From the Lübeck Institute of Experimental Dermatology

of the University of Lübeck

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Neonatal sepsis in a low-income country's Teaching Hospital

Population structure, clonal relatedness, antibiotics and biocide resistance profiles of coagulase-negative staphylococci (CoNS) in the neonatal intensive care unit of a developing country

Dissertation

for Fulfillment of

Requirements

for the Doctoral Degree

Of the University of Lübeck

From the Department of Natural Sciences

Submitted by

Innocent Afeke

from Lübeck

Lübeck, 2021

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Date of oral examination: 4th of August 2021

Approved for printing: 9th August 2021, Lübeck

ABBREVIATIONS

BSI	Bloodstream infections
BV	Bacterial vaginosis
CARD	Comprehensive antibiotic resistance database
CoNS	Coagulase-negative staphylococci
CRC	Colorectal cancer
CSTs	Community state types
EML	Essential Medicines List
EONS	Early-onset neonatal sepsis
HAIs	Healthcare-associated infections
HLMR	High-level mupirocin resistance
HTH	Ho Teaching Hospital
IBDs	Inflammatory bowel diseases
IBS	Irritable bowel syndrome
ICUs	Intensive care units
LMICs)	Low and middle-income countries
LONS	Late-onset neonatal sepsis
MDR	Multi-drug resistant
MICs	Minimum inhibitory concentrations
MLST	Multi-locus sequence typing
MRSA	Methicillin-resistant staphylococcus aureus
MRSE	Methicillin-resistant *staphylococcus epidermidis*
MS	Mupirocin susceptible
NGASs	Non-genome assembly strains
NICUs	Neonatal intensive care units
PFGE	Pulsed-field gel electrophoresis
PPROM	Preterm premature rupture of membranes
PTB	Preterm birth
VLBWI	Very low birth weight infants
VRE	Vancomycin-resistant enterococci
WGS	Whole-genome sequencing
WHO	Wold health organization

ABSTRACT

Infection in neonates remains a significant problem of contemporary medicine. Bacteria are responsible for approximately 90% of all healthcare-associated infections. However, there is limited data on bacterial species' molecular characterisation to determine neonatal sepsis risk factors in low- and middle-income countries. In this study, maternal vaginal microbiota were investigated as a risk factor for preterm birth with subsequent neonatal sepsis. Findings from this study revealed that bacteria associated with vaginal community state type (CST) IV were the only community members identified in all six participants studied, regardless of gestation type and the type of sepsis their neonates had. Also, genus *Ruminococcus* 2 (*Blautia*) was detected in the vaginas of the mothers who had spontaneous preterm deliveries but not in those who had term births, indicating that this genus may be used as a marker in the prognosis of spontaneous preterm birth among the population in which the study was performed. Furthermore, the genus *Acinetobacter* was detected in the vaginas of two of the six women who had previous babies die during their neonatal age. These findings might not be by chance and call for further large scale studies in these directions. Another aspect of the study investigated *S. epidermidis* and *S. haemolyticus* possible transmission sources to neonates in the neonatal intensive care unit of Ho Teaching Hospital, Ghana. The data suggested that clinical staff are more likely to transmit *S. epidermidis* to the studied neonates, whilst mothers are more likely to transmit *S. haemolyticus*. This study isolated, sequenced, and assembled four *S. epidermidis* non-genome assembly strains isolated from neonates' blood samples. Possible transmission sources of these strains were investigated, but the study could not clearly identify the sources. This study provides insight into the mechanisms of resistance of tigecycline of *S. haemolyticus* cultivated from the non-glycylcycline-exposed hospital. The data suggested that co-detection of the genes *msr*A-*mph*C, *mec*A-*msr*A, *tet*(M)-*tet*(S), *tet*(L)-*tet*(45) and *fus*B-*far*1 on the genome of *S. haemolyticus* predicts resistance to tigecycline. Three high-level mupirocin-resistant coagulase-negative staphylococci (CoNS) were isolated from the non-mupirocin-exposed hospital; their genomes revealed that none of them harboured the genes for mupirocin resistance. Their molecular mechanism(s) of resistance to this antimicrobial is unclear. Five novel multi-locus sequence types were identified: two *S. epidermidis* and three *S. haemolyticus*. Staphylococcal species analysed in this study were readily susceptible to chlorhexidine with minimum inhibitory concentrations ranging from <0.25 to 4mg/L. Gene carriage that confers reduced chlorhexidine susceptibility was low among these staphylococcal isolates. These findings served as baseline data for the studied hospital before the start of chlorhexidine ointment treatment of babies' umbilical cords to reduce neonatal sepsis.

ZUSAMMENFASSUNG

Infektionen bei Neugeborenen bleiben ein bedeutendes Problem der modernen Medizin. Bakterien sind für etwa 90 % aller Infektionen im Zusammenhang mit dem Gesundheitswesen verantwortlich. Es gibt jedoch nur wenige Daten zur molekularen Charakterisierung von Bakterienspezies zur Bestimmung von Risikofaktoren für neonatale Sepsis in Ländern mit niedrigem und mittlerem Einkommen. In dieser Studie wurden die mütterliche vaginale Mikrobiota als Risikofaktor für eine Frühgeburt mit anschließender neonataler Sepsis untersucht. Die Ergebnisse dieser Studie zeigten, dass Bakterien, die mit dem vaginalen Community State Type (CST) IV assoziiert sind, die einzigen Gemeinschaftsmitglieder waren, die bei allen sechs untersuchten Teilnehmerinnen identifiziert wurden, unabhängig vom Schwangerschaftstyp und der Art der Sepsis, die ihre Neugeborenen hatten. Außerdem wurde die Gattung *Ruminococcus* 2 (*Blautia*) in den Vaginas der Mütter nachgewiesen, die spontane Frühgeburten hatten, aber nicht bei denen, die reguläre Geburten hatten, was darauf hindeutet, dass diese Gattung als Marker für die Prognose spontaner Frühgeburten in der Bevölkerung, in der die Studie durchgeführt wurde, verwendet werden könnte. Außerdem wurde die Gattung Acinetobacter in den Vaginas von zwei der sechs Frauen nachgewiesen, deren frühere Babys während der Neugeborenenzeit gestorben waren. Diese Befunde sind möglicherweise nicht zufällig und erfordern weitere groß angelegte Studien in diese Richtung. Ein weiterer Aspekt der Studie untersuchte mögliche Übertragungsquellen von *S. epidermidis* und *S. haemolyticus* auf Neugeborene in der neonatologischen Intensivstation des Ho Teaching Hospital, Ghana. Die Daten deuten darauf hin, dass das klinische Personal mit größerer Wahrscheinlichkeit *S. epidermidis* auf die untersuchten Neugeborenen überträgt, während die Mütter mit größerer Wahrscheinlichkeit *S. haemolyticus* übertragen. In dieser Studie wurden vier *S. epidermidis*-Stämme, ohne bisher bekannte Genomassemblierung, aus Blutproben von Neugeborenen isoliert, sequenziert und assembliert. Mögliche Übertragungsquellen dieser Stämme wurden untersucht, aber die Studie konnte die Quellen nicht eindeutig identifizieren. Diese Studie gibt einen Einblick in die Mechanismen der Tigecyclin-Resistenz von *S. haemolyticus*, der aus einem nicht mit Glycylcyclin exponierten Krankenhaus kultiviert wurde. Die Daten legen nahe, dass der gemeinsame Nachweis der Gene *msrA-mphC, mecA-msrA, tet(M)-tet(S), tet(L)-tet(45)* und *fusB-far1* auf dem Genom von *S. haemolyticus* die Resistenz gegen Tigecyclin vorhersagt. Drei hochgradig Mupirocin-resistente Koagulase-negative Staphylokokken (CoNS) wurden aus dem nicht Mupirocin-exponierten Krankenhaus isoliert; die Genome zeigten, dass keines von ihnen die bekannten Gene für Mupirocin-Resistenz trugen. Die molekularen Mechanismen der Resistenz gegen dieses Antibiotikum sind unklar. Es wurden

fünf neue Multilocus-Sequenztypen identifiziert: zwei *S. epidermidis* und drei *S. haemolyticus*. Die in dieser Studie untersuchten Staphylokokken-Spezies waren sehr empfindlich gegenüber Chlorhexidin mit minimalen Hemmkonzentrationen von <0,25 bis 4mg/L. Das Gen für reduzierte Chlorhexidin-Empfindlichkeit war bei diesen Staphylokokken-Isolaten gering. Diese Ergebnisse dienten als Ausgangsdaten für das untersuchte Krankenhaus bevor die Behandlung der Nabelschnur von Säuglingen mit Chlorhexidin-Salbe begann, um die neonatale Sepsis zu reduzieren.

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1 INTRODUCTION

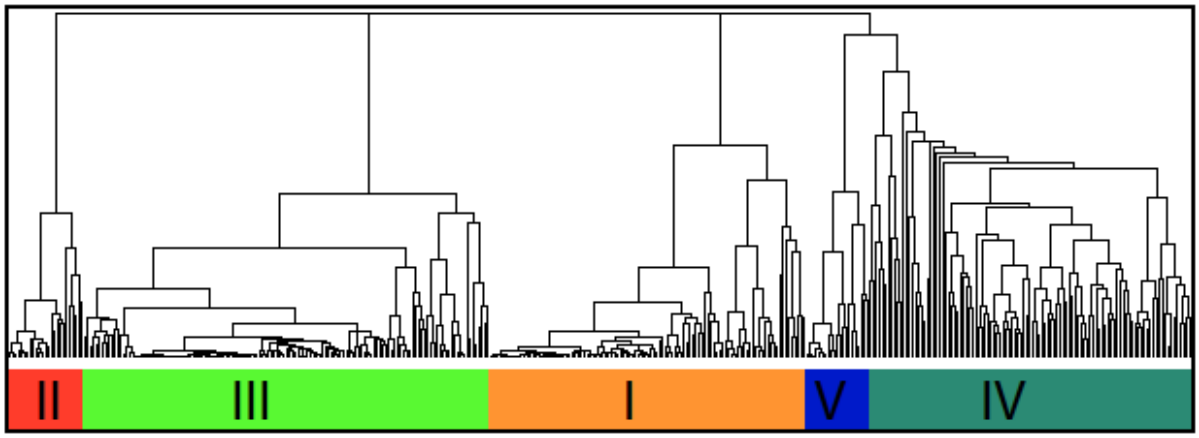
Infection in neonates remains a significant problem of contemporary medicine. Identifying risk factors associated with neonatal bloodstream infections could provide significant insights leading to new findings for neonatal sepsis prevention, early diagnosis, alternative or better treatment, thereby reducing morbidity and mortality among neonates in the NICU. Risk factors associated with neonatal sepsis could be maternal related, neonatal-related, and healthcare-related, including hospital environment, administration of intervention, and burnout among hospital staff [1,2].

Generally, risk factors associated with neonatal sepsis are poorly described in Africa and, more specifically, in Ghana. There is evidence that some of the maternal characteristics like prolonged rupture of membranes, foul-smelling liquor, intrapartum fever, urinary tract infection or sexually transmitted infection and group B streptococcal (gut and vaginal) colonization likely play essential roles in EONS [3,4]. However, modern studies of the role of microbiome diversity and its variation in the incidence and susceptibility to an infection during the neonatal period have primarily not been done in most LMICs.

1.1 The vaginal microbiome

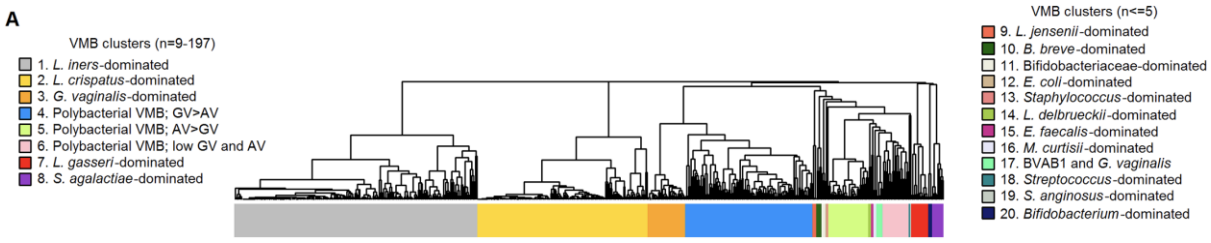
Studies have shown that the vaginal microbiome harbours diverse microorganisms known as vaginal flora, which impact women's health and their newborns[5–7]. Ravel *et al*. sequenced the 16S rRNA gene of samples collected from 396 asymptomatic North American women who represented four ethnic groups, namely, Asian, Black, Hispanic, and White. Their data suggest five microbiota groups (I to V) among these women (Figure 1-a), distinguishable both by the dominance of *Lactobacillus* species and by the presence of a particular *Lactobacillus* species[8]. In group I, communities are dominated by *L. crispatus*, whereas communities in groups II, III, and V are dominated by *L. gasseri*, *L. iners*, and *L. jensenii*, respectively. Communities in group IV are the most diverse and have a higher proportion of strictly anaerobic bacteria combined with *Lactobacillus* species. In group IV, communities were not dominated by the *Lactobacillus* species *L. iners* and *L. crispatus*; however, these were detected in 78.7% and 51.9% of this group, respectively. The researchers also identified a sub-group among the

communities in group IV, in which a small number (4) of the subjects lacked detectable *Lactobacillus* species in their vaginas. Those communities were dominated by *Prevotella, Sneathia*, *Megasphaera* or *Streptococcus*. Community group I was the most common group amongst women of European ancestry, whereas group IV was the most common among African American women. These observations were similar to the findings (Figure 1-b) of the current work done by researchers at Virginia Commonwealth University, USA, where they also analysed the microbiome of 960 African American women and 330 women of European ancestry[5]. Eventually, Borgdorff and colleagues came up with 20 multiple community state types (CSTs) representing species-dominated clusters (Figure 1-b)[9].



Community Groups

Figure 1- a): **Complete linkage clustering of samples based on the species composition and abundance of vaginal bacterial communities that define community groups I-V.** The figure was adapted and modified from[8].



Community Groups

Figure 1- b): **Hierarchical clustering of participants by vaginal microbiota composition.** AV: *Atopobium vaginae*; BVAB1: BV-associated bacterium 1; GV: *Gardnerella vaginalis*; L: *Lactobacillus*. The figure was adapted and modified from[9].

1.2 Dynamics of the vaginal microbiome from pregnancy to postpartum

The normal gravid vaginal microbiome compositions are dynamic during gestation for all women. Studies have reported an increase in four *Lactobacillus* species (*L. crispatus, L. jensenii, L. gasseri, and L. vaginalis*) and a decrease in the number of anaerobic species such as *Atopobium*, *Prevotella*, *Sneathia*, *Gardnerella*, *Ruminococcaceae*, *Parvimonas*, and *Mobilincus*[10,11]. This was suggested to reflect normal changes in the vaginal flora during pregnancy to transition to another *Lactobacillus* community. This stability would protect against ascending infections through the genital tract[10]. A Danish cohort study (COPSAC 2010) analysed vaginal samples from pregnant women at weeks 24 and 36 of gestation and at birth after rupturing the membrane, and reported that vaginal community structure dramatically changed bacterial diversity taxonomic distribution (Figure 2). However, they found that participants carried an individual-specific signature. They further explained that the relative abundance of most bacterial taxa increased stepwise from week 24 of pregnancy until birth, with a gradual decline of *Lactobacillus*[12]. A mixed British cohort study performed throughout pregnancy and six weeks postpartum of women who had term delivery showed that vaginal microbiome composition dramatically changes postpartum to become fewer *Lactobacillus* species-dominant with increased alpha-diversity of the community structure during pregnancy and independent of ethnicity[13]. This study was among the few studies that report on vaginal microbiome composition postpartum. One other study from Africa that analysed vaginal swabs taken postpartum from a cohort of 1,107 women in rural Malawi reported that bacteria associated with CST IV-1 remained the most dominant community members in all participants, even years after delivery when vagina was sampled. Moreover, *G. vaginalis* remained the dominant organism seen in the vaginal microbiota, even over a year postpartum[14].

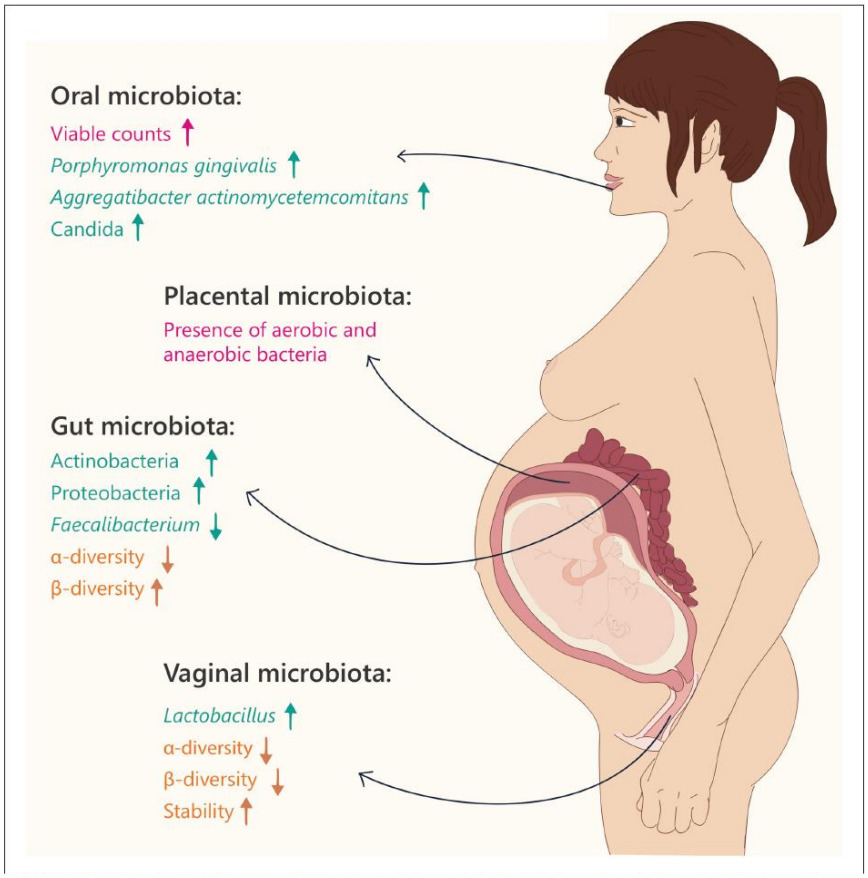


Figure 2- a): **Microbiome changes during pregnancy.** Text and arrows refer to general changes (pink); changes in specific taxonomy (green); and community diversity (orange). Adapted from[15].

1.3 Human vaginal microbiota composition and its association with preterm delivery with risk of early-onset neonatal sepsis

Preterm birth (PTB) and its associated early-onset neonatal sepsis (EONS) are the most significant challenges facing modern medicine obstetrics. They are the world's leading cause of childhood mortality and are associated with 80% of all neonatal morbidity, resulting in a high financial and emotional cost to families and society[16]. In the United States, clinical diagnoses have revealed that African Americans are more frequently affected by bacterial vaginosis (BV) and have a threefold greater risk of very preterm birth (<32 weeks gestation) compared with women of European ancestry[17]. The cause of racial differences in the rate of BV and adverse pregnancy outcomes is not exact.

Dysbiosis of the human microbiome is a known characteristic of various inflammatory disease states and has been linked to spontaneous preterm birth and other adverse pregnancy outcomes[18]. Dysbiosis of the vaginal microbiota is characterized by decreased lactic acid-producing microbiota and increased diverse anaerobic bacteria accompanied by an elevated pH>4.5. Previous data have shown that when the degree of fluctuation becomes too severe, these communities' microbial relationships shift from symbiotic to pathogenic (disease)[19]. Preterm premature rupture of membranes (PPROM) was associated with the instability of bacterial community structure during pregnancy and a shift toward higher diversity during the second trimester[20]. However, not all studies reported an association between vaginal microbiota and PTB with its associated EONS risk. For example, Romero and colleagues reported no bacterial taxa differed in relative abundance between women who had a spontaneous preterm delivery and those who delivered at term[21]. Likewise, a recent study conducted in Brazil[22] also reported no differences in microbial diversity associated with the spontaneous preterm and full-term outcomes; the microbial composition was distinct for these groups (Figure 3).

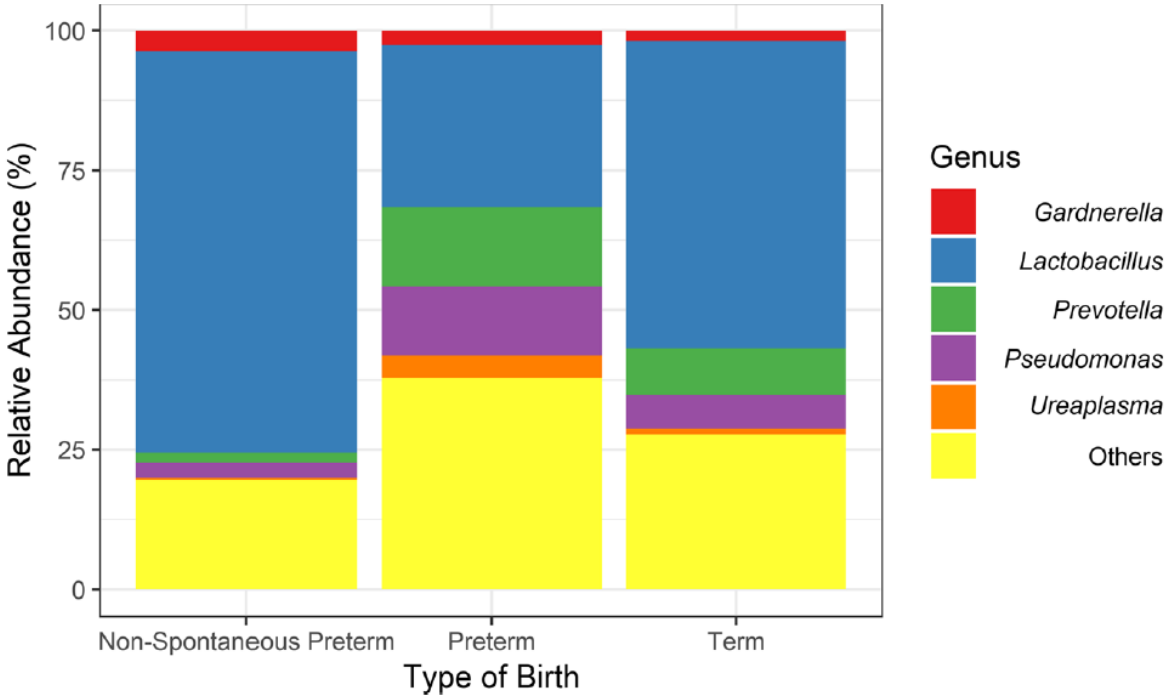


Figure 3- a): **Percentage of the five most abundant microbial genera found in vaginas of the three tested groups.** Adapted from[22].

1.4 Roles of butyrate-producing bacteria in the human vagina

The role that butyrate-producing bacteria of the genera *Faecalibacterium*, *Ruminococcus* and *Eubacteria* play in the human vagina is unknown and needs to be researched. However, their roles in the gut have been intensively documented. A comprehensive review of *F. prausnitzii* revealed that its levels were reduced in patients suffering from several syndromes and diseases such as irritable bowel syndrome (IBS), colorectal cancer (CRC), inflammatory bowel diseases (IBDs), celiac disease and obesity[23–27]. In a search for the mechanism by which *F. prausnitzii* can induce anti-inflammatory conditions, studies have shown that it increased lymphocyte T regulatory (Treg) population *in vivo* after a colonic chemical challenge[28]. Also, *F. prausnitzii* has been identified as a significant inducer of a specific IL-10-secreting Treg subset called CD4CD8α lymphocytes present in the human colonic lamina propria. However, deficient secretion of pro-inflammatory cytokines like IL-12 and IFN-γ was observed in the blood, which are deficient in IBD patients[29,30]. Recent studies have shown that characteristic trends were observed in dysbiosis in chronic heart failure patients' gut microbiota, where *Faecalibacterium* species decrease whilst *Ruminococcus* species increase[31]. Gut dysbiosis of infants with an abundance of *R. gnavus* induces Th2-biased immunity in the colon. Its subsequent effectors exploit the gut-pulmonary axis to evoke allergic asthma in these infants[32]. Restoration of serotonin, which was reported[33] as a key neurotransmitter in the gastrointestinal tract that affects motility, to average levels has been evidenced in murine models treated with either *F. prausnitzii* or its supernatant[34]. Furthermore, this species anti-nociceptive effect in non-inflammatory IBS syndrome-like murine models has been recently evidenced[35]. Because of its essential role in gastrointestinal tract homeostasis, *F. prausnitzii* is now considered a potential next-generation probiotic.

1.5 Healthcare-associated infections

Healthcare-associated infections (HAIs) are a serious patient safety issue that results in increased morbidity and mortality and excessive health resource utilization[36]. The CDC estimates that approximately 1.7 million hospitalized patients annually acquire infections while being treated for other conditions. More than 98,000 of these patients (or 1 in 17) will die due to the acquired infection[37]. Also, estimates from the United States show that on any given day,

approximately 1 of every 25 inpatients in acute care hospitals has at least one HAI[38]. A report from Europe indicated that HAIs also represent a considerable burden, with more than 2.5 million cases occurring each year, resulting in approximately 2.5 million disability-adjusted life years[39]. Given the significant burden of HAIs with the potential for adverse outcomes in patients, there is much interest in understanding their transmission, prevention, and control. Evidence-based research has shown that the hands of healthcare workers mainly cause infections[40,41]. Although this connection is widely known, hand hygiene compliance in neonatal intensive care units (NICUs) has been reported to be as low as 40%, meaning 60% of recommended hand hygiene steps were not fulfilled[42]. Higher activity levels and burnout among staff were associated with lower compliance with hygiene standards[42].

1.6 Molecular typing systems used to determine population structure and clonal relatedness among CoNS in a hospital setting

Clonal diversity among coagulase-negative staphylococcus (CoNS) species varies and is much less studied than *S. aureus*. There are a variety of approaches to analysing these genomic data for epidemiologic and infection control purposes. Pain *et al.* have used comparative genome analysis to reveal key hospital adaptation and pathogenicity among *S. haemolyticus* isolates cultured from a hospital setting[43]. At a high level, phylotyping may support epidemiological investigations to determine the source and routes of infections, trace cross-transmission of healthcare-associated pathogens and identify virulent antibiotic-resistant lineages or subpopulations[44]. However, it is more appropriate for some species CoNS with stable genomic configuration than others. For example, in *S. haemolyticus*, extreme plasticity of the genome was reported, and a high abundance of insertion sequence elements was found, conferring the frequent genomic rearrangement characteristics found in this species[45,46].

1.6.1 **Pulsed-field gel electrophoresis**

Pulsed-field gel electrophoresis (PFGE) has been used to determine genomic diversity. For CoNS, it was used to establish that *S. epidermidis* is characterized by more genomic diversity than other CoNS species, such as *S. haemolyticus* and *S. lugdunensis*[47]. However, PFGE is no longer the preferred method. It has certain intrinsic disadvantages, such as being technically demanding and time-consuming, having poor reproducibility among different technicians, and not discriminating between all unrelated isolates. For the short-term surveillance of *S. epidermidis* in outbreak situations, PFGE targeting the entire bacterial genome can be regarded as an appropriate and powerful tool[48]. However, PFGE results were reported to have correlated poorly with the actual relatedness of isolates[49–51], especially among more distantly related strains[52].

1.6.2 **Single gene typing approach: *tuf*, 16S rRNA and rpoB genes**

In 2012, a study group proposed a refined classification of staphylococci using a combination of Bayesian and maximum likelihood analysis of multilocus data based on four loci, including *tuf*, non-coding 16S rRNA, *rpo*B and *dna*J[53]. As proposed by Lamers and colleagues, 16S rRNA gene typing has emerged as one of the significant typing systems used to determine clonal diversity among bacterial species. Additionally, the *rpoB* gene has been used as an epidemiological target for CoNS of typing[54]. However, for CoNS, recent findings have shown that the *tuf* gene cluster, which is located in the short tandem repeat region on the bacterial chromosome, shows significant diversity among them[55]. For the *tuf* gene, its small size and conserved location in bacterial chromosome have contributed to its superiority in DNA sequencing compared with 16S rRNA for the construction of a phylogenetic tree on species and genus level in staphylococci[56,57]. On this note, a study group has emphasized the value of partial *tuf* gene sequence to identify all staphylococcal species[58]. Comparative analysis of the *tuf* gene among staphylococci proved to be more discriminative. For CoNS, it provides a reference method with high accuracy for recognizing hospital infections related to *S. epidermidis* and *S. haemolyticus* in critical care units[59,60].

1.6.3 **Multiple genes typing approach: multilocus sequence typing**

Multiple gene nucleic acid-based typing approaches such as multilocus sequence typing (MLST)[61] or the use of DNA arrays[62,63] have been proven useful over the years to assess epidemiological relatedness among bacterial strains, especially healthcare-associated microbial species[64]. However, most infections in the clinical setting are caused by bacterial strains belonging to a relatively restricted number of lineages, especially for highly prevalent methicillin-resistant staphylococcus aureus (MRSA)[65]. Notably, such strains cannot always be differentiated in sufficient detail when employing the classical DNA-based methods[64,66]. High-resolution typing of *S. epidermidis* based on MLST was used to investigate the hospital spread of multidrug-resistant clones[67]. Multilocus variable-number tandem-repeat and MLST were successfully used to determine the genetic relatedness of staphylococcus in the gut and skin of preterm neonates and breast milk of their mothers[68].

1.6.4 **Whole-genome sequencing**

Recently, whole-genome sequencing (WGS) has represented a relatively new and increasingly accessible means of tracking disease outbreaks that have had success in multiple applied contexts[69–71]. Whole-genome sequencing will drastically enhance our knowledge by improving the resolution of the genetic organization of CoNS species and (as shown in initial applications for *S. aureus*) their clonal distribution[72]. Findings suggest that using DNA sequencing technologies makes it possible to examine complete or nearly complete bacterial isolates' genomes. Whole-genome sequencing can theoretically distinguish strains that differ at only a single nucleotide. The limited number of studies where direct comparisons with PFGE have been performed has provided more excellent resolution[73–75]. Among the methods, WGS-based strain typing is seeing increasing use in the epidemiologic analysis of bacterial pathogens in both public health and more localized infection control settings[44].

1.7 The Acess,Watch, Reserve (AWaRe) classification of antimicrobials by the World Health Organization

Microorganisms rapidly develop resistance to existing drugs; hence antimicrobial agents of new chemical groups are introduced, and the combined drugs are then used[76]. However, microorganisms' resistance grows faster than new antimicrobials are created. Considering the scale of the problem, the World Health Organization (WHO) has developed a document entitled 'WHO Global Strategy for the Containment of Antibiotic Resistance'[77]. It states that excessive and inappropriate use of antibiotics is considered one of the major causes of the spread of resistance to antimicrobial drugs. Given this, in March 2017, the WHO Essential Medicines List (EML) Working Group classified antibiotics in the EML for Children (EMLc) into three groups: Access, Watch, and Reserve[78] (Table 1). The Access group generally contains narrow-spectrum antibiotics recommended as the first and second choice for most common clinical infection syndromes. They are used for commonly encountered susceptible pathogens and show lower resistance potential than antibiotics in the other groups. The Watch group contains generally broader spectrum antibiotic classes. This group includes antimicrobials with higher resistance potential. It includes most of the highest priority agents among the Critically Important Antimicrobials for Human Medicine[79] and antibiotics at a relatively high risk of selecting bacterial resistance. Antibiotics in the Watch group are suggested to be prioritized as key targets of stewardship programs and monitoring. The Reserve group consists of last-resort antibiotics for targeted use in multidrug-resistant infections. This group includes antimicrobial classes that should be reserved for treatment of confirmed or suspected infections due to multi-drug-resistant organisms. Antibiotics in the Reserve group are to be treated as "last resort" options; they should be accessible, but their use should be tailored to highly specific patients and settings, when all alternatives have failed or are not suitable. To preserve their effectiveness, antibiotics in this group could be protected and prioritized as key targets of national and international stewardship programs involving monitoring and utilization reporting.

Table 0: **New classification of antimicrobials based on access and recommendation on conditions for their use**

Access group antimicrobials

Beta-lactam	*Other antimicrobials*
Amoxicillin	Amikacin
Amoxicillin + clavulanic acid	Azithromycin*
Ampicillin	Chloramphenicol
Benzathine benzylpenicillin	Ciprofloxacin*
Benzylpenicillin	Clarithromycin*
Cefalexin	Clindamycin
Cefazolin	Doxycycline
Cefixime*	Gentamicin
Cefotaxime*	Metronidazole
Ceftriaxone*	Nitrofurantoin
Cloxacillin	Spectinomycin (EML only)
Phenoxymethylpenicillin	Sulfamethoxazole+ trimethoprim
Procaine benzylpenicillin	Vancomycin (oral)*
Piperacillin+ tazobactam*	Vancomycin (parenteral)
Meropenem*	

Watch group antimicrobials

Quinolones & fluoroquinolones: Ciprofloxacin, levofloxacin, moxifloxacin, norfloxacin
Cephalosporins of 3rd generation (with or without beta-lactamase inhibitor): Cefixime, ceftriaxone, cefotaxime, ceftazidime
Macrolides: Azithromycin, clarithromycin, erythromycin
Glycopeptides: Teicoplanin, vancomycin
Anti-pseudomonal penicillins with beta-lactamase inhibitor: Piperacillin+ tazobactam
Carbapenems & penems: Meropenem, imipenem+ cilastatin, faropenem

Reserve group ('last-resort') antimicrobials

Cephalosporins of 4th generation: Cefepime	Others:
Cephalosporins of 5th generation: Ceftaroline	Fosfomycin (intravenous)
Polymyxins: Polymyxin B, colistin	Aztreonam
Oxazolidinones: Linezolid	Tigecycline
	Daptomycin

*Watch group antibiotics included in the EML/EMLc only for specific, limited indications.
Table adapted and modified from[80].

1.7.1 **Antibiotics resistance among CoNS**

Staphylococci, especially CoNS, have a documented history of developing resistance to antimicrobial agents. HAIs are associated with multi-drug resistant (MDR) bacteria, which increases the risk of therapeutic failure due to the limited choice of available antibiotics. HAIs caused by CoNS also lead to an extended duration of admission, increased medical costs, morbidity and mortality[81].

1.7.1.1 Antibiotics' modes of actions against CoNS

Different antibiotics have different modes of action, owing to their structure and degree of affinity to specific target sites within bacterial cells. Table 2 summarizes various antibiotics' mechanism of action.

Table 1: **Site and mode of action of antibiotics**

Site of action	*Mode of action*	*Antibiotics*
Cell wall	Inhibition of precursors for the peptidoglycan synthesis	Fosfomycin Cyloserine
	Stopping the transport of cell wall precursors through the membrane cell	Bacitracin Mueridomycins
	Blocking the polymerization and crosslinking processes of wall peptidoglycan at the level of penicillin binding proteins (PBP's)	β-Lactams (penicillin derivates, cephalosporins, etc.), glycopeptides (vancomycin and teicoplanin)
Cytoplasmic membrane	Increasing the membrane permeability with the subsequent loss of small metabolites.	Polymyxins
	Depolarization of cytoplasmic membrane that reduces the protein and DNA synthesis	Lipopetides (daptomycin)
	Alteration of the membrane by formation of pores	Ionophores (valinomycin, tirocydins) and gramicydins
Protein synthesis	Inactivation of the protein activation process	Mupirocin,
	Inhibition of the protein synthesis initiation	Oxazolidiones and aminoglycosides
	Blocking the tRNA amino acid complex to ribosomes	Tetracycline and glycylcyclines
	Modification of the protein final elongation stages by blocking the peptidyl transferase on the 50S ribosome subunit	Amphenicols, lincosamides, macrolides, ketolides
DNA synthesis	Alteration of the DNA copying processes at the DNA-dependent RNA polymerase	Nitroimidazoles and nitrofurans
	Inactivation final DNA coiling process	Quinolones
Resistance mechanisms	Protects against bacterial enzyme β-lactamases that provide resistance to β-lactam antibiotics and/or blocks the antibiotic active efflux process.	Clavulanic acid, sulbactam and tazobactam

Adapted from [82]

1.7.1.2 Mechanisms of antibiotics' resistance in CoNS and their associated resistant genes

The use of antibacterial drugs has become widespread over several decades. These drugs have been extensively misused in both humans and food-producing animals in ways that favour the selection and spread of resistant bacteria. Consequently, antibacterial drugs have become less effective or even ineffective, resulting in an accelerating global health security emergency that is rapidly outpacing available treatment options.

A microorganism's ability to survive at a given concentration of an antimicrobial agent at which the microorganism's average population would be killed is called the "epidemiological breakpoint". A microorganism's ability to survive treatment with a clinical concentration of an antimicrobial agent in the body is called the "clinical breakpoint". The ability to identify specific genes that are responsible for resistance to antibiotics helps to understand the resistance mechanism for those antibiotics. Table 3 summarizes the mechanisms of antibiotic resistance to various antibiotic classes.

Table 2: **Summary of the mechanisms of antibiotic resistance in CoNS and their associated resistant genes**

Antibiotic class	Resistance type	Resistance mechanism	Genes involved
	Altered PBP	PBP 2a	*mec*A
	Efflux	membrane transporters	RND, ABC
Beta-lactams	Enzyme degradation	Penicillinase	*bla*-Z, -R1, -I
Glycopeptides	Altered target	D-Ala-Ala to D-Ala-D-Lac	
	Decreased uptake	change outer membrane	
	Enzyme modification	AMEs	APH
Aminoglycosides	Efflux	membrane transporters	MexXY, ABC
	Efflux	membrane transporters	Shown in Figure 4
	Altered target	enzymatic inactivation	Shown in Figure 4
Tetracyclines	Ribosomal protection		Shown in Figure 4
	Enzymatic inactivation	Antibiotic inactivation	*mph*C, *Inu*A, *vgb* & *vat*
Macrolides	Efflux	Membrane transporters	*msr*, *vga*
	Altered target	mutation leading reduced binding to the active site	
Oxazolidinones	Plasmid coded	Ribosomal methylation	*cfr*
	Efflux	Membrane transporters	
Quinolones	Altered target	mutation leading to reduced binding to the active site	*gyr*A, *nor*A
Sulfa/Trimethoprim drugs	Altered target Overproduction of substrate	Mutation of genes encoding DHPS K	*dfr*-A, D, G,
Rifampicin	Point mutation	Mutation in *rpo*B gene	*rpo*B
Mupirocin	Chromosomal and plasmid coded		*ile*S, *mup*A$^{\varepsilon}$,*mup*B$^{\varepsilon}$

PBP: penicillin-binding proteins; AMEs: aminoglycoside modifying enzymes; ε: Plasmid coded. Adapted and modified from[83].

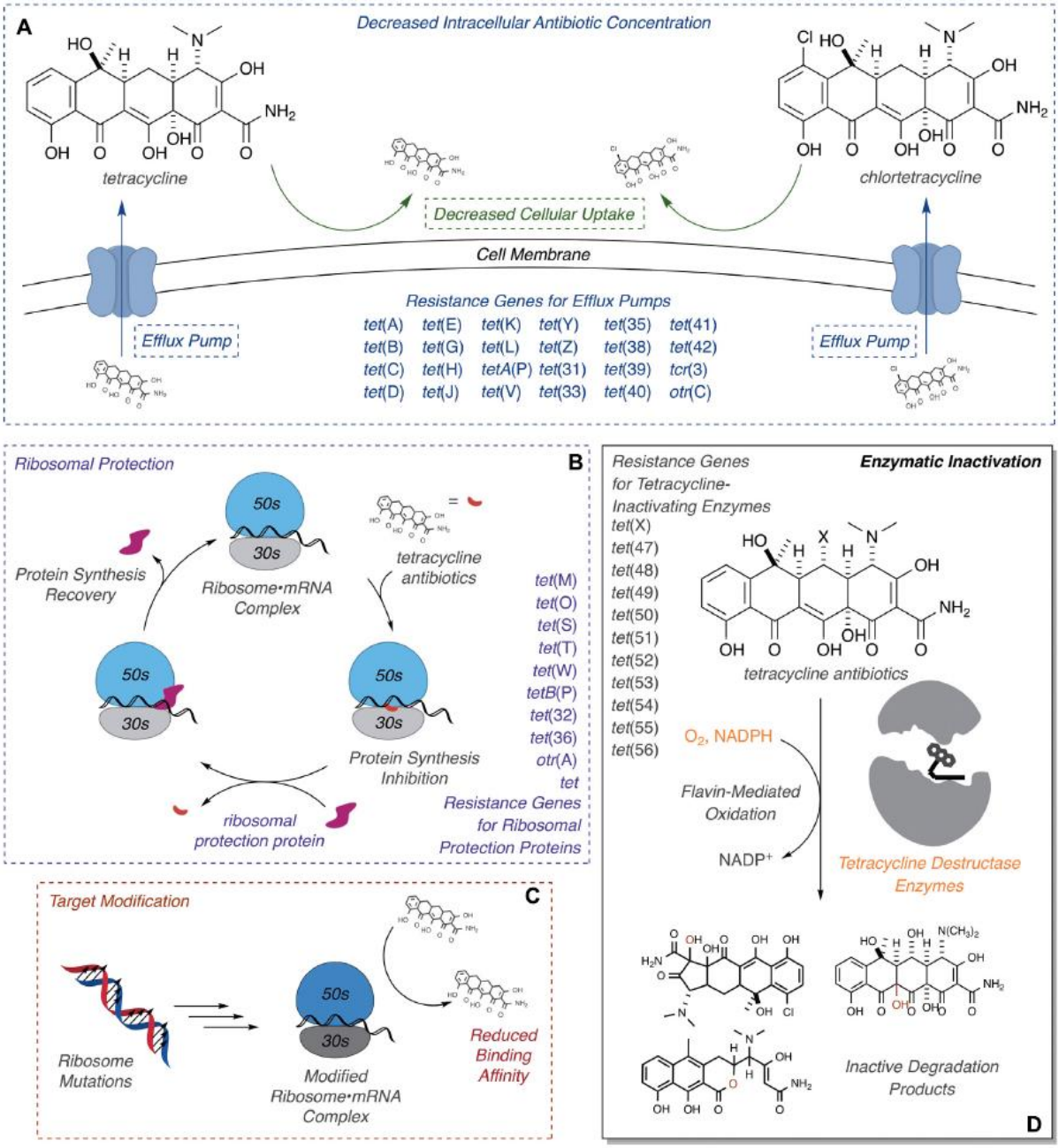


Figure 4- a): **Molecular mechanisms of tetracycline resistance.** (A) Efflux, exclusion; (B) ribosome protection; (C) ribosome modification; and (D) enzymatic inactivation. Documented antimicrobial resistance genes associated with each type of tetracycline resistance is indicated. Figure adapted from Markley and Wencewicz[84].

Tigecycline is a member of the glycylcyclines, which are protein synthesis-inhibiting antibiotics that exhibit activity against a broad spectrum of gram-positive and gram-negative organisms, including MRSA, vancomycin-resistant *Enterococcus* spp., and other difficult-to-treat pathogens[85]. As a derivative of minocycline, tigecycline inhibits bacterial protein synthesis by binding to the 30S subunit of the ribosome. However, it is not affected by classical mechanisms of resistance to tetracyclines, such as specific efflux pumps and ribosome protection[86,87]. As a last resort drug, tigecycline is highly regarded for its activity against *S. aureus*. Recently, multiple studies based on data from the Tigecycline Evaluation and Surveillance Trial, a global surveillance program, reported that the resistance of *S. aureus* isolates to tigecycline in many regions of the world remained extremely low[88,89]. However, multiple studies have also reported the emergence of tigecycline-resistant *S. aureus* in clinical settings and laboratories[90–92]. There is limited data on tigecycline susceptibility patterns among CoNS.

1.7.2 **Prevalence of chlorhexidine resistant genes in staphylococci**

There are 11 genes known to encode efflux-mediated resistance to biocides[93], and more are being discovered. Not all these genes have been identified in staphylococci. The eleven (11) efflux-mediated genes include *qac*A, B, E, EΔ1, F, G, H, J, Z, *smr* and *norA*. The significant genes for chlorhexidine resistance are *qacA/B*. Prevalence of *qacA/B* genes in CoNS varied between 12% and 49%[94,95]. It was estimated higher in isolates from nurses than from the general population (57% versus 14%, respectively; $P<0.001$)[96]. Several, but not all, studies have suggested horizontal transfer of plasmids carrying the *qacA/B* genes among strains of *S. aureus* and CoNS[97,98]. A prospective study carried out with 237 *S. aureus* isolates identified a statistically significant association between isolates carrying the *qacA/B* genes and resistance to the following antibiotic agents: ciprofloxacin ($p=0.005$), trimethoprim/sulfamethoxazole ($p=0.001$), clindamycin ($p=0.023$) and tetracycline ($p=0.01$). No significant association between the *qacA/B* genes and resistance to gentamicin, fusidic acid or erythromycin was identified[96]

1.8 OBJECTIVES

This thesis aimes to investigate to decipher 3 objectives.

Objective 1: High preterm birth with its associated neonatal sepsis and high mortality is higher among the Black race. However, few studies investigate maternal vaginal microbiota composition as a risk factor among indigenous Black women. Therefore, this part of the study attempted to investigate maternal vaginal dysbiosis as a risk factor for spontaneous preterm delivery with subsequent EONS among indigenous Black women who gave birth at a tertiary hospital in a low-income country.

Objective 2: CoNS, primarily *S. epidermidis* and *S. haemolyticus*, are common etiologic agents in neonatal sepsis in low and middle-income countries (LMICs). There is epidemiological evidence that *S. aureus* strains resistant to some of the 'Watch' and 'Reserve' WHO classified antimicrobial groups are emerging from LMICs where these antimicrobial agents are rarely used due to cost. Data on CoNS, especially isolates in the NICUs, are mostly missing. Therefore, in this part of the study delivers insight into *S. epidermidis* and *S. haemolyticus* species' clonal relatedness to predict their source(s) of transmission. It further determined antimicrobial susceptibility patterns of some of the 'Watch' and 'Reserve' group antimicrobials and mupirocin for these bacterial species cultivated from a resource-limited hospital, where there were no prior exposures of these antimicrobials. Antimicrobial gene carriage in these isolates was screened and used to predict mechanisms of resistance to these antimicrobials.

Objective 3: A clinical trial performed in a low-income country revealed that the application of chlorhexidine ointment on umbilical cords of neonates has significantly reduced neonatal mortality due to sepsis. The WHO has recommended chlorhexidine for neonatal umbilical cord in countries worst affected by neonatal mortality due to sepsis. Thus, this part of the study established baseline chlorhexidine minimum inhibitory concentrations (MICs) and screen for biocide resistance genes *qacA/B* in staphylococcal isolates cultured from a tertiary hospital in Ghana before commencement of chlorhexidine ointment usage in the hospital.

2 METHODS

2.1 Methods for Objective 1

2.1.1 Study design, study population and participant selection

This observational, cross-sectional and case-control study was a sub-study taken from a larger study (Ghana Neonatal Sepsis Study) conducted in the Ho Teaching Hospital (HTH), Ghana, from March to June 2018. All of the 96 women whose babies were diagnosed with sepsis or who were at risk of sepsis were accepted as eligible for our larger study following informed consent (Supplementary data 6.3 show flow chart of neonates recruitment and study outcomes). After applying exclusive criteria that the mother must not have vaginal bleeding or have given birth by caesarean section, must not have a history of chronic disease like hypertension, and must not be on antibiotic medication, only 24 mothers were eligible. However, when we used the inclusive criterion that the baby must have blood culture-proven sepsis (EONS), only six mothers' swab samples were used. Four gave birth to preterm babies (Case) and two gave birth to full term babies (Control).

2.1.2 Vaginal swab samples collection, transport and storage

A nurse collected the sample by inserting a wooden cotton swab approximately 6 cm deep past the vaginal introitus, rotated it three times back and forth and then removed the swab and placed it into the tube. Two swab samples were taken. One was used for vaginal microbiota and the other to culture for bacterial isolation and identification. The swab was aseptically broken into a screw-cup vial containing 1 ml of nuclease-free distilled water and then frozen at -20 ^{o}C. The swab samples were transported on dry ice from Ghana to Germany and then stored at -80 ^{o}C until used for DNA extraction.

2.1.3 **16S rRNA gene library preparation and sequencing**

DNA was extracted from vaginal swab samples with a QIAamp®DNA Microbiome kit (QIAGEN, MD, USA) following the manufacturer's protocol without deviation. Briefly, a swab sample in 1 ml of transport medium was dried off by being pressed against the tube wall multiple times. To the 1 ml sample, 500 µL of buffer AHL was added and then incubated at room temperature in a thermomixer at 600 rpm. The sample was then centrifuged at 10,000xg for 10 min and the supernatant carefully removed without disturbing the pellet. To the pellet, 200 µL of buffer ATL containing DX was added. The suspension was mixed, and the whole volume transferred into a Pathogen Lysis Tube (PLTube). Bacterial cells were lysed using the Tissuelyser for 10 min at 50HZ. The PLTube was centrifuged at 10,000xg for 1 min and the supernatant transferred into a fresh microcentrifuge tube. An aliquot of 40 µl of proteinase k was added to this suspension, vortexed and incubated at 56 ^{o}C for 30 min at 600 rpm in a heating block. Buffer APL2; 200 µL was added to the suspension, mixed by pulse vortexing for 30 sec and then incubated at 70 ^{o}C for 10 min with intermittent spinning of the tube. The suspension was then loaded onto the QIAamp UCP Mini Column and then centrifuged at 6,000xg for 1 min. The column was washed first with 500 µL buffer AW1 followed by AW2 and centrifuged at 6,000xg for 1 min and 20,000xg for 3 min. The column was dried by centrifuging further at 20,000xg for 1 min. DNA was eluted by adding 50 µL of buffer AVE to the column, incubated at room temperature for 5 min and then centrifuged at 6,000xg for 1 min. The eluted DNA was stored at -20 ^{o}C until used for polymerase chain reaction (PCR).

Samples were assigned to primer pairs with unique combinations of Multiplex identifiers (MIDs) to allocate an individual sequence to the respective sample after next-generation sequencer (NGS) has sequenced the library. The 16S rRNA gene was amplified using uniquely barcoded primers flanking the V3 and V4 hypervariable regions with fused MiSeq adapters in a 25 µL PCR volume.

Forward Primer = 5'
TCGTCGGCAGCGTCAGATGTGTATAAGAGACAGCCTACGGGNGGCWGCAG and
Reverse Primer = 5'
GTCTCGTGGGCTCGGAGATGTGTATAAGAGACAGGACTACHVGGGTATCTAATC
C were used. The compositions of each reaction mixture and PCR program were outlined (Table 4-a&b).

Table 4-a): **Reaction mix for PCR amplification of V3-V4 region 16S rRNA gene**

Reaction component	Volume	Final concentration/amount
RT-PCR Grade Water	10.25 µL	-
5X Phusion HF Buffer	5 µL	1X
dNTPs (10 mM each)	0.5 µL	200 µM each
Forward Primer (2 µM)	4 µL	0.32 µM
Reverse Primer (2 µM)	4 µL	0.32 µM
Template DNA	1 µL	-
Phusion Hot Start II DNA Polymerase (2U/µL)	0.25 µL	0.5 units
Total volume	**25 µL**	

The plate was covered with an adhesive PCR plate seal, gently vortexed, and spun down.

PCR amplification was performed with the following conditions:

Table 4-b): **PCR program for V3-V4 16S rRNA gene amplification**

Cycle step	Temperature	Duration	
1. Initial denaturation	98°C	30 sec	
2. Denaturation	98°C	9 sec	
3. Annealing	55°C	30 sec	
4. Extension	72°C	45 sec	32 cycles
Final extension	72°C	10 min	
6. Hold	12°C	∞	

2.1.4 **Quantification and normalization of PCR amplicons**

PCR products of the 16S rRNA gene fragments with an estimated size of approximately 460 bp were separated by agarose gel electrophoresis. Agarose gels (1.5%) prepared with TAE buffer (40 mM Tris-HCl, 20 mM acetic acid, 1 mM EDTA) containing SYBR® Safe DNA Gel Stain (SYBR, Thermo Fisher Scientific) were loaded with 5 µL sample supplemented with 1 µL 6X Loading Dye (Thermo Fisher Scientific). As a fragment size marker, 1 µL GeneRuler

100 bp Plus DNA Ladder (Thermo Fisher Scientific) was mixed with 1 µL 6X Loading Dye and 4 µL ddH2O and loaded on the gel. Electrophoresis was performed at 120 V for 5 min and continued at 110 V for another 70 min.

PCR fragment intensity was then assessed with the QUANTUM ST4 1100 imaging system (Vilber Lourmat Deutschland GmbH, Eberhardzell, Germany). The fragment bands were analysed with the software Quantum Capt v16.04 (Vilber Lourmat Deutschland GmbH, Eberhardzell, Germany). With the known concentration of the size marker bands, the PCR products' relative concentration was estimated with the 500 bp marker band. Samples analysed on the same gel image were then pooled together at equimolar ratios using aliquots from the original PCR products. The PCR products' initial sub-pools were separated on another agarose gel as described above to separate residual primer and potential off-target fragments. The desired 16S rDNA gene fragments were cut out from the gel with X-TRACTA Tips, placed into 2 mL tubes and purified using the GeneJET Gel Extraction Kit (Thermo Fisher Scientific).

To this end, samples were supplemented with 400 µL of Binding Buffer and incubated for 10 min at 60 °C to melt the gel slices. 400 µL of 100% isopropanol were added and the mixtures mixed by vortexing. The volume of 800 µL of the mixtures was loaded to the GeneJET purification columns, and the columns were centrifuged at 12,000 g for 1 min. The flow-through was discarded, and the step was repeated with the remaining sample mixture. Another 100 µL of Binding Buffer was added, and the tubes were centrifuged for 1 min at 12,000 g. The flow-through was discarded, and 700 µL of Wash Buffer was added to each column. Samples were centrifuged at 12,000 g for 1 min, and the flow-through discarded. The column was centrifuged for 1 min, turned by 180° and centrifuged for another minute to remove the residual buffer from the filter. The GeneJET purification columns were placed into clean 1.5 mL reaction tubes, and 15-20 µL of Elution Buffer were added to each column. Samples were centrifuged at 12,000 g for 1 min. The eluate was again placed on the column membrane and centrifuged a second time to increase the yield. The purified DNA was stored at -20 °C until further use. Materials and equipment are listed in Supplementary data 6.1.

2.1.5 **16S rRNA gene NGS library purification**

PCR products were purified using the AMPure XP magnetic beads (Agencourt) at a ratio of 1.8 beads (MagnaMedics Diagnostics, Geleen, the Netherlands) to sample (v/v). The manufacturer's protocol was followed without any modification. Briefly, the Agencourt AMPure XP bottle was allowed to attain room temperature and then vortexed to resuspend any magnetic particle that might have settled. An aliquot of 1.8 x volumes of the beads was added to the PCR product in a PCR plate and then mixed thoroughly by pipette mixing 10 times. The suspension was incubated at room temperature for 10 min and then placed in a Magnet Plate for 2 min to separate beads from the solution. The clear solution was aspirated and discarded. The plate was removed from the magnetic stand, and the washing was done with freshly prepared 75% ethanol as follows: 200 µl of the ethanol was added and mixed by pipetting up and down 10 times. The suspension was incubated for 30 sec at room temperature and then placed on the magnetic stand for 2 min. The ethanol was removed and discarded. The washing step was repeated, and the beads were dried at room temperature for about 10 min. The plate was removed from the magnetic stand, and 20 µl of Qiagen PowerSoil kit solution C (elution buffer) was added, mixed by pipetting 10 times, and incubated at room temperature for 2 min. The PCR plate was placed on the magnetic stand for 2 min to separate beads from the solution. The clear solution was transferred into a new tube and stored at -20 °C until further use.

2.1.6 **Library quantification and quality check**

Quantification of libraries using qPCR was done using a commercial kit (NEBNext Library Quant Kit by New England Biolabs®, MA, USA) and Mastercycler® ep realplex^2 (Roche Ltd). Following the manufacturer's guidelines, dilution series were made for all libraries and run parallel with the provided standards. A set of three dilutions (1:1,000, 1:10,000 and 1:100,000) was made for all libraries and compared to three standards and negative control (respective concentrations of 10 pM, 1 pM and 0.1 pM). A PCR reaction mixture total volume of 20 µl (comprising 16 µl NEBNext Library Quant Master Mix with primers and 4 µl of either sample or standard) was used. All samples and standards were run in triplicate and subjected to PCR cycles as follows: initial denaturation at 95 °C for 1 min followed by 35 cycles of denaturation at 95 °C for 15 sec, extension at 63 °C for 45 sec and a holding temperature of 4 °C. The machine automatically generated a standard curve, and it was used to estimate concentrations

of libraries. Final library concentration was calculated using the following formula: calculated concentration x 399/library size (bp). The final concentration of the library was diluted to 4 Nm. The library's quality was checked using the Agilent Bioanalyzer 2100 (Santa Clara, CA, USA). See Supplementary data 6.2 for the quality control results.

2.1.7 **Final preparation of library and 16S rRNA sequencing**

The 16S rRNA gene fragment NGS library was prepared for analysis on a MiSeq desktop sequencer (Illumina, San Diego, USA) using the MiSeq Reagent Kit v3 (Illumina, San Diego, USA) as described by Miodovnik and colleagues[99]. The reagent cartridge and the HT1 buffer were removed from the freezer and thawed at room temperature before the library preparation. The volume of 5 µL of the 16S rRNA gene fragment NGS library (sample library) was mixed with 5 µL of a 0.2 N NaOH solution, briefly vortexed and incubated for 5 min at room temperature to denature the DNA. 990 µL of ice-cold HT1 buffer was added, and the library was further diluted in HT1 buffer to the final concentration of 15 pM (450 µL denatured DNA library + 150 µL HT1 buffer). An internal quality control, the PhiX control library, was prepared by mixing 2 µL of the 10 nM PhiX library with 3 µL of 10 mM Tris-HCl (pH 8.5) containing 0.1% Tween 20. The 4 nM PhiX control library was denatured by mixing 5 µL PhiX control library with 5 µL 0.2 N NaOH, vortexed briefly and centrifuged at 280 x g for 1 minute and incubated for another 5 min at room temperature. Then 990 µL of the HT1 buffer were added, and the PhiX control library was diluted to a final concentration of 12.5 pM (375 µL of 20 pM denatured PhiX control library + 225 µL HT1 buffer).

The sample library and the PhiX control library were then combined by mixing 540 µL of the 15 pM denatured sample library with 60 µL of the 12.5 pM denatured PhiX control.
The custom-made primers, 27F, Index and 338R, were diluted to 0.5 µM by adding 3 µL of 100 µM primer stock solution to 597 µL HT1 buffer. On the reagent cartridge, the reservoir positions 12,17,18,19 and 20 were opened with a sterile pipette tip. The read 1-primer in position 12 was taken out and transferred into a new tube, and 60 µL of the read 1-primer were combined with 540 µL of the forward primer (0.5 Mm). The diluted and denatured sample library (containing 1.25 Pm PhiX control library) was transferred into the reservoir position 17. The forward primer mixed with the read 1-primer was loaded to reservoir position 20 of the reagent cartridge. The FlowCell was cleaned and inserted into the MiSeq desktop sequencer.

The bottle with the incorporation buffer and the reagent cartridge were inserted into the sequencer machine. A digital sample sheet was uploaded onto the machine's software application, and the run was started.

2.1.8 **16S rRNA gene sequence analysis**

Raw sequenced data were processed using USEARCH version 8.0.1623[100], and overlapping reads were merged into contigs. To perform taxonomic classification, RDP version 14 was used. Alpha diversity (Cha1) was estimated using Vegan package version 2.2-1 in R (R Foundation, Vienna, Austria).

2.2 Methods for objectives 2 and 3

2.2.1 **Sources of bacterial isolates**

2.2.2 **Neonates blood cultures**

Bacterial cultures were done in the HTH, UHAS Microbiology Laboratory, Ho, Ghana. Blood samples were collected by aseptic procedures and inoculated directly into BACTEC Peds Plus/F (Becton Dickinson Company, Maryland, USA) blood culture bottles. Blood samples were transported from the ward immediately or within 2 hours of collection and were placed in the BACTEC™ 9050 blood culture instrument. The inoculated culture bottles were loaded into the BACTEC™ 9050 instrument per the manufacturer's guide. The culture bottles were arranged in the three concentric rings designated A, B and C. The culture bottles were incubated at 35 ^{o}C with continuous agitation for a pre-determined time for maximum recovery of organisms. An indicator light flagged positive cultures on the instrument's front, along with an audible alarm, and a display on the LCD screen. Positive culture bottles were sub-cultured onto 5-10% sheep blood agar, harvested, and stored at -20 ^{o}C in labelled sterile screw-cap vials until transported to Germany for further analyses. Blood smears from the cultures were stained with Gram stain, and microscopy was done to identify the isolates' Gram reactions. For the Gram-stained method, heat-fixed bacteria on an object slide were covered with crystal violet (Gentiana violet solution) for 3-5 min. Washed and dried slides were covered in Lugol's

solution for 2-3 min, dried and destained with ethanol (96% v/v). Counterstaining with safranin O (0.25% w/v) for 1 min was followed by drying and examination under the light microscope.

2.2.2.1 Bacterial culture from swab samples from mothers, clinical staff, students and objects

Nasal mucosae swab samples collected from the clinical staff, mothers, medical and nursing students (Supplementary data 6.4 and 6.5 show the demographic characteristics of clinical staff and students, respectively) and inanimate objects were inoculated on 5% sheep blood agar plates and incubated aerobically at 37 °C, for 24 hours. Plates with no growth after 24 hours were re-incubated for another 24 hours. Colonies on blood agar plates were subjected to colony identification and Gram staining for Gram-positive cocci identification. The top surface of represented colonies was touched with a straight wire and then sub-cultured on new blood agar plates. The second Gram staining was performed, and confirmed Gram-positive coccus cells were harvested and stored in Brain Heart Infusion (BHI) (Oxoid Ltd, England) with 15% glycerol at -20 °C for further research.

2.2.3 **Bacterial isolates identification (MALDI-TOF)**

All the bacterial isolates were identified in the Institute of Clinical Microbiology at the University of Lübeck, Germany, using Bruker Daltonik MALDI-TOF Biotyper® GmbH. Bacterial isolates were revived from glycerol-preserved stocks by seeding them on a 5-10% sheep blood agar plate and incubated at 37 ^{o}C for 24 hours or until visible growth was observed on the plate. To avoid sporulation (by spore-forming bacteria), MALDI-TOF Mass Spectrometry was performed immediately after visible growth was observed on blood agar. Bacterial isolates were spotted from a single colony onto a MALDI-TOF MS 48 well target plate using a sterile toothpick following Bruker specifications. One microliter of 70% formic acid was layered on top of the sample and air-dried. After that, 1 µl of the α-cyano-4-hydroxycinnamic acid matrix in 50% acetonitrile-2.5% trifluoroacetic acid was added to each spot and air-dried. The processed plate was then put into the machine for identification of bacterial isolates.

2.2.4 **Antimicrobial susceptibility testing (VITEK2)**

Overnight cultured bacterial isolates on blood agar media were observed for purity, and 0.5 McFarland concentrations were made with the manufacturer's diluent and checked with a bench-top Turbidimeter. The inoculum was added to a VITEK 2 AST card according to the manufacturer's instructions. The reagent card was inserted into the machine for analysis. A purity check plate was performed by plating the diluted suspension on blood agar, incubated aerobically at 37 ^{o}C overnight. The MICs of 17 antibiotics were determined for these strains by VITEK 2®machine (bioMérieux, Durham, USA). *S. aureus* NCTC 12493 was included as a susceptible quality control strain. The MIC results were interpreted according to the 2018 European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints. The MICs of mupirocin, teicoplanin, vancomycin, and tobramycin were also tested using gradient strips (E-test®; Liofilchem® s.r.l., Italy) using Mueller-Hinton E agar (bioMérieux SA, Strasbourg, France). For this procedure, represented-isolated colonies from an overnight agar plate were suspended in the diluent medium to achieve the recommended McFarland standard. To verify that the procedure gave the correct inoculum density in terms of CFU/mL (a 0.5 McFarland approximately corresponds to 1-2 x 108 CFU/mL for E. coli), the optical density of suspension was measured using the Turbidimeter. A sterile swab was dipped in suspension and squeezed on the test tube walls to eliminate excess liquid. The swab was streaked over the entire agar surface. This procedure was repeated by streaking two more times, rotating the plate approximately 60° each time to ensure an even distribution of suspension to streak the inoculum over the entire agar surface efficiently. Excess moisture was allowed to dry on the surface of the agar plate completely. The strip was applied to the agar surface with the scale facing upwards and the code of the strip was applied to the outside of the plate by pressing with sterile forceps on the agar's surface and ensuring that the antibiotic's whole length gradient was in complete contact with the agar surface. The agar plate was incubated in an inverted position aerobically at 37 ^{o}C overnight. The MIC was read where the relevant inhibition ellipse intersects the strip.

2.2.5 **Bacterial isolates and chlorhexidine susceptibility testing**

A total of 410 staphylococcal isolates (from a larger study: Neonatal Sepsis in a Low-income-country) obtained from neonates' blood samples, nasal mucosae and skin of the babies' mothers, clinical staff and newly admitted medical and nursing students who had no contact with the hospital (control) was analysed. Isolation of bacterial isolate cultures was previously described. In the absence of an agreed standardized procedure, chlorhexidine MIC and MBC were determined for all the isolates using the sensitized microtiter plate broth dilution method as described by Wand and colleagues[101] with a small modification. Briefly, the stock chlorhexidine (20%w/V; Sigma Aldrich, USA) was diluted to 128 mg/L. Bacterial isolates were cultured in Mueller-Hinton broth incubated at 37 ^{o}C for 24 hours, and their concentrations were adjusted to 0.5 McFarland turbidity standard. The MICs were determined using an overnight Mueller-Hinton broth culture in a microdilution method with a concentration range of 0-128 mg/L chlorhexidine. All broth microdilution cultures were incubated at 37 ^{o}C for 18-20 h. The MIC was determined by visual inspection (by three technical personnel) against the control, and for the MBC, 25 µl of non-turbid wells were seeded on 10-15% sheep blood agar and incubated at 37 ^{o}C for 24 hours. *Staphylococcus aureus* ATCC 29213, NCTC 12493 and *E. coli* ATCC 25922 were included as the susceptibility quality control strain.

2.2.6 **DNA extraction from bacterial cells for *tuf* gene (and whole-genome) sequencing**

DNA was extracted for 15 isolates using a DNeasy Blood and Tissue Kit (Qiagen, Germany). One sterile inoculation loop (~3mm^2) of the plated overnight culture was resuspended in 100 µl of ultrapure water in a 1.5 ml microcentrifuge tube and mixed by pipetting. The bacterial DNA extraction protocol described in the kit for Gram-positive bacteria was followed without modification. The 100 µl bacterial suspension was centrifuged for 10 min at 7500 rpm, and the pellet resuspended in 180 µl enzyme lysis buffer (20 mM Tris-Cl pH 8.2, 2 Mm Na EDTA, 1.2% Triton®X-100, Lysozyme 20 mg/ml). The suspension was incubated for 30 min at 37 ^{o}C. To this, 25 µl proteinase k and 200 µl buffer AL were added, mixed, and incubated at 56 ^{o}C for 30 min. Then, 200 µl of molecular grade ethanol (96-100%) was added. The mixture was vortexed and transferred into a DNeasy Mini spin column placed in a collection tube, followed by centrifugation for 1 min at 8000 rpm. The column was then washed with 500 µl AW1 followed by 500 µl AW2 buffers, centrifuged at 8000 rpm for 1 min and 14,000 rpm for 3 min,

respectively. The column was placed in a sterile 1.5 ml microcentrifuge tube, 100 µl AE buffer was added, and it was centrifuged for 1 min at 8000 rpm to elute purified bacterial DNA.

2.2.7 **PCR amplification and sequencing of the *tuf* gene**

PCR amplification of the *tuf* gene was performed on a C1000 Touch™ Thermal Cycler (Bio-Rad) by applying a set of primers 5'-GCCAGTTGAGGACGTATTCT-3' and 5'-CCATTTCAGTACCTTCTGGTAA-3', which amplify a 412 bp fragment of the *tuf* gene. PCR conditions were optimized as follows: a total reaction mixture of 50 µl contained 25 µl of DreamTaq Master Mix (10x buffer, 10mM dNTPs and 5U/µl DreamTaq by Thermo Fisher Scientific, Bremen, Germany), 2.5 µl each of the primers, 18 µl of PCR water, and 2 µl of genomic DNA template. PCR was done in a DNA thermal cycler using the following program, as shown in Table 5.

Table 5: **PCR program for tuf gene amplification**

Cycle step	Temperature	Duration	
1. Initial denaturation	95°C	3 min	
2. Denaturation	95°C	30 sec	
3. Annealing	56°C	30 sec	
4. Extension	72°C	45 sec	35 cycles
Final extension	72°C	10 min	
6. Hold	12°C	∞	

The PCR products were aliquoted (46 µl) into 1 ml Eppendorf tubes, sealed, and shipped to GENEWIZ-Brooks Life Sciences, Leipzig, Germany, for *tuf* gene sequencing. DNA sequencing was done by the Sanger method. The obtained sequences of the *tuf* gene for each isolate were aligned separately by MEGA 5 (Molecular Evolutionary Genetics Analysis) software and compared with all existing sequences of CoNS annotated in the GenBank database.

Whole-genome sequencing (Illumina Novaseq6000)

Novogene UK Ltd, Cambridge, performed whole-genome sequencing. Briefly, library preparation was performed with the NEB Next Ultra DNA Library Prep Kit (New England Biolabs, Ipswich MA, USA) according to the manufacturer's directions. The genomic DNA was randomly fragmented to a size of 350 bp by shearing. DNA fragments were end-polished, A-tailed, and ligated with the NEBNext adapter for Illumina sequencing and further PCR enriched by P5 and indexed P7 oligos. The PCR products were purified (AMPure XP system), and the resulting libraries were analysed for size distribution by an Agilent 2100 Bioanalyzer and quantified using real-time PCR. Library validation was done on a Fragment Analyzer System (Agilent Technologies, California, USA) to control library quality and quantified using qPCR via ABI QuantStudio 12K Flex (Thermo Fisher Scientific). Whole-genome sequencing was performed with an Illumina NovaSeq6000 (Illumina, California, USA) to generate 150 bp paired-end reads. The genomes were sequenced at a minimum coverage of 100x.

2.2.8 **Bioinformatics analyses**

Paired reads of the wild-type isolates' FASTQ files were processed to remove adaptor sequences, to trim low-quality ends, and to remove short reads using fastp v0.20.0 [102]. To validate the isolates' purity, the isolates were taxonomically classified on the basis of the sequencing reads using Kraken v2 [103] with the default taxonomy database. Sequencing reads were assembled using MEGAHIT v1.2.9 [104]. Gene prediction and functional annotation were performed using Prokka v1.14.6 [105] with the BLAST, Pfam, and NCBI databases. The aforementioned software packages were used with default parameters. Assembled genomes were submitted to MLST search online www.cge.cbs.dtu.dk/services/MLST-2.0, as described by[106]. Antibiotic resistance genes were searched for via the websites www.card.mcmaster.ca/rgi and www.ifr48.timone.univ-mrs.fr/blast/arg-annot_v6. For CARD, the detection of antimicrobial resistance genes uses so-called "protein homolog models" where BLAST sequence similarity is determined to detect functional homologs[107]. For the detection of mutations associated with antimicrobial resistance, so-called "protein variant models" are applied. Searches can be applied using two criteria: the default (perfect and strict hits only) or discovery (perfect, strict, and loose hits) setting. For outbreak analyses, the default setting is endorsed. This tool's developers placed a disclaimer stating that constant curation changes to the database and cut-off values could potentially affect results. Hence, caution should be exercised when interpreting results[108]. For antibiotic resistance genes screening, the default was set for perfect or strict hits (≥95% identity with gene sequences in the CARD database), after which it was set for loose hits. This was done to identify antibiotic resistance genes for a particular antimicrobial agent to better understand the mechanism of resistance to that antimicrobial agent. Staphylococcal cassette chromosome *mec* (SCC*mec*) type was determined using the website www.cge.cbs.dtu.dk/services/SCCmecFinder. Plasmids were screened for on the website https://bitbucket.org/genomicepidemiology/plasmidfinder.git using the raw sequenced data. Supplementary data 6.6 shows the sequences of plasmids identified on the genomes of isolates studied in this study

2.2.9 **Whole-genome data availability**

This Whole Genome Shotgun project has been deposited at DDBJ/ENA/GenBank under the accession numbers, as stated in Table 6.

Table 6: **Whole-genome sequences accession numbers**

ID	Staphylococcal species	BioProject accession No.	GenBank accession No.	BioSample accession No.
HESN016B	*epidermidis*	PRJNA668279	JADCSG000000000	SAMN16402347
HESN038B	*epidermidis*	PRJNA668279	JADCSK000000000	SAMN16402351
HESN074B	*epidermidis*	PRJNA668279	JADCSI000000000	SAMN16402349
HESN090B	*epidermidis*	PRJNA668279	JADCSE000000000	SAMN16402345
hHES103B	*epidermidis*	PRJNA668279	JADCSS000000000	SAMN16402359
HESN035b	*epidermidis*	PRJNA668279	JADCSM000000000	SAMN16402353
HESS022	*epidermidis*	PRJNA668279	JADCST000000000	SAMN16402360
HESN036B	*haemolyticus*	PRJNA668279	JADCSF000000000	SAMN16402346
HESN094B	*haemolyticus*	PRJNA668279	JADCSC000000000	SAMN16402343
BABY089B	*haemolyticus*	PRJNA668279	JADCSN000000000	SAMN16402354
BABY162B	*haemolyticus*	PRJNA668279	JADCSH000000000	SAMN16402348
HESMS017b	*haemolyticus*	PRJNA668279	JADCSD000000000	SAMN16402344
HESMS053a	*haemolyticus*	PRJNA668279	JADCSO000000000	SAMN16402355
HESN035b	*haemolyticus*	PRJNA668279	JADCSR000000000	SAMN16402358
HESN072a	*haemolyticus*	PRJNA668279	JADCSJ000000000	SAMN16402350
MW015	*haemolyticus*	PRJNA668279	JADCSL000000000	SAMN16402352

3 RESULTS

3.1 Investigate maternal vaginal dysbiosis as a risk factor for spontaneous preterm delivery with subsequent EONS

One of the aims of the Vaginal Microbiome Study was to map the human vaginal microbiota to understand better the dysbiosis or infections caused by its imbalance to offer more appropriate treatment. One of the study's objectives was to address whether the vaginal microbial composition destined a woman to have preterm delivery (case) and subsequent vertical transfer of bloodstream bacterial infection is different from that of a woman who delivers term (control) also with a bloodstream infection.

3.1.1 **Maternal demographics**

The maternal demographic characteristics are described in Table 7-a.

Table 7-a: **Demographic characteristics of mothers**

ID	Age (years)	Occupation	Gravida	Parity	No. Of PBD	Chronic diseases	Antibiotics*
HESNO16	27	Trader	3	2	1	G6PD	No
HESN021	23	Trader	2	2	0	No	No
HESN025	21	Student	1	1	0	No	No
HESN032	26	Farmer	3	3	2	No	No
HESN026	29	Hairdresser	4	4	0	No	No
HESN044	28	Trader	2	2	0	No	No

PBD: previous babies deceased, G6PD: Glucose-6-phosphate dehydrogenase deficiency

Young maternal age at childbearing (≤19 years) and advanced maternal age (≥35 years) are associated with increased risk of spontaneous preterm birth with subsequent infant mortality[109,110]. In the current study, all mothers fall within childbearing age (20s to early 30s), suggesting that age was not a risk factor for giving birth to preterm babies. There is no clear-cut association between maternal gravida and parity with spontaneous preterm birth. However, some maternal chronic diseases like diabetes mellitus, preeclampsia, chronic hypertension, and systemic lupus erythematosus are known risks for spontaneous preterm birth. One mother was G6PD; however, the literature has no associated G6PD with spontaneous preterm bir

th[110].

3.1.2 **Babies demographics**

The babies' demographics and clinical characteristics are described in Table 7-b.

Table 7-b: **Characteristics of babies**

ID	Gestation (weeks)	Birth weight (Kg)	Age (days)	Apgar score (1 min)	Body Temp. (oC)	Antibiotics given	Major clinical diagnoses
HESNO16	24	1.1	1	5	35	No	Prematurity
HESN021	28	2	6*	NK	38.7	No	Prematurity/Neonatal sepsis
HESN025	36	2	1	9	37.5	No	Respiratory distress syndrome
HESN032	32	1.6	<1	6	37.9	No	Hypoxic ischemic encephalopathy
HESN026	37	3.3	2	7	37.3	No	Neonatal sepsis/Hyperbilirubinemia
HESN044	40	3.6	15	NK	37.4	No	Neonatal sepsis

NK: Unknown, *: EONS was first defined as the onset of sepsis less than seven days but later redefined as <3 days, especially for preterm neonates.

Classification of preterm based on the WHO system of classification revealed that one of the neonates falls within extremely preterm (less than 28 weeks), another one very preterm (28-32 weeks), and two within moderate to late preterm (32-37 weeks). All three 'case' neonates have low birth weight while both babies in the 'control' group have an average birth weight. Four of the neonates' sepsis is EONS, and the remaining two are late-onset neonatal sepsis (LONS) (Table 7-b). NB: *: EONS was first defined as the onset of sepsis less than seven days but later redefined as <3 days, especially for preterm neonates. Supplementary data 6.3 shows data on the mothers and neonates' demographic, neonatal sepsis and study endpoints for all babies enrolled in the study and risk factor for neonatal sepsis.

3.1.3 **Taxonomic classifications of bacteria detected in the vaginas of the mothers**

A

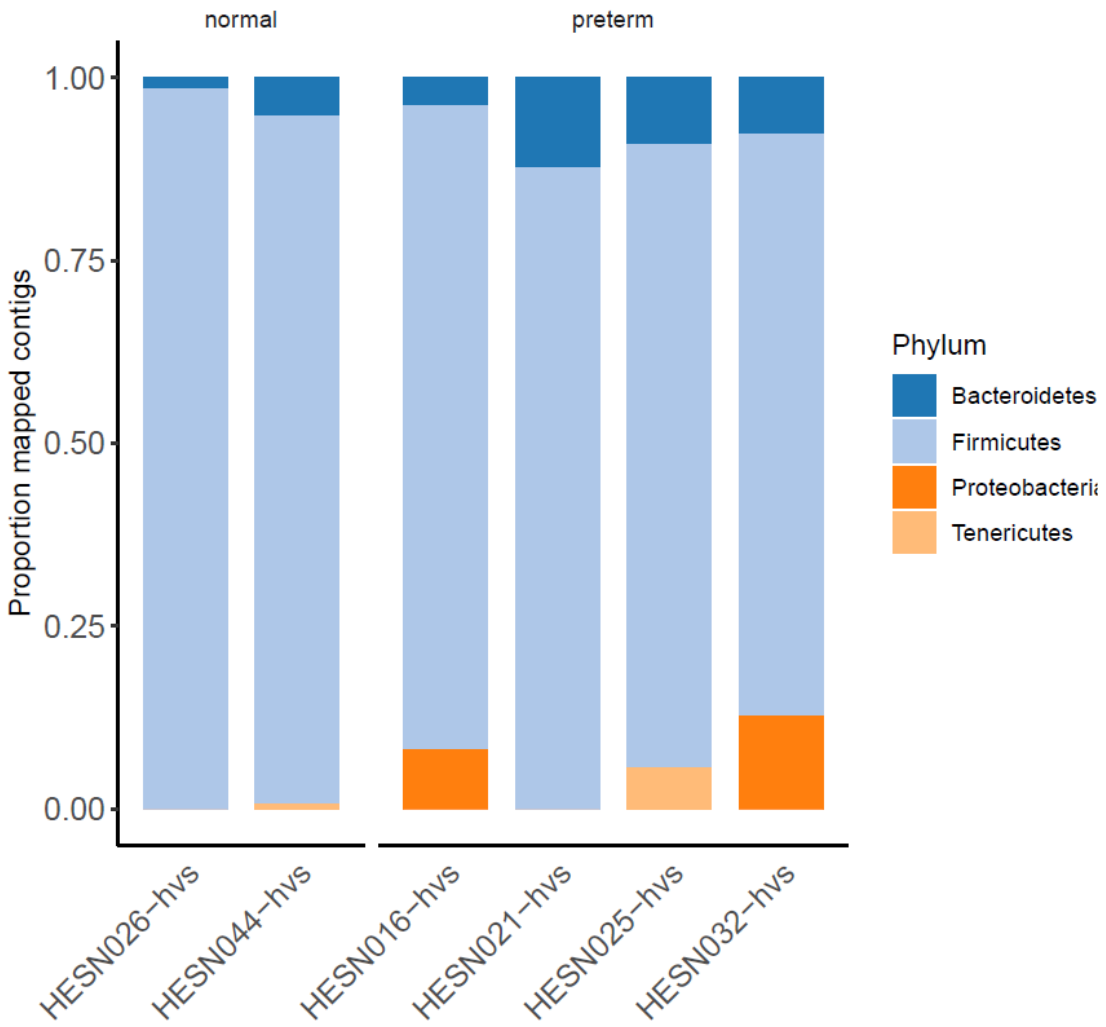


Figure 5- a): **Taxonomic classifications of maternal vaginal bacteria into phyla**

This study analysed taxonomic classification at the phylum level (Figure 5-a) and found that most of the samples mainly consisted of four phyla, namely, *Firmicutes*, *Bacteroidetes*, *Proteobacteria*, and *Tenericutes*. The phylum *Firmicutes* predominates.

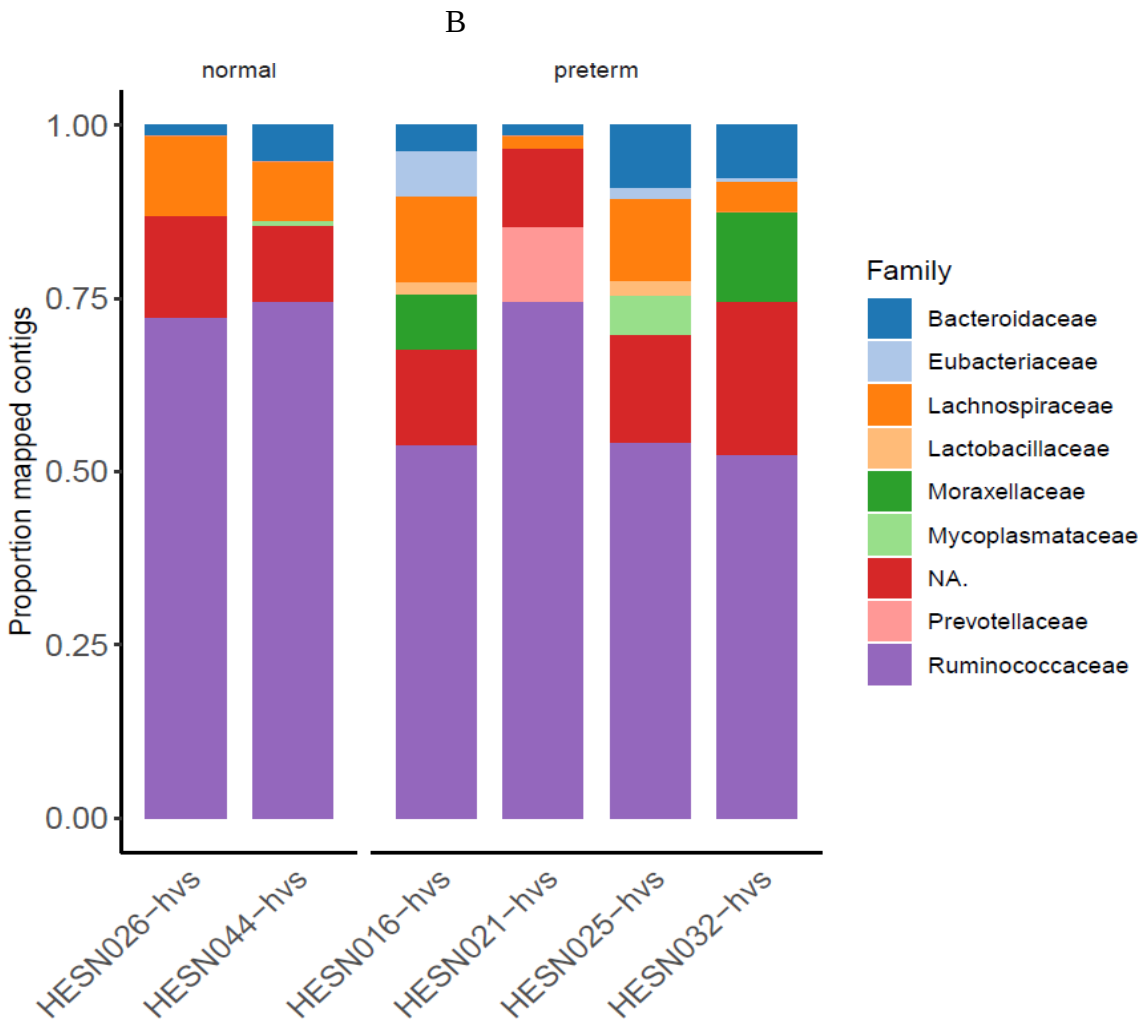


Figure 5- b): **Taxonomic classifications of maternal vaginal bacteria into families**

Among the Firmicutes identified, the represented families include *Ruminococcaceae*, *Lactobacillaceae*, *Lachnospiraceae*, and *Eubacteriaceae*. Among these families, *Ruminococcaceae* are most presented (abundance) in the vaginal samples of the studied women.

C

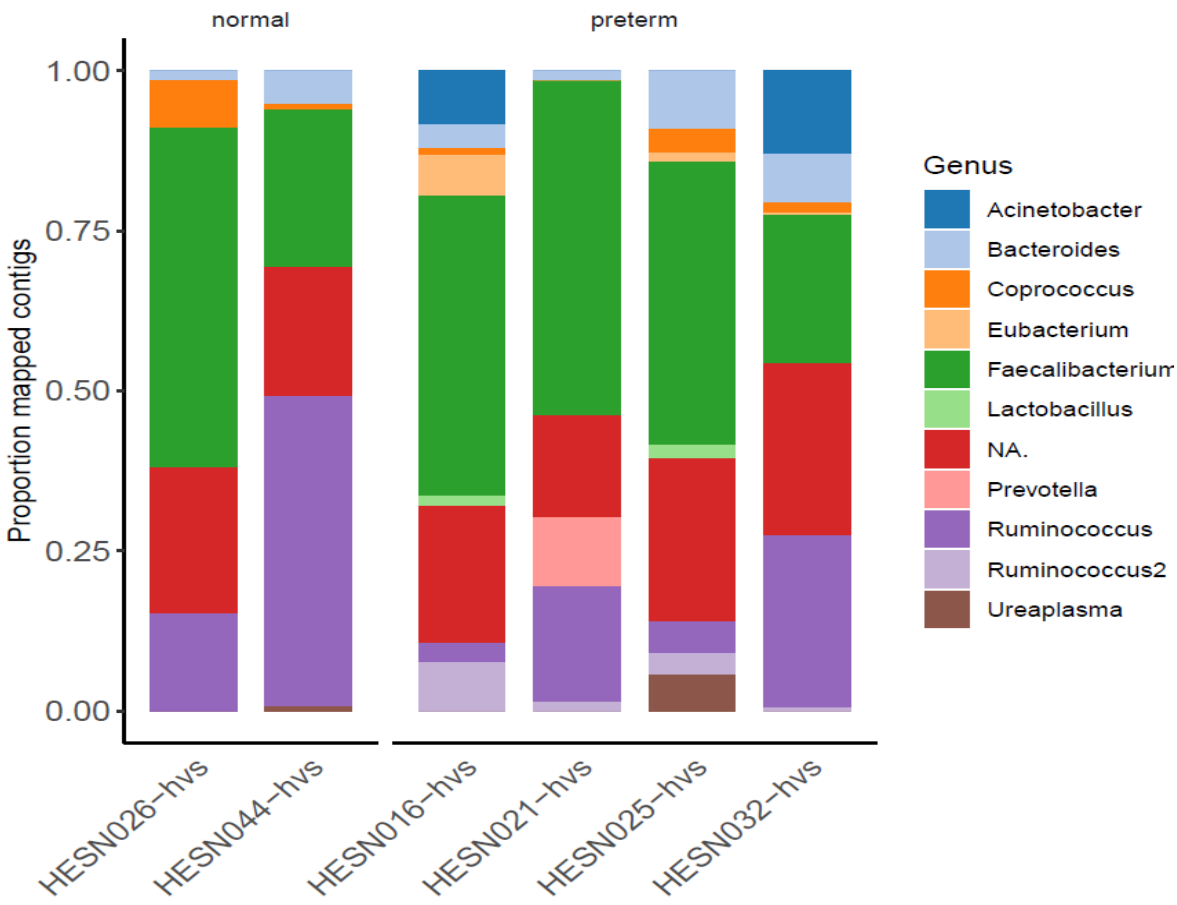


Figure 5- c): **Taxonomic classifications of maternal vaginal bacteria into genera**

Data were further analysed at the genus level of taxonomic classification (Figure 5-c) and revealed that among the *Ruminococcaceae* family, *Faecalibacterium* and *Ruminococcus* were the abundant genera in the studied mothers' microbiota. Generally, the vaginal communities of all six mothers at the genus level fall within community group IV, with the majority likely to be sub-group IV, which had no detectable *Lactobacillus* in their vaginas. The study compared the case and the control groups at the genus level. The data suggest that there were noticeable dysbioses in the vaginal microbiota of all six mothers with very few or undetectable levels of *Lactobacillus* species. However, the butyrate-producing species, *Faecalibacterium* and *Ruminococcus*, increased in abundance. Of the *Ruminococcus*, two genera were identified. These include *Ruminococcus* and *Ruminococcus* 2 (in some taxonomic classification known as *Blautia*). The difference between the two species is that whilst *Ruminococcus* species are facultative anaerobes, *Ruminococcus* 2 *(Blautia)* are known to be strictly anaerobic. The latter is carbohydrate fermenters, and some species are H_2/CO_2-utilizing acetogens, acetate, formate, succinate, lactate, and ethanol produced as by-products of fermentation and cellulose is degraded by some species. Of note, *Ruminococcus* 2 was detected in all of the case group but was absent in the control group. The two mothers in the case group, who had significantly detectable genus *Acinetobacter*, reported at least one of their babies died during their neonatal period.

Table 8: **Results of Shannon Index of diversity and dominant genus**

Participant ID	**(Shannon Diversity Index)**	**Lactobacillus**	**Dominant genus (genera)**	**Ruminococcus 2**
HESNO16	1.89	Very few	Faecalibacterium	Detected
HESN021	1.57	Undetected	Faecalibacterium	Detected
HESN025	1.99	Very few	Faecalibacterium	Detected
HESN032	1.98	Undetected	Faecalibacterium / Ruminococcus 1	Detected
HESN026	1.60	Undetected	Faecalibacterium	Undetected
HESN044	1.74	Undetected	Ruminococcus 1	Undetected

The analysis of Shannon diversity indexes for the vaginal microbiota in this work identified that three mothers who had preterm births with subsequent EONS had a higher diversity index than the control group (Table 8). One mother classified among the case group (HESN021), but her baby had LONS, had a similar lower index as those of the control group. She was selected among the case group because the study first defined EONS as onset from birth to seven day. However, this was later redefined as onset of sepsis from birth to three days of life. Both case and control groups have substantial dysbiosis of their vaginal microbiota.

Results 3.1: **Summary**

- Bacteria associated with vaginal CST IV were the only community members in all six participants regardless of gestation type and their neonates' type of sepsis.

- Genus *Ruminococcus* 2 (*Blautia*) was detected in the vaginas of the mothers who had spontaneous preterm deliveries but not in those who had term births (control group).

- A commonality between two participants who had at least one baby die during the neonatal period was detection of the genus *Acinetobacter* in their vaginas.

3.2 Clonal relatedness of *S. epidermis* and *S. haemolyticus* isolates to predict the source of transmission of these bacterial species to neonates in the Ho Teaching Hospital, Ghana

In Ghana, neonatal mortality is a huge problem. The latest national survey conducted in 2011 estimated the country's prevalence as 32 deaths per 1,000 live births[111], with some regions having a higher prevalence than others. The Volta Region happened to have the highest neonatal mortality rate of 47 deaths per 1,000 live births. The Volta Region is one of Ghana's 16 administrative regions, with Ho designated as its capital. It has four urban and 21 rural settlements.

A previous retrospective study performed in the Volta Regional Hospital of Ghana, now the Ho Teaching Hospital (HTH), revealed that early neonatal mortality is still high, especially among preterm babies and babies born with low birth weight.[112] Therefore, we sought to study the epidemiology (estimate prevalence, aetiology, and mortality) of neonatal sepsis in the HTH to suggest measures to reduce neonates' and infants' sepsis-related deaths in this hospital and places where similar pathogen profiles can be presumed. Neonatal sepsis results are shown in Supplementary data 6.1.

This study determined the possible source(s) of transmission of the two most common CoNS species using various molecular techniques.

3.2.1 Maximum likelihood phylogenetic analysis of the *tuf* gene of *S. epidermidis* and *S. haemolyticus* to determine clonal relatedness

1. S. epidermidis

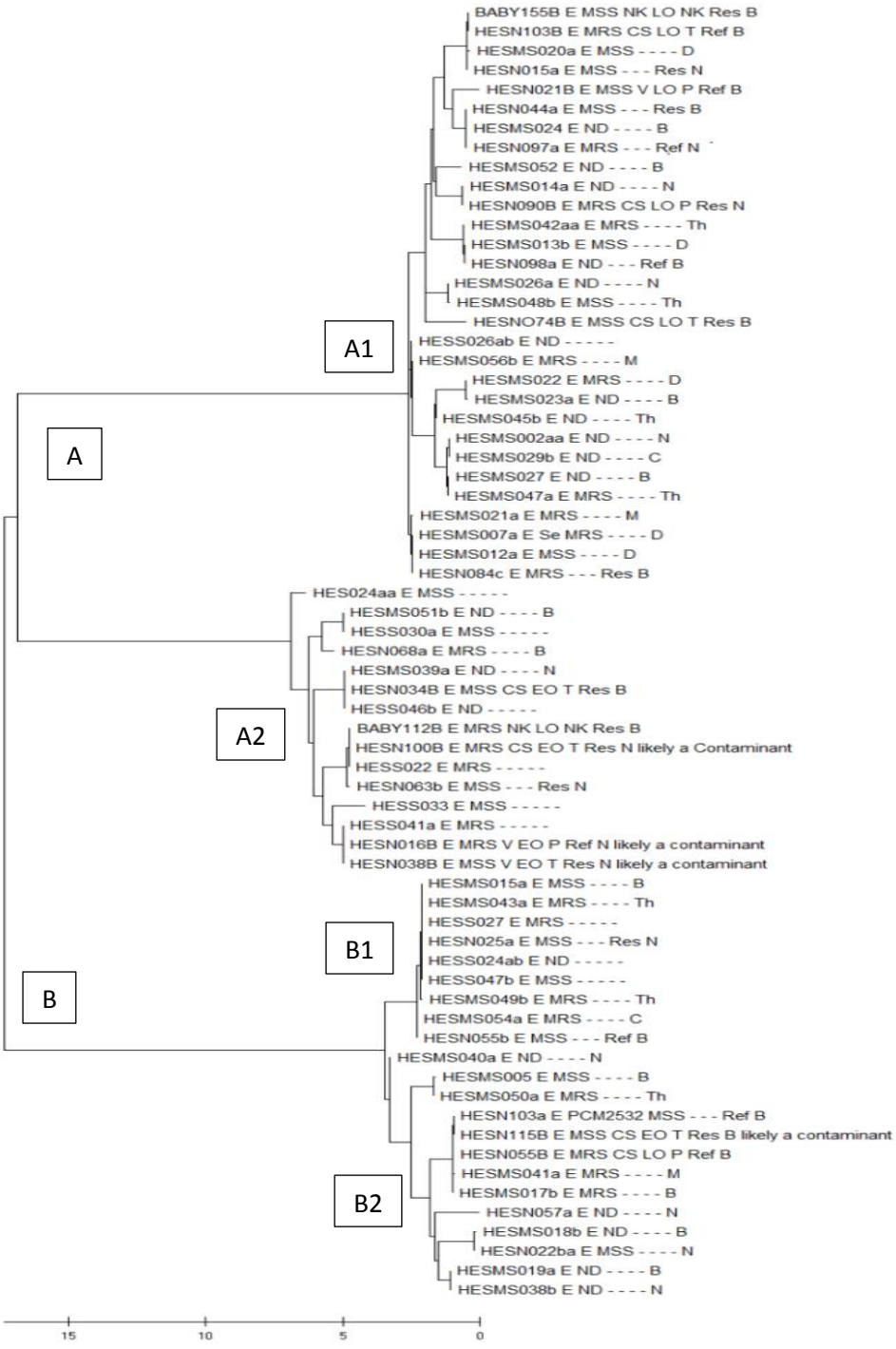


Figure 6- a): **Maximum likelihood phylogenetic tree obtained using the *tuf* genes of the 67 *S. epidermidis*.** E: Epidermidis; MSS: Methicillin susceptible staphylococcus; MRS: Methicillin-resistant staphylococcus; CS: Caesarean section; V: Vaginal delivery; EO: Early-onset neonatal sepsis; LO: Late-onset neonatal sepsis; P: Preterm; T: Term; Res: Residence; Ref: Referral; B: Baby unit; C: Children's ward; M: Maternity ward; N: Neonatal intensive

care unit; Th: Theatre; ND: Not done. Isolates labels: HESNXXXB-Neonate's blood sample; HESNXXX-Mother's nasal mucosa; HESMSXXX-Clinical staff's nasal mucosa; HESSXXX-Medical or nursing student's nasal mucosa; and BABYXXX-achieved bacterial isolates cultured from neonates' blood samples in 2016 at the HTH microbiology laboratory.

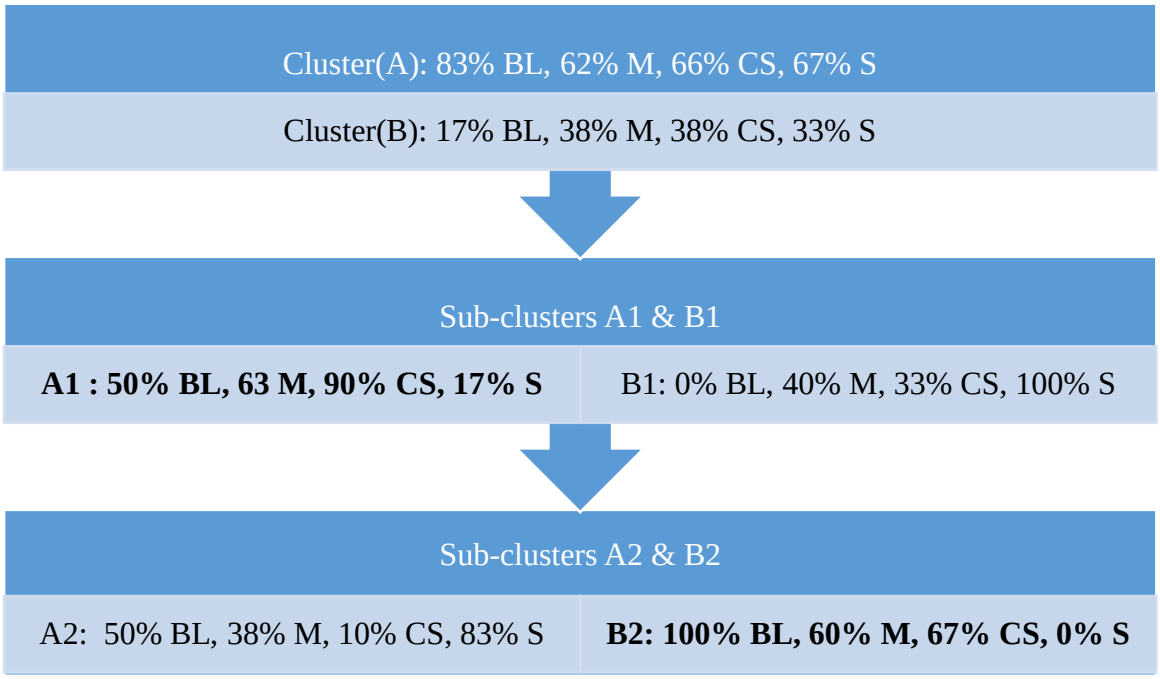


Figure 6- b): **Percentage distribution of *S. epidermidis* isolates in the major clusters and sub-clusters based on participant type.** BL: baby; M: mother; CS: clinical staff; S: student. The bolded sub-clusters are likely hospital endemic clones.

A dendrogram of the 67 *S. epidermidis* isolates cultivated from the HTH revealed two major clusters, labelled A and B (Figure 6-a). Each major cluster has two sub-clusters indicated by A1, A2 and B1, B2. Analysis of percentages of the participants' isolates that fall into each sub-cluster showed that for each major cluster, a sub-cluster is more likely to have hospital-clones that might be causing bloodstream infection among the neonates (sub-clusters A1 and B2). For other sub-classes this is less likely (sub-clusters A2 and B1) (Figure 6-b). The study quantified the percentage of isolates that paired with isolates cultivated from neonates' blood samples. It

used pair-matched analysis for all 67 *tuf* gene sequences of the *S. epidermidis* isolates. The results are shown in Figure 6-c. The pair-match of neonates' blood isolates with isolates from nasal mucosae of clinical staff was estimated to be the highest, at about 55%. The pair-match of neonates' isolates with those of other neonates and of students (control group) was the lowest, at about 9% (Table 9-a).

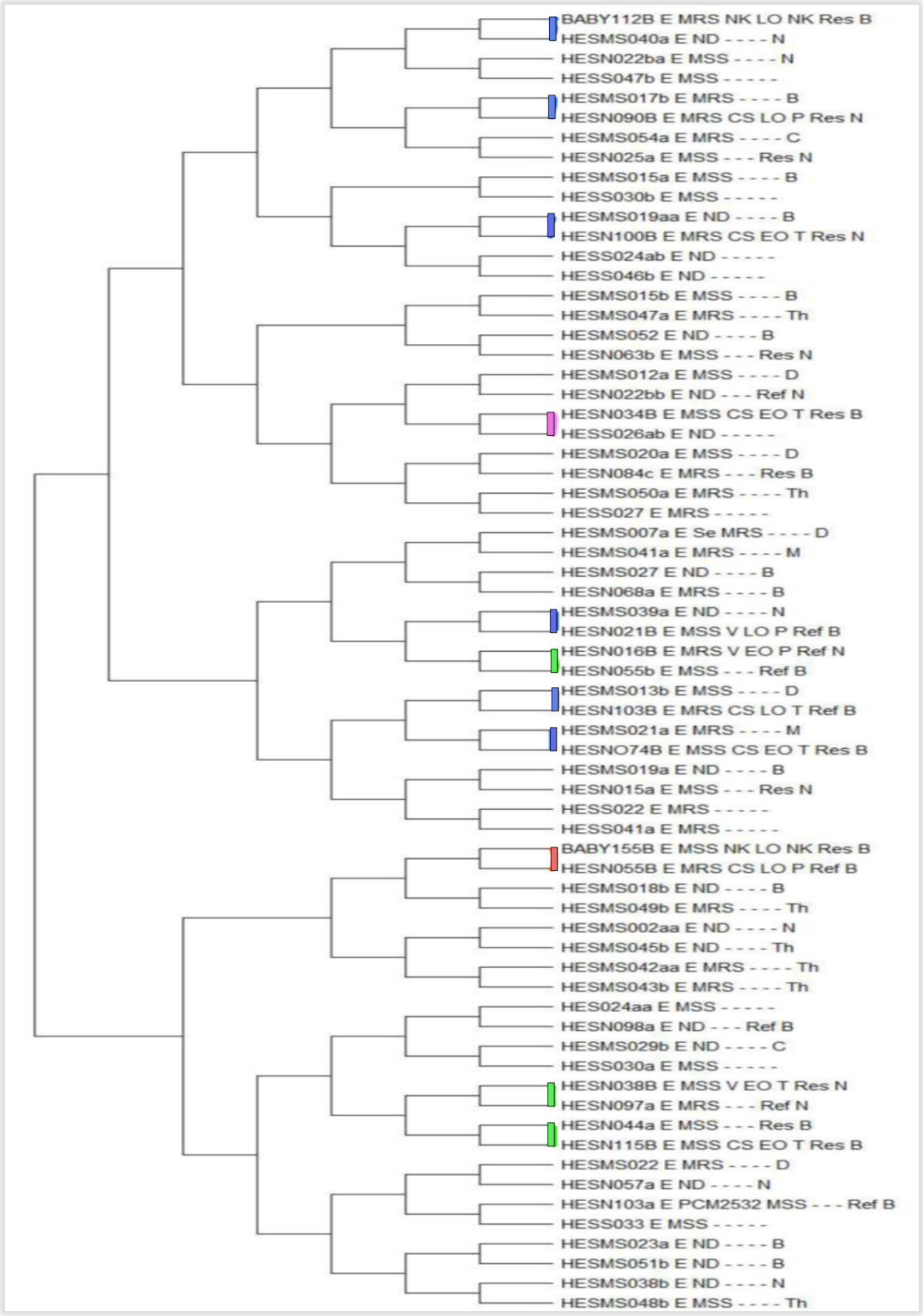


Figure 6- c): **Dendrogram showing pair-match of the 67 *S. epidermidis tuf* genes.**
E: Epidermidis; MSS: Methicillin susceptible staphylococcus; MRS: Methicillin-resistant staphylococcus; CS: Caesarean section; V: Vaginal delivery; EO: Early-onset neonatal sepsis; LO: Late-onset neonatal sepsis; P: Preterm; T: Term; Res: Residence; Ref: Referral; B: Baby

unit; C: Children's ward; M: Maternity ward; N: Neonatal intensive care unit; Th: Theatre; ND: Not done; Blue: Baby-Clinical staff paired isolates; Green: Baby-mother paired isolates; Pink: Baby-student paired isolates; Red: Baby-baby paired isolates.

Table 9-a)**: Percentage of pair-matched *tuf* genes of *S. epidermidis* isolates from babies' blood samples with other sources**

Pair type	Number pair-matched (%) N=11
Isolates from baby's blood pair-matched with isolates colonizing a mother	3 (27)
Isolates from baby's blood pair-matched with another baby's blood isolates	1 (9)
Isolates from baby's blood pair-matched with isolates colonizing a clinical staff member	6* (55)
Isolates from baby's blood pair-matched with isolates colonizing a medical or nursing student	1 (9)

N: total number of pairs (percentages in parenthesis); *: four nurses (one male and three females) and two medical doctors (both males)

Analysis of the paired babies' isolates with their mothers, clinical staff and students' isolates revealed that the clinical staff are more likely to transmit *S. epidermidis* to the babies. Of their six isolates matched with the babies' isolates, four were LONS and two were labelled EONS. A critical check of source data showed that for the two EONS, one was less than a day old before the onset of sepsis, and the other was a six-day-old neonate. EONS was first defined as less than seven days old at onset of sepsis but was later revised to less than three days old at onset of sepsis. This implies the six-day-old babies had LONS and not EONS. With this observation, only one baby had EONS among the clinical staff and babies with matched *S. epidermidis* isolates. Three isolate-matched were seen in babies-mothers combinations. All three matches were EONS. Two of these babies were a day old, while the other was less than a day old.

3.2.2 **Maximum likelihood phylogenetic tree obtained using the *tuf* genes of the 39 *S. haemolyticus*.**

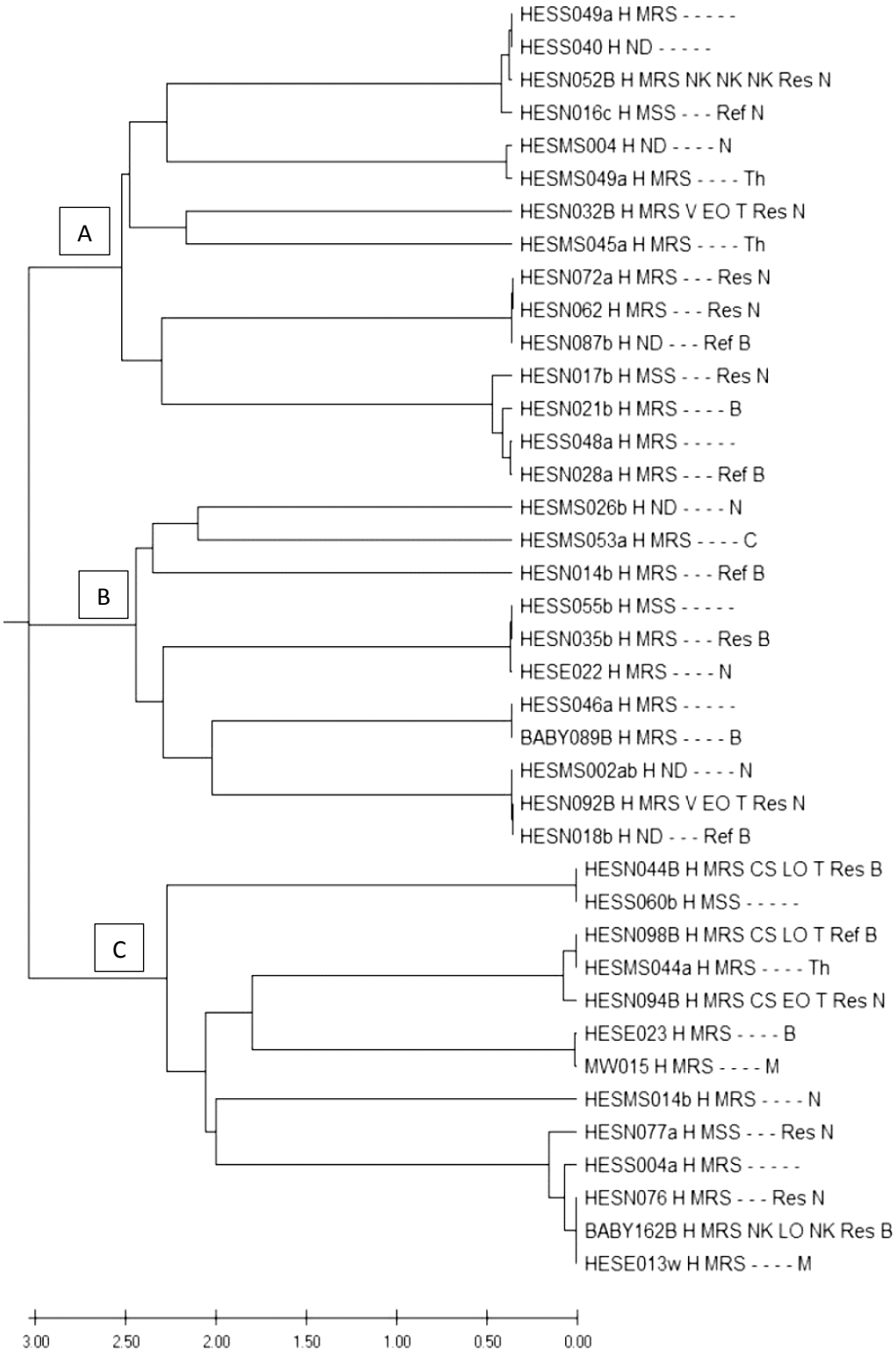


Figure 7- a): **Maximum likelihood phylogenetic tree obtained using the *tuf* genes of the 39 *S. haemolyticus*.** H: Haemolyticus; MSS: Methicillin susceptible staphylococcus; MRS: Methicillin-resistant staphylococcus; CS: Caesarean section; V: Vaginal delivery; EO: Early-

onset neonatal sepsis; LO: Late-onset neonatal sepsis; P: Preterm; T: Term; Res: Residence; Ref: Referral; B: Baby unit; C: Children's ward; M: Maternity ward; N: Neonatal intensive care unit' Th: Theatre; ND: Not done. Isolates labels: HESNXXXB-Neonate's blood sample; HESNXXX-Mother's nasal mucosa; HESMSXXX-Clinical staff's nasal mucosa; HESSXXX-Medical or nursing student's nasal mucosa; HESEXXX/MWXXX-Object in the hospital; BABYXXX-achieved bacterial isolates cultured from neonates' blood samples in 2016 at the HTH microbiology laboratory.

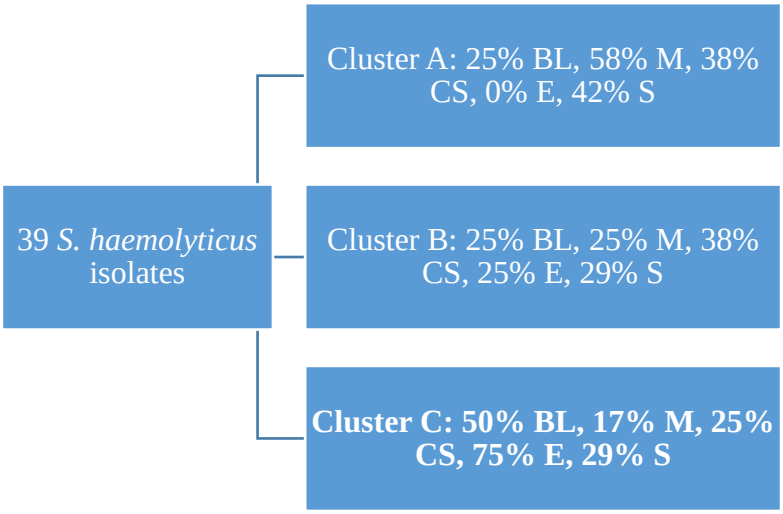


Figure 7- b): **Percentage distribution of *S. epidermidis* isolates into three major clusters based on participant type**. BL: baby; M: mother; CS: clinical staff; S: student.

2. Staphylococcus haemolyticus

For the 39 *S. haemolyticus* isolates analysed, their *tuf* gene sequences dendrogram showed three major clusters, indicated as A, B, and C (Figure 7-a), and each major cluster with about five sub-clusters. Percentages analysis among the major cluster showed that cluster C, with 50% of the neonates' isolates, 75% of isolates from an object in the hospital and 25% of clinical staff's isolates, is more likely to be hospital-acquired transmission than the other two major clusters (Figure 7-b). However, the percentage estimated from pair-matched analysis (Figure 7-c) revealed that mothers are more likely sources of transmission (about 63%) of *S. haemolyticus* to their neonates than the clinical staff (38%) and control group (students) (0%) (Table 9-b).

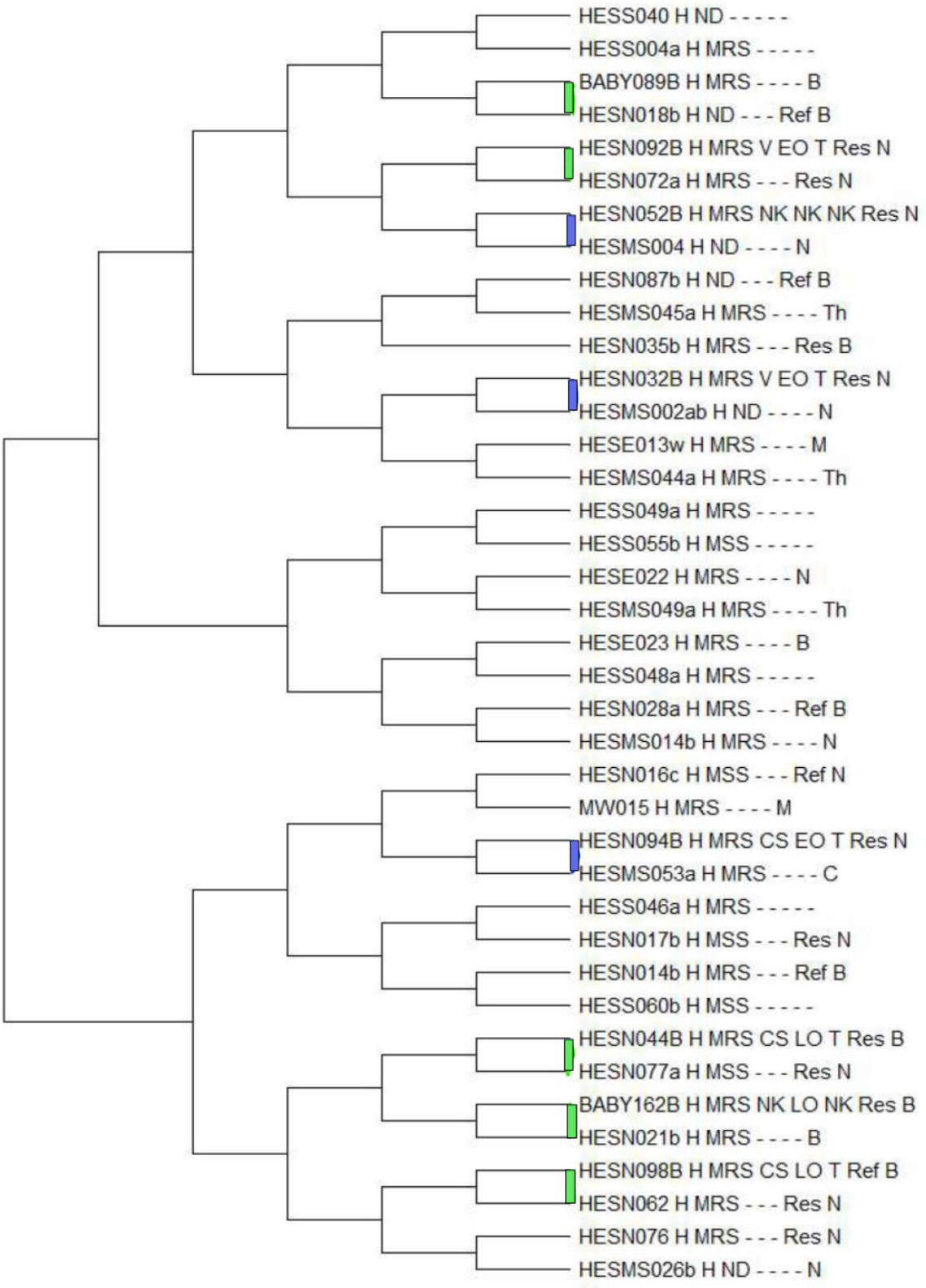


Figure 7- c): **Dendrogram showing pair-matched of the 39 S. haemolyticus tuf genes.** E: Epidermidis; MSS: Methicillin susceptible staphylococcus; MRS: Methicillin-resistant staphylococcus; CS: Caesarean section; V: Vaginal delivery; EO: Early-onset neonatal sepsis; LO: Late-onset neonatal sepsis; P: Preterm; T: Term; Res: Residence; Ref: Referral; B: Baby unit; C: Children's ward; M: Maternity ward; N: Neonatal intensive care unit; Th: Theatre; ND: Not done; Blue: Baby-Clinical staff paired isolates; Green: Baby-mother paired isolate.

Table 9-b): **Percentage pair-matched of *tuf* genes of *S. haemolyticus* isolates from babies' blood samples with other sources**

Pair type	Number pair-matched (%) N=8
Isolates from baby's blood pair-matched with isolate colonizing a mother	5 (63)
Isolates from baby's blood pair-matched with another baby's blood isolates	0 (0)
Isolates from baby's blood pair-matched with isolate colonizing a clinical staff member	3ɔ (38)
Isolates from baby's blood pair-matched with isolates colonizing a medical or nursing student	0 (0)

N: total number of pairs (percentages in parenthesis); ɔ: two nurses (both female) and a medical doctor (male)

The data suggest that mothers are more likely sources of transmission of *S. haemolyticus* species to their babies than the clinical staff. Of note, only one out of the five matches was EONS. This finding reflects postnatal transmission more than intrauterine. For the clinical staff-baby match, two out of the three were EONS and for the other the data on the type of sepsis was unknown. The two babies had their sepsis onset at less than a day old.

3.2.3 **Determine clonal relatedness for *S. epidermidis* and *S. haemolyticus* using their multilocus sequence type analysis**

For the few *S. epidermidis* species of which multilocus sequence types were analysed, two out of the five isolates (40%) cultivated from the neonates' blood samples have MLS type 490. Two of these isolates (40%) had no match in the MLS database and were assigned new MLS types 993 and 994 by www.pubmlst.org. One mother's isolate had MLS type 48 (Table 10). For *S. haemolyticus* isolates, three out of the four isolates (75%) cultivated from neonates' blood samples have MLS type 1, and the other one had no match in the database, although it was close to MLS type 30 (Table 10). Two clinical staff nasal mucosae isolates have MLS types 1 and unknown (close to MLS type 60). Two of the mothers' isolates analysed have MLS types 3 and 30. All unknown MLS types but one were assigned novel MLS types as highlighted in Table 10. The *S. epidermidis* isolate that MLS Type could not be assigned because of missing sequence for one of the housekeeping staff (yqiL). A check from the Global database of new MLS types submitted from various geographic areas revealed that the three new MLS types identified in this study for *S. haemolyticus* were the only submissions from Ghana (Figure 8-a). The two new MLS types of *S. epidermidis* reported in this study were the two among three submitted to the Database from Ghana (Figure 8-b).

Table 10: **Molecular characterization of selected *S. epidermidis* and *S. haemolyticus* based on their multilocus sequence types**

Staphylococcus epidermidis	Sample ID	MLS Type	Nearest MLS Type(s)	MLS Type assigned
	HESN035b	48	NA	NA
	HESS022*	Unknown	866	None
	HESN038B	Unknown	558, 861,872	**994**
	HESN090B	490	NA	NA
	HESN074B	Unknown	290, 889,924	**993**
	HESN016B	490	NA	NA
	HESN103B	226	NA	NA
Staphylococcus haemolyticus				
	HESN036B	1	NA	NA
	HESN094B	1	NA	NA
	HESN035a	30	NA	NA
	HESN072a	3	NA	NA
	HESMS053a	1	NA	NA
	BABY089B$^{\beta}$	Unknown	30	**90**
	MW015	Unknown	30	**91**
	HESMS017b	Unknown	60	**89**
	BABY162B$^{\beta}$	1	NA	NA

MLS: multilocus sequence; NA: not applicable; *: MLS Type not assigned because of missing sequence for one of the housekeeping staff (yqiL); $^{\beta}$: achieved bacterial isolates cultured from neonates' blood samples in 2016 at the HTH microbiology laboratory. Highlights: new MLS type assigned by http://pubmlst.org/shaemolyticus/ and https://pubmlst.org/organisms/staphylococcus-epidermidis

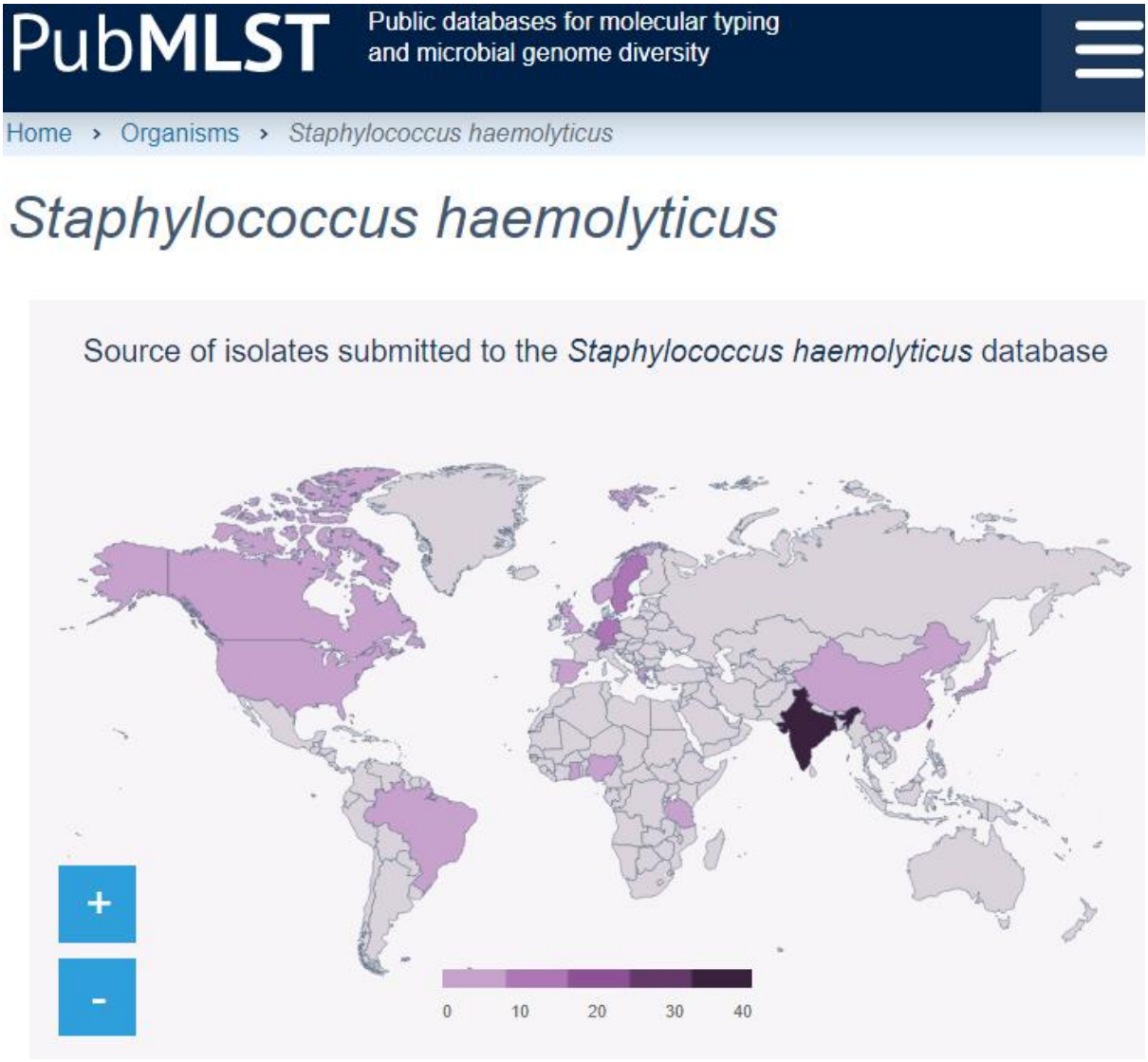


Figure 8- a): ***Staphylococcus haemolyticus*** **multilocus sequence type database**
Countries and number of isolates: Belgium (2), Brazil (1), Canada (1), China (3), Germany (9), **Ghana (3) from this study**, Greece (1), India (37), Japan (8), Nigeria (3), Norway (6), Spain (2), Sweden (13), Switzerland (10), Taiwan (20), UK (8), USA (1), United Republic of Tanzania (1)

Adapted from [113] Last updated 23 February, 2021.

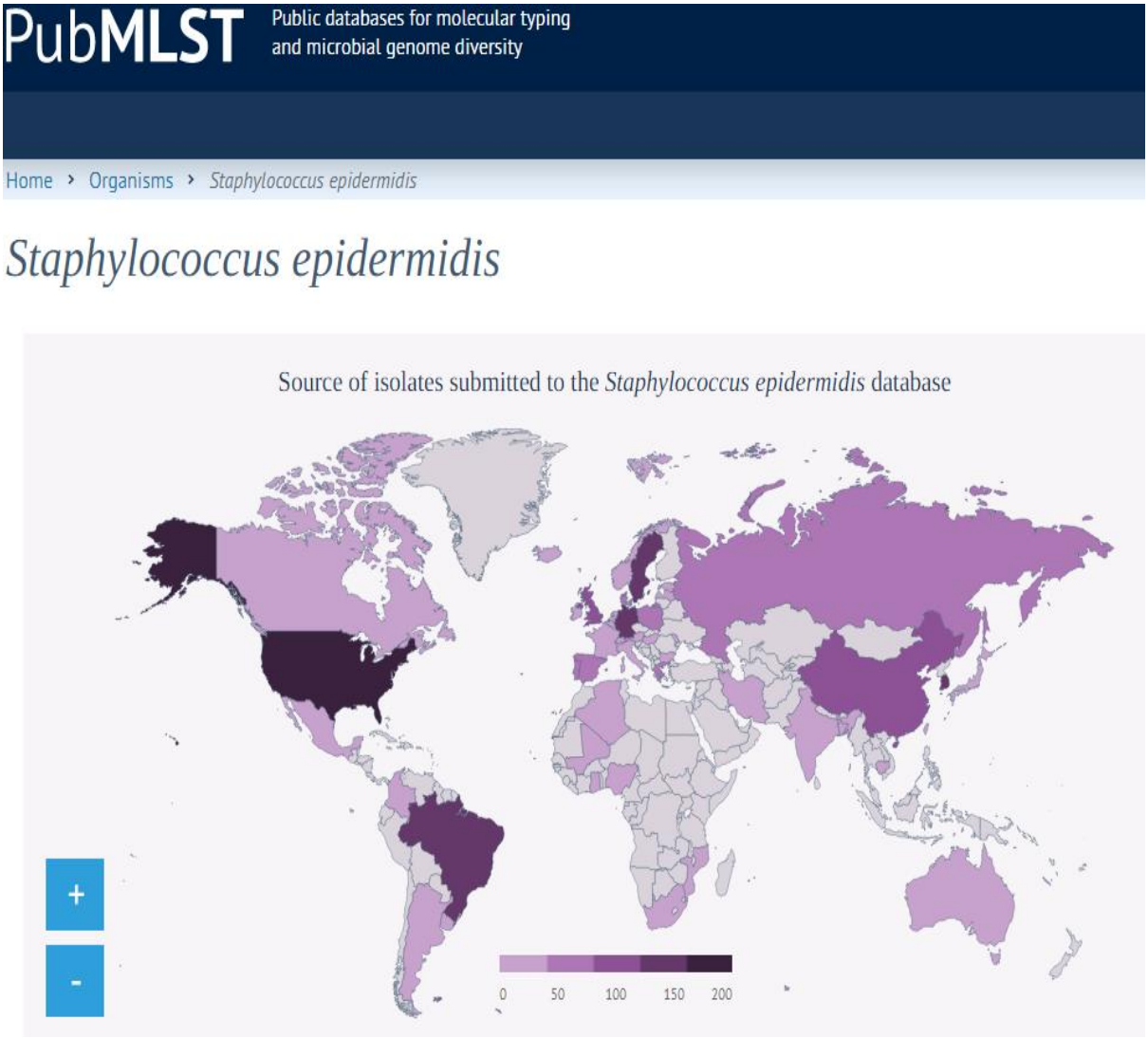


Figure 8- b): ***Staphylococcus epidermidis*** **multilocus sequence type database**
Countries and number of isolates: Algeria (5), Argentina (5), Australia (1), Bangladesh (1), Brazil (139), Bulgaria (5), Cambodia (13), Canada (8), China (101), Colombia (3), Denmark (59), Estonia (13), France (5), Germany (145), **Ghana (3) two from this study**, Greece (48), Hungary (6), Iceland (25), India (31), Iran (17), Ireland (37), Italy (16), Japan (28), Latvia (11), Mali (6), Mexico (14), Moldova (1), Mozambique (4), Nigeria (10), Norway (35), Poland (64), Portugal (51), Russia (62), South Africa (16), South Korea (129), Spain (45), Sweden (154), Taiwan (6), UK (87), USA (179).

Adapted from [113] Last updated 09 March, 2021.

3.2.4 Using whole-genome sequence data of selected *S. epidermidis* and *S. haemolyticus* to determine cluster among neonates' and clinical staff's isolates

Heuristic cluster analysis using whole-genome sequences for the nine selected *S. epidermidis* and five *S. haemolyticus* showed an exact distance between the two staphylococcal species. For *S. epidermidis* isolates, two clusters were observed with at least an isolate from clinical staff closely clustered with isolates cultivated from neonates' blood samples (Fig. 9-a). For *S. haemolyticus* isolates, although the neonates' isolates cluster together, they were relatively distanced from those of the clinical staff.

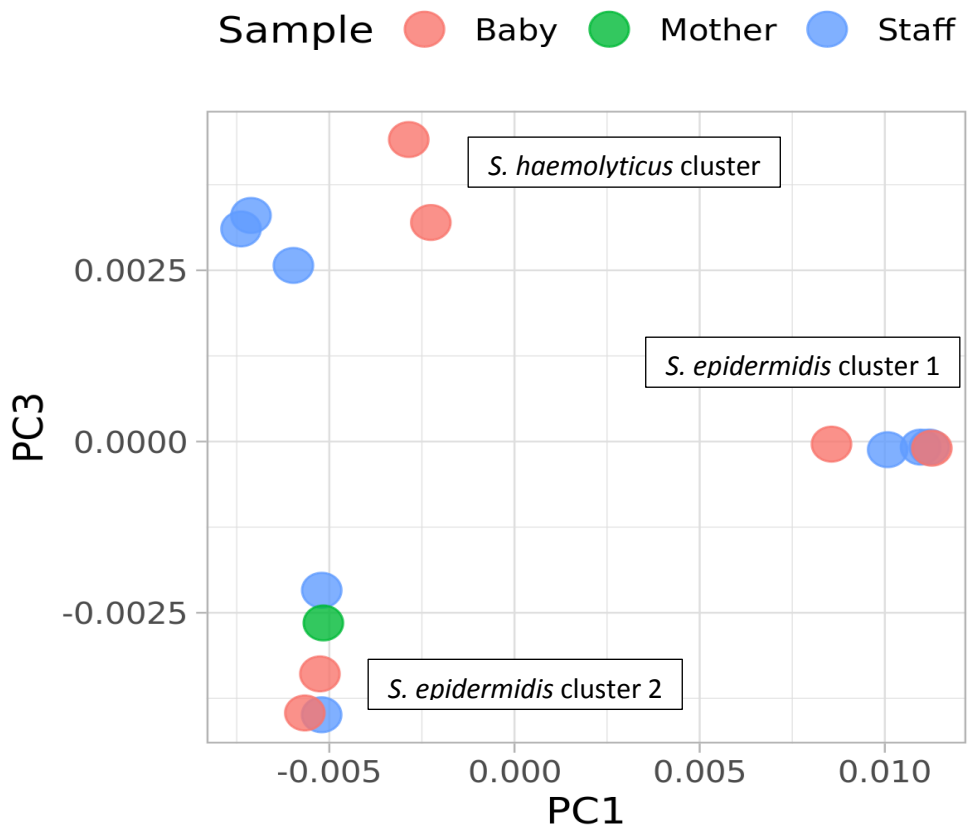


Figure 9- a): **Whole-genome scatter plot of 14 isolates (9 *S. epidermidis* and 5 *S. haemolyticus*)**

3.2.5 **Prediction of the source(s) of infection using *tuf* gene sequences of *S. epidermidis* and *S. haemolyticus* identified to the strain level**

Standard nucleotide BLAST was performed for all the *tuf* gene sequences at the website https://blast.ncbi.nlm.nih.gov/Blast.cgi?PROGRAM on 27 January 2020. The default was set for highly similar sequences (megablast) and searched standard databases. A total score of ≥600, query cover of ≥95% and the highest identity of ≥97% were used to accept isolates at the strain level. Table 11 show the distributions of *S. epidermidis* and *S. haemolyticus* isolates among the participant types at the strain level.

Table 11: **Distribution of staphylococcal strains among the participant type**

		Participant type				
Species	Strain	Baby	Mother	Clinical staff	Student	Environment
	FDAARGOS_529	1	0	2	2	0
	Non-genome assembly	**4**	**0**	**0**	**0**	**0**
	PCM2532	4	8	29	7	0
	Se	2	5	4	2	1
Epidermidis	SeMCV12	1	1	2	2	0
	FDAARGOS_517	3	1	1	0	0
	PK-01	0	1	4	1	0
Haemolyticus	VB19458	6	10	3	7	6

The current study identified four *S. epidermidis* non-genome assembly strains (NGASs) cultivated from neonates' blood samples only and not from other participant sources at the HTH. *S. epidermidis* is a CoNS, a permanent member of the human microbiota commonly colonizing the skin and mucous membranes[48]. In the vulnerable patients, *S. epidermidis* had become an important opportunistic pathogen and is reported as the leading causative agent of nosocomial infections[114]. *S. epidermidis* is the most prevalent CoNS commonly isolated from bloodstream infections in NICUs (3). We have isolated, sequenced and assembled four *S. epidermidis* NGASs from neonates' blood samples. Molecular typing of the *tuf* gene revealed them (out of 77 *S. epidermidis* isolates cultured from the HTH environment) to be peculiar strains isolated from blood culture samples and they had the highest number of identities similar to a strain accession number LR735440.1 deposited at the GenBank. Their transmission source is unclear. This study further analyses these strains in more detail and sequences their whole genomes. Table 12 shows the phenotype and genotype characterizations of these isolate.

Table 12: **Phenotypic and molecular characterization of the four *S. epidermidis* non-genome assembly strains**

ID	HESN016B	HESN038B	HESN074B	HESN103B
Gestation	Preterm(24 weeks)	Term	Term	Term
Mode of delivery	Vaginal	Vaginal	C-section	C-section
Admission type	Referral	Residence	Residence	Referral
Ward	NICU	NICU	Babies'	Babies'
MIC (mg/L)	[susceptibility category]*			
Cefoxitin	2[Negative]	2[Negative]	2[Negative]	>8[Positive]
Oxacillin	>2[N/A]	0.25[N/A]	2[N/A]	>2[N/A]
Erythromycin	0.5[S]	0.25[S]	0.5[S]	>2[R]
Clindamycin	>1[R]	0.25[S]	0.25[S]	>1[R]
Amikacin	4[S]	4[S]	8[S]	8[S]
Ampicillin	2[N/A]	2[N/A]	2[N/A]	>8[N/A]
Gentamicin	2[S]	1[S]	>4[R]	>4[R]
Tetracycline	>2[R]	0.5[S]	0.5[S]	>2[R]
Fosfomycin w/G6P	>64[R]	16[S]	16[S]	16[S]
Ciprofloxacin	2[S]	0.25[S]	0.25[S]	4[S]
Rifampicin	>1[R]	0.25[S]	0.25[S]	0.25[S]
Trimethoprim/Sulfamethoxazole	4/76[S]	4/76[S]	>4/76[R]	>4/76[R]
Tobramycin	2[S]	1[S]	>4[R]	>4[R]
Penicillin G	>0.25[N/A]	0.0625[N/A]	>0.25[N/A]	>0.25[N/A]
Teicoplanin	1[S]	1[S]	1[S]	1[S]
Vancomycin	0.5[S]	1[S]	0.5[S]	1[S]
Mupirocin	>256[R]	1[S]	1[S]	1[S]
Genome size(bp)	2411715	2682678	2439254	2431156
Contigs	22	115	30	25
Largest contig (bp)	453937	297254	335917	569583
N_{50} value	155338	78190	148419	233414

GC content (%)	32.11	31.8	32.01	32
rRNA	6	8	8	8
CDS	2241	2508	2238	2233
tRNA	52	51	52	49
tmRNA	1	None	1	1
MLST	ST490	Unknown	Unknown	ST226
SCCmec type	Vc(5C2&5)	None	V(5C2&5)	None
Resistance genes & Biofilm forming genes	APH(3'), *bla*I, *bla*R1, *bla*Z *dfr*C, *dfr*G, *dfr*K, *nor*A, *gyr*B, *IS*1272 & *ica*BCD	APH(3'), *dfr*C, *nor*A, *gyr*B, *IS*1272	APH(3'), dfrC, *far*1, *fus*B, *nor*A, *gyr*B & *mec*A	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*C, *dfr*G, *dfr*K, *nor*A, *gyr*B & *IS*1272
Plasmids	None	rep19c, rep20	None	rep7a(PKH17), rep10, rep22, rep24c

MIC: minimum inhibitory concentration; R: resistant; S: susceptible; N/A: not applicable-no breakpoint available; C-section: caesarean; NICU: neonatal intensive care unit; MLST: multilocus sequence typing; SCCmec: staphylococcal cassette chromosome mec; *: the MIC results were interpreted according to 2018 European Committee on Antimicrobial Susceptibility Testing (EUCAST) clinical breakpoints.

A search for pathogenicity genes on these four isolates' genomes revealed that two had SCCmec sub-type Vc(5C2&5). For these two isolates, one (strain HESN016B) had biofilm-forming genes (*ica*BCD), whilst the other also had the *mec*A gene, which is known for multidrug resistance in bacterial species. The other two isolates, strain HESN038B and HESN103B, both had multiples of rep plasmids. However, no data suggest the involvement of rep family plasmids in the pathogenicity of bacterial species. This study further analysed the phenotype and genotype of these four strains, and the data suggest that they are not likely to be from the same clone since they all have different MLST types. However, their source(s) of transmission to neonates in the HTH is still unclear.

Results 3.2: **Summary**

- For *S. epidermidis* isolates, maximum likelihood phylogenetic analysis of their *tuf* genes suggested that clinical staff are the most (6/11) common sources of transmission and this was equivocal with the whole genome cluster model, where most of the isolates from the neonates' blood samples cluster with those colonizing clinical staff. MLS type 490 was identified as the common type among the isolates cultured from the babies' blood samples. Two novel MLS types were identified.

- For *S. haemolyticus* isolates, the data suggest that mothers are the most (5/8) common sources of transmission by the *tuf* gene model and this was supported by the distance observed between the neonates' blood isolates and those of the clinical staff when whole genome cluster analysis was performed. MLS type 1 was highly presented among the blood isolates. Three novel MLS types were identified.

- Molecular typing of the *tuf* genes followed by a BLAST search from the GenBank database of *S. epidermidis* isolates revealed four strains which were cultivated from neonates' blood samples and whose identities were similar to a strain in the GenBank data, non-genome assembly strain. Two of these isolates had few pathogenic genes on their genomes, whilst the other two had multiples of rep-family plasmids. The source of transmission of these isolates in the HTH is unclear.

3.3 Antimicrobial susceptibility patterns for *S. epidermidis* and *S. haemolyticus* and their molecular characterization

Antibiotics are the most frequently used medications in neonates. The NICU houses an immunocompromised newborn who is highly susceptible to overwhelming infections. In the HTH's NICU and Baby unit early and decisive treatment with potent antibiotics for neonates with suspected infection is the preferred clinical doctrine owing to the fear of potentially disastrous consequences. The high associated mortality from infections leads neonatal care providers to initiate empirical antibiotic therapy in this hospital. However, antibiotics are often continued in clinical situations where a clear indication of benefit has not been demonstrated. As has already been reported, empiric antibiotic use for 'rule-outs' is a significant contributor to overall antibiotic use in neonatal units, making finding strategies for safe antibiotic restriction challenging, especially among preterm infants[115]. An ideal approach to early empirical antibiotic therapy would be one that accurately identifies and treats those at high risk while sparing those at low risk. However, the Committee on Foetus and Newborn management guidelines (2012) for EONS recommended empirical treatment with broad-spectrum antibiotics for all critically ill infants, irrespective of gestational age and risk factors[116]. In this study, antimicrobial data were obtained from the HTH's pharmacy database. Antimicrobial agents supplied to the NICU and the Baby unit a year before starting the study, during the study period and a year after the study. The routine antibiotics used in the HTH for neonates and infants diagnosed with sepsis or at risk of sepsis are a combination of either amikacin or gentamycin with ciprofloxacin. Metronidazole is given to babies with suspected anaerobic infections. Figure 9 shows antibiotics supplied to the HTH's NICU and Baby unit from 2017 to 2019.

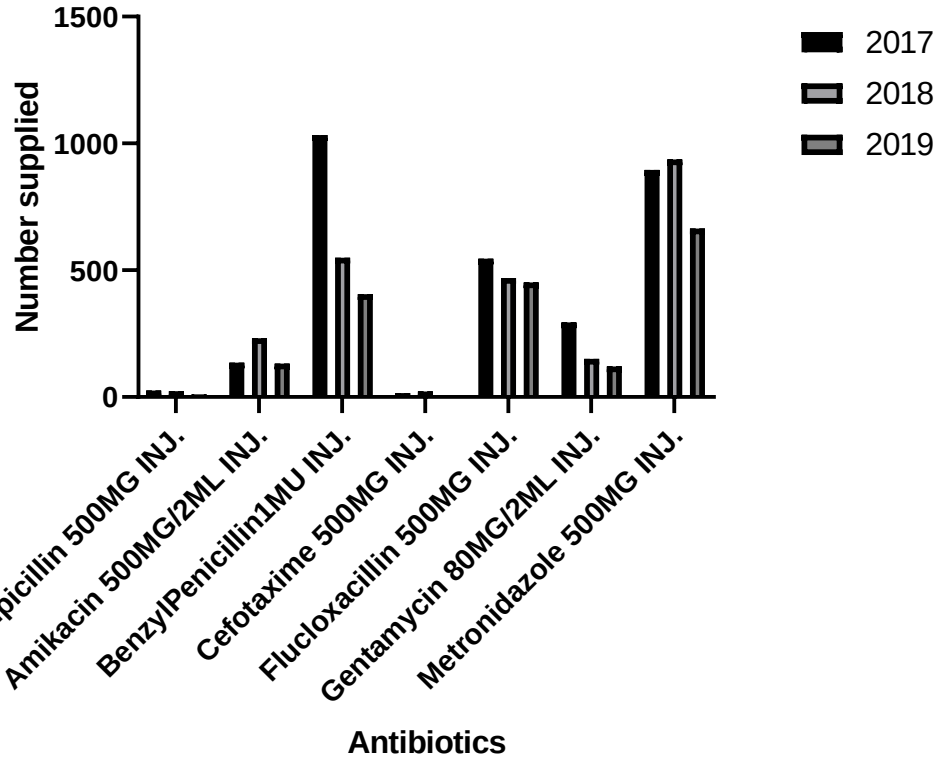


Figure 10- a): **Antibiotics supplied to the HTH's NICU and Babies' unit from 2017 to 2019.**
Source: Archives of the Pharmacy Department of Ho Teaching Hospital, Ho, Ghana

Antimicrobials supplied to the HTH's NICU and Baby during a 3-year period revealed that all antibiotics supplied were in the 'Access' group of antibiotics classified by the WHO Essential Medicine List (EML) Working Group. Of note, apart from ciprofloxacin, none of the 'Watch' or 'Reserve' group antimicrobials has been supplied by the HTH Pharmacy Department (personal communication with the pharmacy department head). A study[117] reported no resistance in Ghanaian MRSA isolates for several antibiotics, including glycopeptides (classified in the 'Watch' group), daptomycin, linezolid and tigecycline (all classified in the 'Reserve' group). There is limited data on antibiotics' resistance profiles for CoNS, especially isolates in the NICUs of Ghanaian hospitals involved in bloodstream infections among babies. The current study determined antimicrobial susceptibility profiles for *S. epidermidis* and *S. haemolyticus* isolates cultivated from babies' blood samples, nasal mucosae of babies' mothers, clinical staff, and students who had no contact with the HTH wards. Table 13 (a & b) shows phenotypes of percentage antimicrobial resistance for the various participant types based on the WHO EML classification of antimicrobials.

Table 13-a): **Percentage antimicrobial resistance for *Staphylococcus epidermidis* isolates**

1. *Staphylococcus epidermidis*

		% resistance for participants types			
Classification	Antimicrobial agent	Babies' Blood	Clinical Staff's nasal mucosae	Mothers' nasal mucosae	Students' nasal mucosae
Methicillin-susceptibility	Cefoxitin	42	65	25	30
	Oxacillin	58	65	25	20
Access	Amikacin	8	25	17	5
	Ampicillin	30	67	50	20
	Clindamycin	25	35	33	10
	Gentamicin	50	35	17	5
	Penicillin G	100	83	90	83
	TRI-SUL	58	25	25	30
	Erythromycin	33	40	25	5
Watch	Ciprofloxacin	10	20	17	0
	Levofloxacin	20	43	18	0
	Moxifloxacin	20	36	17	0
	Teicoplanin	0	0	0	10
	Vancomycin	0	0	0	0
Reserve	Daptomycin	0	0	0	0
	Linezolid	0	0	0	0
	Fosfomycin	17	25	8	20
	Tigecycline	0	0	0	0
Unclassified	Mupirocin	8	0	0	0
	Tetracycline	67	40	91	40
	Rifampicin	17	35	18	20

TRI-SUL: Trimethoprim/sulfamethoxazole

Table 13-b): **Percentage antimicrobial resistance for *Staphylococcus haemolyticus* isolates**

2. *Staphylococcus haemolyticus*

		% resistance for participant types			
Classification	Antimicrobial agent	Babies' Blood	Clinical Staff's nasal mucosae	Mothers' nasal mucosae	Students' nasal mucosae
Methicillin-susceptibility	Cefoxitin	100	100	82	63
	Oxacillin	100	100	82	63
Access	Amikacin	10	18	13	5
	Ampicillin	90	63	80	50
	Clindamycin	36	50	36	13
	Gentamicin	73	63	55	25
	Penicillin G	91	90	90	80
	TRI-SUL	100	75	73	50
	Erythromycin	55	75	46	25
Watch	Ciprofloxacin	55	42	25	20
	Levofloxacin	36	63	36	13
	Moxifloxacin	36	63	36	13
	Teicoplanin	9	0	9	0
	Vancomycin	0	0	0	0
Reserve	Daptomycin	0	0	0	0
	Linezolid	0	0	0	0
	Fosfomycin	18	14	73	63
	Tigecycline	8	5	17	0
Unclassified	Mupirocin	8	5	0	0
	Tetracycline	82	63	82	38
	Rifampicin	27	50	18	5

TRI-SUL: Trimethoprim/sulfamethoxazole

This study has identified resistance to one 'Watch' antimicrobial group (teicoplanin), one 'Reverse' group (tigecycline) and mupirocin, an unclassified group (Table 14). The resistance to tigecycline and mupirocin by CoNS isolates cultivated from non-glycylcyclines and the non-mupirocin-exposed hospital was investigated. The three isolates' identified mechanism of resistance for teicoplanin was not investigated because their whole genomes were not sequenced.

Table 14: **Resistance to mupirocin, 'watch' and 'reserve' antimicrobial groups**

Antibiotic	No. of resistant isolates	Confirmed resistance*	Distribution among participant type				
			NBS	CCS	CM	CS	HE
Linezolid	3	0	0	0	0	0	0
Mupirocin[ɐ]	8	3	2	1	0	0	0
Teicoplanin	12	3	1	0	1	1	0
Tigecycline	5	5	1	1	2	0	1
Vancomycin	6[δ]	0	0	0	0	0	0

*: Minimum Inhibitory Concentrations were obtained on an automated analyser and then confirmed with Epsilometer Test; δ: reduced susceptibility to vancomycin with MIC >4 mg/L; NBS: Bacterial isolates from neonate's blood sample; CCS: Colonizing clinical staff; CM: Colonizing mothers; CS: Colonizing students; HE: Bacterial isolate from the hospital environment; ɐ: WHO Essential Medicines List Working Group unclassified antimicrobial

3.3.1 **Investigating mechanism(s) of tigecycline resistance of five *S. haemolyticus* cultivated from a non-previously tigecycline exposed hospital setting**

Five *S. haemolyticus* isolates cultivated from a neonate's blood culture, nasal mucosa swabs of a clinical staff, mothers, and a swab sample of a baby's cot in the HTH NICU. The strains were resistant to methicillin and tigecycline, the first manufactured drug in the antibiotics' glycylcycline class. There was no prior exposure to glycylcycline antibiotics in the HTH. The detection rate of tigecycline-resistant *S. haemolyticus* in our study was 5/47. The detection rates among the various categories of participants are as follows: 1/11 of babies' blood samples; 2/12 mothers' nasal mucosae; 1/11 clinical staff nasal mucosae; and 0/5 medical and nursing students' nasal mucosae (control group) and 1/5 swab samples from NICU environment. Of note, 78 *S. epidermidis* species isolated in our study were also phenotypically screened with tigecycline, and they were all susceptible to this drug. Our current data suggest that the tigecycline-resistant *S. haemolyticus* might have evolved in the hospital and are hospital endemic. The mechanism through which these *S. haemolyticus* strains develop resistance to tigecycline in a non-glycylcycline antibiotics exposure environment warrants further investigation.

Tigecycline was the first glycylcycline compound derived from minocycline. It is highly active against many multidrug-resistant organisms, including MRSA, methicillin-resistant *staphylococcus epidermidis* (MRSE), vancomycin-resistant enterococci (VRE), *Acinetobacter baumannii,* and anaerobic pathogens[118,119]. It is approved to treat complicated intra-abdominal infections, and preclinical studies showed antiplasmodial activity superior to other tetracyclines[120]. With these properties, tigecycline stands among other antimicrobials as a promising drug that could save children's lives in the tropical regions where both sepsis and malaria co-infection are typically observed. Tigecycline is considered a last-resort antibiotic for treating multidrug-resistant bacteria[121]. It was designed to bypass fundamental bacterial resistance mechanisms that have affected previous antibacterial drug use, including ribosomal protection, macrolide or tetracycline efflux pumps, target-site modification beta-lactamases, and DNA gyrase mutations[122–124]. However, enzymatic inactivation has emerged as a new concern for the next-generation tetracyclines (tigecycline, eravacycline, and omadacycline)[125]. Tigecycline blocks the entry of amino-acyl transfer RNA (t-RNA) molecules into the A site of the 30S ribosomal subunit, thus preventing protein synthesis[122]. It has an excellent treatment spectrum against Gram-positive pathogens for which the resistance seems very rare[118,119,126].

Very few studies have reported the tigecycline susceptibility profile among CoNS[127], especially *S. haemolyticus*.

This study compared the antibiotic resistance phenotypes and genotypes of the five tigecycline-resistant isolates with three other *S. haemolyticus* isolates susceptible to the antibiotic.

Table 15: **Molecular characterization of the five tigecycline-resistant and three tigecycline-susceptible *Staphylococcus haemolyticus* strains**

	ID	Genome size(bp)	Contigs	Largest contig (bp)	N_{50}value	GC content (%)	rRNA	CDS	tRNA	tm RNA	MLST	SCCmec type
Tigecycline - Resistant	BABY089	2453213	69	228898	65362	32.75	7	2404	44	1	**ST90**	None
	HESN035b	2660314	170	286012	42729	32.74	5	2569	80	1	ST30	None
	HESN072a	2758447	114	221483	61871	32.5	6	2717	59	1	ST3	None
	HESMS053a	2396859	69	192779	60967	32.66	6	2334	61	1	ST1	None
	MW015	2873520	190	207830	55396	32.6	7	2809	58	1	**ST91**	None
Tigecycline - Susceptible	HESN036B	2557090	67	205888	63822	32.55	6	2526	58	1	ST1	Vc(5c2&5)
	HESN094B	2630890	90	320731	83068	32.49	6	2568	49	1	ST1	Vc(5c2&5)
	HESMS017b	2462495	20	467572	260253	32.78	5	2382	57	1	**ST89**	None

MLST: Multilocus sequence typing, ST: Sequence type, SCCmec: Staphylococcal cassette chromosome *mec*

Analysing the tigecycline-susceptible and -resistant groups based on their complete genome characterization, the data suggest no significant difference between the characteristics studied. The tigecycline-resistant group had relatively higher values (3/6 had number contigs more than 100) for their contigs than those for the tigecycline-susceptible group (Table 15). There was no clear pattern of the MLST types between the two groups; hence, MLST cannot be used to differentiate them. Three novel MLST types are identified, two from tigecycline-resistant isolates and one tigecycline-susceptible isolate. The website http://pubmlst.org/shaemolyticus/ has assigned the new MLST types identified in this study.

Table 16: **MICs of antibiotics tested against five tigecycline-resistant and three tigecycline-susceptible *S. haemolyticus* strains**

Tigecycline susceptibility type	ID	CEF	OXA	ERY	CLI	GEN	TET	TIG	LIN	MOX	RIF	TEI	VAN	DAP
Tigecycline - Resistant	BABY089	>8[R]	>4[R]	>8[R]	>8[R]	0.5[S]	**>16[R]**	**1[R]**	1[S]	0.25[S]	>32[R]	2[S]	0.5[S]	0.12[S]
	HESN035b	ND	>4[R]	>4[R]	0.25[S]	4[R]	**>16[R]**	**1[R]**	4[S]	1[R]	0.5[S]	4[S]	1[S]	1[S]
	HESN072a	>8[R]	>4[R]	0.25[S]	0.25[S]	4[R]	**>16[R]**	**1[R]**	2[S]	0.25[S]	>32[R]	2[S]	1[S]	0.25[S]
	HESMS053a	>8[R]	>4[R]	>8[R]	>8[R]	>16[R]	**>16[R]**	**1[R]**	2[S]	>8[R]	>32[R]	4[S]	1[S]	1[S]
	MW015	>8[R]	>4[R]	>8[R]	0.25[S]	0.5[S]	**>16[R]**	**>2[R]**	2[S]	0.25[S]	0.5[S]	2[S]	0.5[S]	0.12[S]
Tigecycline - Susceptible	HESN036B	>8[R]	>4[R]	>8[R]	>8[R]	4[R]	>**16[R**]	0.5[S]	1[S]	1[R]	0.25[S]	2[S]	1[S]	1[S]
	HESN094B	>8[R]	>4[R]	0.25[S]	0.25[S]	4[R]	2[S]	0.12[S]	2[S]	0.25[S]	0.25[S]	2[S]	0.5[S]	1[S]
	HESMS017b	>8[R]	>4[R]	>8[R]	0.5[S]	2[S]	0.5[S]	0.12[S]	2[S]	0.5[S]	0.5[S]	1[S]	2[S]	1[S]

CEF: Cefoxitin, OXA: Oxacillin, ERY: Erythromycin, CLI: Clindamycin, GEN: Gentamicin, TET: Tetracycline, TIG: Tigecycline, LIN: Linezolid, MOX: Moxifloxacin; RIF: Rifampicin, TEI: Teicoplanin, VAN: Vancomycin, DAP: Daptomycin, [S]: susceptible, [R]: resistance, ND: not done

All the bacterial isolates in both groups were phenotypically methicillin resistant. However, when considering their tetracycline class of antibiotic phenotype, the results show that all five isolates in the tigecycline-resistant group were resistant to both the first (tetracycline) generation and the third (tigecycline) generation tetracyclines. For the tigecycline-susceptible group, only one isolate out of the three was resistant to first-generation tetracyclines (Table 16). This one isolate happened to be a multidrug-resistant *S. haemolyticus*. The current study investigated the antibiotic resistance genes that this isolate lacks but which are present in the tigecycline-resistant isolates that made the latter resistant to tigecycline at the molecular level.

Table 17-a): **Antibiotic resistance genes, biofilm genes and plasmids detected on the genomes of the five tigecycline-resistant and three tigecycline-susceptible *S. haemolyticus* strains**

Tigecycline susceptibility type	ID	Antibiotic resistance genes	Plasmids	Biofilm genes
Tigecycline - Resistant	BABY089	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, *tet*(45), *tet(*L)& *IS*1272	rep10, rep20, rep21, rep23	None
	HESN035b	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, *tet(*M), *tet(*S), *mph*C, *msr*A & *IS*1272	rep5e, rep7(C&D), rep10b, rep20, rep21, repUS19, repUS43,	None
	HESN072a	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, , *far1*, *fus*B & *IS*1272	None	None
	HESMS053a	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, , *mph*C, *msr*A & *IS*1272	rep10	None
	MW015	APH(3'), *dfr*G, *dfr*K, *msr*A, *mec*A	rep5e,rep7(C&D), rep10b, rep39	None
Tigecycline - Susceptible	HESN036B	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, *mec*A & *IS*1272	rep5b, rep7a, rep10, rep21	None
	HESN094B	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, mecA, *IS*1272	rep10, rep21, rep39	None
	HESMS017b	APH(3'), *Nor*A & *fos*B	rep7(C&D)	None

Table 17-a represents antibiotic genes and plasmids detected on genomes of analysed *S. haemolyticus* isolates and the mechanisms of action of these genes. The study compared the presence of these antibiotic genes among the tigecycline-susceptible and -resistant groups. The current study identified a trend of common antibiotic genes like APH(3') *bla*I, *bla*R1, *bla*Z, *dfr*G, and *dfr*K for both groups. For each tigecycline-resistant *S. haemolyticus isolate*, the mechanism of resistance was predicted. Bacterial strain BABY089 has two antibiotic efflux genes [*tet*(45), *tet(*L)] present in its genome. However, tigecycline was designed to bypass fundamental bacterial resistance mechanisms that have affected previous antibacterial drug use, including ribosomal protection, macrolide or tetracycline efflux pumps, target-site modification beta-lactamases, and DNA gyrase mutations[122–124]. With this bacterial strain resistance to tigecycline, this study hypothesises that the presence of two or more tetracycline efflux genes on the genome of *S. haemolyticus* confers tigecycline resistance. Considering isolate strain MW015, apart from the common antibiotic resistance genes identified, it harboured *msr*A and *mec*A genes. When this strain is compared with isolate strain HESN036B, which is multidrug-resistant with the *mec*A gene, it is evident that the *mec*A gene alone cannot confer tigecycline resistance.

Moreover, the *msr*A gene, the mechanism of action of which is via antibiotic target protection, is unlikely to confer tigecycline resistance alone. Also, current studies report that the third (tigecycline) and fourth (eravacycline and omadacycline) generation tetracyclines overcome resistance via ribosome protection[123,124]. This study, therefore, predicted that the combination of *msr*A and *mec*A genes in *S. haemolyticus* confers tigecycline resistance. For bacterial isolate strain HESMS053a, the two unique genes identified are *mph*C and *msr*A genes. The *mph*C gene is associated with macrolide antibiotics enzyme inactivation. A study has reported that, for the next-generation tetracyclines, enzymatic inactivation has emerged as a new concern for their resistance[125]. The following genes have been identified: *tet*(X), t*et*(47-56)[84]. This study hypothesises that tigecycline resistance in *S. haemolyticus* could be conferred when both *mph*C and *msr*A genes are present on its genome. Bacterial isolate strain HESN072a has *far1, fus*B genes as its unique genes among the isolates compared in this study. While the *far1* gene is noted for the antibiotic inactivation of penicillin and β-lactam antibiotics, the *fusB* gene is involved in antibiotic target protection, mainly in fusidic acid. Their combination in *S. haemolyticus* also suggested conferring resistance to tigecycline. Finally, isolate strain

HESNO35b has two tetracycline target protection genes (*tet*M and *tet*S) besides *mph*C and *msr*A genes, hence it stands a greater chance of conferring tigecycline resistance. Figure 11 represents a network of antibiotic genes that might predict resistance to tigecycline in *S. haemolyticus.*

Table 17-b): **Resistance mechanisms of the various antibiotic resistance genes identified in the *S. haemolyticus* isolates**

Resistance gene	Resistance mechanism	Drug class
APH(3')	antibiotic inactivation	aminoglycoside antibiotic, e.g. gentamicin, tobramycin, amikacin
*bla*I,*bla*R1,*bla*Z, *far*1	antibiotic inactivation	penicillin G, β-lactam antibiotics
*dfr*C, *dfr*G, *dfr*K	antibiotic target replacement	diaminopyrimidine antibiotic, e.g. trimethoprim
tet(45), *tet*(L), *tet*(K)	antibiotic efflux	tetracycline antibiotic
tet(M), *tet*(S)	antibiotic target protection	tetracycline antibiotic
*mph*C	antibiotic inactivation	macrolide antibiotics, e.g. erythromycin, clarithromycin
*msr*A	antibiotic target protection	a macrolide antibiotic, lincosamides antibiotic, streptogramins antibiotic, tetracycline antibiotic, oxazolidinone antibiotic, phenicol antibiotic, pleuromutilin antibiotic
*fus*B	antibiotic target protection	fusidic acid
*fos*B	antibiotic inactivation	fosfomycin resistance
*mec*A	antibiotic target replacement	penicillin G, β-lactam antibiotics
*ile*S	antibiotic target alteration	mupirocin
*rpo*B	antibiotic target alteration, antibiotic target replacement	rifamycin antibiotic

Table 17-b shows various antibiotics' resistance genes and their mechanisms of action. The genes *tet*(X), t*et*(47-56)[84] have been identified as causing resistance by the mechanism of enzymatic inactivation in tetracyclines. However, none were detected in the genomes of the studied *S. haemolyticus*, so they are not included in Table 17-b. Other genes that are known to be related to tetracycline and glycylcycline resistance which are not listed in this table are *mep*R; *mep*A, *Yaj*C, *ade*R, *ram*A, *mar*A and *Sox*R.

Table 18: **Glycylcyclines resistance genes identified on the genomes of the *S. haemolyticus* isolates with percentage identities less than 95% in the CARD database**

Susceptibility type	ID	Tetracyclines and Glycylcyclines resistance genes detected using loose default for identification in the CARD database							
	BABY089	*mar*A (31)*	*mep*A (85)	mepR (50)*	YajC (37)	none	none	none	None
	HESN035b	*mar*A (31)	*mep*A (85)*	mepR (50)	YajC (37)	ramA (21)	soxR (33)	adeR (31)	None
	HESN072a	*mar*A (31)*	*mep*A (85)*	mepR (50)	YajC (37)	None	soxR (33)	adeR (30)	None
	HESMS053a	*mar*A (30)*	*mep*A (85)*	mepR (50)	YajC (37)	None	soxR (33)	None	None
Tigecycline -Resistant	MW015	*mar*A (30)	*mep*A (85)	mepR (50)*	None	ramA (21)	soxR (33)	adeR (30)	tetX(50)*
	HESN036B	*mar*A (31)*	*mep*A (76)	mepR (50)	YajC (37)	ramA (21)	None	adeR (29)	None
	HESN094B	*mar*A (21)	*mep*A (85)*	mepR (50)	None	None	None	None	None
Tigecycline - Susceptible	HESMS017b	*mar*A (30)	*mep*A (77)	mepR (50)	YajC (37)	ramA (21)	soxR (33)	None	None

Percentage identity in (x); Mechanism of action: *mep*A, *Yaj*C, *mep*R, *ade*R: antibiotic efflux; *ram*A, *mar*A: antibiotic efflux & reduced permeability to antibiotic; *sox*R: antibiotic target alteration & antibiotic efflux; *tet*X: antibiotic inactivation; *: multiple detection of gene but the highest percentage identity stated

The study attempted to detect antibiotic genes associated with tetracyclines and glycylcyclines resistance using the default to include loose identity after searching for perfect and strict identities on the CARD website. Table 18 represents the antibiotic resistance genes that were identified. Apart from the *mep*A gene, which has an identity very close to the set identity (≥95% identity), all the genes' identities were extremely low.

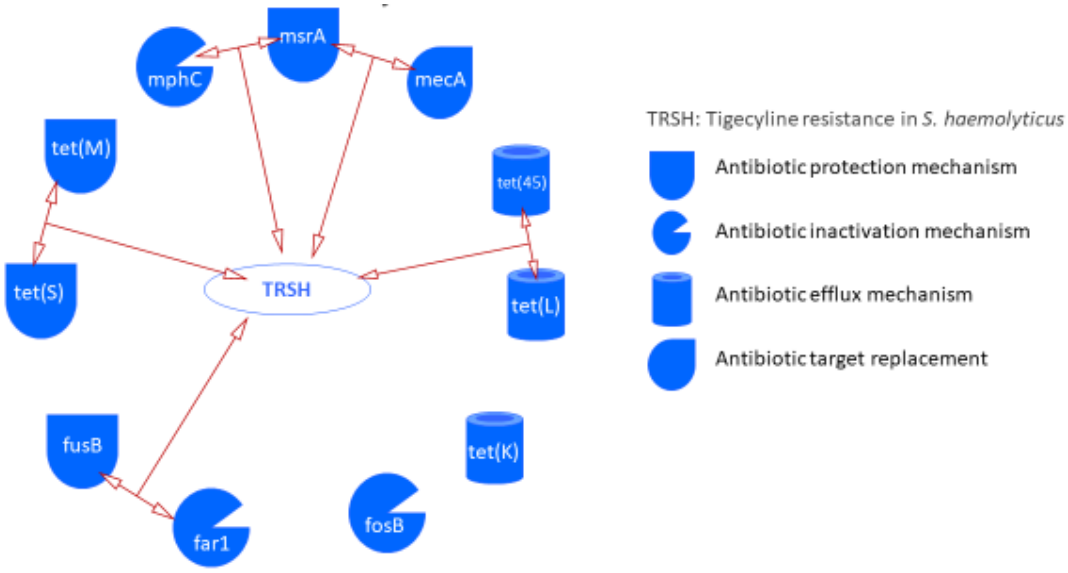


Figure 11- a): **The proposed network of antibiotic genes that might predict resistance to tigecycline of *S. haemolyticus*.**
TRSH: Tigecycline resistance in *S. haemolyticus*

Another area of predicting tigecycline resistance in *S. haemolyticus* is mobile genetic elements, typically transferred through horizontal gene transfer. Association between rep-family plasmid type and antimicrobial resistance in *S. aureus* has been recently reported[128]. Table 19 shows associations of some rep-families with some classes of antibiotics, as reported by Neyaz et al.[128].

Table 19: **Summary of the association of rep types with phenotypic antibiotic resistance in *S. aureus* isolates**

Type				
rep5	97% PEN	77% TET	71% OXA	71% ERY
rep7	75% PEN	67% TET	-	-
rep10	72% PEN	67% TET	-	-
rep20	98% PEN	73% TET	-	60% ERY
rep21	93% PEN	79% TET	63% OXA	65% ERY

PEN: Penicillin, TET: Tetracycline, OXA: Oxacillin, ERY: Erythromycin

Table extracted from Neyaz *et al.* 2020 [128].

Despite years of study, the current understanding of plasmids and how they are distributed within staphylococcal species populations remains lacking. McCarthy and Lindsay[129] found a strong association between plasmid groups containing the rep15 sequence and *tetK* occurrence . In contrast, another study found the same rep type in *tet*R *S. aureus* isolates[130]. This study does not identify any association between tigecycline resistance in *S. haemolyticus* and the type of rep plasmid detected in the isolates. Almost all the rep plasmid types detected were presented in both tigecycline- resistant and -susceptible groups.

3.3.2 **Investigating mechanism(s) of high-level mupirocin resistance in coagulase-negative staphylococcus species cultivated from a non-mupirocin exposed NICU of Ho Teaching Hospital, Ghana**

Topical agents remain an essential integral part of infection control measures to reduce HAI, especially in the NICUs. The application of mupirocin nasal decolonization combined with chlorhexidine skin disinfection has been effective against *S. aureus* infections in a hospital setting[131].

Mupirocin (pseudomonic acid A), a polyketide antibiotic naturally produced by *Pseudomonas fluorescence* strain NCIMB 10586, is used topically to treat skin infections, prevent surgical site infections, and eradicate *S. aureus* carriage. It inhibits bacterial protein synthesis by interfering with isoleucyl-tRNA synthetase activity.

Molecular data on CoNS, major bacterial species implemented in neonatal sepsis, are mostly limited to high-income countries. This study investigated mechanism(s) of high-level mupirocin resistance in three CoNS species cultured from a non-mupirocin exposed NICU in an low-income country (LIC). Two of the isolates were cultured from blood samples of neonates and were identified as *S. epidermidis* and *S. haemolyticus*. The other was cultured from the nasal mucosa of clinical staff and identified as *S. haemolyticus*. The three isolates are methicillin-resistant (phenotype) and also showed high-level mupirocin resistance (HLMR). The development of high-level mupirocin resistance in a non-mupirocin-exposed environment coupled with these isolates' ability to cause bloodstream infections in neonates presents a real threat to preventing bloodstream infections in babies in this NICU. Therefore, the current study decided to study the strains in more detail and sequenced their genomic DNA. This study compared the antibiotic resistance phenotypes and genotypes of the three high-level mupirocin-resistant isolates with three other *S. haemolyticus* and four *S. epidermidis* isolates susceptible to mupirocin.

Table 20: **Molecular characterization of the three high-level mupirocin resistant and seven mupirocin susceptible CoNS strains**

Susceptibility type	ID	Genome size(bp)	Contigs	Largest contig (bp)	N_{50} value	GC content (%)	rRNA	CDS	tRNA	tm RNA	MLST	SCCmec type
HLMR-*S. haemolyticus*	HESMS017b	2462495	20	467572	260253	32.78	5	2382	57	1	**ST89**	None
	HESN036B	2557090	67	205888	63822	32.55	6	2526	58	1	ST1	Vc(5c2&5)
	HESMS53a	2396859	69	192779	60967	32.66	6	2334	61	1	ST1	None
	HESN094B	2630890	90	320731	83068	32.49	6	2568	49	1	ST1	Vc(5c2&5)
MS-*S. haemolyticus*	BABY162B	2397901	66	192779	64263	32.64	6	2337	51	1	ST1	None
HLMR-*S. epidermidis*	HESN016B	2411715	22	453937	155338	32.11	6	2241	53	1	ST490	Vc(5c2&5)
	HESN038B	2682678	115	297254	78190	31.80	8	2508	51	None	**ST994**	none
	HESN074B	2439254	30	335917	148419	32.01	8	2238	52	1	**ST993**	Vc(5c2&5)
	HESN090B	2417530	41	514126	129621	32.09	6	2256	51	1	ST490	IVa (2B)
MS-S. epidermidis	HESN103B	2431156	25	569583	233414	32.00	8	2233	49	1	ST226	none

HLMR: high-level mupirocin resistance, MS: mupirocin susceptible, MLST: Multilocus sequence typing, ST: Sequence type, SCCmec: Staphylococcal cassette chromosome *mec*

Molecular characteristics like total genome size, percentage GC content, number of rRNAs, number of tRNAs, and tmRNA number are similar within species and between the two staphylococcal species. Two out of the three HLMR-CoNS had relatively lower numbers of contigs compared with the MS-CoNS (Table 20). Of note, the tmRNA, a bifunctional RNA with properties of a tRNA and an mRNA, was not detected in one of the MS-S *S. epidermidis*. For the *S. haemolyticus*, all but one (the new assigned) had MLST type 1. In *S. epidermidis* isolates, two new MLST types have been assigned (assigned by https://pubmlst.org/organisms/staphylococcus-epidermidis.) Two other isolates were ST490. One SCCmec type (IVa) was identified among the *S. epidermidis* isolates. This SCCmec type has been previously reported to have been identified in *S. epidermidis* isolates cultured from nasal mucosae of patients presented at a healthcare system in France[132].

Table 21: **MICs of the three high-level mupirocin resistant and seven mupirocin susceptible CoNS strains**

Susceptibility type	ID	CEF	OXA	ERY	CLI	GEN	TET	FOSF	CIP	RIF	TEI	VAN	TRI	MUP
HLMR-*S. haemolyticus*	HESMS017b	>8[R]	>2[R]	>8[R]	0.5[S]	2[S]	0.5[S]	ND	0.5[S]	0.5[S]	1[S]	2[S]	1/19[S]	**>256[R]**
	HESN036B	>8[R]	>2[R]	>8[R]	>8[R]	>4[R]	>16[R]	32[S]	>4[R]	0.25[S]	2[S]	1[S]	>4/76[R]	**>256[R]**
MS-*S. haemolyticus*	HESMS53a	>8[R]	>2[R]	>8[R]	>8[R]	>4[R]	>16[R]	64[S]	>4[R]	>32[R]	4[S]	1[S]	>4/76[R]	1[S]
	HESN094B	>8[R]	>2[R]	>4[R]	>8[R]	>4[R]	>16[R]	32[S]	>4[R]	0.25[S]	2[S]	1[S]	>4/76[R]	1[S]
	BABY162B	>8[R]	>2[R]	>8[R]	0.25[S]	>4[R]	>16[R]	16[S]	>4[R]	>32[R]	>4[R]	2[S]	>4/76[R]	1[S]
HLMR-*S. epidermidis*	HESN016B	2[S]	>2[R]	0.5[S]	>8[R]	2[S]	>16[R]	>64[R]	2[S]	>32[R]	1[S]	0.5[S]	4/76[S]	**>256[R]**
MS-S. *epidermidis*	HESN038B	2[S]	0.25[S]	0.25[S]	0.25[S]	1[S]	0.5[S]	16[S]	0.25[S]	0.25[S]	1[S]	1[S]	4/76[S]	1[S]
	HESN074B	2[S]	2[S]	0.5[S]	0.25[S]	>4[R]	0.5[S]	16[S]	0.25[S]	0.25[S]	1[S]	0.5[S]	>4/76[R	1[S]
	HESN090B	ND	>2[R]	>4[R]	>8[R]	>4[R]	>16[R]	16[S]	>4[R]	0.25[S]	2[S]	1[S]	>4/76[R	1[S]
	HESN103B	>8[R]	>2[R]	>4[R]	>8[R]	>4[R]	>16[R]	16[S]	4[S]	0.25[S]	1[S]	1[S]	>4/76[R]	1[S]

CEF: Cefoxitin, OXA: Oxacillin, ERY: Erythromycin, CLI: GEN: Gentamicin, TET: Tetracycline, FOSF: Fosfomycin with Glucose-6-Phosphate, CIP: Ciprofloxacin, RIF: Rifampicin, TEI: Teicoplanin, VAN: Vancomycin, TRI: Trimethoprim/sulfamethoxazole, MUP: Mupirocin, [S]: susceptible, [R]: resistance, ND: not done

The data suggest that, phenotypically, all the *S. haemolyticus* isolates are methicillin-resistant. For the two HLMR-*S. haemolyticus*, one is multidrug-resistant. Likewise, multidrug resistance is seen among the MS-*S. epidermidis* isolates. The one HLMR-*S. epidermidis* was susceptible to cefoxitin but resistant to oxacillin (Table 21), making its methicillin status challenging to interpret. In a case like this, the interpretation depends on the individual laboratories' guidelines for interpreting discord results of oxacillin and cefoxitin MICs. The CDC guideline for determining methicillin susceptibility suggested that, although oxacillin is more likely to detect heteroresistant strains, which made it better than methicillin, cefoxitin is a better inducer of the *mecA* gene. Tests using cefoxitin give more reproducible and accurate results than tests with oxacillin https://www.cdc.gov/mrsa/lab/index.html. Two out of the four MS-S. *epidermidis* are readily susceptible to the various antibiotics tested, whilst the other two are multidrug-resistant isolates. The three CoNS reported under this section have their mupirocin MICs for broth dilution as >256, and that of the solid medium E-test was >1024.

Table 22: **Antibiotic resistance genes, biofilm genes and plasmids detected on the genomes of the three high-level mupirocin resistant and seven mupirocin susceptible CoNS strains**

Susceptibility type	ID	Antibiotic resistance genes	Plasmids	Biofilm genes
HLMR-*S. haemolyticus*	HESMS017b	APH(3'), *Nor*A & *fos*B	rep7(C&D)	None
	HESN036B	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, *mec*A & *IS*1272	rep5b, rep7a, rep10, rep21	None
	HESMS53a	APH(3'), *bla*I, *bla*R1, *bla*Z, dfrG, *dfr*K, *mph*C, *msr*A & *IS*1272	rep10	None
	HESN094B	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*G, *dfr*K, *mec*A & IS1272	rep10, rep21, rep39	None
MS-*S. haemolyticus*	BABY162B	APH(3'), *bla*I, *bla*R1, *bla*Z, dfrG, *dfr*K, *mph*C, *msr*A & *IS*1272	None	None
HLMR-*S. epidermidis*	HESN016B	APH(3'), *bla*I, *bla*R1, *bla*Z *dfr*C, *dfr*G, *dfr*K, *nor*A, *gyr*B & *IS*1272	None	*ica*B,C,D
	HESN038B	APH(3'), *dfr*C, *nor*A, *gyr*B, *IS*1272	rep19c, rep20	None
	HESN074B	APH(3'), dfrC, *far*1, *fus*B, *nor*A, *gyr*B & *mec*A	None	None
	HESN090B	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*C, *dfr*G, *dfr*K, *tet*(K), *nor*A, *gyr*B & *IS*1272	rep7a (C), rep10, rep20	*ica*B,C,D
MS-*S. epidermidis*	HESN103B	APH(3'), *bla*I, *bla*R1, *bla*Z, *dfr*C, *dfr*G, *dfr*K, *nor*A, *gyr*B & *IS*1272	rep7a(PKH17), rep10, rep22, rep24c	None

HLMR: High-level mupirocin resistance, MS: Mupirocin susceptible

Phenotypically, all five *S. haemolyticus* isolates are methicillin-resistant. However, only two of them carried the *mec*A gene on their genomes (Table22). This phenomenon is not uncommon in staphylococcal species. Although *mecA* gene expression is usually a prerequisite for methicillin resistance, *mecA* expression alone does not appear to be sufficient to guarantee phenotypic methicillin resistance, which suggests the existence of additional molecular targets that could be associated with the susceptibility to oxacillin in certain strains[133–135]. The opposite of this occurrence is seen with the MS-*S. epidermidis* strain HESNO74B where the *mec*A gene was identified, but the isolate was phenotypically susceptible to most of the antibiotics. A study has investigated this phenomenon and reported that mutations in various genes might have been responsible for this observation[133].

For the current molecular resistance mechanism (HLMR) investigated by this study, the data revealed that the three HLMR-CoNS were isolated. None harboured the three major genes *ile*S (responsible for low-level resistance), *mup*A and *mup*B responsible for HLMR. These observations have made the understanding of the mechanism of these HLMR CoNS isolates challenging. For this reason, the default for the search of the antibiotic resistance gene on the CARD platform was altered to include the loose resistance genes detections. Table 23 shows that all the isolates have traces of the three genes responsible for mupirocin resistance but with a low percentage of identities and coverages. Attempting to look for trends of fragmentation of the *mup*A or *mup*B genes resulting from multiple detections of the same gene on an isolated genome yields no results since both the HLMR and MS isolates have similar trends of multiple detections of these two genes.

Table 23: **Mupirocin resistance genes identified on the genomes of the ten CoNS isolates with percentage identities less than 95% in the CARD database**

Susceptibility type	ID			
HLMR-*S. haemolyticus*	HESMS017b	*ileS* (30)	*mupA* (24)	*mupB* (30)*
	HESN036B	None	*mupA* (24)	*mupB* (31)*
	HESMS53a	None	*mupA* (24)	*mupB* (31)*
	HESN094B	None	*mupA* (24)	*mupB* (31)*
MS-*S. haemolyticus*	BABY162B	None	*mupA* (24)	*mupB* (31)*
HLMR-*S. epidermidis*	HESN016B	*ileS* (28)	*mupA* (30)*	*mupB* (24)
	HESN038B	*ileS* (28)	*mupA* (29)*	None
	HESN074B	None	*mupA* (29)*	*mupB* (25)
	HESN090B	*ileS* (28)	*mupA* (30)*	*mupB* (24)
MS-*S. epidermidis*	HESN103B	*ileS* (28)	*mupA* (29)	*mupB* (25)

Percentage identities in (x), HLMR: High –level mupirocin resistance, MS: Mupirocin susceptible, *: multiple detections of the gene but the highest percentage identity state

Results 3.3: **Summary**

- This study identified resistance to one 'Watch' group antimicrobial (teicoplanin), one 'Reserve' group; (tigecycline) and one WHO Essential Medicines List Working Group unclassified antimicrobial (mupirocin) of CoNS cultivated from non-previously exposed of these antimicrobials hospital in low-income country.

- In attempt to predict molecular mechanism of resistance of five *S. haemolyticus* isolates *to* tigecycline in non- glycylcyclines-exposed hospital revealed that co-detection of the following genes *msr*A-*mph*C, *mec*A-*msr*A, *tet*(M)-*tet*(S), *tet*(L)-*tet*(45) and *fus*B-*far*1 on the genome of *S. haemolyticus* predict resistance to tigecycline. Current finding calls for *in vitro* experiment to confirm these resistance mechanisms in *S. haemolyticus*.

- The three High-level mupirocin resistant CoNS identified in this study harboured no genes of mupirocin resistance hence their molecular mechanism(s) of resistance to this antimicrobial is unclear to current study.

3.4 Chlorhexidine susceptibility patterns for staphylococcal species and their molecular characterization

Chlorhexidine has become a primary HAIs prevention tool, as it is used to bath patients before admission or as a daily prevention procedure in Intensive Care Units (ICUs)[136,137], skin antisepsis before line placement and surgical procedures[138,139], as a component of some antimicrobial-impregnated catheters and wound dressings[140–142], and for oral care[143]. Following the chlorhexidine cord treatment cluster-randomized trial results in southern Nepal [141], chlorhexidine has now been included on the WHO list of priority medicines for application to the umbilical cord to prevent neonatal sepsis in countries with a high rate of neonatal mortality[144].

Concerns have been raised concerning biocide resistance or tolerance in recent years. Elsewhere in the United Kingdom, where chlorhexidine bath of patients is being practiced, there is a current report of increased MICs of 32mg/L and more for clinical staphylococcal isolates[145]. Bacteria may be described as susceptible, insusceptible, phenotypically tolerant, tolerant or resistant to biocides. As with antibiotics, resistance to biocides can be either intrinsic or acquired. Bacteria can use intrinsic resistance mechanisms such as alteration in cell wall thickness, alteration in surface porins, efflux-pump systems, biofilm production and hydrophobicity to decrease their sensitivity to biocides.

The results obtained in this study for the chlorhexidine MICs for the staphylococcal isolates are shown in Figures 12 (A, B, C, D, E, & F). The data suggest very high chlorhexidine susceptibility among the 410 staphylococcal species cultivated from the hospital and the students. Chlorhexidine MIC ranges from <0.25 to 4mg/L. Bartlett's test revealed a very high significant difference ($p < 0.0001$) between MIC distributions among the various groups, with most isolates from the students' group having the lowest range of ≤1.0 mg/L.

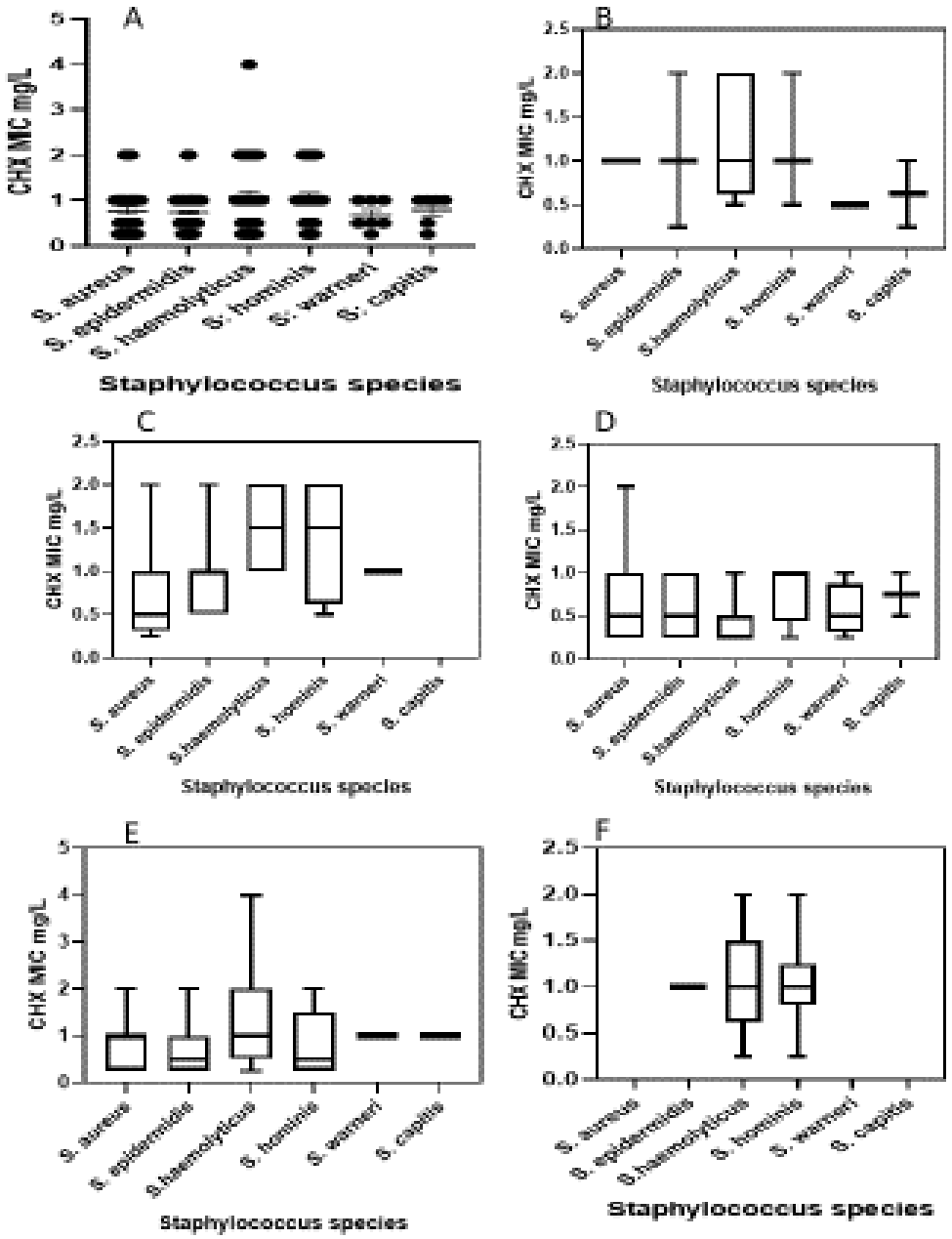


Figure 12- A-F): **Chlorhexidine minimum inhibitory concentrations for staphylococcal species**

A: General chlorhexidine MICs for staphylococcal isolates

B: MICs for isolates cultivated from babies' blood samples

C: MICs for isolates colonizing mothers' nasal mucosae

D: MICs for isolates colonizing students' nasal mucosae

E: MICs for isolates colonizing clinical staff`s nasal mucosae

F: MICs for isolates from hospital objects

Statistical analysis

Bartlett's test	
Bartlett's statistic (corrected)	29,45
P value	<0,0001
P value summary	****

Table 24: **Phenotypic and genotypic characterization of the fifteen CoNS isolates whole-genome sequenced**

ID	Staphylococcal species	Methicillin susceptibility	MIC (MBC)mg/L	*qac* genes type present	*ica* genes present	other plasmids
HESN016B	*epidermidis*	MRS(-)	1.0 (1.0)	none	*ica*B,C,D	None
HESN038B	*epidermidis*	MSS(-)	0.5 (0.5)	none	none	rep19c, rep20
HESN074B	*epidermidis*	MSS(+)	1.0 (1.0)	None	none	None
HESN090B	*epidermidis*	MRS(-)	2.0 (2.0)	*qac*H	*ica*B,C,D	rep7a (C), rep10, rep20
hHES103B	*epidermidis*	MRS(-)	2.0 (2.0)	***qac*A**	none	rep7a(PKH17), rep10, rep22, rep24c
HESS022	*epidermidis*	MRS(-)	0.25 (0.5)	none	none	rep7a (C, L & pSBK203), rep13
HESN036B	*haemolyticus*	MRS(+)	0.5 (0.5)	None	none	rep5b, rep7a, rep10, rep21
HESN094B	*haemolyticus*	MRS(+)	2.0 (2.0)	none	none	rep10, rep21, rep39
BABY089B	*haemolyticus*	MRS(-)	1.0 (1.0)	*qac*E	none	rep10, rep20, rep21, rep23
BABY162B	*haemolyticus*	MRS(-)	2.0 (2.0)	none	none	None
HESMS017b	*haemolyticus*	MRS(-)	0.5 (0.5)	none	none	rep7(C&D)
HESMS053a	*haemolyticus*	MRS(-)	ND	*qac*C	none	rep10
HESN035b	*haemolyticus*	MRS(-)	1.0 (1.0)	none	none	rep5e, rep7(C&D), rep10b, rep20, rep21, repUS19, repUS43
HESN072a	*haemolyticus*	MRS(-)	1.0 (1.0)	*qac*J	none	None
MW015	*haemolyticus*	MRS(+)	1.0 (1.0)	*qac*H, *qac*J	none	rep5e,rep7(C&D), rep10b, rep39

ND: not done, (+): *mec*A positive, (-): *mec*A negative

For the fifteen (15) isolates selected for whole-genome sequencing, only one *a* gene (*qac*A) related to chlorhexidine reduced susceptibility was detected (Table 24). No *qac*B gene was detected. The other four (*qac*C, *qac*E, *qac*H, *qac*J) *qac* gene types were identified among the analysed isolates' sequences. These other four identified *qac* gene types have not been implemented in reduced chlorhexidine susceptibility of staphylococcal species. The isolate that harboured the *qac*A gene is phenotypically methicillin resistant but has no *mec*A gene identified on its genome.

A known attribute of certain CoNS species strains that makes them more pathogens than just commensals is production of biofilms. Biofilm formation facilitates resistance against host immunity[146–149] and also confers antimicrobial and biocide resistance[150]. Two of the *S. epidermidis,* both cultivated from neonates' blood samples, harboured the biofilm-forming genes, *ica*B, C, D. Their chlorhexidine MICs are 1.0 and 2.0 mg/L.

Many isolates harboured different rep-family plasmids (Table 24); however, these plasmid types' role in reducing staphylococcal species' susceptibility to chlorhexidine is unknown.

Results 3.4: **Summary**

- Staphylococcal species cultivated from the environment of the HTH before the commencement of chlorhexidine ointment umbilical cord treatment for neonates in an attempt to reduce neonatal sepsis were readily susceptible to chlorhexidine, with MICs ranging from <0.25 to 4mg/L.

- Only one out of the fifteen CoNS isolates genome sequences screened harboured the *qac*A gene known for reduced chlorhexidine susceptibility. No *qac*B gene was identified on these genome sequences of the isolates screened.

4 DISCUSSION

4.1 Investigate maternal vaginal dysbiosis as a risk factor for spontaneous preterm delivery with subsequent EONS

One of the Vaginal Microbiome Study aims was to map the human vaginal microbiota to better understand the dysbioses or infections caused by its imbalance to offer more appropriate treatment[151]. However, modern studies of the role of microbiota diversity and its variation in the incidence and susceptibility to an infection during the neonatal period have not been done in most LMICs. As rightly reported by Doyle and colleagues, studies to date have concentrated on relatively small numbers of American and European populations, which may not capture the full complexity of the community nor adequately predict what constitutes a healthy vaginal microbiota in all population[14]. Furthermore, there is growing evidence that the vaginal microbiome varies within races and even within different geographic regions due to different genetics and cultural, nutritional and other human practices.

This study analysed the vaginal microbiota of indigenous African women who were less than 24 days into their postpartum period and whose neonates were diagnosed with culture-proven sepsis. Our data revealed that these women's microbiota consisted of five phyla, namely, *Firmicutes*, *Bacteroidetes*, *Proteobacteria* and *Tenericutes*. Of note, *Firmicutes* predominates in terms of phylum richness. Among these phyla, this study identified four families: *Ruminococcaceae*, *Lactobacillaceae*, *Lachnospiraceae* and *Eubacteriaceae*. Among these families, *Ruminococcaceae* are most frequently presented in the vaginal samples of the studied women. Analysing taxonomic classification at the genus level, we found that among the *Ruminococcaceae* family, *Faecalibacterium* (known butyrate-producing, anti-inflammatory bacteria) and *Ruminococcus* (known butyrate-producing, proinflammatory bacteria) were genera with higher richness. The overall assessment of taxonomic analysis of these women's microbiota at the genus level suggests that all six women resemble gut microbiota since *Faecalibacterium Ruminococcus* are well-known gut bacterial genera. This finding is equivocal with a current report by Ceccarani and colleagues, which stated that after delivery, the vaginal microbiota becomes more similar to the gut microbiota, some *Lactobacillus* species

are lost, diversity increases, and vaginosis-associated bacteria are more abundant[152]. A few studies report on postpartum vaginal microbiota analyses, especially during the first month after delivery. Possibly, the incidence of vaginal bleeding, antibiotic medication, trauma after giving birth, among others, might be the reasons why most researchers may not like to search for this category of women. One study from Africa, which analysed vaginal swabs taken postpartum from a cohort of 1,107 women in rural Malawi, reported that bacteria associated with vaginal CST IV-1 remained the most dominant community members in all participants regardless of the sampling time after vaginal delivery. Furthermore, they observed *G. vaginalis* to have remained the dominant organism seen in the vaginal microbiota, even over a year postpartum[14]. As reported by Ravel and colleaques[8], communities in group IV are the most diverse and have a higher proportion of strictly anaerobic bacteria in combination with *Lactobacillus* species. From previous studies[8,9], it is known that *Lactobacillus* species did not dominate communities in group IV. Also, a sub-group among the communities in group IV lacked detectable *Lactobacillus* species in their vaginas. These descriptions of CST IV match with the vaginal community members observed in this work, suggesting our finding is similar to that of the Malawian study. However, their observation that *G. vaginalis* remained the dominant bacterial species in the vaginal microbiota of their studied women was not seen in our study. This difference might be because our study population was a sub-group of women in their postpartum period, i.e. women who have delivered and whose neonates were diagnosed with sepsis (mainly EONS), whilst their study recruited a more heterogeneous group of women, i.e. all women who have delivered. Also, their study was a sub-study of a clinical trial assessing the impact of lipid-based nutrient supplements given to mothers during pregnancy and the first six months of lactation. Although both studies were done in Africa, there may be regional differences in vaginal microbiota of women due to cultural, nutritional and other human practices.

One of this study's objectives was to address whether the vaginal microbial composition of a woman destined to deliver preterm (case) with subsequent vertical transfer of bloodstream bacterial infection is different from that of a woman who delivers term (control) and also with bloodstream infection. We observed an increase in vaginal bacterial diversity (alpha diversity) in the case group compared with the control group. This finding is well documented in recent studies that have found an association between vaginal microbiota and preterm delivery[20,153–155]. However, we did not observe an increase in the *Lactobacillus* species in the control arm,

as reported by other studies[10,13]. MacIntyre and Romero's studies could explain this difference between Brazilian and American populations, respectively. This explanation could be supported with Ravel and colleagues' study, which has revealed that the vaginal microbiome of women could be classified into five cluster groups, namely groups I-V. Four of these groups were dominated by lactobacilli: group I, *Lactobacillus crispatus*; group II, *Lactobacillus gasseri*; group III, *Lactobacillus iners*; group V, *Lactobacillus jensenii*. They further explained that group IV was a heterogeneous group of strict anaerobes[8] and may or may not have detectable *Lactobacillus* species. Their analysis suggests that group I was the most common group amongst women of European ancestry, whereas group IV was the most common in African American women. Our study was conducted among indigenous African women, explaining the low levels of *Lactobacillus* species detection.

Currently, only vaginal microbiota diversity and richness of specific *Lactobacillus* species are reported to be associated with preterm delivery, although not all studies have identified this association. We have identified the detection of *Ruminococcus* 2 (*Blautia*) in the vaginal microbiota of all the members of the case group but not in the control group, which suggests that this bacterial genus might have an association with preterm delivery with subsequent bacterial bloodstream infection. *Ruminococcus* 2 is a group of bacterial species in the genus *Ruminococcus* which were re-classified as *Blautia* on the basis that unlike *Ruminococcus, Blautia* are known to be strictly anaerobic carbohydrate fermenters, some species are H_2/CO_2 utilizing acetogens, acetate, formate, succinate, lactate and ethanol are produced as by-products of fermentation and cellulose is degraded by some species[156–158]. However, in most of the literature they are still called *Ruminococcus*. A major setback of the study was that the sample size was small, suggesting a large scale study in the study region to confirm the association. However, in infants' gut dysbiosis, an abundance of *Ruminococcus* species has been shown to induce Th2 partial immunity in the colon. Its subsequent effectors exploit the gut-pulmonary axis to evoke allergic asthma in these infants[32]. A recent study has also shown that characteristic trends were observed in dysbiosis in chronic heart failure patients' gut microbiota, where *Faecalibacterium* species decrease whilst *Ruminococcus* species increase[31]. In the case of the vaginal microbiota, data from a study conducted among women with common genital tract infections have shown that *Faecalibacterium* species was significantly increased in both women who presented with *Chlamydia trachomatis* and vulvovaginal candidiasis, but not in BV[152]. The role these bacterial species play in the pathogeneses of these diseases is not

clear. Also, the presence and function of *Ruminococcus* species and *Faecalibacterium* in the vagina have not been explored. However, a comprehensive search on *Faecalibacterium* revealed that its gut levels had been reported to be reduced in patients suffering from several syndromes and diseases such as IBS, CRC, IBDs, celiac disease and obesity[23–27].

As observed in this work, the genus *Acinetobacter* is present in a microbial community of the vagina of mothers who have history of previous neonate(s) death. The two mothers in this study whose medical records indicated that they had lost their neonates in their previous deliveries had *Acinetobacter* in their vaginal microbiota, whereas the other mothers did not. Although our study's power is limited due to the small sample size, this observation might not be by chance and calls for further research. *Acinetobacter* species infections in neonates are not uncommon but are rarely studied[159]. Studies have shown that *Acinetobacter* species infections appear to be predominant in some regions, while the incidence is very low in other regions[160,161]. A systematic review report suggests that PROM was observed in 13-21% of neonates with *Acinetobacter* infections[162]. In a previous study, prematurity and LBW were reported as predisposing factors for *Acinetobacter* species infections, with a 3-10 fold higher incidence of infection than full-term infants[4]. A current report from Northern Taiwan has shown that 95% of Acinetobacter-infected newborns were premature with low birth weights. Moreover, 65% had prolonged intubation and required a percutaneous central venous catheter, and 95% had long-term usage of total parenteral nutrition or intravenous lipid[159]. These findings suggest that *Acinetobacter* species infections in neonates could be mostly transmitted vertically but have some aspects of HAIs (LONS), so it may not be clear if the infections were transmitted from a mother and presented late or if they came from the hospital environment.

This aspect of the current study has some limitations. There is no reference data on vaginal microbiota of the general population in the studied region or country for comparison. Also, the study power is low due to the limited sample size; hence we cannot make concrete conclusions on our findings. Furthermore, the 16S rRNA sequenced yields were low due to miss dilution of libraries during the library purification process; however, reasonable phyla sizes were represented. These are likely be close to the actual fingerprint of the microbial DNA in these women’s vaginas.

4.2 Clonal relatedness of *S. epidermis* and *S. haemolyticus* isolates to predict the source of transmission

Despite the importance of CoNS as a cause of HAIs, limited information has been available regarding their reservoirs, distribution, and transmission mode within the hospital environment[163]. This section of the study aimed to investigate possible transmission sources of *S. epidermidis* and *S. haemolyticus* species in the HTH NICU using modern molecular techniques. For 67 *S. epidermidis* isolates, this study using *tuf* gene molecular analysis demonstrated two major clusters that may represent the community's clone. The genetically heterogeneous isolates in the two major clusters may have originated from the native flora of individuals from the community. Each of these two clusters has two sub-clusters, one of each of which were identified as hospital-endemic clones. The clusters are considered endemic clones because some isolates isolated from neonates' blood samples two years before the current study clustered well with isolates from clinical staff and current neonates' isolates, indicating that they are endemic in the hospital environment. The identified hospital-endemic clones may have been selected by the antibiotic treatment given in the hospital or other hospital practices like disinfection. However, in the absence of a specific definition for the classification of genetic similarity between isolates, it cannot be excluded that some of the isolates in both sub-clusters may have a clonal relationship. Analysis of these endemic clones based on their distribution in the various wards found that they were not only in the NICU but also in all the other wards like maternity, children's, and delivery unit, and the hospital's theatre. Three major clusters were identified for the 39 *S. haemolyticus*, and each has about five small sub-clusters. However, one of the major clusters with 50% of the neonates' isolates, 75% of isolates from objects in the hospital, is likely to be the hospital-endemic clones. Biochemical and molecular typing studies have demonstrated that clusters of CoNS may be distributed among both neonates and hospital staff, while isolates associated with sepsis may be more homogeneous[164–166]. For NICUs, in particular, it has been shown that single clones of multi-resistant *S. epidermidis* and *S. haemolyticus* strains that produce biofilms are associated with colonization and disease among preterm neonates[167]. The clonal spread of endemic, multidrug-resistant CoNS within a hospital was also detected in non-neonatal ICUs and wards[168,169]. Within 11 years, one molecular cluster emerged as the predominant cause of CoNS sepsis in a Dutch neonatal ICU[166]. Moreover, possible inter-hospital spread has been demonstrated[169]. In contrast, a pronounced genetic diversity of *S. epidermidis* was found in healthy, non-hospitalized persons[170].

The current study differed from other cited reports in some aspects. This section of the study's primary objective was to identify the possible source(s) of transmission of *S. epidermidis* and *S. haemolyticus* to neonates and not to evaluate the clinical significance of isolated CoNS. Given this, the *tuf* gene sequenced data were analysed to determine the possible pairs of the neonates' isolates with those of the mothers, clinical staff, students and the hospital objects. The findings were compared with MLST typing results and whole-genome scatter graph analysis to predict transmission sources better. Analysis of the *tuf* gene data revealed that clinical staff are more likely to transit *S. epidermidis* to babies in the HTH NICU and Baby unit. The whole-genome sequence analysis results equivocally identified the clinical staff's isolates as having clustered with those of the neonates'. This finding is not surprising because *S. epidermidis* is the most frequently recovered staphylococcal species on humans' bodies. These bacteria species colonise the body surface, particularly in moist areas, such as the axillae, inguinal and perineal areas, anterior nares, conjunctiva, and toe webs[171]. Evidence-based research has shown that hands of healthcare workers [40,41] are the main cause of transmission of pathogens within and between patients. Although this connection is widely known, hand hygiene compliance in NICUs has been reported to be as low as 40%, meaning 60% of recommended hand hygiene steps were not fulfilled[42]. Higher activity levels were shown to be associated with lower compliance with hygiene standards[42].

In the NICU, critically ill infants often require fast-paced, complex and precise care, resulting in an increased propensity toward errors along with increased vulnerability. Research shows that HAIs are a significant cause of morbidity and mortality among infants in the NICU[172,173]. Infants hospitalized in the NICU have the highest rates of HAIs among the paediatric population, with infection rates ranging from 6 to more than 30 infections per 100 patient discharges[174]. Bloodstream infections (BSI) are the most common nosocomial infections in very low birth weight infants (VLBWI)[175–177]. The median BSI rate for VLBWI was reported to be 10.9 per 1000 patient days in NICUs in the US[178], 3.3 per 1000 patient days in the German NEO-KISS network[179] and 2.5 per 1000 patient days in a tertiary hospital, Vienna[180]. A growing body of evidence suggests that burnout among ICU nurses[181,182] and ICU physicians[183] is a remarkable result of the demanding and continuously high-stress work environment. The prevalence of burnout in Western countries within the general working population ranges from 13% to 27%[184]. However, healthcare professionals are referred to as being at increased risk of

suffering burnout[185], compared with non-healthcare professions. Prevalence is documented to be as high as 70% worldwide amongst physicians[186], with 30%–50% of nurses reaching clinical burnout levels on self-report measures[182,187]. This study investigated burnout among HTH clinical staff using the 'gold standard' for measuring burnout syndrome in empirical research (the Maslach Burnout Inventory[188]) and found the overall burnout among HTH clinical staff in this study was 34.7% (Supplementary data 6.4). This result buttresses the current report of burnout among healthcare workers in LMICs[189]. To compare the burnout levels between doctors and nurses, we found a significant difference in burnout levels between nurses and doctors at the HTH. The doctors appeared to have registered less (10.6%) burnout than the nurses (49.2). Burnout among the clinical staff might be responsible for the high rate of *S. epidermidis* transmission to babies by this hospital's clinical staff. These findings call for measures in the HTH to reduce burnout among clinical staff to reduce the rate of HAIs among neonates admitted to this hospital. Another important aspect of investigating the infection rate in this hospital was determining types and rates of disinfectant usage among the clinical staff. About 75% of the clinical staff frequently used alcohol-based and phenolic-based (red cake soap) to disinfect (Supplementary data 6.4).

Regarding *S. haemolyticus* transmission among the studied neonates, *tuf* gene analysis revealed that mothers are more likely to transmit this staphylococcal species than the clinical staff. This observation supported the findings from the whole-genome sequencing analysis, which showed a relative distance of neonates' isolates from those of the clinical staff, but did not show that they cluster with the mothers' isolates since none of the mothers' isolates was analysed. However, MLST revealed that all but one (of unknown ST) of the four neonates' isolates belong to ST1, indicating a likely clone. For the two isolates from clinical staff, one was also ST1 and the other was an unknown ST. In the two mothers' isolates, each has a different ST (ST3 and ST30), indicating the possibility of getting heterogeneous STs from the mothers. For *S. haemolyticus* transmission, there must be a close and continuous contact with some anatomical parts like axillae and pubic areas which are high in apocrine glands [190,191]. This contact is more likely to have occurred with a mother than a clinical staff. Hence the findings of *tuf* gene model of this study that suggest that mothers are likely sources of transmission of *S. haemolyticus* is partially explained by the likely contact with some anatomical parts with their babies. However, the results of the MLST queried mothers as the primary sources of transmission of *S. haemolyticus* and hence made the source of transmission of this species

unclear. The study has some limitations in that whole-genome sequencing was performed on only a few *S. haemolyticus* isolates of mothers, clinical staff, and students, making inferences from the MLST whole-genome sequencing data unavailable or inappropriate.

4.3 Antimicrobial susceptibility patterns for *S. epidermidis* and *S. haemolyticus* and their molecular characterization

To better characterize phenotype-genotype mapping for drug resistance, this aspect of the study analysed drug-resistant gene carriage of CoNS to predict resistance to the 'Watch' and 'Reserve' antimicrobial groups and mupirocin, which have not been previously exposed to the HTH. A previous study demonstrated that the acquisition of resistance to one drug drastically changed resistance and susceptibility to other drugs. This finding suggests that the resistant strains' phenotypic changes were not always restricted to specific factors, such as modifying the drug target protein structure but instead caused changes in several intra-cellular properties[192]. The acquisition of drug resistance is a phenomenon that involves changes in various components, including the genome, transcripts and metabolites, meaning a complex interaction network is involved[192]. Exposure to antibiotics has been considered the most critical factor influencing the emergence and spread of antibiotic resistance[193]. This view emphasizes the influence of natural (Darwinian) selection in the evolution of resistance, such that antibiotic-resistant organisms survive and have progeny while their susceptible counterparts become extinct[194].

This study isolated and sequenced genomes of five tigecycline-resistant *S. haemolyticus* cultured from the HTH. The study investigated the possible molecular resistance mechanism to tigecycline since it has not been used in this hospital. It is highly active against many multidrug-resistant organisms, including MRSA, MRSE, VRE, *Acinetobacter baumannii*, and anaerobic pathogens [118,195] . Bacterial resistance to tigecycline is very rare [119]. Recent updates on tigecycline revealed that enzymatic inactivation has emerged as a new concern for the next-generation tetracyclines (tigecycline, eravacycline, and omadacycline)[125] resistance. Analysis of the five isolates' whole-genome sequences did not reveal the *tet*X, *tet*(47-56) genes[84] known

for resistance by the mechanism of enzymatic inactivation in tetracyclines. This finding implies that a genetic resistance determinant by the presence of the enzyme responsible for antibiotic inactivation among the five isolates is unlikely. A recent study suggested that mutations in the *mep*RAB efflux system contribute to the *in vitro* development of tigecycline resistance in *S. aureus*[196]. This study did not identify these genes when the CARD site was searched for antibiotic resistance genes. However, when the search's default was changed to include loose gene detection, some of these genes were seen but with identities less than 95%. When the trend of identifying *mep* genes was compared between tigecycline-resistant and -susceptible isolates, this study did not observe a difference in the distribution of these genes among the two groups. This observation indicated that these genes (*mep*A and *mep*R) might not be involved in the tigecycline resistance observed in the isolates. However, the current study did not search for specific gene mutations on these genes, as reported by Fang et al.[196].For Fang and colleagues' study, substitution mutations were detected in the transcriptional repressor *mep*R and the efflux pump gene *mep*A. A K57M amino acid substitution occurred in the ribosomal S10 protein-encoding gene *rps*J in *S. aureus*[196]. Moreover, the *mep*R and *mep*A genes were the only genes among other loose antibiotic genes detected that were of relatively higher identities of about 85% and 50%, respectively. In comparing the antibiotic resistance genes patterns of the tigecycline-resistant and -susceptible *S. haemolyticus* isolates, the data revealed the co-detection of the following genes: *msr*A-*mph*C, *mec*A-*msr*A, *tet*(M)-*tet*(S), *tet*(L)-*tet*(45) and *fus*B-*far*1 on the genome of *S. haemolyticus* isolates. The data suggest the co-detection of these genes predicts resistance to tigecycline. The study cannot tell whether the presence of the genes APH(3'), *dfr*G and *dfr*K are required to observe resistance for the co-existing antibiotic genes implemented in this study since they seemed to be harboured by these isolates. As suggested by Hughes et al., after decades of genetic analysis of antibiotic resistance, both *in vitro*-selected strains and clinical isolates, it has become apparent that there is very frequently an interplay between multiple genetic alterations involved in shaping a resistance phenotype[197]. These findings call for further detailed *in vitro* studies to investigate these resistance mechanisms to tigecycline seen in these *S. haemolyticus* isolates.

Another resistance mechanism investigated was the mechanism of HLMR in CoNS cultivated from a non-previously mupirocin-exposed hospital system. Three categories of mupirocin susceptibility have been described for *S. aureus*[198]. *S. aureus* is considered mupirocin susceptible at MIC of 4 g/ml or less. MICs of 8 to 64 g/ml refer to low-level resistance and are

usually due to nonsynonymous changes in the native isoleucyl-tRNA synthetase gene, *ile*S. Isolates with MIC of 128 or 256 g/ml are uncommon and are also considered to demonstrate low-level resistance[199]. High-level mupirocin resistance (MIC of ≥ 512 μg/ml) is mediated by the expression of *mup*A (*ile*S2) and currently identified *mup*B gene seen in a high-level resistant isolate which did not harbour *mup*A but the relatively associated gene *mup*B[199]. The molecular mechanism of low-level mupirocin resistance involves point mutations in the *ile*S gene; V588F and V631F are two common mutations associated with this phenotype[200]. Other point mutations reported for *S. aureus* include G593V, R816C, H67Q and F563L[201]. Of note, these mutations are identified in *S. aureus* and not CoNS. There is the possibility of identifying different mutations in CoNS. Moreover, this might be a reason for detecting *ile*S genes in this study but of lower identities than in the CARD database. The data on the molecular mechanism of low-level mupirocin resistance in CoNS are limited. For HLMR, the molecular mechanism is mediated by the plasmid encoded genes *mup*A and *mup*B, which encode an alternative Isoleucyl-tRNA synthease (ileS2) targeted by mupirocin[199]. Plasmid-mediated high-level mupirocin resistance can spread clonally and horizontally, even between different staphylococcal species[198,202]. This study isolated three HLMR CoNS from the HTH NICU. A search for the three mupirocin resistance genes on the three isolates' genome sequences indicated that none harboured these genes. This observation made the mechanism of HLMR of these isolates unclear. The literature review suggests that many but not all studies which screened for *mup*A or *mup*B among HLMR staphylococcal isolates (including CoNS) cultivated from mupirocin-exposed hospital settings have identified either of these genes in about 99% of the isolates[202–204]. Of note, these studies used detection by conventional PCR methods but not whole-genome sequencing. One study identified *mup*A in 81 out of 82 CoNS isolates that were phenotypically HLMR[204]. They have not investigated the mechanism of resistance of the HLMR isolate, which harboured neither the *mup*A nor the *mup*B genes. This study attempted to analyse the antibiotic resistance genes' patterns to elucidate the resistance mechanism of this HLMR but did not identify any clue. Thus, the mechanism of HLMR of these three CoNS remains unclear to this study.

4.4 Chlorhexidine susceptibility patterns for staphylococcal species and their molecular characterization

Members of all five major families of efflux pumps are upregulated in response to chlorhexidine exposure, both in Gram-negative and Gram-positive bacteria, leading to increased tolerance to it[205]. Also, a study has shown that mutation in *Nor*A and *Nor*B, efflux pumps associated with chlorhexidine and fluoroquinolone efflux, has also increased over time[145]. Furthermore, the detection of the *qacA/B* genes was associated with higher chlorhexidine MICs and unsuccessful decolonization during an ICU-based topical chlorhexidine intervention[206,207]. Tolerance of chlorhexidine via the *qacA/B* efflux system in staphylococcus, especially *S. aureus*, has been studied in depth[145,208]. In this study, only one isolate out of the fifteen isolates analysed harboured the *qacA* gene, indicating that this gene's prevalence among the CoNS isolates in the HTH is low. This finding agrees with the low range of chlorhexidine MICs obtained in this study (0.25-4 mg/L). With only one *qacA* gene detected, an association between *qacA/B* and phenotype of multidrug-resistant isolates cannot be analysed in this study.

Biofilm formation is another mechanism by which most pathogenic bacteria become resistant or tolerant to chlorhexidine. Two of the isolates harboured the biofilm-producing genes and have their chlorhexidine MICs of 1 and 2 mg/L. The data are limited to determine an association between detection of biofilm-forming genes and levels of chlorhexidine MICs in this study.

4.5 Concluding remarks

The current study came up with two null-hypotheses about the risk of maternal vaginal microbiota dysbiosis that need further investigation. First, the genus *Ruminococcus* 2 (*Blautia*) detected in the vaginas of mothers from the study population does not predispose them to spontaneous preterm deliveries. Secondly, the detection of the genus *Acinetobacter* in the vaginas of mothers from the study population does not pose a risk of them losing their babies during the neonatal age. Furthermore, this study identifies the co-existence of certain antibiotic genes on the genome of *S. haemolyticus* species that could be used to predict resistance to tigecycline. This antibiotic is known to have rare resistance to many microorganisms. These findings could be integrated into current automated techniques used to identify resistance of bacterial species to tigecycline in a clinical setting. However, there is a need for further molecular studies to confirm these findings. The three HLMR CoNS identified in this study harboured no genes for HLMR; hence, their molecular mechanism(s) of resistance to this antimicrobial is unclear to the current study. However, the *ile*S genes detected with low identities in this study needed further bioinformatics analyses to identify possible mutation in CoNS that might be attributed to mupirocin resistance. Five novel multilocus sequence types were identified, two *S. epidermidis* and three *S. haemolyticus*. There are limited data on multilocus sequence types published from LMICs. These new MLS types are added to the global database and will help to better understand geographical distribution of MLS types. Also, the current study has obtained baseline chlorhexidine MICs and the prevalence of genes associated with decreased chlorhexidine susceptibility for staphylococcal isolates cultivated from the environment of the HTH. These findings will help in some aspect of the future evaluation of chlorhexidine ointment use in this hospital to reduce neonatal mortality due to HAIs.

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6 SUPPLEMENTARY DATA

6.1 **Materials and Equipment**

Materials	Vendor
6x DNA Loading Dye	Thermo Fisher Scientific, Dreieich, Germany
96-well plate, PCR grade	Sarstedt AG & Co., Nümbrecht, Germany
Antibiotic gradient strips	E-test®; Liofilchem®s.r.l, Italy
BACTEC Peds Plus/F blood culture bottles	Becton Dickinson Company, Maryland, USA
Biozym LE Agarose	Biozym Scientific GmbH, Hessisch Oldendorf, Germany
Bis-Tris	Sigma Aldrich, Darmstadt, Germany
Brain Heart Infusion (BHI)	Oxoid Ltd, England
DNeasy Blood and Tissue kit	Qiagen, Germany
DreamTaq	ThermoFisher Scientific, Bremen, Germany
EDTA solution 0.5M pH 8	AppliChem GmbH, Darmstadt, Germany
Ethanol 96%	Carl Roth GmbH & Co. KG, Karlsruhe, Germany
Ethanol, absolute for analysis	Merck Millipore Merck KGaA, Darmstadt, Germany
GeneJET Gel Extraction Kit	Thermo Fisher Scientific, Dreieich, Germany
GeneJET Genomic DNA Purification Kit	Thermo Fisher Scientific, Dreieich, Germany
GeneRuler 100 bp Plus DNA Ladder	Thermo Fisher Scientific, Dreieich, Germany
Isopropanol (100%)	Carl Roth GmbH & Co. KG, Karlsruhe, Germany
Methanol	Carl Roth GmbH & Co. KG, Karlsruhe, Germany
MiSeq Reagent Kit v3	Illumina, San Diego, USA
Mueller-Hinton E agar	bioMérieux SA, Strasbourg, France
NEBNext Library Quant Kit	New England Biolabs®, MA, USA
PCR plate seal, adhesive	Sarstedt AG & Co., Nümbrecht, Germany
Phusion Hot Start II High-Fidelity	Thermo Fisher Scientific, Dreieich, Germany
Pipette tips	SARSTEDT, Germany
Powersoil DNA Isolation Kit	MO BIO Laboratories, West Carlsbad, USA
Proteinkinase K, lyophilized	Roche Diagnostics GmbH, Germany
QIAamp®DNA Microbiome kit	(QIAGEN, MD, USA
Qubit® dsDNA HS Assay Kit	Thermo Fisher Scientific, Dreieich, Germany
RT-PCR Grade Water	Thermo Fisher Scientific, Dreieich, Germany
Sodium chloride	Merck KGaA, Darmstadt, Germany
Sodium hydroxide	Merck KGaA, Darmstadt, Germany
Stock chlorhexidine	Sigma Aldrich, USA
SYBR® Safe DNA Gel Stain	Thermo Fisher Scientific, Dreieich, Germany
Triton X-100	Carl Roth GmbH & Co. Germany
Tween 20	Sigma-Aldrich, Darmstadt, Germany
Whatman paper	Bio-Rad Laboratories GmbH, Munich, Germany

Equipment source	Supplier
Agilent 2100 Bioanalyzer	Agilent Technologies
Allegra® X-15R Centrifuge	Beckman Coulter
Analytical scale ABS/ABJ-BA-def-1019	Kern & Sohn GmbH, Balingen, Germany
BACTEC™ 9050 blood culture instrument	Becton Dickinson Company, Maryland, USA
Bruker Daltonik MALDI-TOF	Biotyper®GmbH
Centrifuge 5810R	Eppendorf AG, Hamburg, Germany
Freezer -20˚	Liebherr Hausgeräte GmbH, Ochsenhausen, Germany
Freezer -80˚	Thermo Fisher Scientific GmbH, Dreieich, Germany
Fridge: Comfort	Liebherr, Germany
GeneAmp® PCR System 9700	Applied Biosystems
Laminar hood	NuAire, Plymouth, Minnesota, USA
Mastercycler ep realplex	Eppendorf AG, Hamburg, Germany
Micro centrifuge Micro Star 17R	VWR International GmbH, Darmstadt, Germany
Microwave: 700 & Grill	Severin, Germany
MiSeq Desktop Sequencer	Illumina, San Diego, USA
NanoDrop 2000c spectrophotometer	Thermo Fisher Scientific GmbH, Dreieich, Germany
pH meter HI208	HANNA instruments, Vöhringen, Germany
Precision balance 440-47N	Kern, Balingen, Germany
QUANTUM ST4 1100 imaging system	Vilber Lourmat Deutschland GmbH, Eberhardzell, Germany
Qubit® Fluorometer	Thermo Fisher Scientific
Refrigerator	Siemens, Munich, Germany
VITEK 2®machine	Biomerieux, Durham, USA
Vortex	Vortex-Genie® 2-Scientific Industries Inc., Bohemia, New-York,USA
Vortex Adapter	MO BIO Laboratories, Inc.

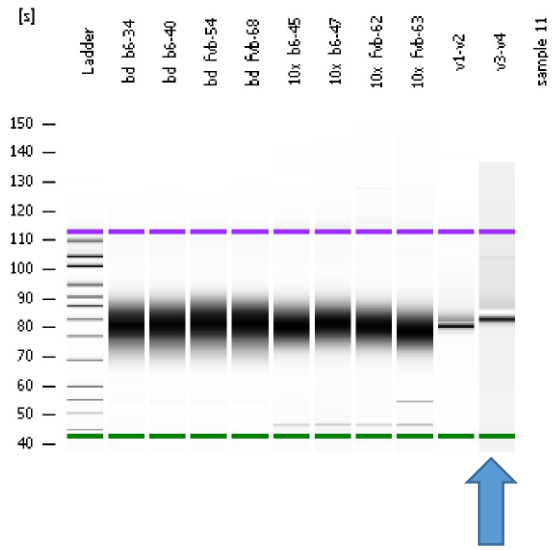
6.2 **Quality control of 16S rRNA gene library and qPCR of library**

2100 expert_High Sensitivity DNA Assay_DE34903614_2019-11-06_12-07-12.xad Page 1 of 19

Assay Class: High Sensitivity DNA Assay
Data Path: C:\...gh Sensitivity DNA Assay_DE34903614_2019-11-06_12-07-12.xad

Created: 06-Nov-19 12:07:12
Modified: 06-Nov-19 12:45:42

Electrophoresis File Run Summary



Instrument Information:

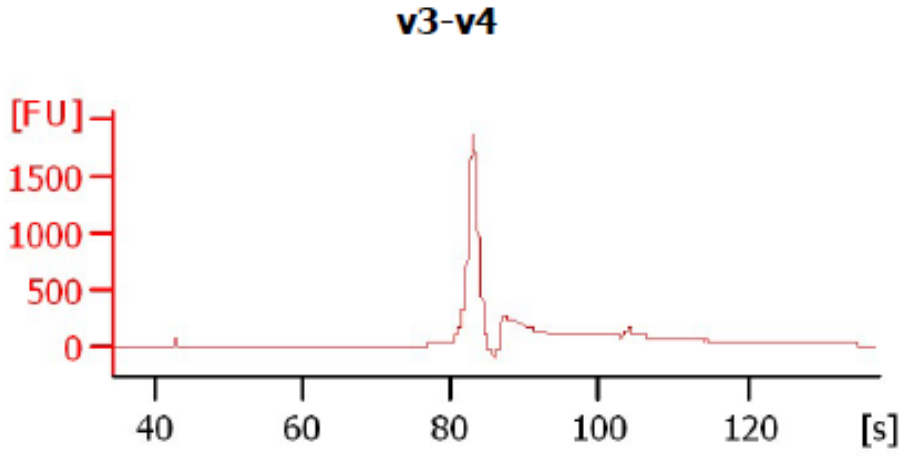
Instrument Name: DE34903614 Firmware: C.01.069
Serial#: DE34903614 Type: G2938C

Assay Information:

Assay Origin Path: C:\Program Files\Agilent\2100 bioanalyzer\2100 expert\assays\dsDNA\High Sensitivity DNA.xsy
Assay Class: High Sensitivity DNA Assay
Version: 1.03
Assay Comments: Copyright © 2003-2010 Agilent Technologies

Chip Information:

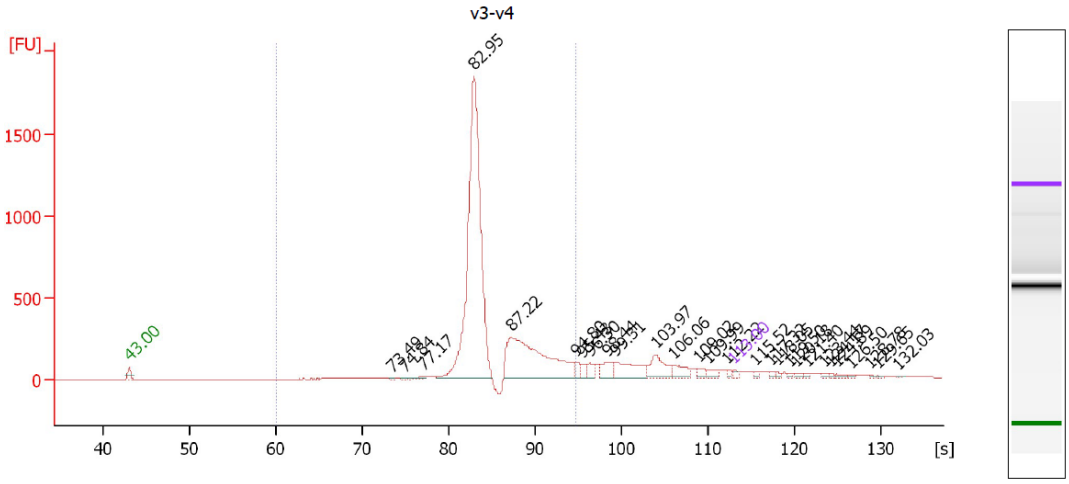
Chip Lot #:
Reagent Kit Lot #:
Chip Comments:



Assay Class: High Sensitivity DNA Assay
Data Path: C:\...gh Sensitivity DNA Assay_DE34903614_2019-11-06_12-07-12.xad

Created: 06-Nov-19 12:07:12
Modified: 06-Nov-19 12:45:42

Electropherogram Summary Continued ...



Overall Results for sample 10 : v3-v4

Number of peaks found:	28	Corr. Area 1:	5,548.1
Noise:	0.5		

Peak table for sample 10 : v3-v4

Peak	Size [bp]	Conc. [pg/µl]	Molarity [pmol/l]	Observations
1	35	125.00	5,411.3	Lower Marker
2	354	20.21	86.5	
3	371	27.39	111.9	
4	400	104.65	396.6	
5	501	14,737.53	44,572.1	
6	595	5,347.36	13,623.9	
7	1,012	263.04	394.0	
8	1,108	193.35	264.3	
9	1,243	285.93	348.6	
10	1,571	430.70	415.5	
11	1,705	965.53	858.1	
12	2,841	786.79	419.6	
13	4,216	410.58	147.5	
14	6,511	154.30	35.9	
15	7,342	183.61	37.9	
16	9,596	67.97	10.7	
17	10,380	75.00	10.9	Upper Marker
18	12,928	0.00	0.0	
19	14,741	0.00	0.0	
20	15,476	0.00	0.0	
21	16,945	0.00	0.0	
22	17,631	0.00	0.0	
23	18,856	0.00	0.0	
24	20,914	0.00	0.0	
25	21,649	0.00	0.0	
26	22,384	0.00	0.0	

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Table 6.2.1. **qPCR of the 16S rRNA gene library**

Pos	Name	Ct SYBR	Ct Mean SYBR	Ct Dev. SYBR	Amount SYBR [pM]
A1	Standart1	8.67			10.0
A2	Standart1	7.47			10.0
A3	Standart1	6.54			10.0
B1	Standart2	12.92			1.00
B2	Standart2	14.13			1.00
B3	Standart2	12.97			1.00
C1	Standart3	15.00			0.100
C2	Standart3	14.87			0.100
C3	Standart3	14.88			0.100
D1	Standart4	18.93			1.000E-2X
E1	NTC	28.07			2.940E-5X
E3	NTC	28.28			2.570E-5X
G2	V3_V4x4	7.29			19.6
G4	V3_V4x5	10.57			2.36
G6	V3_V4x4	7.21			20.7
G8	V3_V4x5				-
G10	V3_V4x4	7.03			23.1
G12	V3_V4x5	10.63			2.28

Analysis Parameters	
Type of Application	Quantification
Dye(s)	SYBR
Inverted Data	OFF
Threshold setting	Noiseband
Threshold level	200
Baseline setting	Automatic
Baseline range (from cycle no. ... to)	n/a
Drift Correction	OFF

Standard curve parameters	
Slope	-3.568
Y-Intercept	11.90
Efficiency	0.91
R^2	0.940

6.3 **Neonatal and infant sepsis**

Table 6.3.1 **Mothers demographic characteristics and risk factors for neonatal sepsis**

Parameter		Blood Culture		Total	p-Value	Odds Ratio (Confidence interval)
		Negative	Positive			
Mother's Age	Teenagers (17-19yrs)	3(100.0)	0(0.0)	3	0.51	1.06 (0.24, 4.71)
	Adults (20-35yrs)	35(66.0)	18(34.0)	53		
	Elderly (>35)	6(66.7)	3(33.3)	9		
	Total	44(67.7)	21(32.3)	65		
Education	No Formal Education	1(100.0)	0(0.0)	1	0.353	2.11 (0.56, 7.97)
	Basic	6(54.5)	5(45.5)	11		
	Secondary	31(81.6)	7(18.4)	38		
	Tertiary	7(46.7)	8(53.3)	15		
	Total	45(69.2)	20(30.8)	65		
Gravida	Primigravida	14(73.7)	5(26.3)	19	0.618	1.358 (0.42, 4.43)
	Multigravida	33(67.3)	16(32.7)	49		
	Total	47(69.1)	21(30.9)	68		
Parity	Primiparous	21(75.0)	7(25.0)	28	0.387	1.615 (0.55, 4.73)
	Multiparous	26(65.0)	14(35.0)	40		
	Total	47(69.1)	21(30.9)	68		
Chronic Disease	No Chronic Disease	26(72.2)	10(27.8)	36	0.444	1.463 (0.49, 4.37)
	Chronic	16(64.0)	9(36.0)	25		
	Unknown	3(60.0)	2(40.0)	5		
	Total	45(68.2)	21(31.8)	66		
UTI	No UTI	29(72.5)	11(27.5)	40	0.301	1.582 (0.32, 7.76)
	UTI	5(62.5)	3(37.5)	8		

	Unknown	10(58.8)	7(41.2)	17		
	Total	44(67.7)	21(32.3)	65		
Antibiotic Prophylaxis	No	30(66.7)	15(33.3)	45	0.466	1.5 (0.27, 8.34)
	Yes	6(75.0)	2(25.0)	8		
	Unknown	7(77.8)	2(22.2)	9		
	Total	43(69.4)	19(30.6)	62		
Antibiotic Medication	No	9(64.3)	5(35.7)	14	0.915	1.37 (0.38, 4.87)
	Yes	32(71.1)	13(28.9)	45		
	Unknown	4(57.1)	3(42.9)	7		
	Total	45(68.2)	21(31.8)	66		
Number of ANC Visits	No ANC Visit	0(0.0)	1(100.0)	1	0.802	0.58 (0.14, 2.4)
	<4	11(84.6)	2(15.4)	13		
	>5	32(68.1)	15(31.9)	47		
	Total	43(70.5)	18(29.5)	61		
Number of Vaginal examinations during ANC	None	8(57.1)	6(42.9)	14	0.118	3.38 (0.52, 21.73)
	3	5(71.4)	2(28.6)	7		
	4 and more	4(100.0)	0(0.0)	4		
	Total	17(68.0)	8(32.0)	25		

Table 6.3.2 **Cross tabulation of blood culture results and baby demographic characteristics**

Parameter		**Blood Culture**		**Total**	**p-Value**	**Odds Ratio (Confidence interval)**
		Negative	***Positive***			
Ward	NICU	42(73.7)	15(26.3)	57	0.079	0.9 (0.51, 1.66)
	Baby	22(56.4)	17(43.6)	39		
	Total	*64(66.7)*	*32(33.3)*	*96*		
Age	0-7 days	50(69.4)	22(30.6)	72	0.285	0.55 (0.13, 2.25)
	8-14 days	4(66.7)	2(33.3)	6		
	15-24 days	1(33.3)	2(66.7)	3		
	25 -50 days	8(57.1)	6(42.9)	14		
	Total	*63(66.3)*	*32(33.7)*	*95*		
Mode of Delivery	CS	34(64.2)	19(35.8)	53	0.566	0.775 (0.33, 1.83)
	SVD	30(69.8)	13(30.2)	43		
	Total	*64(66.7)*	*32(33.3)*	*96*		
Type of Birth	Single	59(65.6)	31(34.4)	90	0.376	0.381 (0.04, 3.4)
	Multiple	5(83.3)	1(16.7)	6		
	Total	*64(66.7)*	*32(33.3)*	*96*		
Birth Weight	ELBW	9(90.0)	1(10.0)	10	0.147	0.93 (0.38, 2.26)
	VLBW	6(75.0)	2(25.0)	8		
	LBW	13(56.5)	10(43.5)	23		
	NBW	32(66.7)	16(33.3)	48		
	Macrosomia	3(50.0)	3(50.0)	6		
	Total	*63(66.3)*	*32(33.7)*	*95*		
Gestational Period	Preterm	25(67.6)	12(32.4)	37	0.87	0.84 (0.35, 2.03)
	Term	35(63.6)	20(36.4)	55		

	Post Term	1(100.0)	0(0.0)	1		
	Total	*61(65.6)*	*32(34.4)*	*93*		
Gender	Female	30(65.2)	16(34.8)	46	0.775	0.88 (0.38, 2.06)
	Male	34(68.0)	16(32.0)	50		
	Total	*64(66.7)*	*32(33.3)*	*96*		
Outcome	Alive	57(70.4)	24(29.6)	81	0.03	
	Deceased	6(46.2)	7(53.8)	13		
	Referred	0(0.0)	2(100.0)	2		
	Total	*64(66.7)*	*32(33.3)*	*96*		

Data presented as frequency and percentages, N=Total numbers of subjects in category, CS=Caesarean section, SVD=Spontaneous vaginal delivery, ELBW = Extremely Low Birth Weight (<1000 g), VLBW = Very Low Birth Weight (>1000 <1500 g), LBW = Low Birth Weight (>1500 <2500 g), NBW = Normal Birth Weight (>2500 g), Macrosomia (>4000 g), NICU= neonatal intensive care unit

A

B

Figures 6.3.1(A&B) **Neonates in the NICU (A) and baby unit (B) of HTH**

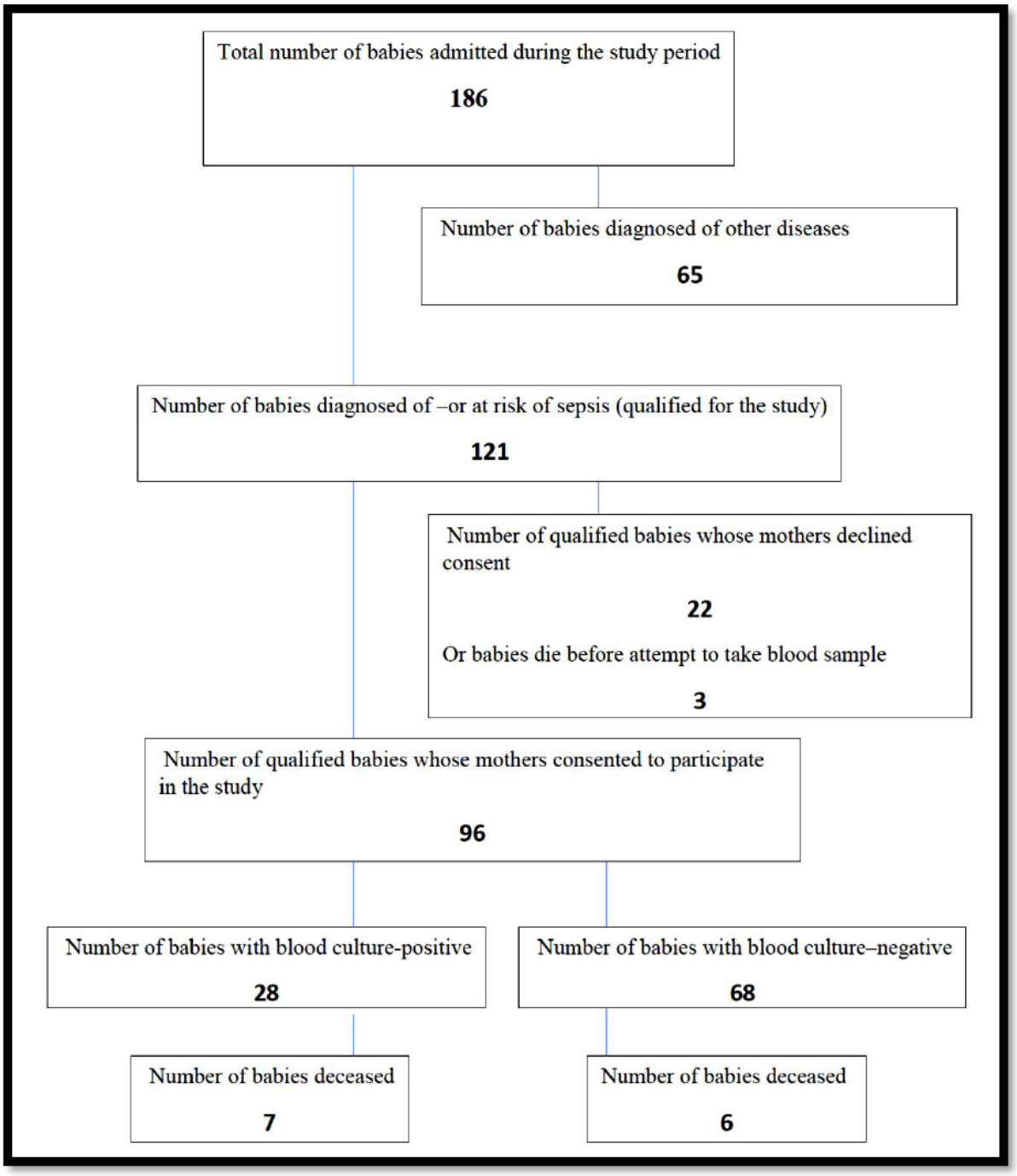

Figure 6.3.2 **Flow chart for neonate recruitment and the study outcomes**

Table 6.3.3 [ì]**Bacterial species cultivated from neonates' blood samples and their clinical outcomes**

Gram reaction	Genus	Species	Total No. of isolates	No. isolated from preterm babies	No. isolated from term babies	No. of neonates Expired
Positive	*Staphylococcus*	*aureus*	1	0	1	0
	Staphylococcus	*capitis*	2*	0	1	0
	Staphylococcus	*cohnii*	3	2	1	0
	Staphylococcus	*epidermidis*	6	3	3	0µ
	Staphylococcus	*haemolyticus*	8*	3	4	2
	Staphylococcus	*hominis*	2	0	2	0
	Staphylococcus	*warneri*	1	1	0	0
	Streptococcus	*agalactiae*	1	0	1	1
Negative						
	Acinetobacter	*bereziniae*	1	0	1	1
	Escherichia	*coli*	1	1	0	1
	Klebsiella	*pneumoniae*	2	0	2	2

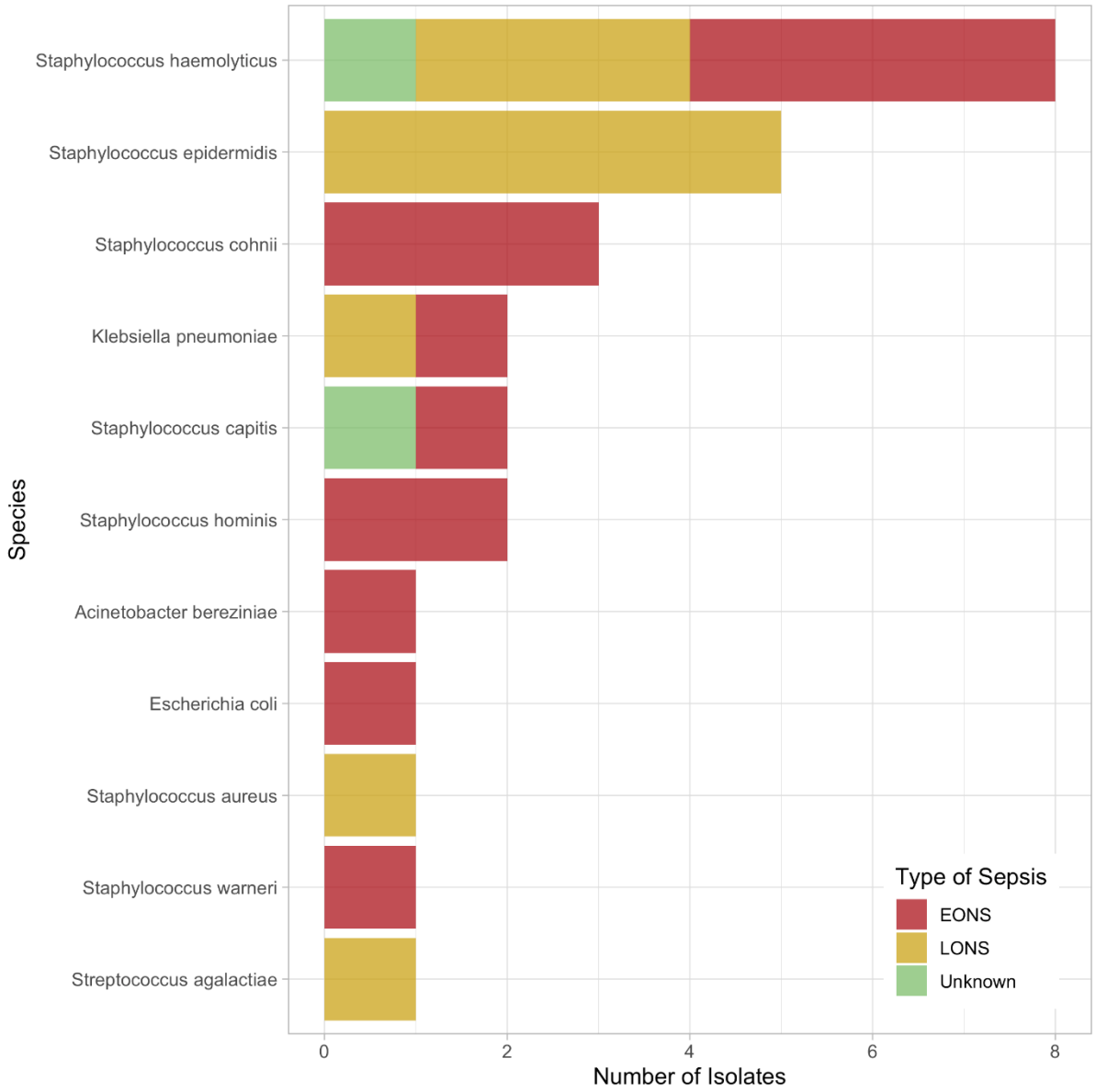

Figure 6.3.3 **Number of isolates based on the type of sepsis**

6.4 **Burnout and rate of disinfectant use among clinical staff of Ho Teaching Hospital**

Table 6.4.1 **Demographic characteristics of clinical staff**

Parameters	**Male** **N=16**	**Female** **N=43**
Age		
20-29	13(81.25)	19(44.19)
30-39	3(18.75)	19(44.19)
40+	0(0.00)	5(11.62)
Profession		
Medicine	11(68.75)	2(4.65)
Nursing	5(31.25)	41(95.35)
Period of working in HTH		
< 1 year	8(50.00)	7(16.25)
1-4 years	7(43.75)	22(51.16)
>5 year	1(6.25)	14(32.56)
Antibiotic taken within last three months		
Yes	2(12.5)	13(30.23)

Table 6.4.2 **Type and rate of disinfectant use among clinical staff of HTH**

Disinfectant	**% of clinical staff used**	**Rate of usage**			
	(N=49)	Always	Very often	Sometimes	Never
Alcohol based	91.5	42.3	32.2	17	8.5
Hypochlorite	86.4	3.3	33.9	49.2	13.6
Phenolic based (red soap)	78	54.2	22	1.7	22
Povidone-iodine	16.9	8.5	3.4	5.1	83.1
Chlorhexidine based	1.7	0	0	1.7	98.3
Thymol based	0	0	0	0	100
Aldehyde based	0	0	0	0	100
Quaternary Ammonium	0	0	0	0	100

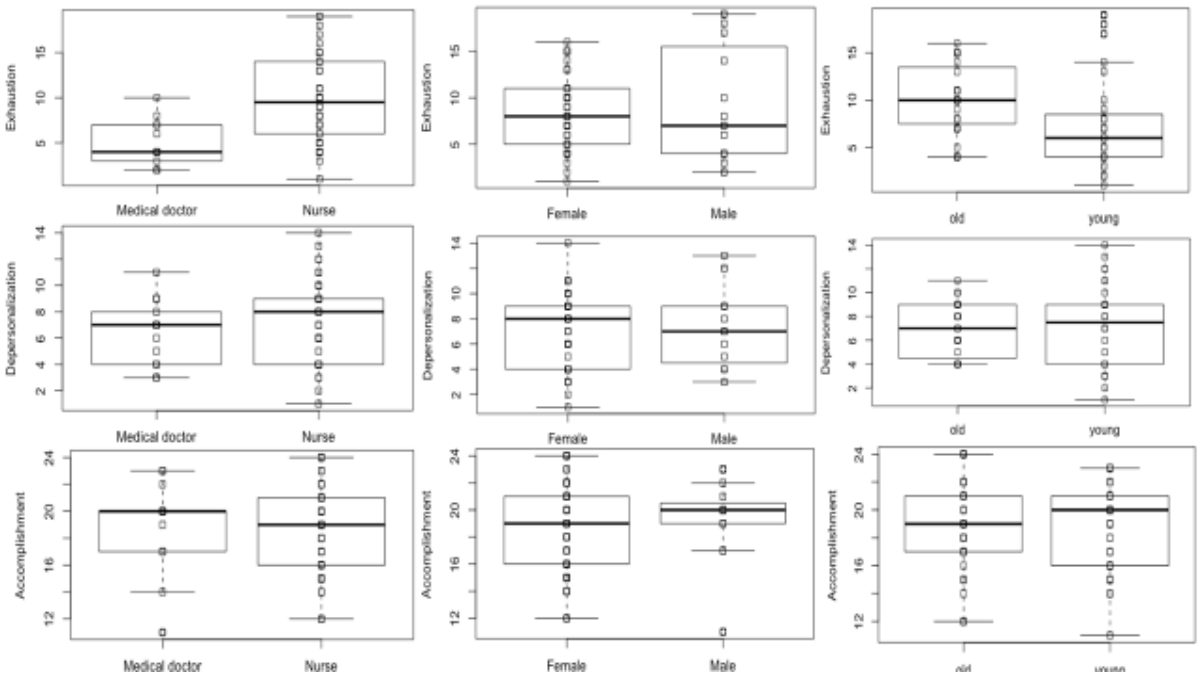

Figure 6.4.1 **Levels of exhaustion, depersonalization and personal accomplishment among the clinical staff**

Table 6.4.3 **Estimation of level of burnout among the clinical staff**

	Overall (%)	Nurses (%)	Doctors (%)	Female (%)	Male (%)	Young staff (%)	Old staff (%)
Exhaustion (E)	57.9	72.4	36.8	57.9	77.6	43.4	71.1
Depersonalization (D)	64.3	64.3	57.1	64.3	64.3	64.3	64.3
Accomplishment (A)	87.5	87.5	83.3	87.5	84.4	87.5	87.5
Burnout (E+D)-A	34.7	**49.2**	**10.6**	34.7	57.5	20.2	47.9

6.5 **Demographic characteristics of medical and nursing students**

Parameters	Male N=40	Female N=20
Age		
16-20	23(57.50)	17(85.00)
21-24	14(35.00)	3(15.00)
25+	3(7.50)	0(0.00)
Programme of study		
Medicine	11(27.50)	9(45.00)
Midwifery	0(0.00)	4(20.00)
Nursing	8(20.00)	3(15.00)
Physician Assistantship	21(52.50)	4(20.00)
Area of residence		
Urban	36(90.00)	16(80.00)
Rural	4(10.00)	4(20.00)
Those who visit hospitals	13(32.50)	8(40.00)
Facilities visited		
VRH	6(15.00)	7(35.00)
Others	7(17.50)	1(5.00)
Reasons for the hospital visit		
Outpatient	11(27.50)	7(35.00)
Visits	2(5.00)	1(5.00)
Taking antibiotics often		
Yes	4(10.00)	3(15.00)
Antibiotic taken within last three months Yes	3(7.50)	1(5.00)
Had a boil recently Yes	5(12.50)	3(15.00)

Data is presented as frequencies with percentages in parenthesis.

6.6 **Sequences of plasmids identified on the genomes of isolates studied in this study**

FDMS202323720 Stain: **HESN036B** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep7a	99.89	936 / 936	NA	NA..NA	repD(pTZ4)	NC010111
rep21	98.41	1005 / 1005	NA	NA..NA	rep(pSK108)	GQ900464
rep10	100	477 / 477	NA	NA..NA	repL(pDLK1)	GU562624
rep5b	99.88	867 / 867	NA	NA..NA	rep(pUR2355)	JQ312422

rep7a_NC010111

```
template
ATGAGTACAGAAAATCATTCAAATTACTTACAAAATAAGGATTTAGACAATTTTTCTAAA
query
ATGAGTACAGAAAATTATTCAAATTACTTACAAAATAAGGATTTAGACAATTTTTCTAAA

template
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query
ACCGGCTACTCTAATAGCCGGTTAAGTGGTAATTTTTTTACCACCCCTCAACCAGAATTA

template
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query
AGTTTTGATGCTATGACAATCGTTGGGAATTTGAACAAAACTAACGCTAAAAAGCTATCT

template
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query
GATTTTATGAGTACAGAGCCACAAATAAGGCTTTGGGATATATTACAAACAAAGTTTAAA

template
GCTAAAGCACTTCAAGAAAAGGTTTATATCGAATATGACAAAGTAAAAGCAGATAGTTGG
query
GCTAAAGCACTTCAAGAAAAGGTTTATATCGAATATGACAAAGTAAAAGCAGATAGTTGG
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template
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template
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template
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query
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template
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rep21_GQ900464

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template
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template
GTCTTAGAGTTCAAGCCGACTGATGAAGGTTATTTGAAGTTACATAAGACATGGTTTTGT
query
GTCTTAGAGTTCAAGCCGACTGATGAAGGTTATTTAAAGTTACATAAGACATGGTTTTGT

template
AAGTCGAAACTCTGCCCAGTTTGTAATTGGAGGCGTGCTATGAAAAATAGTTATCAAGCT
query
AAGTCGAAACTATGCCCAGTTTGTAATTGGAGGCGTGCTATGAAAAATAGTTATCAAGCT

template
CAAAAAGTGATTGAAGAAGTTGTTAAAGAAAAACCAAAAGCGCGTTGGTTATTTTTAACA
query
CAAAAAGTGATTGAAGAAGTGGTAAAAGAAAAACCAAAAGCGCGTTGGTTATTTTTAACA

template
CTTTCAACGAAAAATGCGATAGATGGGGATACTTTAGAACAAAGTTTGAAACATTTAACG
query
CTTTCAACGAAAAATGCGATAGATGGGGATACTTTAGAACAAAGTTTGAAACATTTAGCG

template
AAAGCATTTGATAGGTTAAGTAGATATAAAAAAGTGAAGCAAAATCTTGTTGGGTTTTTG
query
AAAGCATTTGATAGGTTAAGTAGATATAAAAAAGTGAAGCAAAATCTTGTTGGTTTTTTG

template
CGTTCAACGGAAGTAACAGTTAATAAAAATGATGGTAGTTATAATCAACATATGCATGTT
query
CGTTCAACGGAAGTAACAGTTAATAAAAATGATGGTAGTTATAATCAACATATGCATGTT

template
TTATTATGTGTTGAAAATAGTTATTTTAAGAATAAAGCTAATTATATAACTCAAGAAGAA
query
TTATTATGTGTTGAAAATAGTTACTTTAAGAATAAAGCTAATTATATAACTCAAGAAGAA

template
TGGGTTAATTTATGGCAAAAAGCATTACAAGTAAATTATCGACCCGTAGCAAATATTAAA
query
TGGGTTAATTTATGGCAAAAAGCATTACAAGTAAATTATCGACCCGTGGCAAATATTAAA

template
GCGATCAAACCAAATCAAAAAGGCGATAAAGATATTCAAGCAGCTATCAAAGAAACCTCT
query
GCGATCAAACCAAATCAAAAAGGCGATAAAGATATTCAAGCAGCTATCAAAGAAACCTCT

template
AAATATTCGGTTAAGTCATCTGATTTTTTAACTGATGATGATGAAAGAAATCAAGAAATC
query
AAATATTCGGTTAAGTCATCTGATTTTTTAACTGATGATGATGAAAGAAATCAAGAAATC

template
GTGAATGATTTAGAAAAAGGTTTATATCGAAAACGTATGTTGAGTTATGGTGGTTTGCTT
query
GTGAATGACTTGGAAAAAGGTTTATACCGAAAACGTATGTTGAGTTATGGTGGATTGCTT

template
AAACAAAAACATAAGATTTTAAATTTAGATGATGCCGAAGATGGCAATTTGATTAATACA
query
AAACAAAAACATAAGATTTTAAATTTAGATGATGGCGAAGATGGCAATTTGATTAATACA

template
AGTGACGAAGATAAAACAACAGACGAAGAAGAAAAAGCACATTCAATTACGGCAATTTGG
query
AGTGACGAAGATAAAACAACAGACGAAGAAGAAAAAGCACATTCAATTACGGCAATTTGG

template AATTTTGAAAAACAAAATTATTATTTAAAAGATTTGAAACGTTAG
query   AATTTTGAAAAACAAAATTATTACTTAAAAGATTTGAAACGTTAG

rep10_GU562624

template
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT
query
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT

template
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG
query
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG

template
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC
query
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC

template
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA
query
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA

template
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA
query
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA

template
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA
query
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA

template
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA
query
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA

template
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG
query
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG

rep5b_JQ312422

template
TTGAGTGGAGAAACAGTAGTATATAAAAATGATATGAATTTAGTTCCATTGAGAAAATTT
query
TTGAGTGGAGAAACAGTAGTATATAAAAATGATATGAATTTAGTTCCATTGAGAAAATTT

template
AATAATACCGAAGTTAATCTATTTTTTACTTTGTGTAATAAATTAAAAGATAAAGGCAAT
query
AATAATACCGAAGTTAATCTATTTTTTACTTTGTGTAATAAATTAAAAGATAAAGGCAAT

template
TTGACTGTTAATGTGCCATTTGAAGAATTAAAAGAATTAAGTAATTACTATAGTCATGAT
query
TTGACTGTTAATGTGCCATTTGAAGAATTAAAAGAATTAAGTAATTACTATAGTCATGAT

template
AAAAAGCTTTTTATTCAAGATTTAGAAAAATTCTATGATAAAATCTTCTCTTTAACATAT
query
AAAAAGCTTTTTATTCAAGATTTAGAAAAATTCTATGATAAAATCTTCTCTTTAACATAT

template
AGAGAAGAAACTGAGAATGTTATTAGAAAATTTATTCTTTTTACTAAAGTAGAAATTTAT

query
AGAGAAGAAACTGAGAATGTTATTAGAAAATTTATTCTTTTTACTAAAGTAGAAATTTAT

template
AAAGATAAAGAGTATGTGGCTATTGGTGTTAATCCAGATTTAAAACATATTATTAATTCA
query
AAAGATAAAGAGTATGTGGCTATTGGTGTTAATCCAGATTTAAAACATATTATTAATTCA

template
TTAACTAGTAACTTCACTAAATTTGAACTTCGAGAAATGACACACCTTAAATCTACATAT
query
TTAACTAGTAACTTCACTAAATTTGAACTTCGAGAAATGACACACCTTAAATCTACATAT

template
TCTAAGCATATGTTCAGAATACTTAAGCAGTATAAACATACTGGCTATGTAAAAATTAAA
query
TCTAAGCATATGTTCAGAATACTTAAGCAGTATAAACATACTGGCTATGTAAAAATTAAA

template
ATTGATGATTTTAGAGAACGGCTAGATATTCCTAATAGCTACCGTATGACAAATATTAAT
query
ATTGATGATTTTAGAGAACGGCTAGATATTCCTAATAGCTACCGTATGACAAATATTAAT

template
CAAAAAGTATTAGCCCCTATCATTAAAGAATTAGGATTCATTTTTAATAACCTTAATATC
query
CAAAAAGTATTAGCCCCTATCATTAAAGAATTAGGATTCATTTTTAATAACCTTAATATC

template
AATAAAATAAAAGCGAAAAGAGGACGTAAAATCGAGTGGTTAGAGTTTACTTTTGACGCT
query
AATAAAATAAAAGCGAAAAGAGGACGTAAAATCGAGTGGTTAGAGTTTACTTTTGACGCT

template
GAGAAACGCATTCACAACAAGCGACAACCCAAAATGGCGAATGTAGCCCAACCCAAACAA
query
GAGAAACGCATTCACAACAAGCGACAACCCAAAATGGCGAATGTAGCCCAACCCAAACAA

template
TATATCAGTCGTGAGAAAACGCCAAAATGGCTACATGAACGAAATCAAAGTAATACAACT
query
TATATCAGTCGTGAGAAAACGCCAAAATGGCTACATGAACGAAATCAAAGTAATACAACT

template
AGAGAAATGACTGAAGAAGAAAAAGCACTATTAAAAGAACAACAACAAGCATTTAGACAA
query
AGAGAAATGACCGAAGAAGAAAAAGCACTATTAAAAGAACAACAACAAGCATTTAGACAA

template	CAATTAGAACTAGATTGGGAAGATTAG
query	CAATTAGAACTAGATTGGGAAGATTAG

FDMS202323722 Strain: **HESN094B** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep39	99.9	957 / 957	NA	NA..NA	repA(SAP045A)	GQ900402
rep21	98.41	1005 / 1005	NA	NA..NA	rep(pSK108)	GQ900464
rep10	100	477 / 477	NA	NA..NA	repL(pDLK1)	GU562624

6.1.1 *rep39_GQ900402*

```
template
ATGTCTCGTAAAAATATTAAAAATCAAGCAAGTCAAAACTTTTATATGCTACATAAAGCA
query
ATGTCTCGTAAAAATATTAAAAATCAAGCAAGTCAAAACTTTTATATGCTACATAAAGCA

template
TTATTTGTTAATGAAAAATATAAAAAATTAAGTGATAGTGCCAAAGTTACTTATGCAATT
query
TTATTTGTTAATGAAAAATATAAAAAATTAAGTGATAGTGCCAAAATTACTTATGCAATT

template
CTCAACGATAGAGTTAGCTTGTCGATTAAAAATAATTGGGTCGATGATAATGGGGATATA
query
CTCAACGATAGAGTTAGCTTGTCGATTAAAAATAATTGGGTCGATGATAATGGGGATATA

template
TATTTCATTTTTACAAATGAAAGTCTCCAGAATATATTAGACAAAAGCAAGAATACAATT
query
TATTTCATTTTTACAAATGAAAGTCTCCAGAATATATTAGACAAAAGCAAGAATACAATT

template
ACTAAAATAAAAAAAGAACTTCAAGCAGTAGGGTTACTTGAACAAATACGTACAGGATTT
query
ACTAAAATAAAAAAAGAACTTCAAGCAGTAGGGTTACTTGAACAAATACGTACAGGATTT

template
AATAAACCTAATAAATTATATTTGCATGATATAGAAACTAATATTAGTGTAGAAAAAAGT
query
AATAAACCTAATAAATTATATTTGCATGATATAGAAACTAATATTAGTGTAGAAAAAGT

template
ATTCAATCCTCATCTATAACCTACAATGACAAGGAGTCCCAAAATTTGGGACTCCAGAAT
query
ATTCAATCCTCATCTATAACCTACAATGACAAGGAGTCCCAAAATTTGGGACTCCAGAAT
```

template
CCTGAAATTTGGGACTCCAGAAACTCAAAATTTGGGACTCCAGAATCCCAAATTTTAGAC
query
CCTGAAATTTGGGACTCCAGAAACTCAAAATTTGGGACTCCAGAATCCCAAATTTTAGAC

template
CCTAATGATACTGATTATAATGATACTGATTATATTAAGACTGAGAGTAATGATACGGAT
query
CCTAATGATACTGATTATAATGATACTGATTATATTAAGACTGAGAGTAATGATACGGAT

template
GATTTGAATGATAAGAAATTAACATATCCTAATAATCATACAAATCATTCAAATCACGAC
query
GATTTGAATGATAAGAAATTAACATATCCTAATAATCATACAAATCATTCAAATCACGAC

template
AATTCAAACTTTAATAATGAGGCTTTAAAATTCCAATTACTCGAAGAACTACCGCAAAGT
query
AATTCAAACTTTAATAATGAGGCTTTAAAATTCCAATTACTCGAAGAACTACCGCAAAGT

template
ATTCAAAACTATCTAAGTAACTTTGAAGTAACTGAAATTGAAATTATTAAAACTGTATTA
query
ATTCAAAACTATCTAAGTAACTTTGAAGTAACTGAAATTGAAATTATTAAAACTGTATTA

template
TTAAAAGCCAAAACATCTTTCAACAATACGATTGATAGTTATTACTTGTTAGAAGATATG
query
TTAAAAGCCAAAACATCTTTCAACAATACGATTGATAGTTATTACTTGTTAGAAGATATG

template
GAAATCGAAATACTTCATGTTCTTAAACGTTTCAAAGCTATACTTATTCAAAAAAATGAA
query
GAAATCGAAATACTTCATGTTCTTAAACGTTTCAAAGCTATACTTATTCAAAAAAATGAA

template
ACCGTTGAAGCCATGCAAGGATACTTAATGAAATCTCTTAAATCTGAATTCGCTGAAATG
query
ACCGTTGAAGCCATGCAAGGATACTTAATGAAATCTCTTAAATCTGAATTCGCTGAAATG

template
CATACGCTTAATAAACGACGTGATCATTTACCAATCACTTCTTTATTTAATCAATAA
query
CATACGCTTAATAAACGACGTGATCATTTACCAATCACTTCTTTATTTAATCAATAA

6.1.2 ***rep21_GQ900464***

template
ATGCAATATAATACTACTAGATGTATAGACGAAAATCAAGATAACGAAACACTTAAAGAT
query
ATGCAATATAATACTACTAGATGTATAGACGAAAATCAAGATAACGAAACACTTAAAGAT

template
ATGACGAAAAGTGGGAAACAACGCCCATGGAGAGAAAAGAAGATAGATAATGTAAGTTAT
query
ATGACGAAAAGTGGGAAACAGCGCCCATGGAGAGAAAAGAAGATAGATAATGTAAGTTAT

template
GCAGATATACTGGAAATTTTAAAAATAAAAAAGGCTTTTAATGTAAAACAATGTGGTAAC
query
GCAGATATACTGGAAATTTTAAAAATAAAAAAGGCTTTTAACGTAAAACAATGTGGTAAC

template
GTCTTAGAGTTCAAGCCGACTGATGAAGGTTATTTGAAGTTACATAAGACATGGTTTTGT
query
GTCTTAGAGTTCAAGCCGACTGATGAAGGTTATTTAAAGTTACATAAGACATGGTTTTGT

template
AAGTCGAAACTCTGCCCAGTTTGTAATTGGAGGCGTGCTATGAAAAATAGTTATCAAGCT
query
AAGTCGAAACTATGCCCAGTTTGTAATTGGAGGCGTGCTATGAAAAATAGTTATCAAGCT

template
CAAAAAGTGATTGAAGAAGTTGTTAAAGAAAAACCAAAAGCGCGTTGGTTATTTTTAACA
query
CAAAAAGTGATTGAAGAAGTGGTAAAAGAAAAACCAAAAGCGCGTTGGTTATTTTTAACA

template
CTTTCAACGAAAAATGCGATAGATGGGGATACTTTAGAACAAAGTTTGAAACATTTAACG
query
CTTTCAACGAAAAATGCGATAGATGGGGATACTTTAGAACAAAGTTTGAAACATTTAGCG

template
AAAGCATTTGATAGGTTAAGTAGATATAAAAAAGTGAAGCAAAATCTTGTTGGGTTTTTG
query
AAAGCATTTGATAGGTTAAGTAGATATAAAAAAGTGAAGCAAAATCTTGTTGGTTTTTTG

template
CGTTCAACGGAAGTAACAGTTAATAAAAATGATGGTAGTTATAATCAACATATGCATGTT
query
CGTTCAACGGAAGTAACAGTTAATAAAAATGATGGTAGTTATAATCAACATATGCATGTT

template
TTATTATGTGTTGAAAATAGTTATTTTAAGAATAAAGCTAATTATATAACTCAAGAAGAA
query
TTATTATGTGTTGAAAATAGTTACTTTAAGAATAAAGCTAATTATATAACTCAAGAAGAA

template
TGGGTTAATTTATGGCAAAAAGCATTACAAGTAAATTATCGACCCGTAGCAAATATTAAA
query
TGGGTTAATTTATGGCAAAAAGCATTACAAGTAAATTATCGACCCGTGGCAAATATTAAA

template
GCGATCAAACCAAATCAAAAAGGCGATAAAGATATTCAAGCAGCTATCAAAGAAACCTCT

query
GCGATCAAACCAAATCAAAAAGGCGATAAAGATATTCAAGCAGCTATCAAAGAAACCTCT

template
AAATATTCGGTTAAGTCATCTGATTTTTTAACTGATGATGATGAAAGAAATCAAGAAATC
query
AAATATTCGGTTAAGTCATCTGATTTTTTAACTGATGATGATGAAAGAAATCAAGAAATC

template
GTGAATGATTTAGAAAAAGGTTTATATCGAAAACGTATGTTGAGTTATGGTGGTTTGCTT
query
GTGAATGACTTGGAAAAAGGTTTATACCGAAAACGTATGTTGAGTTATGGTGGATTGCTT

template
AAACAAAAACATAAGATTTTAAATTTAGATGATGCCGAAGATGGCAATTTGATTAATACA
query
AAACAAAAACATAAGATTTTAAATTTAGATGATGGCGAAGATGGCAATTTGATTAATACA

template
AGTGACGAAGATAAAACAACAGACGAAGAAGAAAAAGCACATTCAATTACGGCAATTTGG
query
AGTGACGAAGATAAAACAACAGACGAAGAAGAAAAAGCACATTCAATTACGGCAATTTGG

template   AATTTTGAAAAACAAAATTATTATTTAAAAGATTTGAAACGTTAG
query   AATTTTGAAAAACAAAATTATTACTTAAAAGATTTGAAACGTTAG

6.1.3 ***rep10_GU562624***

template
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT
query
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT

template
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG
query
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG

template
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC
query
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC

template
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA
query
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA

template
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA
query
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA

template
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA
query
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA

template
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA
query
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA

template
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG
query
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG

FDMS202323723a Strain : **HESN035b** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep10b	99.14	465 / 465	NA	NA..NA	rep(pSK6)	U96610
rep7a	99.89	955 / 945	NA	NA..NA	repC(Cassette)	AB037671
rep7a	99.68	936 / 936	NA	NA..NA	repD(pTZ4)	NC010111
repUS43	99.92	1206 / 1206	NA	NA..NA	CDS12738 (DOp1)	CP003584
rep21	99.9	999 / 999	NA	NA..NA	rep(pWBG754)	GQ900396
rep5e	98.85	867 / 867	NA	NA..NA	SAP018B003 (SAP018B)	GQ900384
rep20	98.18	936 / 936	NA	NA..NA	repA(p11819p97)	CP003193
repUS19	99.83	585 / 585	NA	NA..NA	rep(pDLK3)	GU562626

6.1.4 ***rep10b_U96610***

```
template
ATGAAAGAACGCTATGGAACAGTATATAAAGGGAAAGAAGAGTTTGTAAATAAAGACTCA
query
ATGAAAGAACGCTATGGAACGGTATATAAAGGGAAAGAGGAGTTTGTAAATAAAGACTCA

template
GGAGAAGTAATACAGTTTGATAAGCTATATAGAGCACAAACAGGTGGAAACTTCGTGAAG
query
GGAGAAGTAATACAGTTTGATAAGCTATATAGAGCACAAACAGGTGGAAACTTCGTGAAG

template
ATGTATATGGAACTGTTTGGAGAAATGTTGGGATTAATGAATAAAAGAGGAGAAGTAATG
query
ATGTATATGGAACTGTTTGGACAAATGTTGGGATTAATGAATAAAAGAGGAGAAGTAATG

template
CAGTACCTTTTTAAAGACTTAAACCTATCAAGTAATACAGTAATAAAAACAGTTCGAGAA
query
CAGTACCTTTTTAAAGACTTAAACCTATCAAGTAATACAGTAATAAAAACAGTTCGAGAA

template
CTTGCTAAAGAAACAAATACAAGTACAAAAACCGTAACAGAAACCCTTAAAATTATGGAA
query
CTTGCTAAAGAAACAAATACAAGTACAAAAACCGTAACAGAAACCCTTAAAATTATGGAA

template
AAAGGAAACATTATAAAAAGAAAGACTGGAGTTATAATGATAAACCCAGCCTTATTAATG
query
AAAGGAAACATTATAAAAAGAAAGACTGGAGTTATAATGATAAACCCAGCCTTATTAATG

template
CGTGGAGATGATAGCAAAAAACGTTATCTCTTACTAGAATTTGAGCAATTCGATAGAGAA
query
CGTGGAGATGATAGTAAAAAACGTTATCTCTTACTAGAATTTGAGCAATTCGATAGAGAA

template    AACGAATTAGAACACGCTTTAAATGAATATGAAAGTTTTAAGTAA
query       AACGAATTAGAACACGCTTTAAATGAATATGAAAGTTTTAAGTAA
```

6.1.5 ***rep7a_AB037671***

```
template
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT
query
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT

template    TTTTCTAAAACCGGCTACTC----------
TAATAGCCGGTTGGACGCACATACTGTGTG
query
TTTTCTAAAACCGGCTACTCTAATAGCCGGTAATAGCCGGTTGGACGCACATACTGTGTG
```

template
CATATCTGATCCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGA
query
CATATCTGATCCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGA

template
CAACGCTCAAGCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATAT
query
CAACGCTCAAGCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATAT

template
TCTTCAAACAAAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAA
query
TCTTCAAACAAAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAA

template
AGTGAAAGCAGATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACT
query
AGTGAAAGCAGATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACT

template
TACACGAGATGAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGG
query
TACACGAGATGAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGA

template
TTTTACAAGATTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAAT
query
TTTTACAAGATTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAAT

template
GTCTGATAAAGCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAA
query
GTCTGATAAAGCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAA

template
ATATTTTGGCGTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACG
query
ATATTTTGGCGTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACG

template
TAAAGATAATGCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACT
query
TAAAGATAATGCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACT

template
TAAAAGAGATATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACC
query
TAAAAGAGATATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACC

template
AGATTGGAAAACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGA

query
AGATTGGAAAACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGA

template
TGAAGAAGAATGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAA
query
TGAAGAAGAATGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAA

template
AGAAATTTCGCCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAA
query
AGAAATTTCGCCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAA

template
ACAATTGCAAAAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
query
ACAATTGCAAAAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG

6.1.6 *rep7a_NC010111*

template
ATGAGTACAGAAAATCATTCAAATTACTTACAAAATAAGGATTTAGACAATTTTTCTAAA
query
ATGAGTACAAAAAATCATTCGAATTACTTACAAAATAACGATTTAGACAATTTTTCTAAA

template
ACCGGCTACTCTAATAGCCGGTTAAGTGGTAATTTTTTTACCACCCCTCAACCAGAATTA
query
ACCGGCTACTCTAATAGCCGGTTAAGTGGTAATTTTTTTACCACCCCTCAACCAGAATTA

template
AGTTTTGATGCTATGACAATCGTTGGGAATTTGAACAAAACTAACGCTAAAAAGCTATCT
query
AGTTTTGATGCTATGACAATCGTTGGGAATTTGAACAAAACTAACGCTAAAAAGCTATCT

template
GATTTTATGAGTACAGAGCCACAAATAAGGCTTTGGGATATATTACAAACAAAGTTTAAA
query
GATTTTATGAGTACAGAGCCACAAATAAGGCTTTGGGATATATTACAAACAAAGTTTAAA

template
GCTAAAGCACTTCAAGAAAAGGTTTATATCGAATATGACAAAGTAAAAGCAGATAGTTGG
query
GCTAAAGCACTTCAAGAAAAGGTTTATATCGAATATGACAAAGTAAAAGCAGATAGTTGG

template
GATAGACGTAATATGCGTGTTGAATTTAATCCAAATAAACTCACACATGAAGAAATGCTT
query
GATAGACGTAATATGCGTGTTGAATTTAATCCAAATAAACTCACACATGAAGAAATGCTT

template
TGGTTAAAACAAAATATTATCGACTACATGGAAGATGACGGTTTTACGAGGTTAGATTTA

query
TGGTTAAAACAAAATATTATCGACTACATGGAAGATGACGGTTTTACGAGGTTAGATTTA

template
GCTTTTGATTTTGAAGATGATTTGAGTGATTACTACGCAATGACTGATAAAGCAGTTAAG
query
GCTTTTGATTTTGAAGATGATTTGAGTGATTACTACGCAATGACTGATAAAGCAGTTAAG

template
AAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGTGTTCGTGAC
query
AAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGTGTTCGTGAC

template
AGTGATAGATTTATTAGAATTTATAATAAAAAACAAGAACGTAAAGATAACGCCGATGTT
query
AGTGATAGATTTATTAGAATTTATAATAAAAAACAAGAACGTAAAGATAACGCCGATGTT

template
GAAGTTATGTCTGAACATTTATGGCGTGTAGAAATTGAATTGAAAAGAGATATGGTTGAT
query
GAAGTTATGTCTGAACATTTATGGCGTGTAGAAATTGAATTGAAAAGAGATATGGTTGAT

template
TACTGGAATGATTGCTTTGATGATTTACACATTTTGAAACCCGATTGGACAACACCAGAA
query
TACTGGAATGATTGCTTTGATGATTTACACATTTTGAAACCCGATTGGACAACACCAGAA

template
AAAGTAAAAGAACAAGCAATGGTTTATTTGTTACTGAATGAAGAAGGCACGTGGGGAAAA
query
AAAGTAAAAGAACAAGCAATGGTTTATTTGTTACTGAATGAAGAAGGCACGTGGGGAAAA

template
CTTGAAAGACATGCTAAATATAAATACAAGCAATTGATTAAAGAAATATCTCCAATTGAT
query
CTTGAAAGACATGCTAAATATAAATACAAGCAATTGATTAAAGAAATATCTCCAATTGAT

template
TTAACGGAATTAATGAAATCGACTTTAAAAGAGAATGAAAAGCAATTGCAAAAACAGATT
query
TTAACGGAATTAATGAAATCGACTTTAAAAGAGAATGAAAAGCAATTGCAAAAACAGATT

template	GATTTTTGGCAACGTGAATTTAGATTTTGGAAGTAA
query	GATTTTTGGCAACGTGAATTTAGATTTTGGAAGTAA

6.1.7 ***repUS43_CP003584***

template
TTGGAGGGATTTTTACTGAATGAACAAACTTGGTTACAGCATTTAAAAGAAAAACGCTTG
query
TTGGAGGGATTTTTACTGAATGAACAAACTTGGTTACAGCATTTAAAAGAAAAACGCTTG

template
GCTTATGGACTATCTCAAAACCGTTTAGCTGTTGCGACTGGTATTACAAGGCAGTATCTA
query
GCTTATGGACTATCTCAAAACCGTTTAGCTGTTGCGACTGGTATTACAAGGCAGTATCTA

template
AGCGATATTGAAACAGGAAAAGTCAAGCCATCAGAGGATTTACAGCAGTCCCTTTGGGAA
query
AGCGATATTGAAACAGGAAAAGTCAAGCCATCAGAGGATTTACAGCAGTCCCTTTGGGAA

template
GCTCTGGAACGCTTCAATCCCGACGCTCCCCTTGAAATGCTGTTTGATTATGTAAGAATT
query
GCTCTGGAACGCTTCAATCCCGACGCTCCCCTTGAAATGCTGTTTGATTATGTAAGAATT

template
CGCTTTCCGACAACAGACGTACAGCAGGTGGTCGAAAACATCTTACAACTGAAACTGTCC
query
CGCTTTCCGACAACAGACGTACAGCAGGTGGTCGAAAACATCTTACAACTGAAACTGTCC

template
TATTTTCTTCATGAGGACTATGGTTTCTATTCTTATTCAGAGCATTATGCTTTAGGCGAC
query
TATTTTCTTCATGAGGACTATGGTTTCTATTCTTATTCAGAGCATTATGCTTTAGGCGAC

template
ATATTCGTCCTTTGCTCCCATGAACTGGACAAAGGAGTTCTGGTGGAATTGAAAGGTCGT
query
ATATTCGTCCTTTGCTCCCATGAACTGGACAAAGGAGTTCTGGTGGAATTGAAAGGTCGT

template
GGGTGCAGACAATTTGAAAGCTATCTTCTGGCACAACAAAGAAGCTGGTATGAGTTCTTT
query
GGGTGCAGACAATTTGAAAGCTATCTTCTGGCACAACAAAGAAGCTGGTATGAGTTCTTT

template
ATGGACGTTTTGGTGGCTGGCGGTGTGATGAAACGCCTTGACCTTGCCATTAACGATAAG
query
ATGGACGTTTTGGTGGCTGGCGGTGTGATGAAACGCCTTGACCTTGCCATTAACGATAAG

template
ACAGGGATTTTAAATATCCCTGTACTCACTGAAAAGTGCCAACAGGAAGAATGTATCTCC
query
ACAGGGATTTTAAATATCCCTGTACTCACTGAAAAGTGCCAACAGGAAGAATGTATCTCC

template
GTCTTCCGCAGTTTTAAAAGCTATCGCAGTGGCGAACTGGTACGCAAAGAGGAAAAGGAA
query
GTCTTCCGCAGTTTTAAAAGCTATCGCAGTGGCGAACTGGTACGCAAAGAGGAAAAGGAA

template
TGTATGGGAAACACCCTCTATATCGGTTCATTACAAAGTGAAGTTTATTTCTGTATCTAT

query
TGTATGGGAAACACCCTCTATATCGGTTCATTACAAAGTGAAGTTTATTTCTGTATCTAT

template
GAAAAGGACTACGAGCAGTACAAGAAAAATGATATTCCCATTGAAGACGCAGAAGTAAAA
query
GAAAAGGACTACGAGCAGTACAAGAAAAATGATATTCCCATTGAAGACGCAGAAGTAAAA

template
AACCGTTTTGAGATTCGATTGAAAAATGAGCGTGCCTATTATGCAGTCCGTGATTTACTC
query
AACCGTTTTGAGATTCGATTGAAAAATGAGCGTGCCTATTATGCAGTCCGTGATTTACTC

template
GTCTATGACAATCCAGAGCATACCGCCTTTAAAATTATCAATCGGTATATCCGTTTTGTA
query
GTCTATGACAATCCAGAGCATACCGCCTTTAAAATTATCAATCGGTATATCCGTTTTGTA

template
GATAAAGACGATTCCAAACCTCGTTCTGATTGGAAACTGAATGAAGAATGGGCTTGGTTT
query
GATAAAGACGATTCCAAACCTCGTTCTGATTGGAAACTGAATGAAGAATGGGCTTGGTTT

template
ATTGGGAACAATCGTGAACGATTAAAACTAACCACAAAACCAGAGCCTTACTCCTTCCAA
query
ATTGGGAACAATCGTGAACGATTAAAACTAACCACAAAACCAGAGCCTTACTCCTTCCAA

template
AGGACGCTGAACTGGCTATCTCATCAAGTTGCCCCGACCTTAAAGGTTGCGATTAAACTT
query
AGGACGCTGAACTGGCTATCTCATCAAGTTGCCCCGACCTTAAAGGTTGCGATTAAACTT

template
GATGAAATCAACCAGACGCAGGTTGTAAAAGACATTCTCGACCATGCGAAACTGACAGAC
query
GATGAAATCAACCAGACGCAGGTTGTAAAAGACATTCTCGACCATGCGAAACTGACAGAC

template
CGACACAAGCAGATTTTGAAGCAACAGTCAGTAAAAGAACAGGACGTGATAACAACAAAA
query
CGACACAAGCAGATTTTGAAGCAACAGTCAGTAAAAGAACAGGACGTGATAACAACAAAA

template AAATAA
query   AA-TAA

6.1.8 ***rep21_GQ900396***

template
ATGCAATATAATACTACAAAATATATAGACGAAAATCAAGATAATGAAACATTGAAAGAT
query
ATGCAATATAATACTACAAAATATATAGACGAAAATCAAGATAATGAAACATTGAAAGAT

template
ATGACTAAAAGTGGGACACAACGCCCATGGAGAGAAAAGAAAATCGACAATGTAAGTTAT
query
ATGACTAAAAGTGGGACACAACGCCCATGGAGAGAAAAGAAAATCGACAATGTAAGTTAT

template
GCAGATATACTAGAAATTTTAAAAATTAAAAAGGCTTTTAACGTGAAGCAATGTGGTAAC
query
GCAGATATACTAGAAATTTTAAAAATTAAAAAGGCTTTTAACGTGAAGCAATGTGGTAAC

template
GTCTTAGAATTTAAGCCGACTGATGAAGGGTATTTAAAACTTTATAAAACATGGTTTTGT
query
GTCTTAGAATTTAAGCCGACTGATGAAGGGTATTTAAAACTTTATAAAACATGGTTTTGT

template
AAGTCTAAATTATGTCCGGTTTGTAATTGGAGGCGTTCAATGAAAAATAGTTATCAAGCT
query
AAGTCTAAATTATGTCCGGTTTGTAATTGGAGGCGTTCAATGAAAAATAGTTATCAAGCT

template
CAAAAAGTCATTGAAGCAGTGGTTAAAGAAAAGCCAAAAGCACGTTGGTTATTCTTAACA
query
CAAAAAGTCATTGAAGCAGTGGTTAAAGAAAAGCCAAAAGCACGTTGGTTATTCTTAACA

template
CTTTCAACAAAAAATGCGATAGATGGTGAGCATTTAGAACAGAGTTTAAAATATATGTCG
query
CTTTCAACAAAAAATGCGATAGATGGTGAGCATTTAGAACAGAGTTTAAAATATATGTCG

template
AAAGCTTTTAACAAGTTAAAAATGTATGCAAAAGTTAAAAAGAATTTAATTGGTTTTATG
query
AAAGCTTTTAACAAGTTAAAAATGTATGCAAAAGTTAAAAAGAATTTAATCGGTTTTATG

template
CGTTCAACTGAAGTTACAGTTAACAAAAATGACGGAAGTTATAATCAACATATGCACGTT
query
CGTTCAACTGAAGTTACAGTTAACAAAAATGACGGAAGTTATAATCAACATATGCACGTT

template
TTATTGTGTGTTGAAAATGCTTATTTCAGAAAAAAAGAGAATTATATAACGCAAGAAGAG
query
TTATTGTGTGTTGAAAATGCTTATTTCAGAAAAAAAGAGAATTATATAACGCAAGAAGAG

template
TGGATCAATTTATGGCAAAAAGCTCTTCAAGTTGATTACAAACCAGTCGCAAATATCAAA
query
TGGATCAATTTATGGCAAAAAGCTCTTCAAGTTGATTACAAACCAGTCGCAAATATCAAA

template
GCAATTAAGCCGAATAAAAAAGGCGATAAAGATATACAAGCTGCAATTAAAGAGACATCA

query
GCAATTAAGCCGAATAAAAAAGGCGATAAAGATATACAAGCTGCAATTAAAGAGACATCA

template
AAATACTCGGTTAAGTCGTCCGATTATTTAACAGGAAACCATGAAAAAGACGCAGAAATT
query
AAATACTCGGTTAAGTCGTCCGATTATTTAACAGGAAACCATGAAAAAGACGCAGAAATT

template
GTTCAAGATTTAGAACAAGGTTTATACAGAAAACGTATGTTAAGTTACGGTGGTTTACTT
query
GTTCAAGATTTAGAACAAGGTTTATACAGAAAACGTATGTTAAGTTACGGTGGTTTACTT

template
AAACAAAAACATAAACTTTTAAATTTAGACGATGCCGAAGAAGGTAATTTAATTCAAACG
query
AAACAAAAACATAAACTTTTAAATTTAGACGATGCCGAAGAAGGTAATTTAATTCAAACG

template
AGCGATGAAGAAAAAACGACTGAAGAAGAACAAAAAGCCCATTCAATTACGGCCATTTGG
query
AGCGATGAAGAAAAAACGACTGAAGAAGAACAAAAAGCCCATTCAATTACGGCCATTTGG

template   AATTTTGAAAAACAAAATTATTTCTTAAAAAATTTGTAA
query   AATTTTGAAAAACAAAATTATTTCTTAAAAAATTTGTAA

6.1.9 *rep5e_GQ900384*

template
ATGTCTGGTGAAACAGTAGTATATAGAAATGAGATGAATTTAGTTCCATTAAGACGTTTT
query
ATGTCTGGTGAAACAGTAGTATATAGAAATGAGATGAATTTAGTTCCATTAAGACGTTTT

template
ACAAGCACTGAAGTAGATTTATTCTTTACTCTATGTAATAAACTTAAAGAGCAAGACACA
query
ACAAGCACTGAAGTAGATTTATTCTTTACTCTATGTAATAAACTTAAAGAGCAAGACACA

template
AGAAAAGTAACTATTCCTTTTGCAGAATTAAAATATTTAAGTAATTACTATACTCGTTCA
query
AGAAAAGTAACTATTCCTTTTGCAGAATTGAAATATTTAAGTAATTACTATACTCGTTCA

template
CAAGAACGTTTTATTAATGATTTAGAACATGTATACGATAAAATGCTTAACTTAACTTAT
query
CAAGAACGTTTTATTAATGATTTAGAACATGTATACGATAAAATGCTTAACTTAACTTAT

template
ATAGAACGTAATGGTAGATCATTTGAAAAATTTATTTTGTTCACTTCCTATAAAGTAGAT
query
ATAGAACGTAATGGTAGATCATTTGAAAAATTTATTTTGTTCACTTCCTATAAAGTGGAT

```
template
TTAGATGAAGAATGTTTATCTATTAGTATTAATTCTGATTTAAAACATATTTTAAATTCT
query
TTAGATGAAGAATGTTTATCTATTAGTATTAATTCTGATTTAAAACATATTTTAAATTCT

template
ATAACTGCCGATTTTACAAAATTTGAGTTGAAGGAAATGACACATCTCAAATCCACCTAT
query
ATAACTGCCGATTTTACAAAATTTGAGTTGAAGGAAATGACACACCTCAAATCCACTTAT

template
GCTAAAAATATGTTTAGGATACTTAAACAATACAAACATACTGGTTATGTAAAAATGAAT
query
GCTAAAAATATGTTTAGGATACTTAAACAATACAAACATACTGGTTATGTAAAAATGAAT

template
TTAGATGATTTTAAAAATCGTCTAGATGTCCCAAAAACTTACCAAATGAATGATATAACT
query
TTAGATGATTTTAAAAATCGTCTAGATGTCCCAAAAACTTACCAAATGAATGATGTAACC

template
AAACGGGTATTAAAACCAATAGTTAATGAACTATCTCAGATTTTCAATAATCTACATATC
query
AAACGGGTATTAAAACCAATAGTTAATGAACTATCTCAGATTTTCAATAATCTACATATC

template
AATAAAATTAAAGCGAAAAAAGGACGTAAAATAGAATGGTTAGAGTTTACTTTTGATGCT
query
AATAAAATTAAAGCGAAAAAAGGACGTAAAATAGAATGGTTAGAGTTTACTTTTGACGCT

template
GAGAAACGCATTCATAGTAAGCGACAACCCAAAATGGCGAATGTAGCCCAACCCAAACAA
query
GAGAAACGCATTCATAGTAAGCGACAACCCAAAATGGCGAATGTAGCCCAACCCAAACAA

template
TATATCAGTCGTGAGAAAACGCCAAAATGGCTACATGAACGAAATCAAAGTAATACAACT
query
TATATCAGTCGAGAGAAAACGCCAAAATGGCTACATGCACGAAATCAAAGTAATACAACT

template
AGAGAAATGACAGAAGAAGAAAAAGCACTATTAAAAGAACAACAACAAGCATTTAGACAA
query
AGAGAAATGACTGAAGAAGAAAAAGCACTATTAAAAGAACAACAACAAGCATTTAGACAA

template    CAATTAGAACTAGATTGGGAAGATTAG
query       CAATTAGAACTAGATTGGGAAGATTAG
```

6.1.10 ***rep20_CP003193***

```
template
ATGCCCAATTTTGAAAAATACAATTTATCACAAGTAAAAACTGAAAGGTTTTATCAACTA
```

query
ATGCCCAATTTTGAAAAATACAATTTATCACAAGTAAAAACTGAAAGGTTTTATCAACTA

template
CCTAAATATTTATTCGAAGATGCATATTTTAAAAAAATGTCGGCGGAAGCCAAAATTATG
query
CCTAAATATTTATTCGAAGATGCATATTTTAAAAAAATGTCGGCGGAAGCCAAAATTATG

template
TATGCGTTATTAAAAGATCGCTTTGAATTATCCATCCAAAATGAATGGGTAGATAAAAAT
query
TATGCGTTATTAAAAGATCGCTTTGAATTATCCATCCAAAATGAATGGGTAGATAAAAAT

template
AATAACATTTACTTTATTTTCAGTAATAAACATTTGTGCGAATACTTAGGTTATGCAGAA
query
AATAACATTTACTTTATTTTCAGTAATAAACATTTGTGCGAATACTTAGGTTATGCAGAA

template
CAAAAAATTATAAAATTAAAAAAAGAGTTAATAAGTTTTAATTTACTAACTCAAGAACGT
query
CAAAAAATTATAAAATTAAAAAAAGAGTTAATAAGTTTTAATTTACTAACTCAAGAACGT

template
GTTGGCCTTAATAAACCAAATAGATTATATTTATTAAAACCTAATTATGACATTAAAGCC
query
GTTGGCCTTAATAAACCAAATAGATTATATTTATTAAAACCTAATTATGACATTAAAGCC

template
AGTCATAGCAAGGAACTTCCAAATTCACAGTTCCAGAACAATGAATTTGGAAGTTCTAGA
query
AGTCATAGCAAGGAACTTCCAAATTCACAGTTCCAGAACAATGAATTTGGAAGTTCTAGA

template
ACTGTGAATTTAAGTGGTCAAGAACTTCCAAATTCACAGTCTAATGATACTGAGAATAAT
query
ACTGTGAATTTAAGTGGTCAAGAACTTCCAAATTCACAGTCTAATGATACTGAGAATAAT

template
GATACTGATTATATTAAGACTGAGAGTAATGATACGAATGATTTGAATGATAATAAACTA
query
GATACTGATTATATTAAGACTGAGAGTAATGATACGAATGATTTGAATGATAATAAACTA

template
ACTTTTCCTAGTAATCATACAAATCATTCAAATCACGACAATTCAAACTTTAATAATGAA
query
ACTTTTCCTAGTAATCATACAAATCATTCAAATCACGACAATTCAAACTTTAATAATGAA

template
GCTTTAAAATTCCAATTACTCGAAGAATTACCACAAAGTATTAAAAACTATCTAAGTAAC
query
GCTTTAAAATTCCAATTACTCGAAGAACTACCGAAAAGTATTCAAAACTATCTAAGTAAC

```
template
TTTGAAGTAGCTGAAATTAAAATTATCAAAACTGTATTATTAAAAGCCAAAACATCTTTC
query
TTTGAAGTAGCTGAAATTAAAATTATCAAATCTGTATTGTTAAAAGCCAAAACATCTTTC

template
AATAATGCGATTGATAGCTACTACTTGTTAGAAGATATGGAAATAGAAATACTTCATGTT
query
AACAATGCGATTGATAGCTACTACTTGTTAGAAGATATGGAAATAGAAATACTTCATGTT

template
CTTAAACGTTTCAAAGCTATGCTTATTCAAAAAAATGAAACTGTTGAATCAATGCAAGGA
query
CTTAAACGTTTTAAAGCCATTCTTATTCAAAAAAATGAAACCATTGAAGCCATGCAAGGA

template
TACTTAATGAAATCTCTTAAGTCTGAATTCGCTGAAATGCATACGCTTAATAAACGACGT
query
TACTTAATGAAATCTCTTAAGTCTGAATTCGCTGAAATGCATACGCTTAATAAACGACGT

template    GATCATTTACCCATCACTTCTTTATTTAATCAATAA
query       GACCATCTACCAATCACTTCTTTATTTAATCAATAA
```

6.1.11 *repUS19_GU562626*

```
template
ATGGCTAATAATACAGAAAAAGATACTAGATCAAAGACATGGAATTTAATTGTTTATCCA
query
ATGGCTAATAATACAGAAAAAGATACTAGATCAAAGACGTGGAATTTAATTGTTTATCCA

template
GAATCAGCACCTGAAGGGTGGAAAGAGTTGCTTGTAGAGGATGGCATATCATTTGTATGT
query
GAATCAGCACCTGAAGGGTGGAAAGAGTTGCTTGTAGAGGATGGCATATCATTTGTATGT

template
AGTCCCTTGCATGATAAGGATATTTTGCCTACAGGTGAGATTAAAAAGGCTCATTGGCAT
query
AGTCCCTTGCATGATAAGGATATTTTGCCTACAGGTGAGATTAAAAAGGCTCATTGGCAT

template
ATTCTTTTGTGTTTTAGTTCCAATAAGACGTTTAAACAAGTGTTAGAAGTATCTGAACGT
query
ATTCTTTTGTGTTTTAGTTCCAATAAGACGTTTAAACAAGTGTTAGAAGTATCTGAACGT

template
TTGAATAGTCCTATACCACAAAAGTCTAAATCAACTGGTGGTAGTATTAGATATATGATT
query
TTGAATAGTCCTATACCACAAAAGTCTAAATCAACTGGTGGTAGTATTAGATATATGATT

template
CATATTGATAGTCCAGATAAAGTTCAATACAAAAAATCTGATATTGAAGTTTATGGAAAT
```

query
CATATTGATAGTCCAGATAAAGTTCAATACAAAAAATCTGATATTGAAGTTTATGGAAAT

template
ATCGATATAGAGCAATATTTTAGAATAACTAGTACTGAAAGATACGATTTAATCCGAGAA
query
ATCGATATAGAGCAATATTTTAGAATAACTAGTACTGAAAGATACGATTTAATCCGAGAA

template
ATGATTGATTTTGTAAGAGAAAATGAAATTGATGAAATCCAAGATTTAATTGATTATGCA
query
ATGATTGATTTTGTAAGAGAAAATGAAATTGATGAAATCCAAGATTTAATTGATTATGCA

template
ATGATAAATCGATTTGATGATTGGTTTCCGTTACTTTGTGATAACTCAACGTTTATCATG
query
ATGATAAATCGATTTGATGATTGGTTTCCGTTACTTTGTGATAACTCAACGTTTATCATG

template AGTAATTACATAAAATCAATTCGACATAGAAAAAAGAGATTTTGA
query AGTAATTACATAAAATCAATTCGACATAGAAAAAAGAGATTTTGA

FDMS202323725 Strain: **HESMS053a** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep10	100	477 / 477	NA	NA..NA	repL(pDLK1)	GU562624

6.1.12 ***rep10_GU562624***

template
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT
query
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT

template
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG
query
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG

template
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC

query
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC

template
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA
query
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA

template
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA
query
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA

template
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA
query
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA

template
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA
query
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA

template
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG
query
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG

FDMS202323726 Strain: **BABY089B** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep10	100	477 / 477	NA	NA..NA	repL(pDLK1)	GU562624
rep20	99.57	936 / 936	NA	NA..NA	repA(SAP105B)	GQ900453
rep23	100	1026 / 1026	NA	NA..NA	rep(pPR9)	GU237136
rep21	100	1005 / 1005	NA	NA..NA	rep(pSK108)	GQ900464

6.1.13 *rep10_GU562624*

template
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT
query
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT

template
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG
query
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG

template
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC
query
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC

template
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA
query
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA

template
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA
query
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA

template
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA
query
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA

template
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA
query
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA

template
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG
query
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG

6.1.14 *rep20_GQ900453*

template
ATGCCCAATTTTGAAAAATACAATTTATCACAAGTAAAAACTGAAAGGTTTTATCAACTA
query
ATGCCCAATTTTGAAAAATACAATTTATCACAAGTAAAAACTGAAAGGTTTTATCAACTA

template
CCTAAATATTTATTCGAAGATGCATATTTTAAAAAAATGTCGGCGGAAGCCAAAATTATG

query
CCTAAATATTTATTCGAAGATGCATATTTTAAAAAAATGTCGGCGGAAGCCAAAATTATG

template
TATGCGTTATTAAAAGATCGCTTTGAATTATCCATCCAAAATGAATGGGTAGATAAAAAT
query
TATGCGTTATTAAAAGATCGCTTTGAATTATCCATCCAAAATGAATGGGTAGATAAAAAT

template
AATAACATTTACTTTATTTTCAGTAATAAACATTTGTGCGAATACTTAGGTTATGCAGAA
query
AATAACATTTACTTTATTTTCAGTAATAAACATTTGTGCGAATACTTAGGTTATGCAGAA

template
CAAAAAATTATAAAATTAAAAAAAGAGTTAATAAGTTTTAATTTACTAACTCAAGAACGT
query
CAAAAAATTATAAAATTAAAAAAAGAGTTAATAAGTTTTAATTTACTAACTCAAGAACGT

template
GTTGGCCTTAATAAACCAAATAGATTATATTTATTAAAACCTAATTATGACATTAAAGCC
query
GTTGGCCTTAATAAACCAAATAGATTATATTTATTAAAACCTAATTATGACATTAAAGCC

template
AGTCATAGCAAGGAACTTCCAAATTCACAGTTCCAGAACAATGAATTTGGAAGTTCTAGA
query
AGTCATAGCAAGGAACTTCCAAATTCACAGTTCCAGAACAATGAATTTGGAAGTTCTAGA

template
ACTGTGAATTTAAGTGGTCAAGAACTTCCAAATTCACAGTCTAATGATACTGAGAATAAT
query
ACTGTGAATTTAAGTGGTCAAGAACTTCCAAATTCACAGTCTAATGATACTGAGAATAAT

template
GATACTGATTATATTAAAACTGAGAGTAATGATACGAATGATTTGAATGATAAGAAATTA
query
GATACTGATTATATTAAAACTGAGAGTAATGATACGAATGATTTGAATGATAAGAAATTA

template
ACATATCCTAGTAATCATACAAATCATTCAAATCACGACAATTCAAACTTTAATAATGAA
query
ACATATCCTAGTAATCATACAAATCACTCAAATCACTACCATTCAAACTTTAATAATGAA

template
GCTTTAAAATTCCAATTACTTGAAGAACTACCTCAAAGTATTCAAAGGTATTTAAGTAAC
query
GCTTTAAAATTCCAATTACTCGAAGAACTACCTCAAAGTATTCAAAGGTATTTAAGTAAC

template
TTTTCTGTAAATGAAATTAAAATCATCAAACCTGTATTATTAAAAGCCAAGACGTCCTTT
query
TTTTCTGTAAATGAAATTAAAATCATCAAACCTGTATTATTAAAAGCCAAGACGTCCTTT

template
AATAATTCTATTGATACATATTACTTATTAGAAGATATGGAAATAGAAATACTTCATGTT
query
AATAATTCTATTGATACATATTACTTATTAGAAGATATGGAAATAGAAATACTTCATGTT

template
CTTAAACGTTTCAAAGCTATGCTTATTCAAAAAAATGAAACCGTTGAAGCCATGCAAGGG
query
CTTAAACGTTTCAAAGCTATGCTTATTCAAAAAAATGAAACCGTTGAAGCCATGCAAGGG

template
TACTTAATGAAATCCCTTAAGTCTGAATTCGCTGAAATGCATACGCTTAATAAACGACGT
query
TACTTAATGAAATCCCTTAAGTCTGAATTCGCTGAAATGCATACGCTTAATAAACGACGT

template GATCATTTACCAATCACTTCTTTATTTAATCAATAA
query   GATCATTTACCAATCACTTCTTTATTTAATCAATAA

6.1.15 *rep23_GU237136*

template
ATGCCAAAAAGTACAACAGCTTATAGAAGTGTAAGAAAATCACATTTTACCCAAATCTCA
query
ATGCCAAAAAGTACAACAGCTTATAGAAGTGTAAGAAAATCACATTTTACCCAAATCTCA

template
AATGACTTATTAAACGATAAAACTATATCATTAGAGGCTAAAGGCTTACTTTCAATCTTT
query
AATGACTTATTAAACGATAAAACTATATCATTAGAGGCTAAAGGCTTACTTTCAATCTTT

template
CTATCAAACAACGATGAATGGGATTTACATATGAGCGAGATTATAAAAAGATCGAAAAAT
query
CTATCAAACAACGATGAATGGGATTTACATATGAGCGAGATTATAAAAAGATCGAAAAAT

template
GGTCGTGACGCACATTACACAGCTTTAAAAAAACTAATAAAAGCTGGTTATATTGCTAGA
query
GGTCGTGACGCACATTACACAGCTTTAAAAAAACTAATAAAAGCTGGTTATATTGCTAGA

template
TTAGAATTCAAACAACTTAGTAATTTTCAATTTCTACATCTTGAATATATTTTTAGTGAT
query
TTAGAATTCAAACAACTTAGTAATTTTCAATTTCTACATCTTGAATATATTTTTAGTGAT

template
AATAAAGAAGATGTAATAAACGGTATAAAAGACGCTCAAAAATTCGCAAATGAAAATGAA
query
AATAAAGAAGATGTAATAAACGGTATAAAAGACGCTCAAAAATTCGCAAATGAAAATGAA

template
CAAATTATTGTTTTAACTTATAAAGATATAGAAGGTCGTAAAATTGAATCTTCTATAGAA

query
CAAATTATTGTTTTAACTTATAAAGATATAGAAGGTCGTAAAATTGAATCTTCTATAGAA

template
AATACAGAAAAAAAGCCGTTTACTGAAAATCCGGATACGGAGGAAAATAGCGAAAATAGT
query
AATACAGAAAAAAAGCCGTTTACTGAAAATCCGGATACGGAGGAAAATAGCGAAAATAGT

template
CCGTTTACTGAAAATCCGGATACGGATAACCCGAATACAGAAAATGCGAATACGGAAAAC
query
CCGTTTACTGAAAATCCGGATACGGATAACCCGAATACAGAAAATGCGAATACGGAAAAC

template
CAGTACAATAATAATACTAATAGCAATAATACCAATATTAATAATACTAATAGTAATAAT
query
CAGTACAATAATAATACTAATAGCAATAATACCAATATTAATAATACTAATAGTAATAAT

template
ACGAATGATATGAATGATAAACAGCAGAATACAGAAAAAGATCATTCATATCATTCAAAT
query
ACGAATGATATGAATGATAAACAGCAGAATACAGAAAAAGATCATTCATATCATTCAAAT

template
CACTTTTCAAATACTCATGATAAAGAATCTCTTAAATATATAGAACTTCAAGAATTACCC
query
CACTTTTCAAATACTCATGATAAAGAATCTCTTAAATATATAGAACTTCAAGAATTACCC

template
GAATTAAGTAAAAGTTATATTAATAATTTCAGCTATGAAGAAGTTAAAAGTATTAAATCT
query
GAATTAAGTAAAAGTTATATTAATAATTTCAGCTATGAAGAAGTTAAAAGTATTAAATCT

template
GTTATTTTAAAAGCTAAAAAATCATTTAATAACAAATACGATACTTTCTATATGTTAGAA
query
GTTATTTTAAAAGCTAAAAAATCATTTAATAACAAATACGATACTTTCTATATGTTAGAA

template
GATATAGACGAAGAATTACTACTAGTTTTAAAACGATTTAAAGGTTACCTCGTTAAAAAA
query
GATATAGACGAAGAATTACTACTAGTTTTAAAACGATTTAAAGGTTACCTCGTTAAAAAA

template
CAAGAAAAAGTAGCAAATATGGAAGGTTATTTAATGAGAAGTATCATTGCTGAACTTGAA
query
CAAGAAAAAGTAGCAAATATGGAAGGTTATTTAATGAGAAGTATCATTGCTGAACTTGAA

template
GAAATGCACTCAACTATTATGAGAAGAAAGAATATGGAAAACAATCCATTATCTTTATTT
query
GAAATGCACTCAACTATTATGAGAAGAAAGAATATGGAAAACAATCCATTATCTTTATTT

template AATTAG
query AATTAG

6.1.16 *rep21_GQ900464*

template
ATGCAATATAATACTACTAGATGTATAGACGAAAATCAAGATAACGAAACACTTAAAGAT
query
ATGCAATATAATACTACTAGATGTATAGACGAAAATCAAGATAACGAAACACTTAAAGAT

template
ATGACGAAAAGTGGGAAACAACGCCCATGGAGAGAAAAGAAGATAGATAATGTAAGTTAT
query
ATGACGAAAAGTGGGAAACAACGCCCATGGAGAGAAAAGAAGATAGATAATGTAAGTTAT

template
GCAGATATACTGGAAATTTTAAAAATAAAAAAGGCTTTTAATGTAAAACAATGTGGTAAC
query
GCAGATATACTGGAAATTTTAAAAATAAAAAAGGCTTTTAATGTAAAACAATGTGGTAAC

template
GTCTTAGAGTTCAAGCCGACTGATGAAGGTTATTTGAAGTTACATAAGACATGGTTTTGT
query
GTCTTAGAGTTCAAGCCGACTGATGAAGGTTATTTGAAGTTACATAAGACATGGTTTTGT

template
AAGTCGAAACTCTGCCCAGTTTGTAATTGGAGGCGTGCTATGAAAAATAGTTATCAAGCT
query
AAGTCGAAACTCTGCCCAGTTTGTAATTGGAGGCGTGCTATGAAAAATAGTTATCAAGCT

template
CAAAAAGTGATTGAAGAAGTTGTTAAAGAAAAACCAAAAGCGCGTTGGTTATTTTTAACA
query
CAAAAAGTGATTGAAGAAGTTGTTAAAGAAAAACCAAAAGCGCGTTGGTTATTTTTAACA

template
CTTTCAACGAAAAATGCGATAGATGGGGATACTTTAGAACAAAGTTTGAAACATTTAACG
query
CTTTCAACGAAAAATGCGATAGATGGGGATACTTTAGAACAAAGTTTGAAACATTTAACG

template
AAAGCATTTGATAGGTTAAGTAGATATAAAAAAGTGAAGCAAAATCTTGTTGGGTTTTTG
query
AAAGCATTTGATAGGTTAAGTAGATATAAAAAAGTGAAGCAAAATCTTGTTGGGTTTTTG

template
CGTTCAACGGAAGTAACAGTTAATAAAAATGATGGTAGTTATAATCAACATATGCATGTT
query
CGTTCAACGGAAGTAACAGTTAATAAAAATGATGGTAGTTATAATCAACATATGCATGTT

template
TTATTATGTGTTGAAAATAGTTATTTTAAGAATAAAGCTAATTATATAACTCAAGAAGAA

```
query
TTATTATGTGTTGAAAATAGTTATTTTAAGAATAAAGCTAATTATATAACTCAAGAAGAA

template
TGGGTTAATTTATGGCAAAAAGCATTACAAGTAAATTATCGACCCGTAGCAAATATTAAA
query
TGGGTTAATTTATGGCAAAAAGCATTACAAGTAAATTATCGACCCGTAGCAAATATTAAA

template
GCGATCAAACCAAATCAAAAAGGCGATAAAGATATTCAAGCAGCTATCAAAGAAACCTCT
query
GCGATCAAACCAAATCAAAAAGGCGATAAAGATATTCAAGCAGCTATCAAAGAAACCTCT

template
AAATATTCGGTTAAGTCATCTGATTTTTTAACTGATGATGATGAAAGAAATCAAGAAATC
query
AAATATTCGGTTAAGTCATCTGATTTTTTAACTGATGATGATGAAAGAAATCAAGAAATC

template
GTGAATGATTTAGAAAAAGGTTTATATCGAAAACGTATGTTGAGTTATGGTGGTTTGCTT
query
GTGAATGATTTAGAAAAAGGTTTATATCGAAAACGTATGTTGAGTTATGGTGGTTTGCTT

template
AAACAAAAACATAAGATTTTAAATTTAGATGATGCCGAAGATGGCAATTTGATTAATACA
query
AAACAAAAACATAAGATTTTAAATTTAGATGATGCCGAAGATGGCAATTTGATTAATACA

template
AGTGACGAAGATAAAACAACAGACGAAGAAGAAAAAGCACATTCAATTACGGCAATTTGG
query
AGTGACGAAGATAAAACAACAGACGAAGAAGAAAAAGCACATTCAATTACGGCAATTTGG

template    AATTTTGAAAAACAAAATTATTATTTAAAAGATTTGAAACGTTAG
query       AATTTTGAAAAACAAAATTATTATTTAAAAGATTTGAAACGTTAG
```

FDMS202323727 Strain: **MW015** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep7a	99.89	945 / 945	NA	NA..NA	repC(Cassette)	AB037671
rep7a	95.5	906 / 933	NA	NA..NA	rep(pKH7)	NC002096
rep5e	98.96	867 / 867	NA	NA..NA	rep(pSHaeC)	AP006719
rep39	100	957 / 957	NA	NA..NA	repA(SAP016A)	GQ900381
rep10b	99.14	465 / 465	NA	NA..NA	rep(pSK6)	U96610

6.1.17 ***rep7a_AB037671***

```
template
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT
query
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT

template
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT
query
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT

template
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA
query
CCAAAATTAAGTTTTGATGCAATGACGATCGGTGGAAATCTCAACCGAGACAACGCTCAA

template
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA
query
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA

template
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA
query
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA

template
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT
```

query
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT

template
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA
query
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA

template
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA
query
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA

template
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC
query
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC

template
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT
query
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT

template
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT
query
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT

template
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA
query
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA

template
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA
query
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA

template
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG
query
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG

template
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA
query
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA

template   AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
query   AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG

6.1.18

6.1.19 ***rep7a_NC002096***

```
template    ATGAGTAAAAAAGAGCAAGAAATCTATGTGAATTTAGAAAATGTTAAATC-
TTCTAAAAC
query       --------------------------
TAAATCAAGAAAATGAACAGTATTCTAAAAC

template
CGGATACTCTAATAGCCGGTTAAGTGGTCAAACTTTGGGAAAATCTCAACCCGAATTAAG
query
CGGATACTCTAATAGCCGGTTAAGTGGTCAAACTTTGGGAAAATCTCAACCCGAATTAAG

template
TTTTGATGCGATGACAATCGTTGGGAATTTGAACAAAACTAATGCTAAAAAGTTATCTGA
query
TTTTGATGCGATGACAATCGTTGGGAATTTGAACAAAACTAATGCTAAAAAGTTATCTGA

template
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query
TTTTATGAGTGTAGATCCACAAATACGACTTTGGGATATACTTCAAACAAAGTTTAAAGC

template
TAAAGCACTTCAAGAAAAAGTTTATATCGAATATGACAAGGTAAAAGCAGATACTTGGGA
query
TAAAGCACTTCAAGAAAAAGTTTATATCGAATATGACAAGGTAAAAGCAGATACTTGGGA

template
TAGACGTAATATGCGTGTTGAATTTAATCCCAATAAACTCACAAGTGAAGAAATGCTTTG
query
TAGACGTAATATGCGTGTTGAATTTAATCCCAATAAACTCACAAGTGAAGAAATGCTTTG

template
GTTAAAACAAAATATTATCGACTACATGGAAGATGACGGTTTTACAAGATTAGATTTAGC
query
GTTAAAACAAAATATTATCGACTACATGGAAGATGACGGTTTTACAAGATTAGATTTAGC

template
TTTTGATTTTGAAGATGATTTGAGCGATTACTATGCAATGACTGATAAAGCAGTTAAGAA
query
TTTTGATTTTGAAGATGATTTGAGCGATTACTATGCAATGACTGATAAAGCAGTTAAGAA

template
AACTGTTTTTTATGGTCGTAATGGCAAGCCAGAAACAAAATATTTTGGCGTTCGTGATAG
query
AACTGTTTTTTATGGTCGTAATGGCAAGCCAGAAACAAAATATTTTGGCGTTCGTGATAG

template
TGATAGATTTATTAGAATTTATAATAAAAAACAAGAACGTAAAGATAACGCAGATGTTGA
query
TGATAGATTTATTAGAATTTATAATAAAAAACAAGAACGTAAAGATAACGCAGATGTTGA
```

template
AGTTATGTCTGAACATCTATGGCGTGTAGAAGTTGAATTAAAAAGAGATATGGTTGATTA
query
AGTTATGTCTGAACATCTATGGCGTGTAGAAATAGAATTAAAAAGAAGTATGGTTGATTA

template
CTGGAATGATTGTTTTAATGATTTACACATTTTGAAACCTGAGTGGACTACTTTAGAAAA
query
CTGGAATGATTGTTTTAATGATTTACACATTTTGAAACCTGAGTGGACTACTTTAGAAAA

template
AATTAATGAGCAAGCTATGGTTTATACTTTGTTGCATGAACAAAGTATGTGGGGAAAGCT
query
AATTAATGAGCAAGCTATGGTTTATACTTTGTTGCATGAAGAAAGTATGTGGGGAAAGCT

template
AAGTAAGAATACTAAGACTAAATTTAAAAAAATGATTAGAGAAATATCTCCAATTGATTT
query
AAGTAAGAATACTAAGACTAAATTTAAAAAAATGATTAGAGAAATATCTCCAATTGATTT

template
AACGGAATTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAAAAACAGATTGA
query
AACGGAATTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAAAAACAGATTGA

template	TTTTTGGCAACGTGAATTTAGGTTTTGGAAGTAA
query	TTTTTGGCAACGTGAATTTAGGTTTTGGAAGTAA

6.1.20 ***rep5e_AP006719***

template
ATGTCTGGTGAAACAGTAGTATATAGAAATGAGATGAATTTAGTTCCATTAAGACGTTTT
query
ATGTCTGGTGAAACAGTAGTATATAGAAATGAGATGAATTTAGTTCCATTAAGACGTTTT

template
ACAAGCACTGAAGTAGATTTATTCTTTACTCTATGTAATAAACTTAAAGAGCAAGACACA
query
ACAAGCACTGAAGTAGATTTATTCTTTACTCTATGTAATAAACTTAAAGAGCAAGACACA

template
AGAAAAGTAACTATTCCTTTTGCAGAATTAAAATATTTAAGTAATTACTATACTCGTTCA
query
AGAAAAGTAACTATTCCTTTTGCAGAATTAAAATATTTAAGTAATTACTATACTCGTTCA

template
CAAGAACGTTTTATTAATGATTTAGAACATGTATACGATAAAATGCTTAACTTAACTTAT
query
CAAGAACGTTTTATTAATGATTTAGAACATGTATACGATAAAATGCTTAACTTAACTTAT

template
ATAGAACGTAATGGTAGATCATTTGAAAAATTTATTTTGTTCACTTCCTATAAAGTAGAT

query
ATAGAACGTAATGGTAGATCATTTGAAAAATTTATTTTGTTCACTTCCTATAAAGTAGAT

template
TTAGATGAAGAATGTTTATCTATTAGTATTAATTCTGATTTAAAACATATTTTAAATTCT
query
TTAGATGAAGAATGTTTATCTATTAGTATTAATTCTGATTTAAAACATATTTTAAATTCT

template
ATAACTGCCGATTTTACAAAATTTGAGTTGAAGGAAATGACACATCTCAAATCCACCTAT
query
ATAACTGCCGATTTTACAAAATTTGAGTTGAAGGAAATGACACATCTCAAATCCACCTAT

template
GCTAAAAATATGTTTAGGATACTTAAACAATACAAACATACTGGTTATGTAAAAATGAAT
query
GCTAAAAATATGTTTAGGATACTTAAACAATACAAACATACTGGTTATGTAAAAATGAAT

template
TTAGATGATTTTAAAAATCGTCTAGATGTCCCAAAAACTTACCAAATGAATGATATAACT
query
TTAGATGATTTTAAAAATCGTCTAGATGTCCCAAAAACTTACCAAATGAATGATATAACT

template
AAACGGGTATTAAAACCAATAATTAATGAACTATCTCAGATTTTCAATAATCTACATATC
query
AAACGGGTATTAAAACCAATAATTAATGAACTATCTCAGATTTTCAATAATCTACATATC

template
AATAAAATTAAAGCGAAAAAAGGACGTAAAATAGAATGGTTAGAGTTTACTTTTGATGCT
query
AATAAAATCAAAGCGAAAAAAGGACGTAAAATAGAATGGTTAGAGTTTACTTTTGATGCT

template
GAGAAACGCATTCATAGTAAGCGACAACCCAAAATGGCGAATGTAGCCCAACCCAAACAA
query
GAAAAACGCATTCATAGTAAGCGACAACCTCACATGGCGAATGTAGGTCAACCTAAACAA

template
TATATCAGTCGTGAGAAAACGCCAAAATGGCTACATGAACGAAATCAAAGTAATACAACT
query
TATATCAGTCGTGAGAAAACGCCCAAATGGCTACATGAACGAAATCAAAGTAATACAACT

template
AGAGAAATGACAGAAGAAGAAAAAGAACTATTAAAAGAACAACAACAAGCATTTAGACAA
query
AGAGAAATGACAGAAGAAGAAAAAGAACTATTAAAAGAACAACAACAAGCATTTAGACAA

template   CAATTAGAACTAGATTGGGAAGATTAG
query   CAATTAGAACTAGATTGGGAAGATTAG

6.1.21 ***rep39_GQ900381***

template
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query
ATGTCTCGTAAAAATATTAAAAATCAAGCAAGTCAAAACTTTTATATGCTACATAAAGCA

template
TTATTTGTTAATGAAAAATATAAAAAATTAAGTGATAGTGCCAAAGTTACTTATGCAATT
query
TTATTTGTTAATGAAAAATATAAAAAATTAAGTGATAGTGCCAAAGTTACTTATGCAATT

template
CTCAACGATAGAGTTAGCTTGTCGATTAAAAATAATTGGGTCGATGATAATGGGGATATA
query
CTCAACGATAGAGTTAGCTTGTCGATTAAAAATAATTGGGTCGATGATAATGGGGATATA

template
TATTTCATTTTTACAAATGAAAGTCTCCAGAATATATTAGACAAAAGCAAGAATACAATT
query
TATTTCATTTTTACAAATGAAAGTCTCCAGAATATATTAGACAAAAGCAAGAATACAATT

template
ACTAAAATAAAAAAAGAACTTCAAGCAGTAGGGTTACTTGAACAAATACGTACAGGATTT
query
ACTAAAATAAAAAAAGAACTTCAAGCAGTAGGGTTACTTGAACAAATACGTACAGGATTT

template
AATAAACCTAATAAATTATATTTGCATGATATAGAAACTAATATTAGTGTAGAAAAAAGT
query
AATAAACCTAATAAATTATATTTGCATGATATAGAAACTAATATTAGTGTAGAAAAAAGT

template
ATTCAATCCTCATCTATAACCTACAATGACAAGGAGTCCCAAAATTTGGGACTCCAGAAT
query
ATTCAATCCTCATCTATAACCTACAATGACAAGGAGTCCCAAAATTTGGGACTCCAGAAT

template
CCCGAAATTTGGGACTCCAGAAACTCAAAATTTGGGACTCCAGAATCCCAAATTTTAGAC
query
CCCGAAATTTGGGACTCCAGAAACTCAAAATTTGGGACTCCAGAATCCCAAATTTTAGAC

template
CCTAATGATACTGATTATAATGATACTGATTATATTAAGACTGAGAGTAATGATACGGAT
query
CCTAATGATACTGATTATAATGATACTGATTATATTAAGACTGAGAGTAATGATACGGAT

template
GATTTGAATGATAAGAAATTAACATATCCTAATAATCATACAAATCATTCAAATCACGAC
query
GATTTGAATGATAAGAAATTAACATATCCTAATAATCATACAAATCATTCAAATCACGAC

template
AATTCAAACTTTAATAATGAGGCTTTAAAATTCCAATTACTCGAAGAACTACCGCAAAGT
query
AATTCAAACTTTAATAATGAGGCTTTAAAATTCCAATTACTCGAAGAACTACCGCAAAGT

template
ATTCAAAACTATCTAAGTAACTTTGAAGTAACTGAAATTGAAATTATTAAAACTGTATTA
query
ATTCAAAACTATCTAAGTAACTTTGAAGTAACTGAAATTGAAATTATTAAAACTGTATTA

template
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query
TTAAAAGCCAAAACATCTTTCAACAATACGATTGATAGTTATTACTTGTTAGAAGATATG

template
GAAATCGAAATACTTCATGTTCTTAAACGTTTCAAAGCTATACTTATTCAAAAAAATGAA
query
GAAATCGAAATACTTCATGTTCTTAAACGTTTCAAAGCTATACTTATTCAAAAAAATGAA

template
ACCGTTGAAGCCATGCAAGGATACTTAATGAAATCTCTTAAATCTGAATTCGCTGAAATG
query
ACCGTTGAAGCCATGCAAGGATACTTAATGAAATCTCTTAAATCTGAATTCGCTGAAATG

template
CATACGCTTAATAAACGACGTGATCATTTACCAATCACTTCTTTATTTAATCAATAA
query
CATACGCTTAATAAACGACGTGATCATTTACCAATCACTTCTTTATTTAATCAATAA

6.1.22 *rep10b_U96610*

template
ATGAAAGAACGCTATGGAACAGTATATAAAGGGAAAGAAGAGTTTGTAAATAAAGACTCA
query
ATGAAAGAACGCTATGGAACGGTATATAAAGGGAAAGAGGAGTTTGTAAATAAAGACTCA

template
GGAGAAGTAATACAGTTTGATAAGCTATATAGAGCACAAACAGGTGGAAACTTCGTGAAG
query
GGAGAAGTAATACAGTTTGATAAGCTATATAGAGCACAAACAGGTGGAAACTTCGTGAAG

template
ATGTATATGGAACTGTTTGGAGAAATGTTGGGATTAATGAATAAAAGAGGAGAAGTAATG
query
ATGTATATGGAACTGTTTGGACAAATGTTGGGATTAATGAATAAAAGAGGAGAAGTAATG

template
CAGTACCTTTTTAAAGACTTAAACCTATCAAGTAATACAGTAATAAAAACAGTTCGAGAA
query
CAGTACCTTTTTAAAGACTTAAACCTATCAAGTAATACAGTAATAAAAACAGTTCGAGAA

template
CTTGCTAAAGAAACAAATACAAGTACAAAAACCGTAACAGAAACCCTTAAAATTATGGAA
query
CTTGCTAAAGAAACAAATACAAGTACAAAAACCGTAACAGAAACCCTTAAAATTATGGAA

template
AAAGGAAACATTATAAAAAGAAAGACTGGAGTTATAATGATAAACCCAGCCTTATTAATG
query
AAAGGAAACATTATAAAAAGAAAGACTGGAGTTATAATGATAAACCCAGCCTTATTAATG

template
CGTGGAGATGATAGCAAAAAACGTTATCTCTTACTAGAATTTGAGCAATTCGATAGAGAA
query
CGTGGAGATGATAGTAAAAAACGTTATCTCTTACTAGAATTTGAGCAATTCGATAGAGAA

template AACGAATTAGAACACGCTTTAAATGAATATGAAAGTTTTAAGTAA
query AACGAATTAGAACACGCTTTAAATGAATATGAAAGTTTTAAGTAA

FDMS202323728a Strain: **HESMS017b** *S. haemolyticus*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep7a	99.89	945 / 945	NA	NA..NA	repC(Cassette)	AB037671
rep7a	98.82	936 / 936	NA	NA..NA	repD(pTZ4)	NC010111

6.1.23 ***rep7a_AB037671***

template
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT
query
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT

template
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT
query
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT

template
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA
query
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA

template
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA
query
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA

template
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA
query
AAGTTTAAAGCTAAAGTACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA

template
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT
query
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT

template
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA
query
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA

template
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA
query
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA

template
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC
query
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC

template
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT
query
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT

template
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT
query
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT

template
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA
query
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA

template
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA
query
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA

template
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG

query
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG

template
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA
query
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA

template AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
query   AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG

6.1.24 *rep7a_NC010111*

template
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query
ATGACTAAAGAAAATCAATCGAATTACTTACAAAATAATGATTTAACGTCTTTTTCTAAA

template
ACCGGCTACTCTAATAGCCGGTTAAGTGGTAATTTTTTTACCACCCCTCAACCAGAATTA
query
ACCGGATACTCTAATAGCCGGTTAAGTGGTAATTTTTTTACCACCCCTCAACCAGAATTA

template
AGTTTTGATGCTATGACAATCGTTGGGAATTTGAACAAAACTAACGCTAAAAAGCTATCT
query
AGTTTTGATGCTATGACAATCGTTGGGAATTTGAACAAAACTAACGCTAAAAAGCTATCT

template
GATTTTATGAGTACAGAGCCACAAATAAGGCTTTGGGATATATTACAAACAAAGTTTAAA
query
GATTTTATGAGTACAGAGCCACAAATAAGGCTTTGGGATATATTACAAACAAAGTTTAAA

template
GCTAAAGCACTTCAAGAAAAGGTTTATATCGAATATGACAAAGTAAAAGCAGATAGTTGG
query
GCTAAAGCACTTCAAGAAAAGGTTTATATCGAATATGACAAAGTAAAAGCAGATAGTTGG

template
GATAGACGTAATATGCGTGTTGAATTTAATCCAAATAAACTCACACATGAAGAAATGCTT
query
GATAGACGTAATATGCGTGTTGAATTTAATCCAAATAAACTCACACATGAAGAAATGCTT

template
TGGTTAAAACAAAATATTATCGACTACATGGAAGATGACGGTTTTACGAGGTTAGATTTA
query
TGGTTAAAACAAAATATTATCGACTACATGGAAGATGACGGTTTTACGAGGTTAGATTTA

template
GCTTTTGATTTTGAAGATGATTTGAGTGATTACTACGCAATGACTGATAAAGCAGTTAAG
query
GCTTTTGATTTTGAAGATGATTTGAGTGATTACTACGCAATGACTGATAAAGCAGTTAAG

```
template
AAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGTGTTCGTGAC
query
AAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGTGTTCGTGAC

template
AGTGATAGATTTATTAGAATTTATAATAAAAAACAAGAACGTAAAGATAACGCCGATGTT
query
AGTGATAGATTTATTAGAATTTATAATAAAAAACAAGAACGTAAAGATAACGCCGATGTT

template
GAAGTTATGTCTGAACATTTATGGCGTGTAGAAATTGAATTGAAAAGAGATATGGTTGAT
query
GAAGTTATGTCTGAACATTTATGGCGTGTAGAAATTGAATTGAAAAGAGATATGGTTGAT

template
TACTGGAATGATTGCTTTGATGATTTACACATTTTGAAACCCGATTGGACAACACCAGAA
query
TACTGGAATGATTGCTTTGATGATTTACACATTTTGAAACCCGATTGGACAACACCAGAA

template
AAAGTAAAAGAACAAGCAATGGTTTATTTGTTACTGAATGAAGAAGGCACGTGGGGAAAA
query
AAAGTAAAAGAACAAGCAATGGTTTATTTGTTACTGAATGAAGAAGGCACGTGGGGAAAA

template
CTTGAAAGACATGCTAAATATAAATACAAGCAATTGATTAAAGAAATATCTCCAATTGAT
query
CTTGAAAGACATGCTAAATATAAATACAAGCAATTGATTAAAGAAATATCTCCAATTGAT

template
TTAACGGAATTAATGAAATCGACTTTAAAAGAGAATGAAAAGCAATTGCAAAAACAGATT
query
TTAACGGAATTAATGAAATCGACTTTAAAAGAGAATGAAAAGCAATTGCAAAAACAGATT

template    GATTTTTGGCAACGTGAATTTAGATTTTGGAAGTAA
query       GATTTTTGGCAACGTGAATTTAGATTTTGGAAGTAA
```

FDMS202323729a Strain: **HESS022** *S. epidermidis*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep13	99.68	924 / 924	NA	NA..NA	rep(pPI2)	AB125342
rep7a	97.04	926 / 945	NA	NA..NA	repC(Cassette)	AB037671
rep7a	98.42	948 / 948	NA	NA..NA	repL(pLUG10)	SLU74623
rep7a	98.84	945 / 945	NA	NA..NA	rep(pSBK203)	U35036

6.1.25 ***rep13_AB125342***

```
template
ATGGATAAGTATACTGAGAAGAAACAAAGAAATCAAGTATTTCAGAAATTTATTAAGCGA
query
ATGGATAAGTATACTGAGAAGAAACAAAGAAATCAAGTATTTCAGAAATTTATTAAGCGA

template
CATGTCAAAGAAGGGCAAATGGATTTGATAAAGGAGTGCAATACATTCTTGAGTTTTGTG
query
CATGTCAAAGAAGGGCAAATGGATTTGATAAAGGAGTGCAATACATTCTTGAGTTTTGTG

template
GCAGATAGAACGTTAGAGAAACAGAAATTGCATAAATCTAATTTGTGTAAAAATCGATTT
query
GCAGATAGAACGTTAGAGAAACAGAAATTGCATAAATCTAATTTGTGTAAAAATCGATTT

template
TGTCCTGTATGTGCATGGCGAAAAGCGAGAAAAGATGCGTTAGGTTTATCATTGATGATG
query
TGTCCTGTATGTTCATGGCGAAAAGCGAGAAAAGATGCGTTAGGTTTATCATTGATGATG

template
CAATATATTAAGCAAAAAGAAGATAAACAATTCATCTTTTTAACACTTACGACACCAAAT
query
CAATATATTAAGCAAAAAGAAGATAAACAATTCATCTTTTTAACACTTACGACACCAAAT

template
GTAACAGTTGAGCATTTGGAAGATGAAATAAAAAATTATAATGAGTCGTTTAGACGATTA
query
GTAACAGTTGAGCATTTGGAAGATGAAATAAAAAATTATAATGAGTCGTTTAGACGATTA
```

template
AGTAATCGTAAACACTTTAAATCTATAGCTAAAGGTTACGTAAGAAAATTAGAAATTACT
query
AGTAATCGTAAACATTTTAAATCTATAGCTAAAGGTTACGTAAGAAAATTAGAAATTACT

template
TACAACAAAAAACGCGATGATTATAATCCACATTTTCATGTTTTGATTGCTGTTAACAAA
query
TACAACAAAAAACGCGATGATTATAATCCACATTTTCATGTTTTGATTGCTGTTAACAAA

template
TCGTATTTTACAGACAAACGATATTATATTAGTCAAAAAGAATGGCTGAATTTATGGCGA
query
TCGTATTTTACAGACAAACGATATTATATTAGTCAAAAAGAATGGCTGAATTTATGGCGA

template
GATGTGACTGGAATTGATGAAATCACACAAGTACATGTTCAAAAAATCAAACAGAACAAC
query
GATGTGACTGGAATTGATGAAATCACACAAGTACATGTTCAAAAAATCAAACAGAACAAC

template
AACAAAGAATTATACGAAATGGCGAAGTATTCTGGTAAAGATAGCGATTATTTAGTTAAT
query
AACAAAGAATTATACGAAATGGCGAAGTATTCTGGTAAAGATAGCGATTATTTAGTTAAT

template
CAAAAAGTGTTCGATACATTTTATAAATCTCTTAAGGGAAAACAAATTCTTGTTTATTCT
query
CAAAAAGTGTTCGATACATTTTATAAATCTCTTAAGGGAAAACAAATTCTTGTTTATTCT

template
GGACTGTTTAAAGAGGCAAGAAAGAAATTAAAAAATGGAGATTTAGATTATCTTAAAGGA
query
GGACTGTTTAAAGAGGCAAGAAAGAAATTAAAAAATGGAGATTTAGATTATCTTAAAGAA

template
GTAGATCCGACAGAATATATTTATCAAATTTTTTATCACTGGAACCAAAAAGAATACTTA
query
GTAGATCCGACAGAATATATTTATCAAATTTTTTATCACTGGAACCAAAAAGAATACTTA

template
GCGAGTGAAATTTTTGATTTGACTGAAGAAGAAAAAAGTAGAATTAATCATCAAATGATT
query
GCGAGTGAAATTTTTGATTTGACTGAAGAAGAAAAAAGTAGAATTAATCATCAAATGATT

template   GATGAAATTGACGAAGAAAAATAA
query   GATGAAATTGACGAAGAAAAATAA

6.1.26 ***rep7a_AB037671***

```
template
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT
query       ------------------
CAAATCATTCAAATCATTTGGAAAACGAAAACTTA---AAT

template
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT
query
TTTTCTAAAACCGGATACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT

template
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA
query
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA

template
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA
query
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA

template
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA
query
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA

template
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT
query
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT

template
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA
query
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA

template
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA
query
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA

template
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC
query
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC

template
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT
query
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT
```

```
template
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT
query
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT

template
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA
query
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA

template
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA
query
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA

template
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG
query
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG

template
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA
query
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA

template    AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
query       AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
```

6.1.27 ***rep7a_SLU74623***

```
template
ATGAGTAAAAATAATCACGCAAATCATTCAAATCACTTACAAAATAAGGATTTAGATAAT
query
ATGAGTAAAAATAATCACGCAAATCATTCAAATCACTTAGAAAATCACGATTTAGATAAT

template
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTAAGTGTACCGATTTGGGACACCCCCCAA
query
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTAAGTGTACCGATTTGGGACACCCCCCAA

template
CCAAAATTAAGTTTTGACGCTATGACAATTGTTGGAAATCTCAGTCGTGACAATGCTCAA
query
CCAAAATTAAGTTTTGACGCTATGACAATTGTTGGAAATCTCAGTCGTGACAATGCTCAA

template
AAACTATCAGAATTTATGAGTATTGAACCACAAATTCGACTTTGGGATATACTACAAACG
query
AAACTATCAGAATTTATGAGTATTGAACCACAAATTCGACTTTGGGATATACTACAAACG

template
AAATTCAAAGCTAAAGCTCTACAAGAAAAGGTTTATATTGAATATGACAAAGTAAAAGCA
```

query
AAATTCAAAGCTAAAGCTCTACAAGAAAAGGTTTATATTGAATATGACAAAGTAAAGGCA

template
GATACATGGGATAGACGTAATATGCGTGTTGAATTTAACCCAAATAAACTTACACATGAA
query
GATACATGGGATAGACGTAATATGCGTGTTGAATTTAACCCAAATAAACTTACACATGAA

template
GAGATGCTTTGGTTAAAACAAAACATTATTGACTACATGGAAGATGACTCGTTTACAAGA
query
GAGATGCTTTGGTTAAAACAAAATATTATTGACTACATGGAAGATGACGGTTTTACAAGA

template
CTAGATTTAGCTTTTGATTTTGAAGATGATTTGAGCGATTACTACGCAATGACTGATAAA
query
CTAGATTTAGCTTTTGATTTTGAAGATGACTTGAGCGATTACTACGCAATGACTGATAAA

template
TCAGTTAAGAAAACTATCTTTTATGGTCGTAATGGTAAGCCTGAAACAAAATATTTCGGT
query
TCAGTTAAGAAAACTATCTTTTATGGTCGTAATGGTAAGCCTGAAACAAAATATTTCGGT

template
GTAAGAGATAGTGATAGATTTATTAGAATTTATAATAAAAAACAAGAGCGTAAAGACAAT
query
GTAAGAGATAGTGATAGATTTATTAGAATTTATAATAAAAAACAAGAGCGTAAAGACAAT

template
GCAGATGTTGAAGTTATGTCTGAACATTTGTGGCGTGTAGAAATTGAATTGAAACGAAAT
query
GCAGATGTTGAAGTTATGTCTGAACATTTGTGGCGTGTAGAAATTGAATTGAAACGAAAT

template
ATGGTTGATTATTGGAATGATTGTTTTGATGATTTACATATTTTGAAACCAGATTATTCA
query
ATGGTTGATTATTGGAATGATTGTTTTGATGATTTACATATTTTGAAACCAGATTATTCA

template
ACAATAGAAAAAATGCTCCAGACCGTCATACAATTTATGGCTTTGTTATTTGATGAAAAC
query ACAATAGAAAAA--GCTCCAGACCGTCATACAATT-
ATGGCTTTGTTATTTGATGAAAAC

template
GAATGGGGAAAATTAGAGCGTAAAAAGAAATACCGAATGAAAAAATTGATGACTGAAATA
query
GAATGGGGAAAATTAGAGCGTAAAAAGAAATACCGAATGAAAAAATTGATGACTGAAATT

template
TCTCCAGTTGATTTAACGGAATTAATGAAATCGACTTTAAGAGAAAATGAAAAACAATTA
query
TCTCCAGTTGATTTAACGGAATTAATGAAATCGACTTTAAGAGAAAATGAAAAACAATTA

template CAAAAGCAAATAGAATTTTGGCAAGCAAAAAGTAAGAAGCTATTTTAA
query CAAAAGCAAATAGAATTTTGGCAGACAAAAAGTAAGAAGCTATTTTAA

6.1.28 *rep7a_U35036*

template
ATGATTAAAAAAGCAGAAGAAATTCAGGCAAAACAAAGCTTAGAAAACGAAAACTTAAAT
query
ATGATTAAAAAAGCAGAAGAAATTCAGGCAAAACAAAGCTTAGAAAACGAAAACTTAAAT

template
TTTTCTAAAACCGGATACTCTAATAGCCGGTTAAACCGACATACTATGTACACCCCGGAA
query
TTTTCTAAAACCGGATACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT

template
CCAAAATTAAGTTTTGACGCTATGACTATTGTTGGAAATCTTAATAAAAATAATGCTCAC
query
CCAAAATTAAGTTTTGACGCTATGACTATTGTTGGAAATCTTAATAAAAATAATGCTCAC

template
AAACTATCTGAATTTATGAGTGTCGAGCCACAAATTCGACTTTGGGATATACTACAAACT
query
AAACTATCTGAATTTATGAGTGTCGAGCCACAAATTCGACTTTGGGATATACTACAAACT

template
AAATTTAAAGCTAAAGCTCTACAAGAAAAAGTTTATATCGAATATGACAAAGTAAAAGCA
query
AAATTTAAAGCTAAAGCTCTACAAGAAAAAGTTTATATCGAATATGACAAAGTAAAAGCA

template
GATACGTGGGATAGACGTAATATGCGTGTTGAATTTAATCCAAATAAACTTACGCATGAA
query
GATACGTGGGATAGACGTAATATGCGTGTTGAATTTAATCCAAATAAACTTACGCATGAA

template
GAAATGCTTTGGTTAAAACAAAACATTATCGACTACATGGAAGACGATGGTTTTACAAGA
query
GAAATGCTTTGGTTAAAACAAAACATTATCGACTACATGGAAGACGATGGTTTTACAAGA

template
TTAGATTTAGCTTTTGATTTTGAATATGATTTAAGTGATTATTATGCAATGACTGATAAA
query
TTAGATTTAGCTTTTGATTTTGAATATGATTTAAGTGATTATTATGCAATGACTGATAAA

template
TCAGTTAAGAAAACTATTTTTTATGGTCGTAACGGTAAACCAGAAACGAAATATTTTGGT
query
TCAGTTAAGAAAACTATTTTTTATGGTCGTAACGGTAAACCAGAAACGAAATATTTTGGT

template
GTTCGTGACAGTGATAGATTTATTAGAATTTATAATAAAAAACAGGAACGCAAAGATAAT

query
GTTCGTGACAGTGATAGATTTATTAGAATTTATAATAAAAAACAGGAACGCAAAGATAAT

template
GCAGATATTAAAATTATGTCTGAACACTTATGGCGTGTAGAAATTGAATTAAAAAGAGAT
query
GCAGATATTAAAATTATGTCTGAACACTTATGGCGTGTAGAAATTGAATTAAAAAGAGAT

template
ATGGTTGATTATTGGAACGATTGTTTTAATGATTTACATATATTACAACCAGATTGGAAA
query
ATGGTTGATTATTGGAACGATTGTTTTAATGATTTACATATATTACAACCAGATTGGAAA

template
ACTATCGAACGTACTTCTGATAGAGCAATGGTTTTTATGTTGTTGAATGATGAAGAAGAA
query
ACTATCGAACGTACTTCTGATAGAGCAATGGTTTTTATGTTGTTGAATGATGAAGAAGAA

template
TGGGGAAAATTAGAAAGACGTACTAAGAATAAATATAAAAAATTAATTAAAGAAATATCT
query
TGGGGAAAATTAGAAAGACGTACTAAGAATAAATATAAAAAATTAATTAAAGAAATATCT

template
CTAATTGATTTAACTGATTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA
query
CTAATTGATTTAACTGATTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA

template AAGCAGATTGATTTTTGGCAACGTGAATTTAGATTTTGGAAGTAA
query AAGCAGATTGATTTTTGGCAACGTGAATTTAGATTTTGGAAGTAA

FDMS2023237231 Strain: **HESN090B** *S. epidermidis*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep10	100	477 / 477	NA	NA..NA	repL(pDLK1)	GU562624
rep20	97.33	936 / 936	NA	NA..NA	repA(VRSAp)	AP003367
rep7a	98.2	933 / 945	NA	NA..NA	repC(Cassette)	AB037671

6.1.29 *rep10_GU562624*

template
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT
query
ATGAAAGAAAGATATGGAACAGTCTATAAAGGCTCTCAGAGGCTCATAGACGAAGAAAGT

template
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG
query
GGAGAAGTCATAGAGGTAGACAAGTTATACCGTAAACAAACGTCTGGTAACTTCGTAAAG

template
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC
query
GCATATATAGTGCAATTAATAAGTATGTTAGATATGATTGGCGGAAAAAAACTTAAAATC

template
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA
query
GTTAACTATATCCTAGATAATGTCCACTTAAGTAACAATACAATGATAGCTACAACAAGA

template
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA
query
GAAATAGCAAAAGCTACAGGAACAAGTCTACAAACAGTAATAACAACACTTAAAATCTTA

template
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA
query
GAAGAAGGAAATATTATAAAAAGAAAAACTGGAGTATTAATGTTAAACCCTGAACTACTA

template
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA
query
ATGAGAGGCGACGACCAAAAACAAAAATACCTCTTACTCGAATTTGGGAACTTTGAGCAA

template
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG
query
GAGGCAAATGAAAAACAAGAAAATGCATTATCTGATTATTATTCTTTCAAGGACTAG

6.1.30 *rep20_AP003367*

template
ATGCCCAATTTTGAAAAATATAATTTATCACAAGTAAAAACTGAAAGATTTTATCAACTG
query
ATGCCCAATTTTGAAAAATATAATTTATCACAAGTAAAAACTGAAAGATTTTATCAACTA

template
CCTAAATATTTATTTGAAGATGCATATTTTAAGAAAATGTCTGCAGAAGCCAAAATTATG

query
CCTAAATATTTATTTGAAGATGCATATTTTAAGAAAATGTCTGCAGAAGCCAAAATTATG

template
TATGCGTTATTAAAAGATCGTTTTGAATTATCCCTCCAAAATGAATGGGTAGATAAAAAT
query
TATGCGTTATTAAAAGATCGTTTTGAATTATCCCTCCAAAATGAATGGGTAGATAAAAAT

template
AATAATATTTACTTTATTTTCAGTAATAAACATTTGTGTGAATACTTAGGTTATGCAGAA
query
AATAATATTTACTTTATTTTCAGTAATAAACATTTGTGTGAATACTTAGGTTATGCAGAA

template
CAAAAAATTATAAAATTAAAAAAAGAGTTAATAAAATTTAATTTACTAACTCAAGAACGT
query
CAAAAAATTATAAAATTGAAAAAAGAGTTAATAAAATTTAATTTACTAACTCAAGAACGT

template
GTTGGCCTTAATAAACCAAATAGATTATACCTATTAAAACCTAATTATGACATTGAAGCC
query
GTTGGCCTTAATAAACCAAATAGATTATACCTATTAAAACCTAATTATGACATTGAAGCC

template
AGTCATATCAAGGAACTTCCAAATTCACAGTTCCAGAACAATGAATTTGGAAGTTCTAGA
query
AGTCATATCAAGGAACTTCCAAATTCACAGTTCCAGAACAATGAATTTGGAAGTTCTAGA

template
ACTGTGAATTTAAGTGGTCAAGAACTTCCAAATTCACAGTCTAATGATACTGATTATAAT
query
ACTGTGAATTTAAGTGGTCAAGAACTTCCAAATTCACAGTCTAATGATACTGATTATAAT

template
GACACTGATTATATTAAGACTAATTATAATGATATGTATGATTTGAATGATAGGAAATTA
query
GACACTGATTATATTAAGACTAATAGTAATGATACGTATGATATGAATGATAAGAAATTA

template
ACATATTCTAGTAATCATACAAATCATTCAAATCACTACTATTCAAAATTCAATGATGAA
query
ACATATTCTAGTAATCATACAAATCATTCAAATCACTACTATTCAAAATTTAATGATGAA

template
GCTTTAAAATTTCAATTACTTGAAGAACTACCACAAAGTATTCAAAGTTATTTAAGTAAC
query
GCTTTAAAATTTCAATTACTCGAAGAACTACCTCAAAGTATTCAAAGTTATTTAGGTAAC

template
TTTTCTGTATCTGAAATTAAACTTATTAAATCTGTGTTATTAAAAGCCAAAACATCCTTC
query
TTTTCTGTAGCTGAAATTAAAATTATCAAAACTGTATTACTAAAAGCCAAAACATCCTTC

```
template
AACAATTCTATTGATGCATATTATTTATTAGAAGATATGGAATTTGAAATTGTTAATGTT
query
AACAATTCTATTGATGCATATTATTTATTAGAAGATATGGAATTTGAAATTGTTAATGTT

template
CTTAAGCGTTTTAAAGCTACATTAATTCAAAAAAATGAAACCGTTGAAGCAATGCAAGGG
query
CTTAAGCGTTTTAAAGCTACATTAATTCAAAAAAATGAAACCGTTGAAGCAATGCAAGGG

template
TACTTAATGAAATCTCTTAAATCTGAATTTGCAGAAGTACATACGCTTAATAAACGACGT
query
TACTTAATGAAATCTCTTAAATCAGAATTCGCAGAAGTACATACGCTGAATAAGAGACGT

template    GATCATTTACCAATCACTTCTTTATTTAATCAATAA
query       GATCATTTACCTATTACATCTTTATTTAATCAATAA
```

6.1.31 *rep7a_AB037671*

```
template
ATGTATAAAAACAATCATGCAAATCATTCAAATCATTTGGAAAATCACGATTTAGACAAT
query       ------------
AATCAAGCAAATCATTCAAGTCATTTaGAAAATCACGATTTAGATAAT

template
TTTTCTAAAACCGGCTACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT
query
TTTTCTAAAACCGGATACTCTAATAGCCGGTTGGACGCACATACTGTGTGCATATCTGAT

template
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA
query
CCAAAATTAAGTTTTGATGCAATGACGATCGTTGGAAATCTCAACCGAGACAACGCTCAA

template
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA
query
GCCCTTTCTAAATTTATGAGTGTAGAGCCCCAAATAAGACTTTGGGATATTCTTCAAACA

template
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA
query
AAGTTTAAAGCTAAAGCACTTCAAGAAAAAGTTTATATTGAATATGACAAAGTGAAAGCA

template
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT
query
GATAGTTGGGATAGACGTAATATGCGTATTGAATTTAATCCAAACAAACTTACACGAGAT

template
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA
```

```
query
GAAATGATTTGGTTAAAACAAAATATAATAAGCTACATGGAAGATGACGGTTTTACAAGA

template
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA
query
TTAGATTTAGCCTTTGATTTTGAAGATGATTTGAGTGACTACTATGCAATGTCTGATAAA

template
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC
query
GCAGTTAAGAAAACTATTTTTTATGGTCGTAATGGTAAGCCAGAAACAAAATATTTTGGC

template
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT
query
GTGAGAGATAGTAATAGATTTATTAGAATTTATAATAAAAAGCAAGAACGTAAAGATAAT

template
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT
query
GCAGATGCTGAAGTTATGTCTGAACATTTATGGCGTGTAGAAATCGAACTTAAAAGAGAT

template
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA
query
ATGGTGGATTACTGGAATGATTGCTTTAGTGATTTACATATCTTGCAACCAGATTGGAAA

template
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA
query
ACTATCCAACGCACTGCGGATAGAGCAATAGTTTTTATGTTATTGAGTGATGAAGAAGAA

template
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG
query
TGGGGAAAGCTTCACAGAAATTCTAGAACAAAATATAAGAATTTGATAAAAGAAATTTCG

template
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA
query
CCAGTCGATTTAACGGACTTAATGAAATCGACTTTAAAAGCGAACGAAAAACAATTGCAA

template    AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
query       AAACAAATCGATTTTTGGCAACATGAATTTAAATTTTGGAAATAG
```

FDMS2023237232 Strain: **HESN038B** *S. epidermidis*

Plasmid	Identity	Query / Template length	Contig	Position in contig	Note	Accession number
rep19c	100	972 / 972	NA	NA..NA	rep(pETB)	AP012467
rep20	98.18	936 / 936	NA	NA..NA	repA(VRSAp)	AP003367

6.1.32 ***rep19c_AP012467***

```
template
ATGTCCAACTTTAACATTAAAGAAATCCAAAAAGAGAAATTTTATCAATTACCTAAAGTG
query
ATGTCCAACTTTAACATTAAAGAAATCCAAAAAGAGAAATTTTATCAATTACCTAAAGTG

template
TTTTTTACGAATCCTAAATATGTTAATTTGTCTAACGATGCAAAAATAACATGGTCAATA
query
TTTTTTACGAATCCTAAATATGTTAATTTGTCTAACGATGCAAAAATAACATGGTCAATA

template
TTAAGAGATCGTTTAGATTTATCTATAAGAAATAATTGGGTAGATAAAAATGGAGATATA
query
TTAAGAGATCGTTTAGATTTATCTATAAGAAATAATTGGGTAGATAAAAATGGAGATATA

template
TTTTTTATTTATACCAATGAAAAGCTTAAATCTATTTTAAATATTAGTAGTCCAAATAAG
query
TTTTTTATTTATACCAATGAAAAGCTTAAATCTATTTTAAATATTAGTAGTCCAAATAAG

template
TTATCTAAAATTAAAAAAGAATTAACTCAAGCTGATTTATTCAATCAAATAAGAGTAGGT
query
TTATCTAAAATTAAAAAAGAATTAACTCAAGCTGATTTATTCAATCAAATAAGAGTAGGT

template
TTAAATAAACCTAATAAATTATATATTAAAAAACCGGAAGTAACAGAAGCTGATGTATAT
query
TTAAATAAACCTAATAAATTATATATTAAAAAACCGGAAGTAACAGAAGCTGATGTATAT

template
TATATTTCACAACAAGAAAATGATATAGAACAGCGTAATAACACGGACGTATCAAATTCA
query
TATATTTCACAACAAGAAAATGATATAGAACAGCGTAATAACACGGACGTATCAAATTCA

template
TACGTCCAGAAATATGATAATGATACATCAAGAAATATTAATTTGATACATCATGACATA
```

query
TACGTCCAGAAATATGATAATGATACATCAAGAAATATTAATTTGATACATCATGACATA

template
TCAAAAGAATACACTAATGATACTGACTTAAGTAATACTGACTATATAGAAACTAAGAAT
query
TCAAAAGAATACACTAATGATACTGACTTAAGTAATACTGACTATATAGAAACTAAGAAT

template
AATGATACGCATGATATGAATGATACATATAACAATTCAACAAACCACAATCATTCGAAT
query
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7 ACKNOWLEDGEMENT

First and foremost I would like to thank Prof. Dr Saleh Ibrahim for providing me with the opportunity to pursue my doctoral thesis in his laboratory and his guidance during my years of work. Thank you very much for your support and open-minded discussions that have helped me to carry out my research study successfully.

I would also like to thank my co-supervisors Dr Misa Hisrose and Dr Mareike Becker for their helpful expertise in molecular techniques and fruitful discussions in the thesis meetings. With that, I would also like to thank Prof. Dr Ibrahim's and Prof. Hauke Busch's research group members for the help they offered me in their laboratory during this study.

We thank the head, Prof. Jan Rupp, and the staff of the Clinic for Infectiology and Microbiology (UKSH) and the HTH laboratory for their support. We are grateful to Dr John Korbuvi of the Pharmacy Department for providing data on the antibiotics supplied to the hospital's NICU.

Special thanks to Prof. Ahmed Moustafa of American University of New Cairo, Dr Axel Künstner and Prof. Inke Regina Koenig for their help in bioinformatics and statistics analyses.

I am grateful to all the clinical staff at the HTH, the babies' mothers, and the medical and nursing students of the University of Health and Allied Sciences who participated in our study. We are also grateful to the administrative staff of the HTH for their help.

The financial support by the Deutsche Forschungsgemeinschaft is gratefully acknowledged.

Last, but not least, I wish to thank my family and my friends for their support, their encouragement, and their patience in waiting for me to complete this program.

8 PUBLICATIONS AND POSTER PRESENTATIONS

1. Publications 2018-up to date

Innocent Afeke, Ahmed Moustafa, Misa Hirose, Mareike Becker, Hauke Busch, Axel Kuenstner, Anke Faehnrich, Anthony S. Ablordey, Christoph Haertel, Kokou Hefoume Amega-Aho, Mohamed Tarek Badr, Jan Rupp, Saleh Ibrahim, ≠. Draft genome sequences and antimicrobial profiles of three *Staphylococcus epidermidis* from neonate blood samples. Microbiol Resour Announc 10:e00170-21. https://

doi.org/10.1128/MRA.00170-21.

Innocent Afeke, Ahmed Moustafa, Mareike Becker, Hauke Busch, Axel Kuenstner, Misa Hirose, Anthony S. Ablordey, Christoph Haertel, Paul Schilf, Adina-Malin Tietje, Graceful Lord Mensah, Jan Rupp, Saleh Ibrahim*. Draft genome sequences of five tigecycline-resistant *Staphylococcus haemolyticus* from neonate blood, nasal mucosae of clinical staff, mothers, and an object in a non-glycylcycline exposed Neonatal Intensive Care Unit of Ho Teaching Hospital, Ghana. Manuscript in process.

Innocent Afeke, Ahmed Moustafa, Misa Hirose, Axel Kuenstner, Hauke Busch, Mareike Becker, Anthony S. Ablordey, Christoph Haertel, Hintermann Kobina Mbroh, Agne Garrett, John Korbuvi, Jan Rupp, Saleh Ibrahim*. Draft genome sequences of three high-level mupirocin-resistant coagulase-negative staphylococcus species cultivated from blood samples of neonates and nasal mucosa of clinical staff in a non-mupirocin exposed Neonatal Intensive Care Unit of Ho Teaching Hospital, Ghana. Manuscript in process.

Innocent Afeke, Misa Hirose, Kokou Hefoume Amegan-Aho, Christoph Haertel, Mareike Becker, Ahmed Moustafa, Paul Schilf, Mohamed Tarek Badr, Graceful Lord Mensah, Hintermann Kobina Mbroh, Jan Rupp & Saleh Ibrahim*. Neonatal and young infant sepsis in a regional hospital in Ghana. January 2021 Open Journal of Pediatrics 11(02):281-300 DOI: 10.4236/ojped.2021.112027

Soyanika Devi Waikhom, **Innocent Afeke**, Grace Sefakor Kwawu, Hintermann Kobina Mbroh, George Yiadom Osei, Bengyella Louis, John Gameli Deku, Emmanuel Senyo Kasu, Prosper Mensah, Charles Yao Agede, Cornelius Dodoo, Emmanuel Akomanin Asiamah, John Tampuori, John Korbuvi, & Japheth Awuletey Opintan,. (2020) Prevalence of vulvovaginal candidiasis among pregnant women in the Ho Municipality, Ghana: species identification and antifungal susceptibility pattern of candida isolates. BMC Pregnancy and Childbirth 20(2020) 131-140

David Adedia, Adjoa A. Boakye, Daniel Mensah, Sylvester Yao Lokpo, **Innocent Afeke** & Kwabene O. Duedu. (2020) Comparative assessment of methods for determining adiposity and model for obesity index. Heliyon 6 e05740

Joseph Adu-Amankwaah, Emmanuel Alote Allotey, David Annor Kwasie, **Innocent Afeke,** Patrick Kwasi Owiafe, Paul Chukwuemeka Adiukwu &Verner N Orish.(2018) Prevalence and Morphological Types of Anaemia among Children Under-Five Years in the Volta Regional Hospital of Ghana. Open Access Library Journal, 5(2) 1-10

Orish V, Amegan Aho K, Ofori-Amoah, Osei-Yobah J, Jamfarum I, **Afeke I**, Mac-Ankrah L, Adzaku F. (2018) Asymptomatic *Plasmodium falciparum* infection and poor school performance in primary school children in the Volta Region of Ghana. (2018) *Ethiop J Health Sci* 28 (6) 749-758

Fernando Miguel Almaguer Acevedo, Verner N Orish, Afram Joseph Kwesi, Obum Edem Kojo, Osisiogu Emmanuel, & **Innocent Afeke**. (2018) Clinical and Microbial Presentations of Ludwig Angina in the Volta Regional Hospital Ho Ghana. PJMHS 12 (1) 463-467

2. Poster presentation

Poster presented at the World Microbe Forum 2021, organized by American Society for Microbiology (ASM) and Federation of European Microbiological Societies (FEMS) collaboration: Title: **Predicting Tigecycline Resistance of *Staphylococcus haemolyticus* Isolates Cultivated from non-Glycylcycline-Exposed Tertiary Hospital in a Low-Income Country. Authors:** Innocent Afeke-1, 2, Ahmed Moustafa-3, Mareike Becker-1, Hauke Busch-1, Axel Kuenstner-1, Misa Hirose-1, Anthony S. Ablordey-4, Christoph Haertel-5, Paul Schilf-1, Kokou Hefoume Amegan-Aho-6 Adina-Malin Tietje-1, Graceful Lord Mensah-6, Jan Rupp-7, Saleh Ibrahim-1*

9 ERKLÄRUNG

Hiermit versichere ich, dass ich die vorliegende Arbeit selbstständig verfasst und keine anderen als die angegebenen Hilfsmittel benutzt habe. Weder vorher noch gleichzeitig habe ich andernorts einen Zulassungsantrag gestellt oder diese Dissertation vorgelegt. Ich habe mich bisher noch keinem Promotionsverfahren unterzogen.

Lübeck, den__16.08.2021_____

I.A

Innocent Afeke

Einverständniserklärung (To submit)

Name, Vorname Surname, given Name	Afeke, Innocent

Adresse adress / destination	Brüder-Grimm-Ring 1, 23560 Lübeck

Sektion Department of Natural Sciences or Department of Engineering / Computer Sciences (former faculty)	Naturwissenschaften

Titel der Dissertation Title of thesis	Neonatal sepsis in a low-income country's Teaching Hospital

Ich erkläre mich damit einverstanden, dass die Zentrale Hochschulbibliothek Lübeck die elektronische Dissertation und die dazugehörigen Daten in Datennetzen zur öffentlichen Nutzung bereitstellt. Die Zentrale Hochschulbibliothek ist berechtigt, die elektronische Dissertation und dazugehörigen Daten an die Deutsche Nationalbibliothek weiterzugeben.

Falls persönliche Daten (Lebenslauf) in meiner Dissertation enthalten sind, bin ich damit einverstanden, dass diese von der Zentrale Hochschulbibliothek Lübeck und der Deutschen Nationalbibliothek maschinell gespeichert und zur öffentlichen Nutzung bereitgestellt werden.

LÜBECK, 13.08.2021 Afmmmt

Ort, Datum Unterschrift
(location, date, signature)