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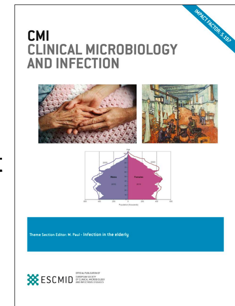

Maternal colonisation and early-onset neonatal bacterial sepsis in The Gambia, West Africa: a genomic analysis of vertical transmission.

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Original Article

Maternal colonisation and early-onset neonatal bacterial sepsis in The Gambia, West Africa: a genomic analysis of vertical transmission.

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Key words: Early-onset, neonatal sepsis; maternal colonisation; vertical transmission; whole genome sequencing; West Africa

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Genomic analysis of neonatal sepsis transmission in Gambia

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1 **Abstract**

2 **Objectives**: To define bacterial aetiology of neonatal sepsis and estimate prevalence of neonatal
3 infection from maternal genital tract bacterial carriage among mother-newborn pairs.

4 **Methods**: We carried out a cross-sectional study of newborns with clinical sepsis admitted to neonatal
5 wards of three hospitals in The Gambia. Neonatal blood cultures and maternal genital swabs were
6 obtained at recruitment. We used whole-genome sequencing (WGS) to explore vertical transmission
7 for neonates with microbiologically confirmed bloodstream infection by comparing phenotypically
8 matched paired neonatal blood culture and maternal genital tract bacterial isolates.

9 **Results**: We enrolled 203 maternal-newborn pairs. Two-thirds (67%; 137/203) of neonates presented
10 with early-onset sepsis (days 0 – 6 after birth) of which 26% (36/137) were due to a clinically-
11 significant bacterial pathogen. Blood culture isolates from newborns with early-onset sepsis due to
12 *Staphylococcus aureus* (n=5), *Klebsiella pneumonia* (n=2), and *Enterococcus faecalis* (n=1),
13 phenotypically matched their maternal genital tract isolates. Pairwise SNV comparisons showed
14 differences of 12 - 52 SNVs only between maternal and newborn *Staphylococcus aureus* isolates,
15 presumably representing vertical transmission with a transmission rate of 14% (5/36).

16 **Conclusions**: We found low prevalence of vertical transmission of maternal genital tract colonisation
17 in maternal-newborn pairs for early-onset neonatal sepsis in west African context. Identifying
18 infection acquisition pathways among newborns is essential to prioritise preventive interventions,
19 which could be targeted at mother or infection control in the hospital environment, depending on the
20 major pathways of transmission.

21 ## Introduction

22 Infections are among the leading causes of newborn deaths globally, and more prevalent in resource-
23 limited settings [1]. In sub-Saharan Africa infections account for nearly one quarter of neonatal deaths
24 [2]. Early-onset neonatal bacterial sepsis occurring day 0 – 6 after birth is often associated with vertical
25 transmission of infection, occurring shortly before or during labour. In resource-limited settings, early-
26 onset infections may include infections acquired horizontally from environmental (home or hospital)
27 sources at birth with lower hygiene measures during delivery and initial care of the baby [3]. Late-
28 onset (7 – 27 days after birth) neonatal sepsis is mostly horizontally acquired.

29 Bacterial flora diversity of the female lower genital tract can change in response to endogenous and
30 exogenous influences including age and pregnancy and is best characterised using culture-independent
31 molecular approaches, including high-throughput sequencing and metagenomics [4, 5]. Vertical
32 transmission of bacterial pathogens from the maternal lower genital tract has traditionally been studied
33 using conventional culture-dependent techniques, such as serotyping, and antimicrobial susceptibility,
34 to compare bacterial isolates from newborn surface contamination and invasive disease, with paired
35 maternal recto-vaginal isolates [6, 7]. Microbiological techniques, however, lack sufficient
36 discriminatory power to adequately delineate vertical from horizontal routes of bacterial transmission
37 to the newborn. Molecular and genomic typing of bacterial pathogens complements culture-based
38 techniques by providing appropriate discriminatory analyses to detect transmission events and the
39 relatedness of strains. Whole genome sequencing (WGS) has been used to demonstrate vertical
40 transmission of maternal Group B Streptococcal (GBS) infection in mother-newborn pairs for both
41 surface contamination and perinatal disease [8]. WGS has also been used to identify and define
42 transmission pathways of GBS [9] and *Staphylococcus aureus* outbreaks in neonatal units. [10, 11]. In
43 this study, we combined traditional bacteriological culture with WGS to assess vertical transmission of
44 maternal colonisation in maternal-newborn dyads with neonatal sepsis in a West African resource-
45 limited setting.

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46 # Methods

47 ## Ethics Approval

48 This study was approved by The Gambian government/MRC Gambia (MRCG) Joint Ethics Committee
49 and the London School of Hygiene & Tropical Medicine (LSHTM) Ethics Committee.
50 Mothers/caregivers of all newborn participants gave written informed consent. We followed STROBE-
51 NI recommendations for reporting observational studies on neonatal infections [12].

52 ## Study Design and Setting

53 This was a secondary analysis of prospectively collected and archived bacterial isolates from mother-
54 newborn pairs that were part of a hospital-based case control study of invasive neonatal infections. The
55 study was carried out on of the Edward Francis Small Teaching Hospital, Banjul (EFSTH) and Kanifing
56 General Hospital (KGH), and the postnatal ward of Brikama District Hospital (BDH) over a period of
57 17 months [April-August 2015 (EFSTH only) and February 2016-January 2017 (all three
58 facilities)].These main public hospitals serve a total population of 1.1 million people (59% of the
59 national population) [13]. Over three-quarters of women in the region deliver in a health facility, with
60 the largest number occurring at EFSTH (~6000 deliveries per year), followed by BDH (~5000 deliveries
61 per year), and KGH (~3000 deliveries per year). National neonatal mortality, stillbirth and preterm birth
62 rates are 26 per 1000 live births, 22 per 1000 births, and 12 per 100 live births, respectively [14].

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63 ## Participants and procedures

64 Inclusion criteria for neonates were postnatal age 0 – 27 days (day 0 being the day of birth), presentation
65 with one or more clinical signs of possible serious bacterial infection (pSBI) **(Supplementary Table
66 S1)**, admission weight of 1000 g or more. Mothers of eligible neonates resident in the study area and
67 presented with documented evidence of having attended at least one antenatal care visit. For all eligible
68 neonatal admissions, peripheral blood was sampled (1.0 - 1.5 mL) drawn following strict aseptic
69 technique [15], before neonatal antibiotic treatment (or within 12 hours for overnight admissions).
70 Supportive care and antibiotic treatment were provided as per the national protocol (**Supplementary
71 Table S2**). We took recto-vaginal swabs from all consenting mothers at time of neonatal recruitment.

A small flocked swab (Copan Diagnostics, Brescia, Italy) was used to wipe the lower third of vaginal mucosa and the anal surface mucosa according to standard procedures [16]. Mothers could withhold consent for having their samples collected permit their infants to be studied. All samples were processed at the MRCG at LSHTM ISO 15189 accredited Clinical Microbiology laboratory and Genomics Core Facility.

Laboratory methods

Bacterial culture

We used automated blood culture (BACTEC 9050) to isolate pathogens. Bacterial strains from cultures were identified with conventional biochemical tests and the API 20E strip test (bioMerieux-Vitek, Hazelwood, MO, USA). We classified blood culture isolates as clinically significant or clinically non-significant (**Supplementary Table S3**) [17, 18]. Recto-vaginal swabs were placed into Skim-milk Tryptone-Glucose-Glycerol (STGG) transport medium, refrigerated, transported in cool containers to the MRCG at LSHTM Clinical Microbiology laboratory and processed by standard methods including subculture on solid media as follows: positive blood cultures (Blood, chocolate, and MacConkey agar); recto-vaginal swabs (Blood agar and MacConkey agar). Priority was given to the identification of known bacterial pathogens associated with neonatal sepsis and meningitis. For each sample up to three morphological similar isolates were sub-cultured for susceptibility testing and further storage; we did not consider presence of multiple species and strains. Phenotypic antimicrobial sensitivity testing was carried out using Kirby-Bauer disc diffusion method with Oxoid antimicrobial susceptibility discs (Thermo Scientific, Waltham, MA) for a panel of antibiotics that are used locally in accordance with 2016 Clinical and Laboratory Standards Institute guidelines (**Supplementary Table S4**).

Bacterial whole-genome sequencing

Bacterial isolates were frozen in 1 ml vials and stored at -80C before subculture onto blood agar plate for 24 – 48h, followed by DNA extraction from a single pure colony using a commercial kit. Sequencing was performed on Illumina MiSeq (Illumina, San Diego, California, USA) using the NEBNext® Ultra™ libraries and protocols (New England Biolabs, UK). Sequence reads were trimmed, and assemblies generated using SPAdes (version 3.13.0), with kmer sizes 21, 33, 55, and 77, and annotated

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99 using Prokka v1.13 [19, 20]. Single-nucleotide variants (SNVs) were determined using Snippy v4.3.6
100 with the following references: *Escherichia coli* str. K-12 MG1655, *Staphylococcus aureus* str. NTC
101 8325, *Klebsiella pneumoniae* str. HS11286 and *Enterococcus faecalis* str. V583. Core genome analyses
102 were done using Roary v3.12.0 [21]. Sequence data were deposited in the NCBI Sequence Read Archive
103 (SRA) under BioProject PRJNA723854 (for isolate accessions see **Supplementary Table S5**).

104 ***Outcomes***

105 We defined three categories of neonatal sepsis: (i) Blood culture-proven bacterial sepsis with a clinically
106 significant pathogen; (ii) Blood culture-proven bacterial sepsis with clinically non-significant pathogen;
107 and (iii) Clinical (culture-negative) sepsis. We defined early-onset sepsis as occurring on days 0–6 after
108 birth (day 0 as day of birth) and late-onset sepsis as that from days 7–27 after birth.

109 We defined maternal colonisation as a positive recto-vaginal bacterial culture (*Staphylococcus aureus*,
110 *Klebsiella pneumoniae*, *Escherichia coli*, Group B *Streptococcus* (GBS), Group A *Streptococcus*,
111 *Pseudomonas* spp., Citrobacter spp., Proteus spp., *Acinetobacter* spp.) without signs or symptoms of
112 infection, as these bacteria are known to cause infections in neonates. Neonatal blood culture and
113 maternal recto-vaginal isolates were considered phenotypically matched if both were identical species
114 and antibiogram.

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115 Statistical Analysis

116 Within the study sample of sick neonates, we compared descriptive data between groups based on blood
117 culture results. Categorical and continuous descriptive variables were compared by χ^2 and Mann-
118 Whitney U tests respectively. Analyses were performed using STATA v16 (StataCorp, College Station,
119 Tx, USA).

120 Results

121 We enrolled 203 mother-newborn pairs including 202 newborns with blood culture (**Figure 1**). Bacteria
122 were isolated from the blood of 45% (91/203) of neonates; 25% (51/203) of all cultures grew a clinically
123 significant bacterial pathogen and 20% (40/203) grew a clinically non-significant pathogen. Two-thirds
124 (67%; 137/203) of all cases presented as early-onset sepsis (days 0 – 6 after birth) of which one quarter

125 (26%; 36/137) were due to a clinically significant bacterial pathogen (**Table 1**). Sixty-two (30%)
126 neonates died; 56 neonates died on or before 27 days postnatal age (three of which died at home after
127 discharge from hospital) and six died after 27 days postnatal age. Overall, neonates with blood cultures
128 positive for a clinically significant pathogen had a higher case fatality compared to those with negative
129 cultures and those with cultures positive for a clinically non-significant pathogen [45% (23/51) *vs* 29%
130 (32/111) *vs* 18% (7/40); $P = 0.02$].

131 *Staphylococcus aureus* was the predominant species isolated, accounting for 6% (8/137) of cases of
132 early-onset neonatal sepsis and 8% (5/66) of late-onset sepsis cases (**Table 2**). One infant had
133 polymicrobial culture with *Escherichia coli* and *Enterobacter* spp. Figure 2 shows the distribution of
134 clinically significant pathogens in the first week (days 0 – 6). Among *Klebsiella* isolates, non-
135 susceptibility to WHO-recommended first-line gentamicin was 89% (8/9) with non-susceptibility to
136 WHO-recommended second-line therapy (third generation cephalosporins) ranging from 67% - 100%
137 (**Supplementary Table S6**).

138 We obtained genital tract cultures from all but one of the infant mothers enrolled in the study. Most
139 (97%) mothers were colonised with at least one potentially pathogenic organism **(Supplementary**
140 **Table S7**). Eight (22%) of 36 neonates with EONS due to a clinically significant bacterial pathogen
141 were born to mothers colonised with a phenotypically matched isolated: five with *Staphylococcus*
142 *aureus* sepsis; two with *Klebsiella pneumoniae* sepsis and one with sepsis due to *E. faecalis* (Table 3).
143 Both maternal-newborn Klebsiella pairs were emergency caesarean deliveries and were highly
144 divergent (> 15,000 single nucleotide variants [SNVs] with different STs and species). Genomic
145 analysis revealed both neonatal isolates (ST1535) to be *Klebsiella quasipneumoniae subspecies*
146 *similipneumoniae*, which along with isolates another six cases of *Klebsiella pneumoniae* (ST 39) sepsis
147 reported here, were identical to *Klebsiella* ST 1535 and ST 39 isolates from a previously reported
148 outbreak of multidrug resistant ESBL-producing *Klebsiella* sepsis in one of the neonatal wards [22].
149 These cases were subsequently excluded from further analyses. All *Staphylococcus aureus* isolates were
150 Methicillin sensitive. Pairwise SNV comparisons between maternal and newborn isolates showed
151 differences of 12 - 52 SNVs, presumably representing vertical transmission with a transmission rate of

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152 14% (5/36). Two of the maternal-newborn *Staphylococcus aureus* pairs were the same ST (ST627) but
153 neonatal isolates from each pair differed by 82 SNVs, possibly reflecting two unrelated occurrences of
154 ST627 in their mothers given the lack of epidemiological links in time and place (delivered at different
155 health facilities and admitted 21 days apart). Paired maternal and newborn E. faecalis isolates were the
156 same ST but differed by 108 SNVs.

157 Discussion

158 Neonatal infections remain an important challenge for child survival and health worldwide. Our
159 understanding of the routes of transmission remains incomplete; yet is critical to develop research
160 priorities and appropriate strategies for prevention. Here, for the first time from a West African setting,
161 we present a comparative genomic analysis of paired maternal and neonatal isolates to evaluate mother-
162 to-newborn transmission events among neonates with culture-confirmed early-onset bacterial sepsis.
163 We found lower prevalence of vertical transmission of maternal bacterial genital tract colonisation for
164 early-onset neonatal sepsis in only 14% (5/36) of neonates, with no genetically near-identical pairs (0
165 SNVs).

166 A systematic review of vertical transmission of early-onset neonatal infection showed that only 1.1%
167 (95% CI 0.2 – 2.0) of newborns of colonised mothers not exposed to intrapartum antibiotics developed
168 laboratory-confirmed bacterial infection [23]. Most studies included in the review focused on maternal
169 GBS colonisation and were from high-income countries. In a more recent GBS-specific review, the risk
170 of early onset GBS disease was 1.1% (95% CI 0.6% - 1.5%) for newborns born to women colonized
171 with GBS in pregnancy in settings without a policy for providing intrapartum antibiotic prophylaxis
172 (IAP) for positive GBS screening. Stratified by region, the risk was reported to be lower in Africa (0.7%;
173 95% CI 0.3% – 1.1%) than in Europe and America (1.34%; 95% CI 0.7 – 2.0) [24]. While invasive
174 bacterial disease risk in neonates of colonised mothers maybe low, in the neonates that do develop early-
175 onset sepsis, the organism may have been part of the maternal vaginal flora. However, a previous study
176 in Uganda found no concordance between organisms recovered from newborn blood and maternal
177 vaginal cultures in the mother-newborn pairs [6]. These data were generated through conventional
178 culture methods rather than genomic approaches used in our study and differed regarding site of

179 maternal swab collection (high or low vaginal swab, rectum, or perianal region), timing of swab
180 collection (during pregnancy), and laboratory methods. Our finding of few confirmed instances of
181 vertical transmission of early onset neonatal sepsis among colonised mothers might contribute to
182 evidence on why IAP and other strategies such as chlorhexidine intravaginal and neonatal wipes have
183 not been highly effective for preventing neonatal sepsis in sub- Saharan Africa [25].

184 In concordance with previous data from West Africa, *Staphylococcus aureus* was the predominant cause
185 of early-onset neonatal sepsis in our setting [26], and the only organism demonstrated to be vertically
186 transmitted. This is in sharp contrast to high-income country settings where perinatal vertical
187 transmission of *Staphylococcus aureus* is reportedly rare, with it rather being a leading cause of
188 outbreaks and healthcare associated infections in neonatal intensive care units [27]. In these settings,
189 decolonization of colonized neonates and healthcare workers has been recommended as a means of
190 preventing transmission and infections due to methicillin resistant *Staphylococcus aureus* [28]. The
191 adoption and success of decolonization in resource limited settings is precluded by limited laboratory
192 capacity for culture-based detection; the short interval between colonization to infection, and high
193 recolonization rates [27]. Outbreaks in hospitalized African neonates are predominantly due to Gram-
194 negative bacteria [29].

195 Despite our genomic analyses, we found that most of newborns with culture positive early-onset sepsis
196 in our cohort did not have a maternal linkage. This might be related to the fact that we only picked and
197 sequenced single colonies, precluding ability to account for within-host diversity and multi-strain
198 colonisation. It is possible that some mothers would have been colonised with multiple strains of the
199 pathogenic bacteria, and in some cases by chance, may not have picked the colony for the strain that
200 was passed to the baby; therefore, absence of culture-positive transmission is not evidence for absence
201 of transmission. Since this study was designed to focus on vertical transmission, we were unable to
202 explore sources elsewhere in the hospital environment, particularly the labour ward. Failures in aseptic
203 technique can lead to neonatal infections, including early onset [3].

204 Our study has strengths and limitations. Strengths include the epidemiological design with mother-baby
205 pairs, consistent case definitions and rigorous genomic methods. Our neonatal sepsis cohort was not

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206 population-based and not representative of all neonatal sepsis cases at participating facilities. Notably
207 very low birthweight babies were excluded because of challenges in obtaining sufficient samples, yet
208 they are the most vulnerable. Even though a quarter of neonatal blood cultures were positive for a
209 clinically significant pathogen, our genomic data is limited to a small number of cases. Our definition
210 of genetic relatedness was based on an arbitrary SVP cut-off as there is little agreement in the literature.
211 However, the presence of a few (tens of) SNVs indicates isolates are closely related and increases
212 likelihood of arising from the same source, whereas the presence of many (hundreds or more) SNVs
213 indicates that isolates are distantly related, implying differing reservoir populations [30]. This depends
214 critically on the pathogen as well as the context – outbreak or non-outbreak settings. Data on
215 comparative genomic analyses of bacterial isolates from maternal carriage and neonatal disease are
216 available for GBS [8]. Evidence is however lacking for pathogen-specific genetic relatedness cut-offs
217 for transmission in similar non-outbreak settings. A recent study [31] attempted to define a genetic
218 relatedness SNP cut-off between any two Methicillin-resistant *Staphylococcus aureus* (MRSA) lineages
219 during an outbreak and proposed a conservative cut-off of 25 whole genome SNPs or 15 core genome
220 SNPs, above which 95% of recent MRSA transmission events can be ruled out within a period of 6
221 months. A major limitation of SNP cut-offs is that they cannot be used to identify sources and recipients
222 of transmission (directionality), or to establish probability of transmission. Application of this threshold
223 to our data would have further reduced the prevalence of likely vertical transmission.

224 In conclusion, neonatal infections remain an enormous issue in The Gambia, and we demonstrated a
225 low prevalence of vertical transmission of maternal colonisation for early-onset neonatal sepsis. Further
226 context-specific research is required to better direct interventions aimed at reducing the burden of
227 infection-specific neonatal mortality in sub-Saharan Africa, and importantly, hospital-acquired
228 infections in newborn care units. One such approach is the use of next generation sequencing
229 technologies and metagenomic approaches to improve characterisation maternal genital tract
230 colonisation, as well as complement surveillance of environmental contamination in hospital facilities.
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245 this study.

246 **Author contributions**

247 UO, JEL, and BK conceptualised the study. UO wrote the first draft of the manuscript, prepared all
248 figures tables. SD, SJ and NK carried out pathogen isolation and antimicrobial sensitivity testing with
249 guidance and support by KLD. AG, TD and MG-J provided patient care. AA, and SJ carried out DNA
250 extraction and sequencing of isolates with technical and administrative support by AKS. SYB
251 performed the bioinformatic analysis. KEH provided guidance on the interpretation of phenotypic and
252 genomic analysis Statistical analysis was done by UO, with advice from JEL and BK and KLD. All
253 authors provided input to the overall direction and content of the paper, and have seen and approved
254 the final version

255 **Conflict of Interest**

256 No author declared a conflict of interest in relation to the submitted work. UO reports grants from the
257 MRC UKRI, Wellcome and Thrasher Foundation outside the submitted work. KH reports numerous

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258 research grants outside the submitted work. BK reports grants from UKRI, Wellcome and NIHR for a
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Figure Legends

Figure 1: Flow chart of participant recruitment**.**

Figure 2. Distribution of blood culture results and clinically significant bacterial isolates by postnatal age at diagnosis

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Table 1. Characteristics of Neonates and Mothers Stratified by Neonatal Blood Culture Result [a]

	All newborns with suspected bacterial sepsis (N=203)	Culture-confirmed bacterial sepsis with a clinically significant pathogen (N=51) [b]	Culture-confirmed bacterial sepsis with a clinically non-significant pathogen (N=40) [b]	Clinical sepsis (N=111) [b]	*P**
Neonatal					
Sex					
Male	123 (61%)	33 (65%)	24 (60%)	65 (59%)	0.76
Female	80 (39%)	18 (35%)	16 (40%)	46 (41%)	
Median postnatal age in days (IQR)	3 (1 – 9)	2 (1 – 8)	2 (1 – 7)	3 (1 – 10)	
0 – 6 days	137 (67%)	36 (71%)	29 (73%)	72 (65%)	0.60
7 – 27 days	66 (33%)	15 (29%)	11 (27%)	39 (35%)	
Median gestational age in weeks (IQR)	38 (36 – 39)	38 (36 – 40)	38 (36 – 39)	38 (36 – 39)	
Preterm (< 37 weeks)	50 (26%)	12/47 (26%)	10/39 (26%)	28/106 (26%)	0.10
Full term (≥ 37 weeks)	143 (74%)	37/47 (74%)	29/39 (74%)	78/106 (74%)	
Median birthweight in kg (IQR)	3000 (2600 – 3400)	3000 (2500 – 3400)	3000 (2800 – 3200)	3000 (2600 – 3400)	
Low birth weight <2500g	33 (18%)	7/48 (15%)	3/38 (8%)	23/101 (23%)	0.10
Normal birth weight ≥2500g	155 (82%)	41/48 (85%)	35/38 (92%)	78/101 (77%)	
Birth location					
Health facility	184 (91%)	48 (94%)	37 (93%)	99 (89%)	0.64
Home/TBA	19 (9%)	3 (6%)	3 (7%)	12 (11%)	
Mode of delivery					
Vaginal delivery [c]	178 (88%)	47 (92%)	38 (95%)	92 (83%)	0.10
Caesarean section	25 (12%)	4 (8%)	2 (5%)	19 (17%)	
Resuscitation at delivery	58 (32%)	16 (32%)	14 (40%)	28 (29%)	
Pre-recruitment antibiotic exposure	34 (17%)	10 (20%)	8 (20%)	16 (14%)	0.60
Median length of admission, days (IQR)	6 (3 – 9)	6 (2 – 9)	6.5 (4 – 9.5)	6 (3 – 9)	0.54
Clinical signs of pSBI					
Fast breathing (%)	103 (51%)	34 (67%)	22 (55%)	46 (41%)	0.01-
Severe chest indrawing (%)	42 (21%)	14 (27%)	6 (15%)	21(19%)	0,30
Feeding problems (%)	79 (39%)	19 (37%)	17 (43%)	43 (39%)	0.20-
Fever (%)	106 (52%)	22 (43%)	17 (43%)	66 (59%)	0.06

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Hypothermia (%)	30 (15%)	9 (18%)	5 (13%)	16 (14%)	0.78
Lethargy or unconsciousness (%)	30 (15%)	16 (31%)	6 (15%)	14 (13%)	0.01
Reported or observed convulsions (%)	52 (26%)	14 (27%)	14 (35%)	24 (22%)	0.24
Outcome					
Died by day 27 of life [d]	56 (30%)	21 (41%)	6 (15%)	29 (26%)	0.03
Died overall	62 (31%)	23 (45%)	7 (18%)	32 (29%)	0.02
Maternal					
Median age at delivery, years (IQR)	27 (22 – 32)	27 (24 – 32)	27 (23 – 32)	27 (22 – 32)	0.65
Education					
Some education (ever attended school)	145 (71%)	37 (73%)	30 (75%)	77 (69%)	0.78
No education	58 (29%)	14 (27%)	10 (25%)	34 (31%)	
Parity					
Multiparous	141 (69%)	39 (76%)	26 (65%)	75 (68%)	0.04
Primiparous	62 (31%)	12 (24%)	14 (35%)	36 (32%)	
Fever before or during labour (by recall)	52 (26%)	16 (31%)	11 (28%)	25 (23%)	0.47
Intrapartum antibiotic exposure (by recall)	4 (2%)	1 (2%)	1 (3%)	2 (2%)	0.90
Genital tract bacterial carriage	195 (97%)	51 (100%)	35 (88%)	108/110 (98%)	0.01

[a] Excluding 1 infant who did not have a blood culture.

[b] Denominators (X/Y) are presented for variables with missing data or otherwise indicated.

[c] Included both unassisted and assisted (forceps, vacuum extraction) vaginal deliveries.

[d] 56 neonates died on or before 27 days postnatal age, 3 of which died at home after discharge from hospital, while 6 died after 27 days postnatal age

* P-values are chi-squared or Fisher's exact, or Kruskal-Wallis (for medians) where appropriate, excluding missing values

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Table 2. Distribution of isolated bacterial pathogens stratified by neonatal characteristics

	Overall prevalence (n=203)	Prevalence within different age groups (%)		Prevalence by birth location (%)		Gestational age <37 weeks (%) (n=50) [a]	Prevalence by mode of delivery (%)		Died (%) (n=62)[c]
		Aged 0 - 6 days (n=137)	Aged 7 – 27 days (n=66)	Hospital (n=184)	Home (n=18)		Vaginal (n=177) [b]	Caesarean (n=25)	
Any positive culture	91 (45%)	65 (47%)	26 (39%)	85 (46%)	6 (33%)	22 (44%)	85 (48%)	6 (24%)	30 (48%)
Clinically significant pathogen									
Staphylococcus aureus	13 (6%)	8 (6%)	5 (8%)	12 (7%)	1 (5%)	2 (4%)	13 (7%)	0	3 (5%)
Burkholderia cepacia	9 (4%)	8 (6%)	1 (2%)	9 (5%)	0	0	9 (5%)	0	5 (8%)
Klebsiella pneumoniae	8 (4%)	7 (5%)	1 (2%)	8 (4%)	0	7 (14%)	6 (3%)	2 (8%)	4 (6%)
Klebsiella oxytoca	1 (<1%)	1 (1%)	0	1 (<1%)	0	0	0	1 (4%)	0
Pseudomonas luteola	6 (3%)	4 (3%)	2 (3%)	6 (3%)	0	0	6 (3%)	0	4 (6%)
Pseudomonas species	1 (<1%)	0	1 (2%)	1 (<1%)	0	0	1 (<1%)	0	0
Enterococcus faecalis	3 (1%)	3 (2%)	0	3 (2%)	0	1 (2%)	3 (2%)	0	2 (3%)
Acinetobacter baumanii	2 (1%)	2 (1%)	0	2 (1%)	0	1 (2%)	2 (1%)	0	1 (2%)
Escherichia coli [d]	2 (1%)	0	2 (3%)	2 (1%)	0	1 (2%)	2 (1%)	0	2 (3%)
Streptococcus species	2 (1%)	2 (1%)	0	2 (1%)	0	0	2 (1%)	0	1 (2%)
Achromobacter xylosoxidans	1 (<1%)	0	1 (2%)	1 (<1%)	0	0	1 (<1%)	0	0
Citrobacter species	1 (<1%)	0	1 (2%)	0	1 (5%)	0	1 (<1%)	0	1 (2%)
Salmonella species	1 (<1%)	0	1 (2%)	0	1 (5%)	0	1 (<1%)	0	0
Pantoea species	1 (<1%)	1 (1%)	0	1 (<1%)	0	0	0	1 (4%)	0
Clinically non-significant pathogen									
Coagulase-negative staphylococci	32 (16%)	22 (16%)	10 (15%)	30 (16%)	2 (11%)	9 (18%)	31 (17%)	1 (4%)	4 (6%)
Viridans streptococci	2 (1%)	2 (1%)	0	2 (1%)	0	0	2 (1%)	0	1 (2%)
Micrococcus species	2 (1%)	2 (1%)	0	2 (1%)	0	0	2 (1%)	0	2 (3%)
Bacilus species	4 (2%)	3 (2%)	1 (2%)	3 (2%)	1 (5%)	1 (2%)	3 (2%)	1 (4%)	0

[a] 10 babies had missing data for gestational age.

[b] Includes spontaneous (172) and assisted [vacuum (3) and breech (2)] vaginal deliveries.

[c] 59 neonates died on admission, 3 died at home after discharge.

[c] One baby had polymicrobial culture with *Enterobacter cloacae.*

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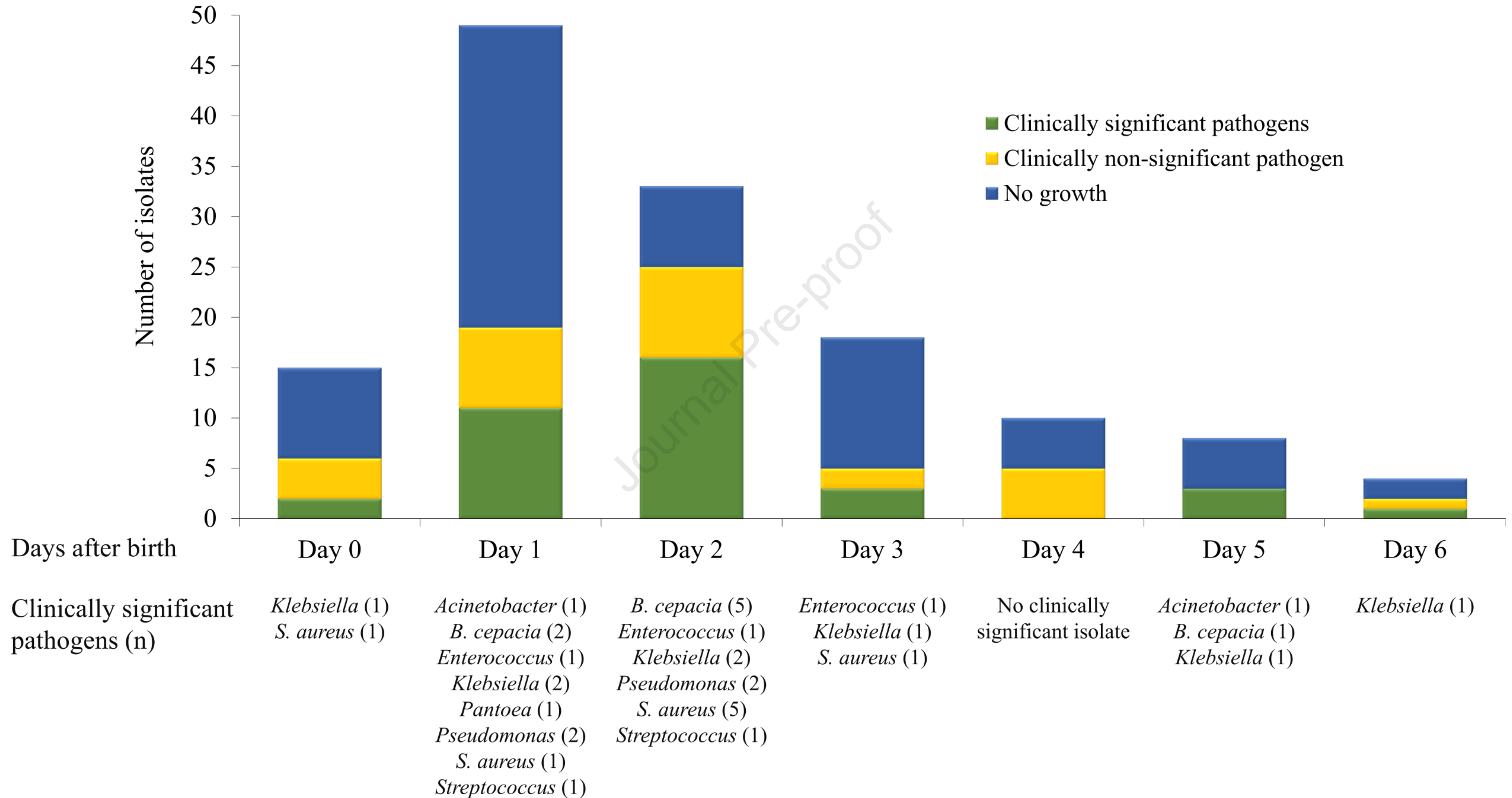
Table 3. Genomic relatedness of phenotypically-matched paired maternal rectovaginal and neonatal blood culture isolates

Pair	Strain	Organism	Age at culture	GA (weeks)	Birth weight (g)	Place of birth	Mode of delivery	Maternal intrapartum antibiotic exposure	Neonatal outcome	MLST	Pairwise SNP distance	Comments
Early-onset Sepsis												
EOS-Pair 1	Maternal	*S. aureus*	28 years			Brikama district Hospital	SVD	No		ST627	12	
	Neonatal	*S. aureus*	2 days	38	2800				Alive	ST627		
EOS-Pair 2	Maternal	*S. aureus*	26 years			SOS Clinic (NGO facility)	SVD	No		ST627	14	
	Neonatal	*S. aureus*	1 day	40	3300				Alive	ST627		
EOS-Pair 3	Maternal	*S. aureus*	26 years			Banjulinding Health Centre	SVD	No		Novel	30	
	Neonatal	*S. aureus*	0 days	38	2400				Died	Novel		
EOS-Pair 4	Maternal	*S. aureus*	26 years			Bakau Health Centre	SVD	No		ST15	52	
	Neonatal	*S. aureus*	2 days	42	3800				Died	ST15		
EOS-Pair 5	Maternal	*S. aureus*	23 years			Banjulinding Health Centre	SVD	No		ST6	41	
	Neonatal	*S. aureus*	2 days	40	2790				Alive	ST6		
EOS-Pair 6	Maternal	*K. pneumoniae*	36 years			Mbowen Clinic (Private facility)	Emergency C/S	No		ST15	15159	Newborn isolates genetically identical to nosocomial outbreak strains
	Neonatal	*K. pneumoniae*	2 days	34	2500				Alive	ST1535		
EOS-Pair 7	Maternal	*K. pneumoniae*	24 years			Mbowen Clinic (Private facility)	Emergency C/S	No		Unknown	42896	Newborn isolates genetically identical to nosocomial outbreak strains
	Neonatal	*K. pneumoniae*	2 days	34	2500				Died	ST1535		
EOS-Pair 8	Maternal	*E. faecalis*	23 years			Brikama district Hospital	SVD	No		646	108	
	Neonatal	*E. faecalis*	3 days	37	2500				Alive	646		
Late-onset Sepsis												
LOS-Pair 1	Maternal	*S. aureus*	28 years			Home	SVD	No		ST1	45168	
	Neonatal	*S. aureus*	21 days	40	4500				Alive	ST152		
LOS-Pair 2	Maternal	*E. coli*	17 years			Brikama district Hospital	SVD	No		ST10	5801	
	Neonatal	*E. coli*	26 days	36	2600				Died	ST10		
LOS-Pair 3	Maternal	*E. coli*	25 years			Pirang Health Centre	SVD	No		ST1193	6044	
	Neonatal	*E. coli*	8 days	39	2400				Died	Unknown		

NA = Not applicable; EOS = Early-onset sepsis; LOS = Late-onset sepsis; GA = Gestational age at birth
SVD = Spontaneous vaginal delivery; C/S = caesarean section



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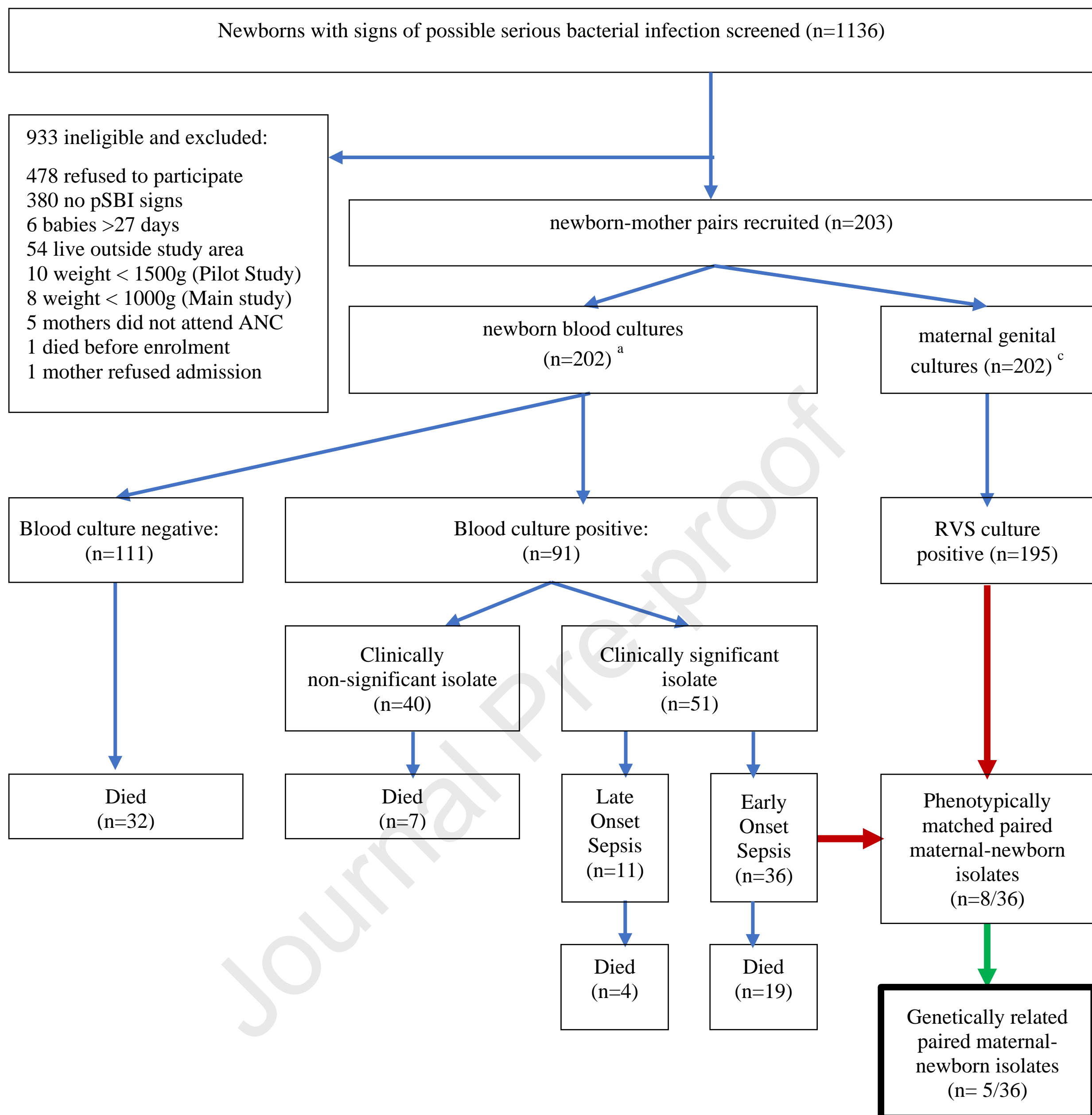

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