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Genomic comparison of *mecC*-carrying methicillin-resistant *Staphylococcus aureus* from hedgehogs and humans in the Netherlands

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Objectives: MRSA carrying the *mecC* gene (*mecC*-MRSA) have been found in humans and animals worldwide. A high carriage rate of *mecC*-MRSA has been described among hedgehogs in different countries. We performed genomic comparison of *mecC*-MRSA from hedgehogs and humans using next-generation sequencing (NGS) to investigate possible zoonotic transmission in the Netherlands.

Methods: Nasal swabs from hedgehogs (*n* = 105) were cultured using pre-enrichment and selective plates. Isolates were sequenced using Illumina NGS platforms. These data were compared with sequence data of *mecC*-MRSA (*n* = 62) from the Dutch national MRSA surveillance in humans.

Results: Fifty hedgehogs were found to be MRSA positive, of which 48 carried *mecC*. A total of 60 *mecC*-MRSA isolates derived from 50 hedgehogs were compared with the human isolates. Fifty-nine *mecC*-MRSA from hedgehogs and all but one isolate from humans belonged to clonal complexes CC130 and CC1943. The *mecC* gene was located within the SCC*mec* XI element. Most *mecC*-MRSA did not carry other resistance genes besides *mecC* and *blaZ*. Two human isolates carried *erm*(C). Isolates differed in the presence of various virulence genes, which were linked to distinct STs and clonal complexes. Some isolates had up to 17 virulence genes, which underlines their pathogenic potential. No genetic clusters of hedgehog and human isolates were found.

Conclusions: *mecC*-MRSA from hedgehogs and humans mainly belonged to the same two clonal complexes, indicating a common source. No firm evidence for recent zoonotic transmission was found. Further studies are needed to investigate the role of hedgehogs in the occurrence of *mecC*-MRSA in humans.

Introduction

In the Netherlands, livestock-associated MRSA (LA-MRSA) mainly comprise isolates belonging to MLST ST398 and carrying the *mecA* gene.[1] LA-MRSA can be transmitted between food-producing animals and humans, especially where there is close contact between humans and animals.[2] In 2011, a new methicillin resistance gene, named *mecC* (initially called *mecA*$_{LGA251}$), was described in MRSA isolates from both humans and bovines.[3] Since then, *mecC*-carrying MRSA (*mecC*-MRSA) have been found in companion animals, livestock and in many different wild animal species in numerous, mainly European, countries.[4] *mecC*-MRSA are found in healthy as well as diseased animals.[5] The *mecC* gene is situated on an SCC*mec* XI element that has

to date been identified in different clonal complexes (CCs) including CC49, CC130, CC425, CC599 and CC1943.[4,5] Resistance to non-β-lactam antibiotics is currently uncommon among *mecC*-MRSA isolates.[4,5] Recent studies show that *mecC*-MRSA are common in European hedgehogs and therefore these animals are considered a natural reservoir for these pathogens.[6–9] In Denmark, 114/188 (60.6%) of hedgehogs tested positive for MRSA and all were *mecC* positive and belonged to CC130 or CC1943.[7] In Sweden, 64% of the 55 tested hedgehogs were found to be MRSA positive.[6] It has been speculated that this high occurrence might be attributed to co-occurrence of penicillin-producing dermatophytes present on the skin of the hedgehogs.[8,10,11] It is unknown whether hedgehogs serve as a reservoir of *mecC*-MRSA for humans. Therefore, hedgehogs

from the Netherlands were tested for MRSA carriage and isolates obtained were sequenced by NGS and compared with data from the national MRSA surveillance in humans.

Materials and methods

Ethics

The authors confirm that they adhered to the ethical policies of the journal. This study included swabs from hedgehogs that either were found dead, had been euthanized because of severe illness, or died of natural causes within hedgehog rehabilitation centres. The study was performed according to the Dutch law on studies with animals.

MRSA isolates from humans were submitted to the National Institute for Public Health and the Environment by the medical microbiology labs participating in the Dutch National MRSA surveillance. Personal data were all pseudonymized in the Type-Ned database that stores the MRSA data within the Dutch National MRSA surveillance. As all data were processed anonymously, informed consent of the patients was not required.

Sample collection and processing

Nasal swabs were taken from 105 dead wild European hedgehogs (*Europeaus erineaus*) that were sent to the Dutch Wildlife Health Centre in 2019 and 2020 for post-mortem examination. Hedgehogs had been found dead or came from hedgehog rehabilitation centres where they had been euthanized because of severe illness or died of natural causes.

Nasal swabs from the hedgehogs were stored at 4°C until analysis. Most samples were analysed within 14 days. However, due to lockdowns during the COVID-19 pandemic, handling times increased in 2020. Therefore the average time between taking the samples and analysing them was 15 days (median 10 days). Samples were incubated in 10 mL of Mueller–Hinton enrichment broth (BD, France) with 6.5% sodium chloride for 18 h at 37°C. A 10 µL loop of the enrichment was plated on Brilliance MRSA 2 Agar (Oxoid, Germany). After 18 h incubation at 37°C, suspected colonies were confirmed as MRSA by multiplex PCR.[12] All MRSA collected from the hedgehogs were sequenced using Illumina platforms (BaseClear, Leiden, Netherlands) and *de novo* assembled using SPAdes 3.15.3 and CLC Genomic Workbench v20.03. All the genomic sequences are available at the European Nucleotide Archive at the European Molecular Biology Laboratory (accession no. PRJEB54087; see Table S1, available as Supplementary data at *JAC* Online).

Molecular analyses

Resistance genes, SCC*mec* types and virulence determinants were identified using ResFinder, SCC*mec*Finder and VirulenceFinder databases from the Center for Genomic Epidemiology (https://bitbucket.org/genomicepidemiology). A threshold of 95% was used for identity and 60% for the minimum length. For comparative analysis, the whole-genome MLST (wgMLST) *Staphylococcus aureus* scheme comprising 2567 genes was used (Ridom SeqSphere+). The wgMLST scheme consists of the MLST+ scheme (version 1.3; 1861 targets) and the Accessory scheme (version 1.2; 706 targets) both curated by Alexander Mellmann and Dag Harmsen (University of Muenster). Genetic clusters were defined as two isolates differing by ≤25 alleles by wgMLST. From these data a dendrogram was created by BioNumerics software (Applied Maths) using the unweighted pair group method with arithmetic mean (UPGMA). For epidemiological context, in this study we included human-retrieved *mecC*-MRSA isolates obtained in the Dutch national MRSA surveillance[13] in the period January 2010 until December 2021 (one *mecC*-MRSA isolate per person with personal identification number, per year; *n* = 184 from a total of 43 859 MRSA isolates), of which 62 *mecC*-MRSA isolates were sequenced by NGS for multiple projects.

Table 1. CCs and STs of *mecC*-MRSA isolates of humans and hedgehogs

CC	ST	Hedgehogs (*n*)[a]	Humans (*n*)[b]
CC130	ST130	13	19
	ST1245	9	25
	ST1945	4	3
	Other[c]	4	6
CC1943	ST1943	1	1
	ST2361	26	5
	ST3566	1	1
	ST3567	0	1
	ST7629	1	0
Other[d]		1	1
Total		60	62

[a]60 *mecC*-MRSA isolates derived from 50 hedgehogs.
[b]62 *mecC*-MRSA isolates derived from 62 humans.
[c]Hedgehog: ST1704, ST7630, ST7628, ST7632. Human: ST3568, ST3568, ST4620, ST4756, ST5341, ST5547.
[d]Hedgehog: ST49 (CC49). Human: ST5116(CC121).

Results

Characterization of mecC-MRSA from hedgehogs and humans

MRSA was found in 50 of the 105 hedgehogs sampled. Depending on the morphology and number of isolates on the plate, one to six colonies per sample were collected, resulting in a total of 176 isolates. Isolates within one sample that showed different sizes of the *spa* gene on the agarose gel using the multiplex PCR described by Stegger *et al.*[12] were included for sequencing. As a result, a total of 62 hedgehog isolates were sequenced (from 10 hedgehogs, two MRSA isolates, and from 1 hedgehog three MRSA isolates were included). Forty-eight hedgehogs carried *mecC*-MRSA, while two hedgehogs carried *mecA*-positive MRSA (see Figure S1 for details on the *mecA*-positive isolates). This resulted in 60 *mecC*-MRSA from hedgehogs.

The 62 *mecC*-positive isolates from humans were collected between 2008 and 2020 from persons 0–93 years of age (median 63 years). Twenty-six persons were female, 34 were male and for two persons no information regarding gender was available. The isolates were cultured from wounds (*n* = 20), urine (*n* = 6), blood (*n* = 2), swabs from nose, throat and/or perineum (*n* = 16), sputum (*n* = 2), purulent material (*n* = 11) and other materials (*n* = 5).

The *mecC*-MRSA isolates from hedgehogs and humans belonged mainly to the same two CCs, CC130 (*n* = 30 and *n* = 53, respectively) and CC1943 (*n* = 29 and *n* = 8, respectively). Within these CCs, different STs were detected (Table 1).

In hedgehogs the most common ST was ST2361 (CC1943) whereas in humans this was ST1245 (CC130). ST130, ST1245 and ST2361 were commonly found in both hedgehogs and humans, while other STs were only found incidentally (Table 1).

The *mecC* gene was located within the SCC*mec* XI(8E) element with an identical genetic organization (flanked by *blaZ* and *mecR* & *mecI*) in all *mecC*-MRSA-carrying hedgehog and human isolates.

The *mecC*-MRSA isolates from hedgehogs had no other resistance genes besides *blaZ* and *mecC*. Most human *mecC*-MRSA
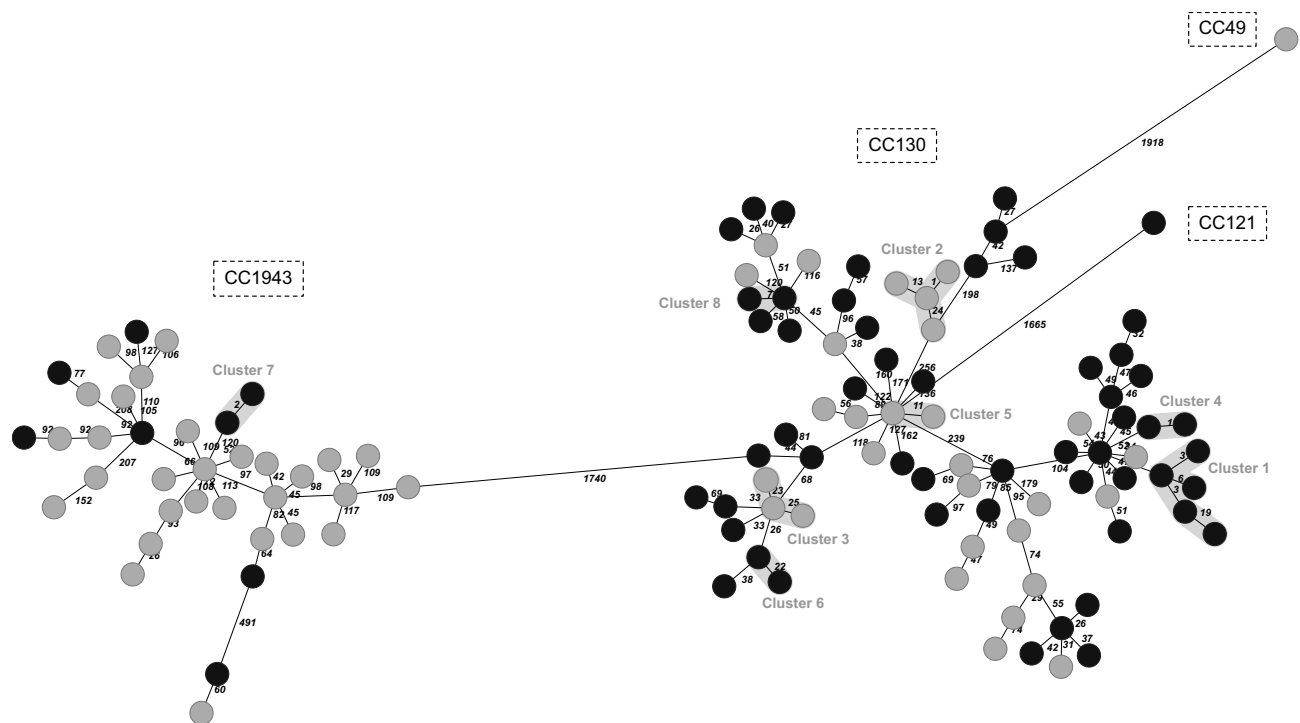
Figure 1. Minimum spanning tree of wgMLST data analysis of MRSA isolates derived from hedgehogs and humans. The wgMLST scheme consists of the MLST+ scheme (Ridom SeqSphere⁺ version 1.3; 1861 targets) and the Accessory scheme (Ridom SeqSphere⁺ version 1.2; 706 targets). Every circle represents one MRSA isolate. The shading displays clusters of isolates that have fewer than 25 allelic differences. Grey circles represent hedgehog *mecC*-MRSA and black circles human *mecC*-MRSA.

carried no other resistance genes, except for two isolates carrying the plasmid-borne erythromycin resistance gene *erm*(C) (Figure S1).

All resistance and virulence genes per isolate can be found in Figure S1. All hedgehog and human MRSA isolates carried the aureolysin gene *aur*, the haemolysin-encoding genes *hlgA, hlgB* and *hlgC*, and the serine protease genes *splA* and *splB*. Isolates belonging to CC1943 however, had disrupted *splA* and *splB* genes. In addition, all but four *mecC*-MRSA from hedgehogs and humans carried the leucocidin genes *lukD* and *lukE*. *lukE* was disrupted in one CC130 isolate and four CC1943 isolates. Most *mecC*-MRSA isolates from humans and hedgehogs belonging to CC1943 carried the enterotoxin-encoding genes *sec, seg, sei, sel, sem, sen, seo* and *seu* and the toxic shock syndrome toxin gene *tst*. All *mecC*-MRSA belonging to CC130 carried the epidermal cell differentiation inhibitor gene *edinB* and the exfoliative toxin gene *ete*. This last gene (*ete*) was disrupted in three isolates. The CC5 isolate carried *sak* and *scn*. None of the isolates carried genes encoding for Panton–Valentine leucocidin (PVL) (Figure S1).

Genetic relationship of hedgehog mecC-MRSA isolates from hedgehogs and human mecC-MRSA and their geographical distribution

All but two *mecC*-MRSA, one from hedgehogs (ST49, CC49) and one from humans (ST5116, CC121), belonged to CC130 or CC1943 (Figure 1). These two CCs differed more than 1740 alleles from each other by wgMLST. The origins of the isolates are

scattered over the Netherlands, with most isolates found in the middle region of the Netherlands (Figure 2). Four pairs and one group of five isolates (*n*=13) of human *mecC*-MRSA clustered together with ≤25 alleles difference (see Figure 1; Cluster 4, 6–8 and Cluster 1, respectively). For the hedgehog isolates, one group of four isolates, one of three isolates and one group containing two isolates clustered together (see Figure 1; Cluster 2, 3 and 5, respectively). Isolates within Clusters 1, 4, 7 and 8 were found within a range of 20 km from each other (Figure 2). Interestingly, Cluster 1 (Figure 1 and Figure S1) included five isolates from at least three persons: a man aged 22 years (wound infection), a man aged 61 years (perineum swab) and a woman aged 58 years (perineum swab). Three isolates from three different persons were cultured in 2011 at the same microbiological lab and they differed by only three and six alleles. All three were living in the same 4-digit postal code area and it cannot be ruled out that they were members of the same household. One isolate from 2012 was from the same woman (same person identifier number). One isolate from 2017 was presumably also from the same woman, as the postal code was the same and the age matched. The isolate from 2017 differed in 19 alleles from that in 2012. The isolates in Cluster 7 (one from 2017 and one from 2019) could also be confirmed as being derived from the same man. These two isolates differed by two alleles.

No human–hedgehog genetic clusters were found when using differences of 25 alleles as cut-off, but Figure 2 shows that although not closely linked, in certain parts of the Netherlands *mecC*-MRSA occurs both in hedgehogs and humans. In addition, some human–
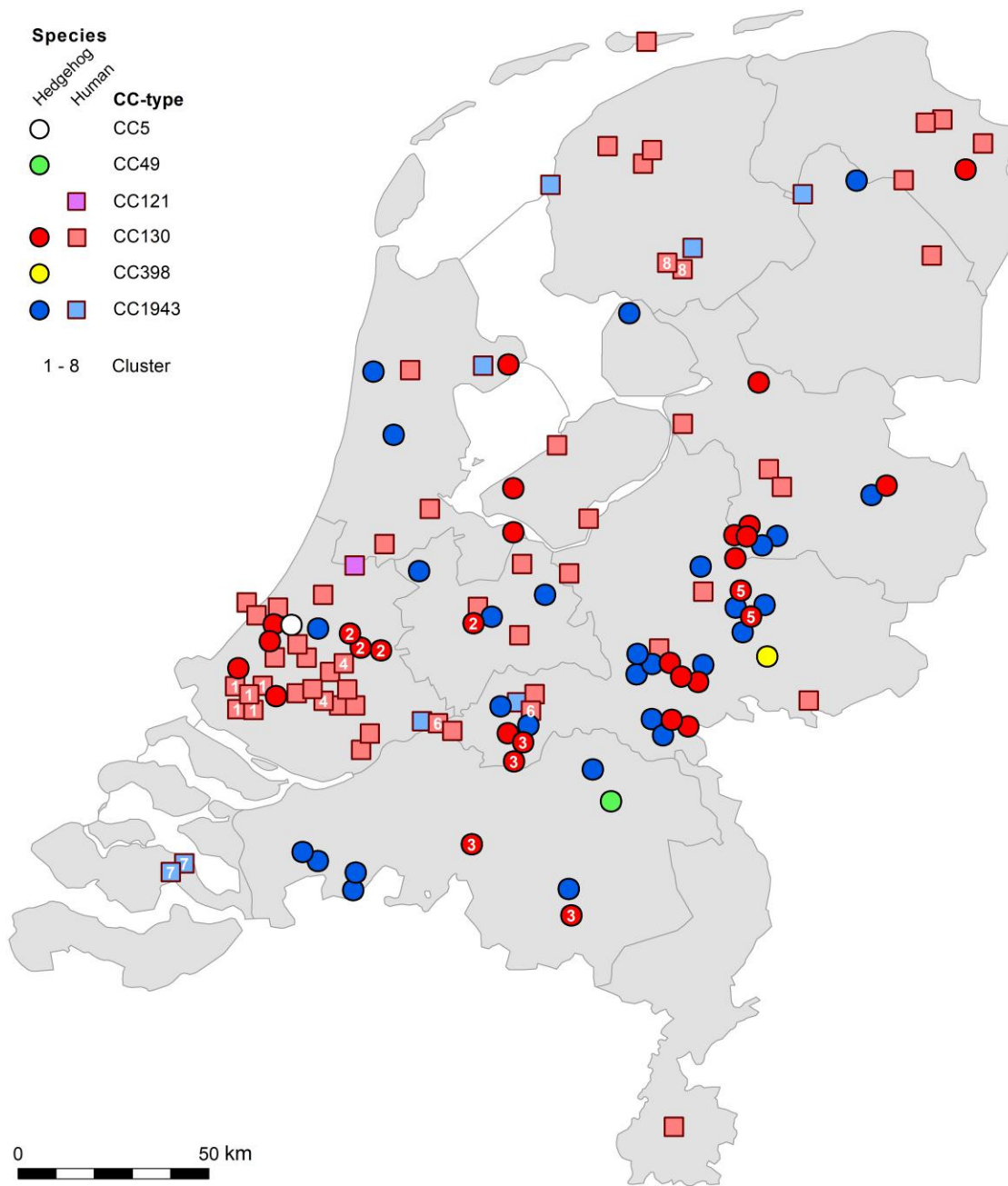
Figure 2. Distribution of hedgehog and human MRSA isolates over the Netherlands. Circles represent hedgehog isolates and squares represent human isolates. The different colours refer to the different CCs (see legend). Isolates carrying the same number (1–8) differ by less than 25 allelic differences to each other. This figure appears in colour in the online version of *JAC* and in black and white in the print version of *JAC*.

hedgehog isolate pairs differed in only 26 or 27 alleles. Remarkably, 10 hedgehogs from which multiple MRSA isolates were sequenced carried *mecC*-MRSA belonging to different CCs (Figure S2), indicating that hedgehogs co-carry different MRSA strains at the same time.

Discussion

The occurrence of MRSA in hedgehogs in the Netherlands was high (48%; 50 out of 105) and all except two MRSA isolates

carried the *mecC* gene. Due to the long storage time before ana-lyses of some samples as a result of lockdowns during the COVID-19 pandemic, MRSA may have lost viability and thus the prevalence might even be higher. Similar high prevalences of *mecC*-MRSA in hedgehogs have been found in the Czech Republic, Denmark, England, Germany, Sweden and Wales.[6–8,14] In a recent study using selective culturing of hedgehog samples, no MRSA was found in France, Greece, Italy, Romania and Spain.[8] The reason why no MRSA was found among hedgehogs in these

countries is unknown. In Greece and Romania, other hedgehog species could be present (e.g. *Europeaus roumanicus*), but it is unknown whether this would influence the presence of MRSA.[15]

In the past, dairy cows were considered to be the most likely reservoir of *mecC*-MRSA and the major source of zoonotic infections in humans, as they were first found in ruminants.[3] Earlier studies suggest that *mecC*-MRSA already existed in the pre-antibiotic era as a co-evolutionary adaptation of *S. aureus* to the colonization of dermatophyte-infected hedgehogs.[10,11] This hypothesis was substantiated by showing the presence of β-lactam production by the hedgehog dermatophyte *Trichophyton erinacei*.[11] Recently, this was molecularly confirmed by Dube *et al.*[8] and Larsen *et al.*[10] Larsen *et al.*[8] also proved the selection of *mecC*-MRSA by penicillin-producing *T. erinacei*. They also investigated the evolutionary history of *mecC*-MRSA and concluded that most *mecC*-MRSA lineages originate from hedgehogs, although domesticated or other wild animals probably could act as intermediate hosts and vectors in zoonotic transmission from hedgehogs to humans.

All *mecC*-MRSA in the present study lacked a staphylococcal pathogenicity island encoding von Willebrand factor-binding protein (vwbSaPI) that is often discovered in MRSA adapted to ruminants (data not shown).[16] In the Netherlands, no *mecC*-MRSA have been found in cattle to date.[17]

In the present study, hedgehog and human *mecC*-MRSA mainly belonged to two distinct CCs, namely CC130 and CC1943 (based on the seven housekeeping gene MLST scheme), indicating a common origin. These two genomic groups differed by more than 1740 alleles from each other in a wgMLST analysis (Figure 1). These genomic groups have also been identified in MRSA isolated from hedgehogs in Denmark and in several other countries.[7,8] No genetic clusters of human and hedgehog isolates were found that differed by fewer than 25 wgMLST alleles. According to Coll *et al.*,[18] with a threshold of >25 SNPs, recent (within 6 months) patient-to-patient transmission is unlikely. A limitation of the use of this cut-off is that we are not studying transmission between patients in hospitals, but potential transmission between different mammalian species. We therefore used a more conservative threshold by using 25 differences in wgMLST alleles instead of 25 SNPs. Another limitation of our study is that we used a relatively small number of 62 human and 60 hedgehog isolates and that the isolates were not all from the same time frame. Therefore it is difficult to draw firm conclusions regarding transmission. We also compared our CC130 and CC1943 MRSA isolates with CC130 and CC1943 MRSA isolates investigated by Larsen *et al.*[8] and Sahin-Tóth *et al.*[9] in order to increase the number of isolates, but found no clustering between human isolates in the Netherlands and hedgehog isolates from other countries (see minimum spanning tree in Figure S3). The molecular differences between human and hedgehog isolates in the Netherlands did not clearly demonstrate recent transmission, although some hedgehog and human isolates only differed by 26 or 27 alleles and transmission in the past cannot be ruled out. More research with larger numbers of isolates is needed to elucidate if transmission between hedgehogs and humans occurs. The metadata from isolates in Clusters 1 and 7 indicate that human-to-human transmission (Cluster 1) as well as prolonged carriage (both Clusters 1 and 7) with evolution of strains in time occurs.

The highest risk of transmission would be anticipated for persons in contact with *mecC*-MRSA-carrying animals. In the Netherlands, there are many hedgehog rehabilitation centres, but persons working in these centres were not included in the study. In Denmark, none of 16 persons working at hedgehog rehabilitation centres carried MRSA,[7] which suggests a low human health risk from direct contact with MRSA-*mecC*-positive hedgehogs. Likewise, the *mecC* gene was absent in eight MRSA-positive persons out of 307 delegates of a Cattle Veterinarian Association Congress.[19] On the other hand, two human cases of *mecC*-MRSA infection have been linked to livestock as the isolates from the humans and ruminants (cow and sheep, respectively) on the farms the patients lived on appeared to be nearly identical as determined by WGS.[20] In one of these patients, *mecC*-MRSA CC130 was cultured from blood, indicating an invasive infection. In the present study, most *mecC*-MRSA from humans were cultured from wounds or were found in screening samples, but two *mecC*-MRSA were cultured from blood. Severe human infections with *mecC*-carrying MRSA have been reported by others.[21, 22] Lozano *et al.*[23] summarized 61 case reports of humans infected or colonized with *mecC*-MRSA. In 56 cases, the *mecC*-MRSA isolates were from infections; the majority were from skin and wound infections (47 cases), but also from joint and bone infections (three cases), respiratory infections (two cases) and bacteraemia (two cases). In conclusion, although the prevalence of *mecC*-MRSA in human infections is low, severe and even fatal cases have been reported.

The proportion of *mecC*-MRSA in humans in the Netherlands was, on average, 0.42% ($n = 184$) from a total of 43 859 isolates analysed from January 2010 until December 2021 (A. P. A. Hendrickx, RIVM, personal communication). In Denmark, the prevalence of *mecC*-MRSA among all MRSA was found to be 1.9% in 2010, increasing to 2.8% in 2011.[5]

The *mecC*-MRSA from hedgehogs and all but two *mecC*-MRSA from humans did not carry additional resistance genes, which corroborates findings on *mecC*-MRSA from other countries.[5] Isolates differed in the presence of various virulence genes, which linked to distinct STs and CCs. Isolates from CC1943 especially often carried many virulence genes, including the enterotoxin-encoding genes *sec*, *seg*, *sei*, *sel*, *sem*, *sen*, *seo* and *seu*, and the toxic shock syndrome toxin 1 gene *tst*, which underlines their pathogenic potential. The exfoliative toxin gene *ete* and the epidermal cell differentiation inhibitor gene *edinB* were found exclusively in isolates belonging to CC130. *mecC*-MRSA belonging to CC130 carrying exfoliative toxin genes have been found incidentally in hedgehogs.[9,24] The high number of isolates (mostly CC1943) carrying *tst* is remarkable, as only 10% of 3331 sequenced isolates from the National MRSA surveillance (all CCs together) carried this gene, most of which belonged to CC22 (L. Schouls, RIVM, personal communication).

Studies have suggested that *mecC*-MRSA is adapted to animals due to the lack of the *scn* gene, which is suggested to be a marker for human-adapted *S. aureus*,[7] All *mecC*-MRSA isolates in the present study were negative for *scn*. The immune modulating genes *chp*, *sak* and *scn* are often found together, as they belong to a phage-encoded immune evasion cluster, IEC-B.[25] Human *mecC*-MRSA isolates described in the literature generally lack the virulence genes *chp*, *sak* and *scn*, except for one ST1945 (CC130) isolate obtained from a screening swab from a patient in

the UK that was positive for *sak* and *scn*, suggesting a possible human origin.[20,26] In the present study, only one *mecC*-MRSA CC130 (ST1945) isolate from a person was positive for *sak*. This gene can also be present on the chromosome.[25]

From a subset of 11 hedgehogs, we sequenced two or three *mecC*-MRSA colonies with different sizes in *spa* gene PCR products. This revealed that hedgehogs frequently carried multiple *mecC*-MRSA strains, belonging to different CCs. The reason for this is unknown, but in future studies on the prevalence and molecular characteristics of MRSA in hedgehogs, it is advised to examine more than one MRSA colony per animal, to get a better overview of the strain diversity of the MRSA in hedgehogs.

In conclusion, a high occurrence of MRSA carriage was found in Dutch hedgehogs. Most were *mecC* positive, belonged to CC130 and CC1943 and carried various virulence genes linked to different CCs. In addition, *mecC*-MRSA were also found in humans and they belonged to the same CCs, indicating a common source. We found no proof of recent human–hedgehog transmission using a threshold of 25 differences in wgMLST alleles, but further studies with larger numbers of isolates are needed to confirm this. In addition, studies on humans in close contact with hedgehogs should be carried out, in order to investigate if contact with hedgehogs increases the risk of *mecC*-MRSA carriage.

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Transparency declarations

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Supplementary data

Figures S1 to S3 and Table S1 are available as Supplementary data at *JAC* Online.

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