,45,77–80], except two patients: one of them was a 34 year-old farm worker with high contact with animals who presented a superficial skin lesion [81], and the other was a healthy 3 year-old child [37]. The average age of patients with *mecC*-MRSA detected in Denmark during 2007–2011 was 51 [24] and the average detected in Sweden in 2005–2014 was 60 [76]. In the Danish study, CA-MRSA *mecC* patients were significantly older than other CA-MRSA cases, indicating that *mecC*-MRSA seems to have a different origin and epidemiology to typical CA-MRSA [24].

3.4. Underlying Chronic Disease

Remarkably, in the 45 human cases detected in Sweden, most patients had some kind of underlying chronic disease (diabetes mellitus, cancer, autoimmune diseases or atherosclerotic diseases), or an existing skin lesion [76]. Infection by *mecC*-MRSA of wounds has also been suggested by others [79]. Moreover, *mecC*-MRSA infections were identified in patients with primary pathologies (diabetes, myelodysplastic syndrome, peripheral arterial occlusion disease, etc.) in one study in Austria [38], and in a patient with an urothelial carcinoma in Spain [80]. Unfortunately, information about other underlying diseases of *mecC*-MRSA positive patients is missing in most of the papers.

4. Characterization of *mecC*-MRSA Human Isolates

4.1. Clonal Lineages of *mecC*-MRSA of Human Origin

As in other hosts, most of the *mecC*-MRSA isolates obtained from human samples belonged to CC130 (Tables 1 and 3) (Figure 1). Other clonal complexes identified were CC49, CC425, CC599, CC1943 and CC2361 [16,24,25,29–31,38,40,41,76] (Table 1) (Figure 1). Worryingly, it has been hypothesized that SCC*mec* XI (the SCC element that contains the *mecC* gene) might have the potential to be transferred to other S. aureus clonal lineages due to the fact that it is bounded by integration site sequence repeats and that it has intact site specific recombination components [16] (Table S1 and S2). Until now, *mecC*-MRSA CC130 isolates have been identified in all countries in which clonal lineages were determined and it was the unique CC detected in Spain, France, Ireland, Slovenia and Switzerland [17,37,45,77–79,81] (Figure 1). Remarkably, in France and Spain there were several human infection reports, but in all of them the *mecC*-MRSA isolates belonged to CC130 (Table 3). After CC130, the clonal complexes CC1943 and CC599 were the most widely detected in humans, being identified in four and three countries respectively [16,25,29,31,38,41] (Figure 1). Conversely, CC49 was only described in one study in Belgium [29]. While CC49, CC130, CC425, CC599 and CC1943 were also identified in *mecC*-MRSA
isolates from a non-human origin, CC2361 has been only described in humans so far [24,76]. Thus, CC130 was described in farm, domestic and wild animals and in food samples; CC49 in horses and small mammals, CC425 in wild animals and food, CC599 in pets and farm animals and CC1943 in pets [8].

Figure 1. Clonal complexes (CCs) detected in mecC-MRSA human isolates.

A large variety of spa types was detected among the human mecC-MRSA isolates (Figure 2). The most predominant spa type was t843, which is associated with CC130 and was identified in a total of 260 human isolates. This spa type was detected in all countries in which human mecC-MRSA isolates were detected, except in Switzerland [45]. Other spa types were also described in several countries. Some of them were identified only in two countries, this is the case of t792, t1773, t5930, t6293, t6386, t7485, t7734, t7945, t7946, t7947 and t9397, but others were more widely spread as t978, t1535, t1736, t3391 or t6220 (Figure 2). Although there is a strong association among spa types and MLST clonal complexes [86], some spa types were associated with different clonal complexes. Two isolates obtained in screen swabs from two patients in two different hospitals from England presented the spa type t11706 [40]; one of these isolates belonged to ST1245 (CC130) and the other one to ST425 (CC425). Moreover, the spa types t978, t2345, t3391 and t8835 were associated in some studies with CC1943 [16,25,29], and in others with CC2361 [24,76]. Nevertheless, the founders of both clonal complexes, ST1943 and ST2361, are Single Locus Variant (SLV) of each other (and only differ at the aroE allele), which could explain these results (Table S1).
4.2. Treatment and Antimicrobial Resistance Profile of mecC-MRSA Human Isolates

Most of the human mecC-MRSA isolates detected were susceptible to all non-beta-lactam antimicrobials tested (Tables 1 and 3). This is in accordance with results obtained in mecC-MRSA isolates from other origins [21]. In one study performed in Spain, isolates using this criterion were selected in order to identify mecC-MRSA or CA-MRSA isolates [69]. Although mecC-MRSA was not detected, this resistance phenotype was a valuable marker for Panton-Valentine Leukocidin (PVL)-producer isolates (Table S1). Nevertheless, the low prevalence of mecC-MRSA isolates in this region could be responsible for this result and the use of this phenotype to suspect the presence of the mecC mechanism should not be discarded.

The most important problem for treating mecC-MRSA infections is that these isolates must be correctly identified. Although mecC isolates are considered to be MRSA, these isolates sometimes show borderline susceptibility results for oxacillin or cefoxitin, being identified as MSSA if the mecA gene is only tested [44]. This could lead to the implementation of inappropriate therapies. Resistance development to other antimicrobial agents could be added to this, considering the capacity of S. aureus to acquire resistance to various antimicrobial agents. Some mecC-MRSA isolates detected in humans have shown resistance to non-beta-lactam antimicrobials [24,33,40,41,76] (Table 1). Fluoroquinolone resistance was identified in two isolates in Germany [33] and in one isolate in Denmark [24]. Macrolide and lincosamide resistance was also detected in some studies: one erythromycin resistant isolated in the UK [41] and one erythromycin and clindamycin resistant isolate in Sweden [76] and England [40]. Regarding resistance mechanisms, in two studies carried out in Ireland, the gene sdrM, which encodes a multidrug efflux pump related to norfloxacin resistance and tet efflux related to tetracycline resistance, were identified in one and two mecC-MRSA CC130 isolates, respectively [17,26]. Although there has only been one study, whose objective was to compare different diagnostic tests, human mecC-MRSA isolates resistant to several antimicrobial families have been
detected [87]. The presence of resistance to non-beta-lactam agents in mecC-MRSA isolates significantly limits our therapeutic options.

4.3. Virulence of mecC-MRSA Human Isolates

The search for virulence genes in human mecC-MRSA isolates has been highly variable from one study to another. In any case, for the moment, the most common virulence genes detected have been hla, hld, hlb, edinB, lukED, cap8 or ica, with these genes being highly associated with CC130 [17,26,31,33,36,38,41]. Fortunately, no mecC-MRSA isolates carrying the PVL genes were detected. However, other clonal lineages associated with animals have been able to acquire this virulence factor [88]. For this, their detection in mecC-MRSA isolates cannot be ruled out in the future. Significantly, some pyrogenic toxin superantigen (PTSAg) genes have been detected in mecC-MRSA isolates [29,31,38,41]. These genes might be related to specific clonal lineages such as CC599, CC1943 or CC2361. Thus, the gene tst encoding the toxic shock syndrome toxin has been found in three CC1943 isolates (two harboring sec gene and one containing seg and sei genes) [29,41], in three CC599 isolates (two of them positive for sel gene and one for sec and sel) [31,38] and in one sec, seg, sei, sel, sen, seo and seu positive CC2361 isolate [31] (Table S1).

5. mecC-MRSA Problem: What is its Origin? Is It an Emerging Problem?

The oldest known mecC-MRSA isolate, dated in 1975, was detected in the retrospective study performed by García-Álvarez et al. [16] This isolate was identified in a human blood sample from Denmark and its detection suggested a possible human origin for the mecC gene [16]. Later, in two other retrospective studies also carried out in Denmark, two mecC-positive isolates were identified in samples dated in 1975 [24,25], both were also identified in human blood samples [24,25]. However, in two of these studies, the oldest sample studied was obtained in 1975, so the presence of older isolates cannot be ruled out [16,25]. With respect to the remaining retrospective studies in which the presence of the mecC gene was sought, the dates of the samples were much later than these three studies, with them being isolates obtained from the year 2000 and later (Table 1). Regarding the earliest reported mecC-MRSA isolate in other hosts, 1975 also seems to be the key date [89,90]. Therefore, this resistance mechanism might have been present for over 45 years.

Moreover, this resistance mechanism is highly associated with CC130 since most of the mecC-MRSA isolates belong to this clonal lineage. A human-to-bovine host-jump of CC130, which occurred ∼5429 years ago, has been suggested [91]. The time and host in which CC130 MSSA isolates acquired the mecC resistance gene remain unknown today. In order to establish a possible human or animal origin for the detected mecC-MRSA isolates in human samples, several studies analyzed the presence of IEC (immune evasion cluster) genes [17,24,26,31,33,36,41,42,78,81] (Tables 1 and 3). In all cases, human mecC-MRSA isolates were negative for sak, chp and scn except for one ST1945 (CC130) isolate obtained from a screen swab from a patient in the UK that was positive for sak and scn (IEC type E), suggesting a possible human origin [41]. Nevertheless, it has been suggested that IEC type E might be a conserved part of ST1945 since mecC MRSA ST1945 isolates from wild animals also showed IEC type E in several studies in Spain [41,63,92].

The newest human mecC-MRSA isolates detected so far in Europe were obtained in 2015, one of them in Germany [27], and the other in England [42]. Both strains showed similarities to those identified in the first studies [16,17] and both belonged to CC130. Nevertheless, after phylogenetic analysis, the strain identified in England seemed not to be highly related to any of the published sequenced mecC-MRSA CC130 isolates [42]. Despite the non-description of mecC-MRSA isolates in humans in the last 5 years in Europe, data provided by previous studies have detected an increasing tendency in the prevalence of mecC-positive isolates [24], indicating that surveillance in detecting this resistance mechanism must be maintained. The lack of detection could be due to the low prevalence of this resistance mechanism and/or problems in mecC diagnostic methods. Important difficulties in the detection of mecC-MRSA isolates have been indicated [44,93]. It has been shown that various clinical
tests used in hospital labs might have failed to identify 0 to 41% of mecC-MRSA isolates [93]. It is important to optimize and develop new testing protocols and redefine currently available phenotypic testing methods [44]. In this regard, several commercial PCR-based tests that detect mecC and mecA genes have been developed. Moreover, recently, mecA/mecC MRSA isolates from cattle have been described [83]. The possible clinical impact of isolates carrying both genes is currently unknown.

6. Implications in Veterinary and Food Safety

Although this review is focused on the human health implications of mecC-MRSA isolates, the effects that these isolates can have on veterinary medicine should not be forgotten. mecC-MRSA isolates causing infections in domestic animals have been identified in several studies [8,94,95]. However, this resistance gene seems to be most frequently detected in livestock animals including cattle, sheep and rabbits [8,21]. Although mecC-MRSA rarely causes clinical disease in these food-producing animals, there are reports of bovine mastitis in several countries [96,97]. As observed in humans, most of the mecC-MRSA isolates detected in other hosts also belong to CC130, with the characteristics of these animal mecC-MRSA isolates being very similar to those detected in humans [8,21].

On the other hand, the presence of mecC-MRSA in dairy animals is highly relevant since it could be a route of entry of these isolates into the food chain. Indeed, milk samples have been identified carrying mecC-MRSA [8] with the consequent risk of colonization for food handlers. In this case, it is worth highlighting one of the clinical cases included in this review in which the patient was a cheese producer [81]. mecC-MRSA zoonotic transmission has been demonstrated in some studies [18], with the correct prevention, detection and control measures in veterinary and food safety laboratories being necessary.

7. Conclusions and Future Problems Associated with mecC

Currently, the prevalence of human mecC-MRSA infections is very low. However, mecC-MRSA isolate transmission between different hosts indicates the great capacity of these isolates for spreading. There is a wide range of reservoirs in wild, livestock and companion animals and zoonotic transmission of these isolates could increase the number of mecC-MRSA human clinical cases. Moreover, SCCmec XI might have the potential to be transferred to other clonal lineages in the future. Their transfer to more virulent and better-adapted human clones would be deeply troubling. Worryingly, the mecC gene has already been detected in clonal lineages in which important virulence genes were identified (CC599, CC1943 or CC2361) or in which IEC was described (ST1945-CC130). Moreover, mecC-MRSA isolates resistant to non-beta lactams have been detected. Acquisition of non-beta lactam resistance by mecC-MRSA isolates significantly limits our therapeutic options. mecC-MRSA should be taken into consideration in hospital and veterinary laboratories and in food safety institutions, and prevention strategies must be implemented in order to avoid possible emerging health problems.

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