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Pathogenic traits of coagulase-negative Staphylococci and *Mammalicoccus* isolated from neonatal sepsis blood cultures in low- and middle-income countries

Jawaria Aziz¹, Kirsty Sands^{1,2}, Ian Boostrom¹, Kathryn Thomson², Rabaab Zahra^{3,4}, Kenneth C. Iregbu⁵, Jean-Baptiste Mazarati⁶, Andrew Whitelaw^{7,8}, Timothy R. Walsh², Owen B. Spiller¹

¹ Division of Infection and Immunity, Department of Medical Microbiology, Cardiff University, University Hospital of Wales, Cardiff UK

² Ineos Oxford Institute for Antimicrobial Research, Department of Biology, University of Oxford, Oxford, UK

³ Department of Microbiology, Quaid-i-Azam University, Islamabad, Pakistan

⁴ Department of Clinical Microbiology, School of Medicine, Trinity College Dublin, St James's Hospital, Dublin 8, Ireland

⁵ Department of Medical Microbiology, National Hospital Abuja, and Department of Medical Microbiology, Faculty of Basic Clinical Sciences, College of Health Sciences, University of Abuja, Nigeria

⁶ The National Reference Laboratory, Rwanda Biomedical Centre, Kigali, Rwanda

⁷ Division of Medical Microbiology, Stellenbosch University, Cape Town, South Africa

⁸ National Health Laboratory Service, Tygerberg Hospital, Cape Town, South Africa

Abstract:

Coagulase-negative staphylococci (CoNS) are increasingly recognised as neonatal pathogens in low- and middle-income countries (LMICs), yet are often dismissed as contaminants. We characterised the genomic landscape, antimicrobial resistance (AMR), and virulence of 48 CoNS isolates recovered as the sole pathogen from neonates with clinical sepsis across seven hospitals in five LMICs. Whole-genome sequencing determined sequence types, resistomes, and virulomes, whilst virulence was assessed using a *Galleria mellonella* *in vivo* model.

Species identified included *Mammaliicoccus sciuri* (n=19; 40%), *S. haemolyticus* (n=15; 31%), *S. epidermidis* (n=11; 23%), *S. saprophyticus* (n=2), and *S. xylosus* (n=1). *M. sciuri* predominated in early-onset sepsis (63%); *S. haemolyticus* (87%) and *S. epidermidis* (64%) dominated late-onset cases. Multidrug resistance (≥ 3 classes) was pervasive in *S. haemolyticus* (93%) and *S. epidermidis* (91%), with 41.7% of all isolates harbouring *mecA*-positive SCC*mec* elements.

In *Galleria*, *S. haemolyticus* induced significantly higher mortality than *S. epidermidis* and *M. sciuri* ($p < 0.01$). Genomically, expanded *cap8* capsular gene cassette carriage in *S. haemolyticus* negatively correlated with pathogenicity ($p = 0.011$), suggesting extensive encapsulation masks acute toxicity. Conversely, *S. epidermidis* exhibited a broader pathogenic arsenal (adherence, exoenzymes, Type VII secretion), wherein adherence-gene burden positively correlated with mortality ($p = 0.035$), whilst biofilm (*icaA-D*) carriage showed no significant association ($p = 0.412$).

The recovery of these isolates challenges their perception as mere contaminants. Whilst *M. sciuri* is associated with early-onset disease, the pronounced virulence of *S. haemolyticus* and the pervasive MDR profiles of both *S. haemolyticus* and *S. epidermidis* highlight them as critical, overlooked pathogens in the neonatal unit.

50

51 **Keywords:** Coagulase-negative staphylococci, *Mammaliicoccus sciuri*, Virulence,
52 *Galleria mellonellae*, Genomics, Neonatal sepsis, multi-drug resistance.

53 **Introduction**

54 Neonatal sepsis is a bloodstream infection causing high morbidity and mortality in
55 newborns (<28 days) and young infants (<60 days) [1]. It accounts for an estimated
56 50% of deaths in children under 5 years, with the highest burden in low- and middle-
57 income countries (LMICs), highlighting vast disparities in neonatal care [2]. In recent
58 decades, coagulase-negative staphylococci (CoNS) have emerged as major
59 pathogens, causing ~50% of late-onset sepsis (LOS) cases in neonatal intensive care
60 units (NICUs) worldwide [3]. *S. haemolyticus* and *S. epidermidis*, the two CoNS
61 species most frequently isolated, are widely reported in association with neonatal
62 sepsis [4,5].

63 While, standard diagnostic criteria recommend isolating the same CoNS strain from
64 two separate blood cultures to distinguish infection from contamination [6], this is often
65 impractical in LMICs. Collecting sufficient blood volume from deteriorating preterm
66 neonates is challenging, and rapid antibiotic administration frequently suppresses
67 bacterial growth in subsequent samples. Susceptibility is primarily driven by immature
68 innate immunity [7], which elevates their susceptibility to infections from nosocomial
69 reservoirs where CoNS are prevalent [8]. Key risk factors include prematurity and very
70 low birth weight (VLBW, <1500g). Breaches in the skin barrier, caused by medical
71 interventions such as catheter insertion and prolonged hospital stays, combined with
72 biofilm formation, significantly increase the risk of infection [9–11]. In preterm
73 neonates, this risk is heightened because the stratum corneum (the skin's primary
74 physical barrier) remains underdeveloped for the first weeks after birth [12].

Furthermore, the vernix caseosa, a waxy coating that confers antimicrobial protection, is produced only at the end of the last trimester; full-term neonates therefore benefit from this additional defence, whereas premature infants do not, placing them at higher risk of CoNS infections [13,14]

The increase of CoNS-related sepsis is concerning due to growing antibiotic resistance, notably to β -lactams [15] and decreased susceptibility to vancomycin [16].

The intense selective pressure from therapeutic and prophylactic antibiotic use in clinical settings favours the emergence and spread of multidrug-resistant (MDR) CoNS isolates. Despite this alarming trend, comprehensive data remain scarce on the diversity of CoNS species and their resistance patterns, particularly in LMICs.

The primary aim of this retrospective study was to characterise the CoNS species isolated from neonatal sepsis cases, including associated antimicrobial susceptibility profiles and underlying resistance mechanisms as determined by whole-genome sequencing (WGS). We assessed regional and national variations in sequence types (ST), especially those linked to local outbreaks, and compared the pathogenic potential of different CoNS species using the *Galleria mellonella* infection model.

Methods:

Study design and sample processing

These samples arise from the 2015–2017 BARNARDS (Burden of Antimicrobial Resistance in Neonates from Developing Societies) study (which will be referred to as BARNARDS-1, to distinguish it from the ongoing follow-up study BARNARDS-2; 2022–2025, in future publications). It was a prospective observational cohort of mother–neonate dyads and infants aged <60 days presenting with suspected sepsis [17]. The original programme focused primarily on Gram-negative neonatal sepsis, particularly

carbapenem resistance. An interim review identified that approximately half of positive blood cultures were reported as Gram-positive, prompting an amendment to the standard operating procedure (SOP) to include retention and collection of Gram-positive isolates. Implementation of this amendment varied between sites, and Gram-positive isolate capture was consequently incomplete, particularly during the earlier stages of the programme. The broader Gram-positive collection has been described previously [17].

Ethical approval was obtained locally for each clinical site: BC=Ethical Review Committee, Bangladesh Institute of Child Health to Samir Kumar Saha reference number BICH-ERC-4/3/2015 on 15/09/2015; NK=Kano State Hospitals Management Board to Kenneth Iregbu reference number 8/10/1437AH on 13/07/2016; NN=Health Research Ethics Committee (HREC), National Hospital, Abuja to Kenneth Iregbu reference number NHA/EC/017/2015 on 27/04/2015; NW=Health Research Ethics Committee (HREC), National Hospital, Abuja to Kenneth Iregbu reference number NHA/EC/017/2015 on 27/04/2015; RK=Republic of Rwanda, National Ethics Committee to Jean-Baptiste Mazarati reference number No342/RNEC/2015 on 10/11/2015; and ZAT=Stellenbosch University and Tygerberg Hospital, Research projects, Western Cape Government to Shaheen Mehtar reference number N15/07/063 on 04/12/2015. The study and all procedures involving human participants adhered to the ethical principles outlined in the Declaration of Helsinki. All mothers provided written informed consent for their and their neonates' participation, utilising consent forms translated into local languages. Participants retained the right to withdraw from the study at any time without affecting their standard of care.

The BARNARDS-I study was a multinational, prospective observational cohort study. Recruitment occurred between November 2015 and December 2017. The study

enrolled two cohorts: (A) In-born (Birth Cohort): Mother-neonate dyads recruited at delivery within the participating facility, followed for 60 days; and (B) Out-born (Admission Cohort): Neonates and young infants (aged <60 days) born elsewhere but admitted to the facility with a primary diagnosis of suspected sepsis. Sepsis was defined by the attending physician using local guidelines or WHO Integrated Management of Childhood Illness (IMCI) criteria (e.g., respiratory rate >60 breaths/min, severe chest indrawing, temperature instability). Upon clinical suspicion, blood samples were collected aseptically prior to the administration of new antibiotics where possible.

Positive blood cultures were initially processed at local site laboratories. Bacterial isolates were preserved on charcoal swabs (Amies transport medium) and transported at ambient temperature to the central reference laboratory (Cardiff University, UK) under UN3373 regulations. Isolates were revived, confirmed for purity, and stored at -80°C. For this specific analysis, CoNS isolates were included only if they were the sole organism isolated from the blood culture, with mixed cultures excluded. This criterion restricted the analysis to monomicrobial cultures but was not considered sufficient to establish true bloodstream infection or exclude contamination..

This analysis includes all 48 CoNS isolates that could be viably recovered from blood cultures collected across seven clinical sites in Bangladesh, Nigeria (three hospitals), Pakistan, Rwanda, and South Africa. To differentiate infection from contamination, only isolates identified as the sole organism in a confirmed positive blood culture were selected for genomic characterisation.

Antibiotic susceptibility testing

CoNS isolates were plated onto Columbia Blood Agar supplemented with 5% sterile horse blood and incubated overnight at 37°C. Purity checks and preliminary visual identification were performed using Chromatic™ Gram-positive agar supplemented with Chromatic™ *Staphylococcus aureus* supplement (Liofilchem, Italy). This medium facilitates the differentiation of mixed cultures by generating distinct colony colours based on species-specific enzymatic activity. Unique observed colour and morphologies for species in this study included: *Mammaliicoccus sciuri*, *Staphylococcus haemolyticus*, *Staphylococcus epidermidis*, *Staphylococcus saprophyticus*, and *Staphylococcus xylosus*, which were all distinctly different from control (*Staphylococcus aureus*). Species were confirmed using the Microflex LT MALDI-TOF MS system (Bruker Daltonik, GmbH, UK). Minimum inhibitory concentrations (MICs) for 23 antibiotics were determined by agar dilution (0.06–128 mg/L) and interpreted with EUCAST v15.0, using ATCC 29213 *Staphylococcus aureus* as a quality control strain (Supplementary data S1).

Whole genome sequencing and bioinformatic analysis

Bacterial pellets were resuspended with 60 µL lysozyme (10 mg/mL) and incubated at 37 °C for 1 h, followed by DNA extraction on a QIAcube (Qiagen) with RNase treatment. DNA yield was measured using a Qubit 4.0 fluorometer (Thermo Fisher Scientific). Short-read libraries were prepared using Nextera XT v2 and sequenced on an Illumina MiSeq (v3 chemistry, 2×300 bp) to achieve >40× coverage. Over 50% of the isolate cohort underwent long-read sequencing: low-yield samples were concentrated with Meg-Bind SPRI beads (1:1 ratio, 15 µL elution) to 40–60 ng/µL, gDNA was barcoded using the Rapid Barcoding Kit (SQK-RBK110.96, Oxford Nanopore Technologies), and the library was sequenced using a MinION R9.4 flow

cell. Genome analyses were conducted via Bactopia v3.0.1 [18]. Raw FASTQ files were quality-filtered with fastp v0.23.4 [19] and assessed by FastQC v0.12.1 [20]. Short-read assembly with SPAdes v3.15.5 [21] within Shovill v1.1.0; and, for selected isolates, hybrid assemblies using Flye v2.9.2-b1786 and Polypolish v0.5.0 [22,23]; short-read-first assembly with Unicycler v0.5.0 [24]. Long reads were base-called and demultiplexed with Guppy v6.5.7 and adapters trimmed by Porechop v0.2.4 [25]. Annotation was performed with Prokka v1.14.6 [26]. Species identification used Mash v2.3 and Sourmash v4.8.2 [27]; MLST via MLST v2.23.0 and mlst-db v2.23.0-20230907 [28]. Resistance determinants were detected with AMRFinder+ v3.11.18 (amrfinderplus-database: 2023-08-08.2) [29] and ABRicate v1.0.0 against CARD [30] and ResFinder [31] plasmids via PlasmidFinder (--db plasmidfinder) [32]; SCCmec types by Staphopia-sccmec v1.0.0 [33]; and IS256 presence by querying ISfinder (<https://isfinder.biotoul.fr>; input=fna). Putative virulence genes were identified by querying Prokka-predicted protein sequences against the Virulence Factor Database (VFDB_setB_pro; downloaded 2026-02-13) using BLASTP (BLAST+ v2.17.0) [34]. The top hit for each query was retained using thresholds of E-value $\leq 1e-5$, $\geq 60\%$ sequence identity, and $\geq 50\%$ alignment coverage. Gene names, functions, and virulence categories were then extracted from VFDB headers to compile comprehensive virulence profiles across all CoNS isolates. All computational workflows were executed on the ARRCA-HAWK HPC cluster at Cardiff University.

Virulence assay

Virulence was assessed using the well-established *Galleria mellonella* infection model, commonly used for *S. aureus* [34]. This assay was used to compare experimental virulence potential among *S. epidermidis*, *S. haemolyticus* and *M. scuri* species within the recovered isolates for this cohort.

Washed bacterial suspensions (sterile saline; pelleting at 2400xg) were standardized to $\sim 10^9$ CFU/mL ($OD_{600nm}=0.7$) and diluted to yield inocula of 10^8 and 10^7 CFU/mL. Larvae (n=30/strain/bacterial load) were injected with 10 μ L via the right posterior proleg. Controls included sterile saline injection and non-injected needle trauma controls. Mortality was recorded at 24, 36, and 72 hours based on the melanisation and mobility. Weighted pathogenicity scores (time vs. dose) were compared using ANOVA with Tukey's post-hoc test, corrected for multiple comparisons (GraphPad Prism). For gene association, gene annotations were normalised, split into individual loci, and deduplicated per isolate. Analysing *S. haemolyticus* and *S. epidermidis* independently, continuous pathogenicity scores were compared against binary gene/cassette carriage using exact two-sided Mann–Whitney U tests (effect direction assessed by medians), and against gene-module burden using Spearman rank correlations. Statistical significance was set at $p < 0.05$.

Results:

Characterisation of CoNS species from neonatal blood samples:

Genomic analysis of 48 isolates identified five species: *M. sciuri* (n=19, 40%), *S. haemolyticus* (n=15, 31%), *S. epidermidis* (n=11, 23%), *S. saprophyticus* (n=2, 4%), and *S. xylosus* (n=1, 2%). The cohort comprised in-born (n=23, 48%) and out-born (n=25, 52%) neonates; only two subjects were aged >28 days (but data missing for 6 patients). LOS (onset >72h post-birth) predominated in out-born cases (n=18, 72%), whereas EOS (onset $\leq$ 72h) was more frequent in in-born cases (n=13, 57%); four cases were undocumented. This suggests links between infant admissions and out-born neonatal sepsis and, the nosocomial environment as a potential source for EOS cases in the birth cohort. Caesarean delivery was not significantly associated with

sepsis onset (LOS 9/19; EOS 6/19; not recorded 4/19); however, species distribution varied by onset: *S. haemolyticus* (n=13, 87%) and *S. epidermidis* (n=7, 64%) were primarily linked to LOS, while *M. sciuri* (n=12, 63%) was common in EOS cases (Figure 1).

Genomic population structure:

MLST identified 25 different STs in three CoNS species (Table 1). Both *S. haemolyticus* and *S. epidermidis* populations were highly diverse, with the majority of isolates identified as singletons representing unique sequence types (STs). While we identified a few small clusters (2–3 isolates; ST30, ST3, ST56 for *S. haemolyticus*; ST983 and ST490 for *S. epidermidis*) sharing the same ST, these lacked sufficient genomic similarity to be considered true clonal lineages (Supplementary data S2). This lack of clonality is further supported by their disparate geographical origins; these isolates were usually recovered from different hospitals across Nigeria. The only exception was a single *S. epidermidis* isolate originating from Bangladesh. Conversely, *M. sciuri* displayed low diversity with 15/19 isolates belonging to a specific lineage associated with a clonal outbreak in Pakistan (Supplementary data S3). Currently no allele-based typing system is available for *S. saprophyticus* or *S. xylosus* (<https://pubmlst.org/organisms>).

Phenotypic resistance linked with genotypic determinants

S. epidermidis and *S. haemolyticus* consistently clustered in the highest MIC range for multiple drug classes, notably β -lactams, macrolides/lincosamides, aminoglycosides, and fluoroquinolones, consistent with MDR phenotypes (Figure 2, Supplementary data S4). *M. sciuri* showed elevated MICs to classical penicillins and first/second-

generation cephalosporins but remained largely susceptible advanced agents including ceftaroline and vancomycin.

In the context of empiric first-line neonatal therapies for low- and middle-income countries, we confirmed a coverage gap for *Staphylococcus* species. Gentamicin resistance (MIC>4 mg/L) was observed in 44% (21/48) of all CoNS isolates. All empiric first-line therapeutics were largely ineffective (Figure 3). All *S. haemolyticus* were gentamicin-resistant; notably, isolates lacking ARGs (n=3) shared the elevated MICs of those carrying *aac(6')-Ie/aph(2'')-Ia 9* and/or *aph(3')-IIIa* genes. *S. epidermidis* resistance was lower (36%). Regardless of *blaZ* presence (67–82%), or alternative *blaI/blaR1* presence, penicillin resistance was confirmed via PK/PD thresholds: no *S. haemolyticus* and only two *S. epidermidis* isolates met clinical efficacy targets (benzylpenicillin ≤ 0.125 mg/L; ampicillin ≤ 2 mg/L), validating phenotypic resistance despite undefined CoNS breakpoints. However, modest β -lactam efficacy would be anticipated in *M. sciuri* (only 9/18 isolates have benzylpenicillin MICs ≥ 8 mg/L). Furthermore, phenotypic resistance to daptomycin was exceptionally high (98%, 47/48). More than half of CoNS were resistant to tetracycline (54%; 26/48), and erythromycin (52%; 25/48). *S. haemolyticus* tetracycline resistance (n=8) was mediated by efflux pump *tet(K)*, and macrolide resistance (n=8) was mediated either by *msrA* (n=6) and/or *ermC* (n=3).

With MDR defined as non-susceptibility to three or more classes [35], 93% (14/15) of *S. haemolyticus*, and 91% (10/11) of *S. epidermidis* were MDR. A single *S. saprophyticus* from Kano, Nigeria, was extensively drug-resistant (XDR), susceptible only to tigecycline. Both *S. saprophyticus* were unusually found to carry 3-4 plasmids (rep7a_22_rep(pSBK203), rep21_3_rep(pS0385), repUS10_1_CDS25(pSSP1), and rep20_1_ORF1(EDINA)), which may be responsible for resistance.

Genomic Determinants of Methicillin Resistance

Methicillin resistance, inferred by cefoxitin MIC ≥ 8 mg/L [36], was observed in all 15 (100%) of *S. haemolyticus* and 5/11 (45%) of *S. epidermidis*. This phenotype correlated strictly with *mecA* carriage, except for two *S. epidermidis* isolates (ST490), that were unexpectedly cefoxitin-susceptible. In contrast, *M. sciuri* predominantly carried the native *mecA1* homolog (18/19; 95%), which neither mediates resistance nor associates with SCCmec cassettes, and was carried adjacent to *fosY*, and *sal(A)*. SCCmec (*staphylococcal cassette chromosome mec*) typing, reliant on gene content and often requiring long-read resolution, highlighted lineage-specific complexity (Table 1). *S. epidermidis* was fully resolved: SCCmec type IV (IVa/IVc) predominated, while ST490 and ST896 displayed mosaicism, co-harboring types V and VII. *S. haemolyticus* was dominated by type IIa (40%), though a single ST3 isolate similarly carried types V and VII; seven *mecA*-positive isolates (and two *M. sciuri*) remained unassigned. The widespread presence of *IS256* (n=18/48) suggests a mechanism for this recombination (Supplementary Table S2).

Genomic Determinants of Virulence

Overall, *in silico* analysis revealed distinct, species-specific virulence profiles. *S. haemolyticus* and *M. sciuri* predominantly exhibited immune modulation strategies, whereas *S. epidermidis* displayed a broader pathogenic arsenal driven by adhesion, exoenzymes, and toxin production.

Across 15 *S. haemolyticus* isolates, we detected 222 total virulence gene occurrences. Immune modulation dominated (n = 107), primarily via capsular polysaccharide synthesis (*cap8C*, *cap8P*, *cap8H*). Secondary mechanisms included exoenzymes mediating tissue damage and immune evasion (n = 40; e.g., *nuc* [thermonuclease], *eno* [phosphopyruvate hydratase], *lip* [triacylglycerol lipase precursor]), and

adherence factors (n = 38; *aae* [bifunctional autolysin/adhesin], *atl* [autolysin], *ebp* [elastin-binding protein]). Nutritional/metabolic factors (n = 27) and stress survival genes (n = 10; notably *katA* [catalase]) were also present.

Conversely, 11 *S. epidermidis* isolates yielded 257 total virulence occurrences spanning wider pathogenic mechanisms. This profile was heavily characterised by adherence genes (n = 82; *atl*, *aae*, *ebp*, and MSCRAMM-family adhesins *sdrG*, *sdrH*, *sdrF*) and diverse exoenzymes (n = 65; e.g., *sspA* [V8 serine protease], *sspB* [staphopain cysteine proteinase]). Uniquely, *S. epidermidis* harboured genes for Type VII secretion system effector delivery (*esaA-G*; n = 30), exotoxins (n = 20; *hly* [beta-hemolysin], *sec* [staphylococcal enterotoxin C precursor], *sell* [staphylococcal enterotoxin L precursor]), and biofilm formation (*icaC*; n = 15), alongside minor stress survival factors (n = 4).

Finally, like *S. haemolyticus*, the predicted pathogenic potential of *M. sciuri* was primarily driven by immune modulation (detailed in Supplementary data S5). However, its secondary profile favoured adherence factors (e.g., *tuf*, *plr/gapA*, *aae*) over the robust exoenzyme arsenal (*nuc*, *lip*) seen in *S. haemolyticus*, alongside unique, albeit minor, occurrences of biofilm (*icaA*, *sasG*) and exotoxin (*plc1*, *plc2*) determinants.

Differential virulence in *Galleria mellonella* model

All isolates were injected into *Galleria* with low (N=30) and high (N=30) bacterial loads, where pathogenicity scores range from 0 (all survive at 72 h) to 201 (rapid mortality at low dose by 24 h). *S. haemolyticus* (109.00 +/- 18.82) demonstrated significantly higher virulence than *M. sciuri* (41.48 +/- 6.65; p < 0.001) and *S. epidermidis* (58.21 +/- 9.77; Figure 4; p < 0.05). In *S. haemolyticus*, expanded *cap8* cassette carriage was significantly associated with a lower pathogenicity score (Mann–Whitney U; p = 0.011,

Spearman's ρ ; $p = 0.009$). Conversely, in *S. epidermidis*, adherence-gene burden positively correlated with higher pathogenicity (Spearman's ρ , $p = 0.035$), whereas *icaA-D* biofilm carriage showed no significant association (Mann–Whitney U, $p = 0.412$). Notably, MDR *S. haemolyticus* clustered at the upper range of the pathogenicity scores, indicating that resistance genes did not incur a significant fitness cost. Recorded patient mortality for this cohort only identified one death in the 60 days post-birth, although outcomes for eight infants were lost to follow-up.

Discussion:

Incorporating pathogenicity indexing, virulence gene profiling, and long-read data analysis provides detailed characterisation of this collection of blood-derived CoNS isolates and supports their potential clinical significance in neonatal sepsis. Our findings are consistent with a recent meta-analysis [37] that evaluated 4,155 CoNS isolates from 65 studies across 16 African countries, in which neonatal bloodstream infections were dominated by *S. haemolyticus*, *S. epidermidis*, and *M. sciuri*. CoNS are commensals of the skin and the mucous membrane of humans and animals [38], and *S. haemolyticus* was recently identified colonising the preterm infant gut [39]. As opportunistic pathogens of humans facilitated by increasing patient- and procedure-related changes compounded by immunological insufficiency inherent to neonates, CoNS represent major nosocomial pathogens worldwide. In addition to available data in Africa [37], a multicentre American neonatal study confirmed 629/1313 (47.7%) LOS in VLBW neonates were CoNS [3].

The importance of CoNS as a *mecA* reservoir is often asserted, underpinned by the homology of ancestral *mecA1* among members of the *M. sciuri* family [40]. We found that 95% of our *M. sciuri* isolates carried *mecA1*, but, interestingly, this did not correlate

with phenotypic resistance to cefoxitin. We found a similar diversity in the *SCCmec* types compared to the CoNS Africa meta-analysis [37] although *mecA* prevalence was much higher in our *S. haemolyticus* (100% versus meta-analysis 34%) and our *S. epidermidis* (64% versus meta-analysis 22%), but lower in *M. sciuri* (5% versus 37%; likely skewed by the outbreak nature of this isolate). The carriage of diverse *SCCmec* cassette types/subtypes (*IIa*, *III*, *V*, *VII*, *IVa*, and *IVc*) among the blood-derived CoNS isolates investigated here has clinical significance, as their role is not confined to causing resistance to β -lactam/methicillin antibiotics, but also serves as reservoirs for ARGs integrated into plasmids, transposons, and insertion sequence inserted in the junkyard (J1-3) regions of *SCCmec* cassette, resulting in the emergence of highly MDR strains of *S. haemolyticus* and *S. epidermidis*. Moreover, in addition to diverse ARGs carried in chromosome cassettes, heavy metal resistance genes are also prevalent in associated plasmids. A pathogenic threat associated with *SCCmec* types *II*, *III* and *VIII*, is the *psm-mec* gene, a toxin-associated virulence factor integrated in the J2 region adjacent to the *mecI* gene of the *mecA* gene complex which contributes to microbial pathogenicity [41]. *M. sciuri* and *S. haemolyticus* may therefore play key roles in the acquisition and donation of ARG, while *S. epidermidis* remains a significant reservoir due to prominent colonisation of the skin. Herein, *S. haemolyticus* isolates carried the highest burden of ARGs with the ability to confer resistance to first-line β -lactam and gentamicin therapeutics, inferring ARG and potential for further transmission, likely accentuated by the presence of highly mobile IS256 [42].

Previous research suggests survival of *Galleria mellonella* following challenge with *S. epidermidis* was slightly lower compared to challenge with MRSA [43]. Only one study of *Galleria* virulence in *S. haemolyticus* exists, and it found that ST42 (lacking in our cohort) was more virulent than the other tested STs and more virulent than *S. aureus*

ATCC29213 within 24 hours [44]. These observations are in agreement with our findings, where *S. haemolyticus* was significantly more virulent compared to *S. epidermidis* and *M. sciuri*, which exhibited lower *Galleria* mortality by 72 h. Moreover, in our study, higher virulence was observed in certain lineages, including ST30, ST49, ST67, and ST56 in *S. haemolyticus* and ST892 in *S. epidermidis*. We also found that lower *S. haemolyticus* virulence was associated with extended capsule cassette carriage, which seems contrary to expectations [44], but previous studies have not explicitly correlated virulence to gene carriage exclusive of ST.

This study has several limitations. Although the isolates were characterised in detail, the collection comprised only 48 strains from seven hospitals in five countries and cannot be considered representative of CoNS associated with neonatal sepsis across these settings. BARNARDS-1 initially focused on Gram-negative organisms, with systematic retention of Gram-positive isolates introduced later in the programme. Variation in implementation between sites, together with incomplete retention and successful recovery of stored isolates, may have introduced selection bias. All available viable isolates meeting the inclusion criteria were investigated, but the small and geographically uneven collection precludes reliable estimates of prevalence or country-level comparisons. The clonal representation of *M. sciuri* from one centre further limits the independence and generalisability of species-level observations. Differences between species and lineages, and associations between gene carriage and experimental virulence, should therefore be interpreted as exploratory findings requiring confirmation in larger, independently collected cohorts. Additionally, clinical evidence of sepsis and aseptic sampling do not definitively exclude blood culture contamination, while antibiotic treatment initiated at the first collection could reduce recovery of susceptible organisms from subsequent samples. Finally, virulence in

Galleria demonstrates pathogenic potential under experimental conditions but does not establish that an isolate caused the infant's illness or directly predict disease severity in neonates.

In conclusion, the combination of higher experimental virulence and prevalent MDR traits among the *S. haemolyticus* isolates investigated supports further evaluation of this species as an important opportunistic pathogen in neonatal populations. The clonal nature of the *M. sciuri* outbreak in one centre [17] also highlights the potential for healthcare-associated dissemination. Resistance to commonly used first-line antibiotics within this collection reinforces the need for prospective CoNS surveillance integrating microbiological characterisation with clinical and epidemiological data. Larger, systematically collected cohorts are required to establish how broadly these findings apply and to clarify the contribution of these organisms to neonatal disease.

Table 1. STs assignment, *SCCmec* typing, along with the presence/absence of IS256 and the type of virulence factor (VF) determinant.

CoNS Species	Number of isolates undergone WGS	STs identified	<i>SCCmec</i> cassette presence/ types/ subtypes	IS256
<i>S. haemolyticus</i>	N=15 NK (n=4), NN (n=7), NW (n=4)	ST30 (n=3)	<i>SCCmec</i> subtype <i>IIa</i>	Yes (2)
		ST56 (n=2)	<i>SCCmec</i> subtype <i>IIa</i>	-
		ST3 (n=2)	<i>SCCmec</i> type <i>V</i> & <i>SCCmec</i> type <i>VII</i> (1)	Yes (1)
		ST49 (n=1)	NT	-
		ST66 (n=1)	NT	-
		ST29 (n=1)	NT	Yes
		ST161 (n=1)	NT	-
		ST42 (n=1)	NT	-
		ST67 (n=1)	NT	Yes
		ST135 (n=1)	<i>SCCmec</i> subtype <i>IIa</i>	-
		ST65 (n=1)	NT	-
<i>S. epidermidis</i>	N=11 NK (n=6), NN (n=4), BC (n=1)	ST896 (n=1)	<i>SCCmec</i> type <i>V</i> & <i>SCCmec</i> type <i>VII</i>	-
		ST893 (n=2)	NA	-
		ST439 (n=1)	<i>SCCmec</i> subtype <i>IVa</i>	-
		ST894 (n=1)	<i>SCCmec</i> subtype <i>IVa</i>	Yes
		ST490 (n=2)	<i>SCCmec</i> type <i>V</i> & <i>SCCmec</i> type <i>VII</i>	Yes (1)
		ST888 (n=1)	NA	Yes
		ST892 (n=1)	<i>SCCmec</i> subtype <i>IVc</i>	-
		ST798 (n=1)	NA	-
		ST2 (n=1)	<i>SCCmec</i> subtype <i>IIIa</i>	-
<i>M. sciuri</i>	N=19 NK (n=1), PP (n=15), BC (n=3)	ST82 (n=15)	NA	Yes (9)
		ST80 (n=1)	NA	-
		ST71 (n=1)	NT	-
		ST135 (n=1)	NA	-
		ST81 (n=1)	NA	Yes
<i>S. saprophyticus</i>	N=2 ZAT (n=1), NK (n=1)	N/A	NA	-
<i>S. xylosus</i>	N=1 RK (n=1)	N/A	NA	-

NT; Not-typeable, NA; Not Present

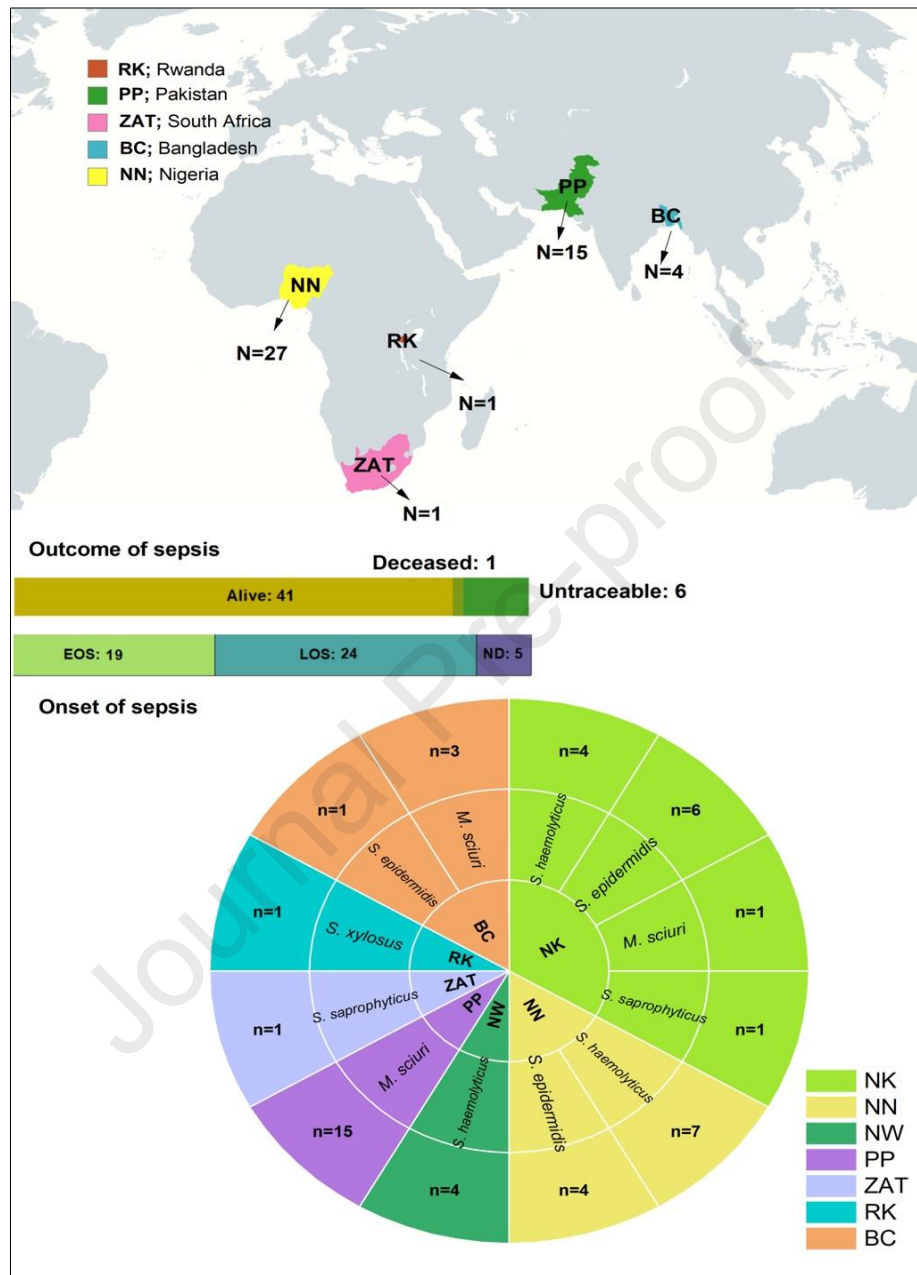


Figure 1. World map of seven clinical sites in five countries showing sepsis onset and outcome. Sunburst diagram: central ring lists sites by country and city (Nigeria: Kano (NK) & Abuja [2 hospitals (NN & NW)], Islamabad, Pakistan (PP); Chittagong, Bangladesh (PC); Cape Town, South Africa (ZAT); Kigali, Rwanda (RK); middle ring shows CoNS species; outer ring shows isolate counts.

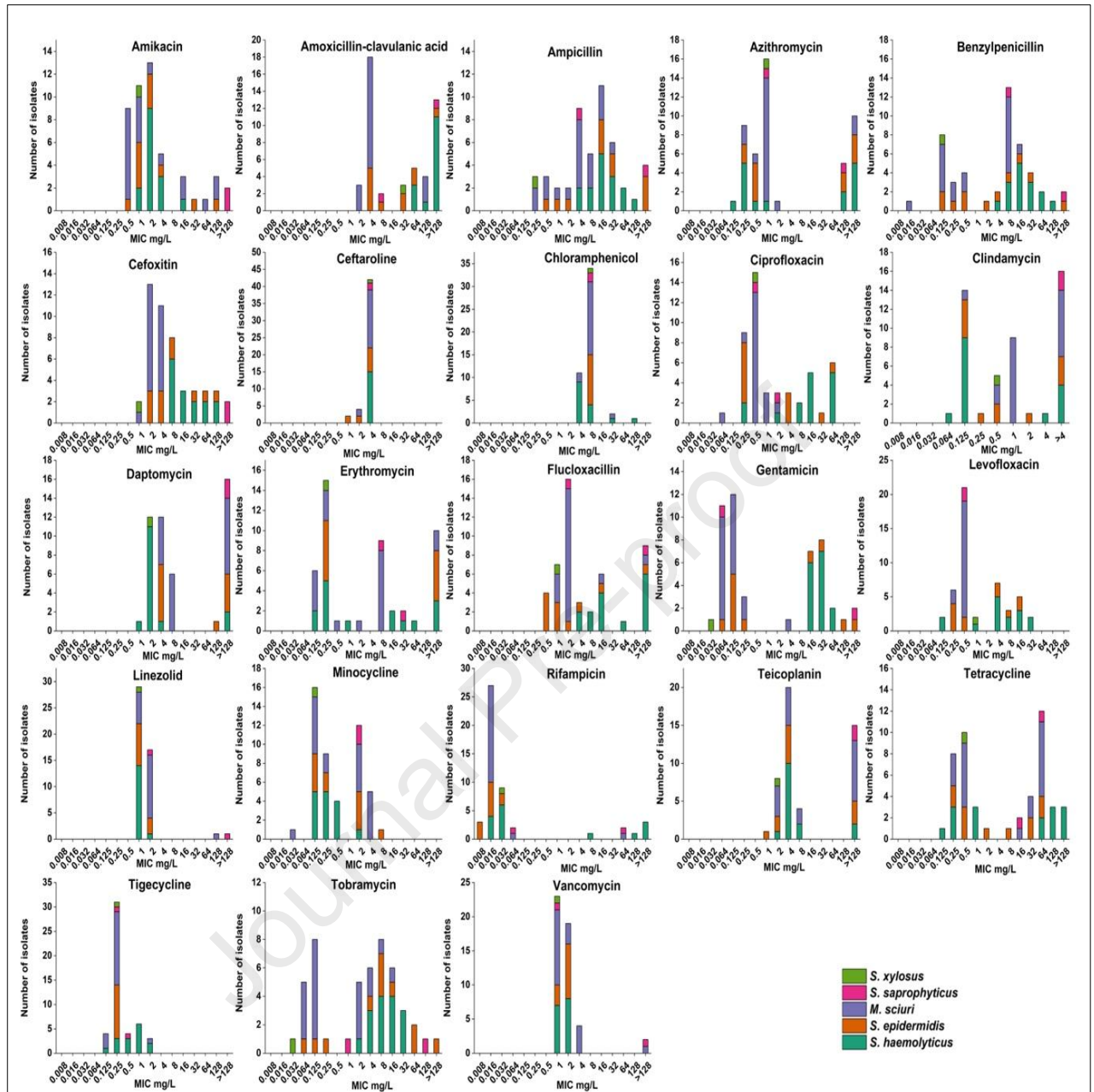


Figure 2. Distributions of minimum inhibitory concentrations (MICs) for the panel of 23 antibiotics tested against the five species of coagulase-negative staphylococci (stacked and colour-coded as *S. haemolyticus*, *S. epidermidis*, *M. sciuri*, *S. saprophyticus* and *S. xylosus*. Thresholds for antimicrobials can be different between species, and are often undefined for many CoNS.

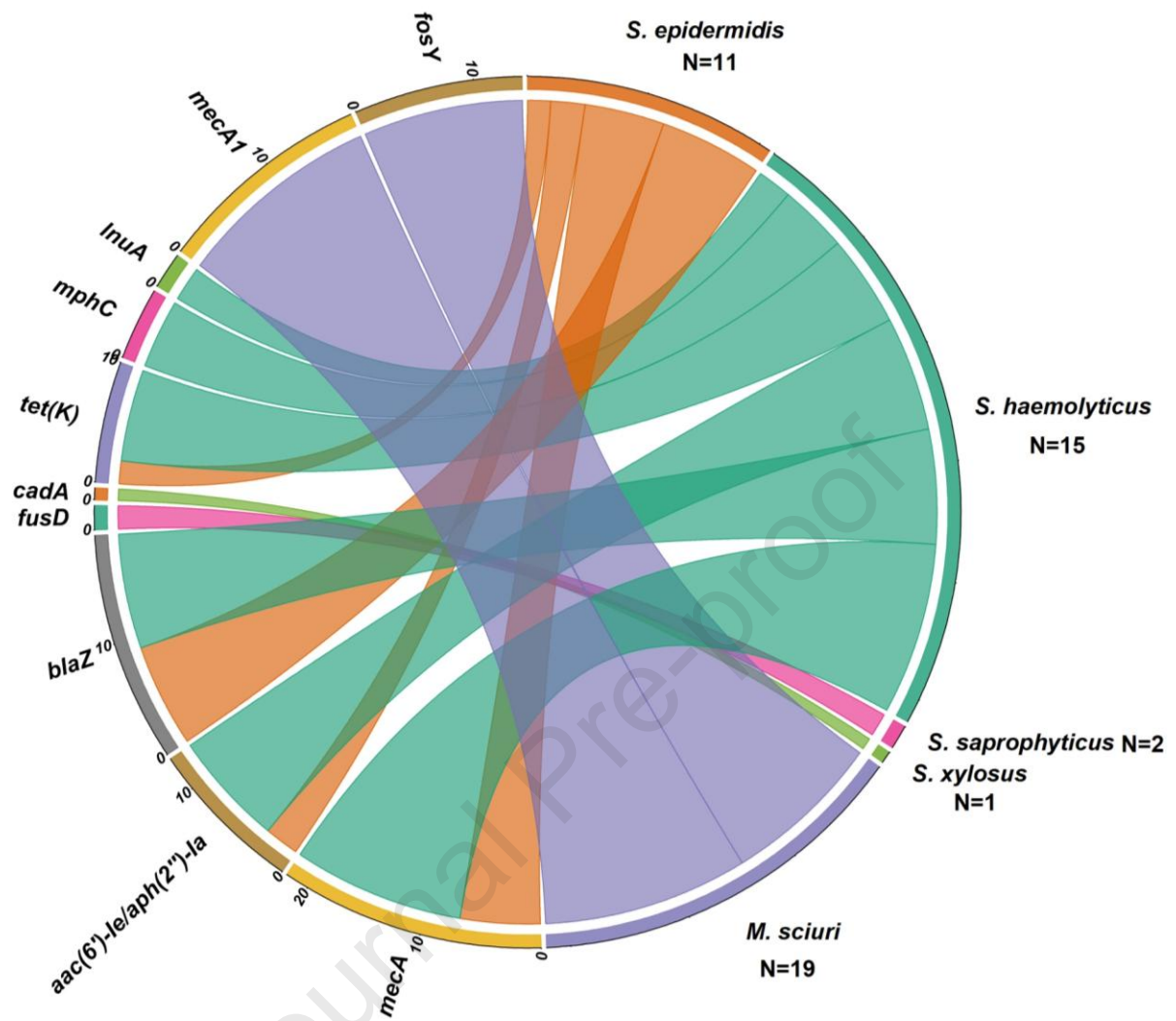


Figure 3. A chord diagram joining CoNS species to relevant ARGs based on numbers of isolates identified as ARG-positive and confirmed by whole genome sequencing.

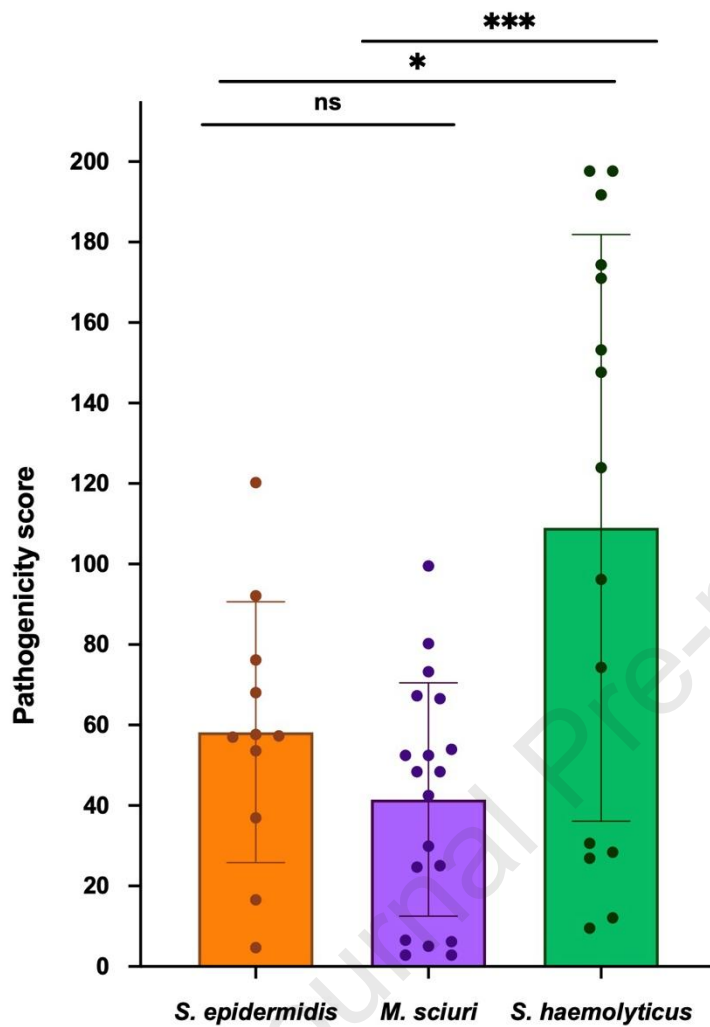


Figure 4. Pathogenicity for three CoNS species in *Galleria mellonella* *in vivo* model. Three groups (n=10 each) were injected with ten microlitres of 10^7 or 10^8 CFU/ml washed bacterial suspension and incubated for 72 hours at 37°C. Weighted pathogenicity scores (time vs. dose) were compared using ANOVA with Tukey's post-hoc test, corrected for multiple comparisons, for weighted pathogenicity scores. *S. haemolyticus* was significantly more virulent than *M. sciuri* ($p=0.0007$; ***) and *S. epidermidis* ($p=0.0318$; *).

Data Availability Statement The whole-genome sequencing data that support the findings of this study are openly available in the NCBI database under BioProject PRJNA1400482, and in the European Nucleotide Archive (ENA) under project PRJEB107080. The authors confirm that all supplementary data the antimicrobial susceptibility testing (AST) and *Galleria mellonella* mortality data supporting the findings of this study are available at <https://figshare.com/s/fee97a93f399b8c3a26b>. [45]

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Competing interests None of the authors have any competing or conflicting interests to declare.

AI use. During the preparation of this work, the author(s) used Google Gemini to reduce word length and improve grammar. The author(s) reviewed and edited the output as needed and take full responsibility for the content of the published article.

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Highlights

- We characterized 48 coagulase-negative staphylococci (CoNS) and *M. scuri* neonatal sepsis isolates.
- *S. haemolyticus* and *S. epidermidis* frequently showed multidrug resistance.
- *S. haemolyticus* showed the highest virulence in an *Galleria mellonella*.
- *S. epidermidis* carried a broader range of putative virulence genes.
- Capsular gene carriage was associated with lower *S. haemolyticus* virulence.