Supplementary material

Contents

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Supplementary table 1. Key variations in the implementation of the SRC across hospitals.

Hospital	**Groups of infants** **(all eligible infants versus infants with risk factors as per NICE)** **(postnatal versus postnatal and neonatal unit)**	**Management for infants at intermediate risk**	**Background incidence used during the study period**
1	All eligible Postnatal ward only	Take blood culture and give antibiotics	0·8/1000
2	All eligible Postnatal ward and neonatal unit	Take blood culture, withhold antibiotics, no additional tests (FBC, CRP) and observations. Antibiotics if clinical signs or blood culture is positive.	1/1000 (Sep 2020 – Nov 2020) 0·8/1000 (from Dec 2020)
3	Infants with risk factors and meeting NICE criteria for antibiotics	Take blood culture and give antibiotics	0·8/1000
4&5	Infants with risk factors and meeting NICE criteria for antibiotics Postnatal ward only	Take blood culture and give antibiotics	0·6/1000
6	Infants with risk factors Postnatal ward only	Take blood culture, withhold antibiotics, measure FBC and CRP. Observe for 36 hours. Antibiotics if the CRP is significantly raised, clinical signs or positive blood culture.	0·8/1000
7	Infants with risk factors and meeting NICE criteria for antibiotics Postnatal ward only	Take blood culture and give antibiotics	0·8/1000
8	Infants with risk factors and meeting NICE criteria for antibiotics. Postnatal ward only.	Take blood culture and give antibiotics	0·8/1000
9	Infants with risk factors Postnatal ward and neonatal unit	Take blood culture, withhold antibiotics, measure CRP, repeat CRP at 18-24 hours. Observe for 36 hours. Antibiotics if CRP is significantly raised, clinical signs or positive blood culture.	0·8/1000
10	All eligible Postnatal ward only	Take blood culture, withhold antibiotics, measure CRP, repeat CRP at 18-24 hours. Observe for 36 hours. Antibiotics if CRP is significantly raised, clinical signs or positive blood culture.	0·8/1000

Supplementary table 2. Data for the hospitals following SRC.

Abbreviations: LNU – local neonatal unit, SCBU – special care baby unit**.** *Combined data for two hospitals provided. **≥34 weeks' gestation.

SRC hospital	**1**	**2**	**3**	**4&5***	**6**	**7**	**8**	**9**	**10**	**Total**
Type of neonatal unit	LNU	Tertiary	LNU	Tertiary & LNU	LNU	LNU	SCBU	Tertiary	Tertiary	
Expected total livebirths	*5225*	*5982*	*3944*	*8860*	*3927*	*3919*	*2496*	*4626*	*5040*	*44019*
Months of available data	12	12	12	24	12	12	7	12	12	115
Livebirths denominator corresponding to months of available data	5225	5982	3944	8860	3927	3919	1429	4626	5040	42952
Number screened ≤24 h, n (%)	537 (10)	356 (6)	349 (8·8)	544 (6·1)	199 (5·1)	359 (9·2)	91 (6·4)	406 (8·8)	456 (9)	3297 (7·7)
Number treated ≤24 h, n (%)	537 (10)	308 (5·1)	349 (8·8)	543 (6·1)	177 (4·5)	351 (9)	90 (6·3)	366 (7·9)	390 (7·7)	3111 (7·2)
Number screened ≤7 days, n (%)	623 (12)	455 (7·6)	422 (11)	646 (7·3)	248 (6·3)	437 (11)	108 (7·6)	485 (11)	507 (10)	3931 (9·2)
Number treated ≤7 days, n (%)	620 (12)	404 (6·8)	421 (11)	643 (7·3)	225 (5·7)	427 (11)	107 (7·5)	467 (10)	457 (9·1)	3771 (8·8)
Missed, culture-proven, n	0	0	1	0	0	0	0	1	0	2
Missed, culture-negative, n (%)	25 (0·5)	17 (0·3)	19 (0·5)	23 (0·3)	25 (0·6)	16 (0·4)	2 (0·1)	44 (1·0)	16 (0·3)	187 (0·4)

Supplementary table 3. Data for the hospitals following NICE.

Abbreviations: LNU – local neonatal unit, SCBU – special care baby unit. *≥34 weeks' gestation.

NICE hospital	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**	**16**	
Type of neonatal unit	Tertiary	Tertiary	SCBU	Tertiary	Tertiary	LNU	LNU	LNU	LNU	SCBU	LNU	Tertiary	LNU	SCBU	LNU	LNU	
Months of available data	12	12	5	12	7	12	12	11	9	1	9	12	12	12	12	10	160
Expected total livebirth denominator	*5351*	*3144*	*1722*	*5509*	*3895*	*4964*	*3305*	*5272*	*3863*	*3852*	*6665*	*4759*	*2119*	*4591*	*4018*	*3577*	*66606*
Livebirths denominator corresponding to months of available data	5351	3144	710	5509	2272	4964	3305	4760	2897	321	4999	4759	2119	4591	4018	3012	56731
Number screened ≤24 h, n (%)	963 (18)	487 (16)	64 (9)	1125 (20)	441 (20)	675 (14)	421 (13)	641 (14)	400 (14)	69 (22)	565 (11)	791 (17)	310 (15)	569 (12)	507 (13)	409 (14)	8437 (15)
Number treated ≤24 h, n (%)	964 (18)	487 (16)	64 (9)	1125 (20)	441 (20)	674 (14)	420 (13)	638 (14)	400 (14)	69 (22)	565 (11)	791 (17)	309 (15)	568 (12)	507 (13)	406 (14)	8428 (15)
Number screened ≤7d, n (%)	1061 (20)	528 (17)	68 (9.6)	1198 (22)	498 (22)	726 (15)	463 (14)	716 (15)	441 (15)	79 (25)	592 (12)	860 (18)	360 (17)	618 (14)	566 (14)	468 (16)	9242 (16)
Number treated ≤7d, n (%)	1060 (20)	527 (17)	68 (9.6)	1197 (22)	495 (22)	726 (15)	462 (14)	712 (15)	441 (15)	79 (25)	591 (12)	860 (18)	360 (17)	618 (14)	566 (14)	464 (15)	9226 (16)
Missed, culture proven, n	0	1	0	2	0	0	0	0	0	0	0	0	1	0	1	0	5
Missed, culture-negative, n (%)	15 (0·3)	7 (0·2)	3 (0·4)	16 (0·3)	6 (0·3)	15 (0·3)	5 (0·2)	2 (0)	9 (0·3)	4 (1·2)	6 (0·1)	26 (0·5)	9 (0·4)	11 (0·2)	13 (0·3)	11 (0·4)	158 (0·3)

Supplementary table 4. Distribution and incidence of organisms isolated.

*Other pathogens included: *Acinetobacter lwoffii, , Enterobacter cloacae, Enterococcus faecalis, Haemophilus parainfluenzae, Listeria monocytogenes, Morganella morganii, Moraxella osloensis, and Staphylococcus aureus*. *Streptococcus dysgalactiae* was not listed in the Vermont Oxford Network Manual of Operations 2021, but biologically similar to *Streptococcus pyogenes* and included as a pathogen after discussion with PTH. Two cases excluded from the total reported as these did not fulfill definition of growth of organism in blood or CSF: 16S PCR in one infant reported *Streptococcus* species matching best to *Streptococcus oralis*; Gram negative bacilli were identified by microscopy in another infant, but failed to grow on culture. One case with *Moraxella osloensis* was not classified as early onset sepsis as the infant had mild symptoms (re-admitted >24 hours for feeding difficulties), was discharged home after 2 days of antibiotics, and the blood culture isolated the organism after 72 hours of incubation. Two infants with bacteraemia were excluded due to congenital skin anomalies predisoposing to postnatal acquisition of infection: *Bacillus cereus* with *Acinetobacter baumanii*, and *Staphylococcus aureus*. **≥34 weeks' gestation.

Organism	SRC	NICE	Total	Incidence per 1000 livebirths ** (95%CI)
Group B Streptococcus	15	29	44	0·44 [0·33-0·59]
Escherichia coli	2	5	7	0·07 [0·03-0·15]
Other pathogens*	3	13	16	0·16 [0·1-0·26]
Contaminants	48	77	125	1·25 [1·05-1·49]

Supplementary table 5. Maternal and infant characteristics of 5 cases of EOS identified >24 hours after birth

*As per the Medical Certificate of Cause of Death following a Coroner's investigation and based on postmortem; blood culture not taken at presentation to the emergency department. **Group B *Streptococcus* colonisation in previous pregnancy. Status in this pregnancy unknown. One case with *Moraxella osloensis* was not classified as early onset sepsis as the infant had mild symptoms (re-admitted >24 hours for feeding difficulties), was discharged home after 2 days of antibiotics, and the blood culture isolated the organism after 72 hours of incubation.

Case	Type of unit	Pathogen/s	Gestational age (weeks)	Birth-weight (g)	Age at antibiotics (hours:minutes)	Re-admission?	Mode of delivery	Length of rupture of membranes (hours)	Highest antepartum temperature	Maternal group B *Streptococcus* status	Clinical information	Duration of intravenous antibiotics (days)	Final outcome
1	SRC	*Group B Streptococcus*	38+0	2600	26:40	No	Vaginal	30	36.8	Unknown	Developed symptoms and admitted to neonatal unit	7	Discharged home
2	NICE	*Escherichia coli* and *Group B Streptococcus*	36+4	2715	30:43	No	Vaginal	Unknown	37.5	Positive	Severe hydronephrosis	21	Discharged home
3	NICE	*Group B Streptococcus**	38+2	2730	-	Yes	Vaginal	6	37.1	Positive**	Cardiac arrest at home on day 3	-	Died
4	NICE	*Haemophilus parainfluenzae*	41+5	3570	65:09	Yes	Vaginal	4	36.8	Positive	Presented with feeding difficulties	7	Discharged home
5	NICE	*Moraxella osloensis* and *Corynebacterium aurimucosum*	41+2	3260	165:25	Yes	Vaginal	1.5	37.2	Unknown	Presented with feeding difficulties	5	Discharged home

Supplementary file 1. Detailed case histories of cases of EOS identified >24 hours after birth.

Case 1: This infant was initially observed on the postnatal ward. EOS score at birth was 0·33. The infant developed symptoms, and received antibiotics just after 24 hours thus meeting the definition for missed case. The CSF was sterile. This infant was born at a hospital following SRC. There was prolonged rupture of membranes (>18 hours) and would have received observations if NICE was followed, but unlikely processes or outcome would have been different. Case 2: This was a female infant with hydronephrosis diagnosed during the antenatal period and was admitted directly to the neonatal unit. She received prophylactic trimethoprim on day 1. Empiric antibiotics were started on day 2 following a raised CRP on routine testing. The CSF was sterile. In case 1, there was no maternal indicators to have prompted earlier antibiotics had the infant been cared in a unit following NICE. Moreover, the NICE guideline and the SRC are aimed at managing risk of EOS in healthy infants, and cannot extend to infants with rare anomalies.

Cases 3 – 5 were discharged home from the postnatal ward and returned to hospital. All 3 were born in hospitals following NICE CG149 and there were no clinical indicators for empiric antibiotics. Case 3: The infant was brought to the emergency department following cardiac arrest at home. The infant had had blood sugar monitoring during the initial postnatal period and discharged home on day 1. There had been insufficient opportunity to obtain blood for culture during resuscitative attempts. The Coronial certified cause of death was GBS sepsis as per the postmortem findings, and this was the diagnosis given to the infant's parents. The mother had GBS colonisation in her previous pregnancy. She was not tested during this pregnancy, and did not receive intrapartum antibiotic prophylaxis. Cases 4 and 5 presented with feeding difficulties and were discharged home. Case 4: The mother had GBS colonisation in this pregnancy, but did not receive intrapartum antibiotic prophylaxis. The CSF was sterile in case 4, and not obtained in Case 5. Case 5: Moraxella and Corynebacterium were isolated. Moraxella is an unusual organism and rare cause of human infection, but included in the list of Bacterial Pathogens as per the Vermont Oxford Network. Corynebacterium can be considered a contaminant. The infant received 5 days of intravenous antibiotics, and included as EOS for the purpose of comprehensive reporting.

Supplementary table 6. Maternal and infant characteristics of 345 cases where empiric antibiotics were commenced >24 hours from birth, for ≥5 days, with negative cultures.

Abbreviations: EOS – early onset sepsis, GBS – group B *Streptococcus*, IQR – interquartile range, ROM – rupture of membranes, SD – standard deviation.

	SRC (n=187)	**NICE (n=158)**	**P value**
Gestational age, weeks, mean (SD)	39·9 (1·7)	39·6 (1·5)	0·57
Birthweight, g, mean (SD)	3394 (573)	3277 (583)	0·07
Male, n (%)	117 (63)	86 (54)	0·13
Vaginal delivery, n (%)	107 (57)	98 (62)	0·37
Highest maternal antepartum temperature, median (IQR) †	37·1 (36·8-37·8)	37·0 (36·7-37·2)	0·05
Maternal GBS status, n (%)			
-Unknown	134 (72)	91 (58)	0·006
-Positive	20 (11)	10 (6·3)	0·15
-Negative	32 (17)	57 (36)	<0·001
ROM, h, median (IQR) ±	13 (2-22)	7 (1–16)	<0·001
Maternal antibiotics, n (%)			
-No antibiotics or any <2h prior to birth	138 (75)	131 (89)	<0·001
-GBS specific antibiotics >2h prior to birth	19 (10)	7 (4·8)	0·06
-Broad spectrum antibiotics 2-3.9h prior to birth	11 (6)	3 (2)	0·06
-Broad spectrum antibiotics >4h prior to birth	16 (8·7)	6 (4·1)	0·09
Age at antibiotics, hours, median (IQR)	36 (28-54)	37 (28–50)	0·70
Days of antibiotics, median (IQR)	5 (5-7)	5 (5-5)	0·15
Initial hospital stay			
-Assigned postnatal care and never admitted, n (%)	118 (63)	84 (53)	0·06
-Assigned postnatal care and later admitted to neonatal unit, n (%)	56 (30)	70 (44)	0·006
-Admitted to neonatal unit from birth centre, n (%)	13 (7)	4 (2·5)	0·06
Re-admission from home, n (%)	33 (18)	39 (25)	0·1
Death, n	0	0	

EOS score at birth, median (IQR)	0·34 (0·15-0·78)	-	

† Highest maternal antepartum temperature missing for SRC 34, NICE 92 infants

± Rupture of membrane timing missing for SRC 14, NICE 47 infants