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# Comparison of missed diagnoses of early onset sepsis associated with use of Sepsis Risk Calculator versus NICE CG149 2020-21: a population cohort study in London, UK



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**Comparison of missed diagnoses of early onset sepsis associated with use of Sepsis Risk Calculator versus NICE CG149 2020-21: a population cohort study in London, UK**

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Keywords: neonatal sepsis, sepsis risk calculator, early onset sepsis

## ABSTRACT

**Objective:** The National Institute for Health and Care Excellence (NICE) neonatal infection (early-onset) guideline CG149 results in large numbers of newborn infants receiving antibiotics. We sought to compare the incidence of missed early-onset sepsis (EOS) in infants ≥34 weeks' gestation in hospitals using the Kaiser Permanente sepsis risk calculator (SRC) with hospitals using the NICE guidance.

**Design and setting:** Prospective observational population-wide cohort study involving all 26 hospitals with neonatal units co-located with maternity services across London (10 using SRC, 16 using NICE). **Study population**: all livebirths ≥34 weeks' gestation between September 2020 and August 2021.

**Outcome measures**: Culture-proven missed EOS was defined as isolation of *a bacterial pathogen in the blood or CSF culture of an infant from 24 hours of age up to 7 days of age.* Culture-negative missed EOS was defined as an infant *commencing intravenous antibiotics from 24 hours of age up to 7 days of age, for at least 5 days,* but with negative blood or CSF cultures.

**Results:** Of 99,683 livebirths, 42,952 (43%) were born in SRC hospitals and 56,731 (57%) in NICE hospitals. The overall incidence of culture-proven EOS (<72 hours) was 0·65/1000 livebirths. The incidence of culture-proven missed EOS was 4·7/100,000 (n=2) for SRC versus 8·8/100,000 (n=5) for NICE (odds ratio 0·5, 95%CI [0·1; 2·7]). The incidence of culture-negative missed cases was 4·4/1000 (n=187) for SRC versus 2·9/1000 (n=158) for NICE (odds ratio 1·5, 95%CI [1·2; 1·9]); 3111 (7%) infants received antibiotics in the first 24 hours of life in SRC hospitals versus 8428 (15%) in NICE hospitals.

**Conclusion:** There was no significant difference in the incidence of culture-proven missed EOS between SRC and NICE hospitals, although more culture-negative cases were missed in SRC hospitals. SRC use resulted in 50% fewer infants receiving antibiotics in the first 24 hours of life.


### Strengths and limitations

Largest UK study with 99,683 livebirths comparing neonatal outcomes following the Kaiser Permanante Sepsis Risk Calculator (SRC) versus National Institute for Health and Care Excellence (NICE) guidance.

Prospective one-year observational population-wide cohort study utilising a network approach to ensure capture of all re-admissions following discharge due to early-onset neonatal sepsis.

Observational study design cannot exclude differences in population and clinical practices at hospitals that may explain the higher incidence of culture-negative missed cases in SRC units.

Data were only obtained for infants who had a blood culture received in a laboratory, and therefore it is possible to have missed a few infants who received antibiotics without a blood culture.

We applied a pragmatic clinician-consensus definition for culture-negative sepsis defined as receipt of at least 5 days of intravenous antibiotics.

**Patient and Public Involvement statement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

## BACKGROUND

Early-onset sepsis (EOS) can be defined as bacteraemia occurring within 72 hours of birth. EOS occurs in around 0·7/1000 livebirths in high income settings,[1] and remains a major cause of morbidity in neonates, particularly those born preterm.[2] As infants can initially be asymptomatic or present with non-specific symptoms, determining who should receive antibiotics can be a challenge, and is a balance between unnecessary use of antibiotics and avoiding harm from delayed antibiotic therapy. In the United Kingdom (UK), most hospitals follow the National Institute for Health and Care Excellence (NICE) guidance CG149 which uses maternal risk factors, clinical indicators and "red flags" [3] to guide decisions on investigations and antibiotics. However, concerns of associated antibiotic overuse[4] have prompted an increasing number of hospitals to adopt the Sepsis Risk Calculator (SRC)[5,6] for infants ≥34 weeks' gestation and within 12 hours of birth.[7]

The SRC was developed in the USA and estimates the risk of EOS based on background incidence, gestational age, highest maternal antepartum temperature, duration of membrane rupture, maternal GBS status, and type and timing of intrapartum antibiotics. The infant's evolving clinical presentation is factored into the second part of the model, which adjusts the prior risk of EOS. Depending on the estimated final risk, the SRC provides recommendations for clinical management (routine care/blood culture/empiric antibiotics) and monitoring of vital signs.[7,8] The SRC was endorsed by the American Academy of Pediatrics in 2018.[9] Whilst the SRC reduces antibiotic usage,[10,11] there have been concerns of the potential for missed or delayed identification of EOS compared to NICE.[12,13] Despite this, the SARS-CoV-2 pandemic accelerated its uptake in the UK; 10 out of 26 hospitals in London adopted the SRC to ration resources and facilitate earlier discharges. In this one-year prospective regional study we aimed to report the incidence of culture-proven and culture-negative missed EOS cases and compare the incidence in hospitals using SRC with hospitals using NICE guidance.

## METHODS

### Design

We applied a pragmatic study design, developed by a multi-professional project team (comprising doctors, nurses, midwives and network managers), supported by the London Neonatal Operational Delivery Network. A common minimum dataset was collected by a network of trainee and consultant paediatricians in the Neonatal Trainee Research and Improvement Projects (NeoTRIPS). The protocol is published on the NeoTRIPS website.[14]

### Setting

All 26 National Health Service (NHS) hospitals within Greater London providing newborn care and co-located with a maternity service participated in this study. These included 9 tertiary neonatal intensive care units (NICU), 13 local neonatal units (LNUs) and 4 special care baby units (SCBUs). 10 hospitals followed SRC and 16 followed NICE guidance. The decision regarding which approach to follow (SRC/NICE) was made by individual hospitals and was not influenced by participation in this study.

The background incidence of EOS used by the SRC hospitals during the study period ranged from 0.6-1/1000. There was variation in the application of SRC; in 9/10 units, it was applied only to subsets of infants meeting specified risk thresholds, and there were differences in the management of infants deemed to be at intermediate risk (Supplementary table 1).

**Participants**

The eligible population was all live births ≥34 weeks' gestation during a 12-month period from 1 September 2020 to 31 August 2021.

**Main outcomes**

The primary outcome was the number of missed EOS cases, compromised of culture-proven and culture-negative cases, as a proportion of livebirths. Culture-proven missed EOS was defined as isolation of a bacterial pathogen in the blood or CSF culture of an infant from 24 hours of age (up to 7 days of age). Bacterial pathogens were categorised as per the Vermont Oxford Network Manual of Operations.[15] Culture-negative missed EOS was defined as an infant commencing intravenous antibiotics from 24 hours of age (up to 7 days of age), for at least 5 days, but with negative blood or CSF cultures. [11] The number of babies receiving intravenous antibiotics in the first 24 hours of life and the number of babies with culture proven EOS in the 1st 72 hours of life were also assessed.

**Data collection**

The number of all livebirths ≥34 weeks' gestation per calendar month at each hospital site was obtained for the duration of the study. Patient-level data were collected for all infants who had a blood culture obtained during the first 7 postnatal days (Figure 1). These infants were identified by reviewing weekly lists of blood cultures from all microbiology laboratories serving these hospitals to ensure all screens for suspected EOS were captured from all settings (postnatal ward, neonatal unit, accident and emergency department). If an infant had more than one blood culture, the timing of the first sample was used.

For each infant who had a blood culture taken, a basic dataset was obtained: time of blood culture (hours of age), receipt of antibiotics and time of administration, admission to a neonatal unit, duration of antibiotics, length of initial hospital stay.

For all culture-proven EOS cases, additional maternal and infant clinical details were collected (Figure 1): gestational age, birthweight, sex, mode of delivery, maternal risk factors (length of rupture of membrane, highest maternal antepartum temperature, GBS status in the current pregnancy, class and timing of intrapartum antibiotics), organisms isolated (blood culture, cerebrospinal fluid (CSF), or both), CSF white cell count, infant's clinical signs during initial hospital stay, whether the infant presented after

discharge home, infant's symptoms upon re-admission from home, duration of antibiotics, and final clinical outcome. In addition, for SRC hospitals, we collected EOS scores at birth and after clinical examination. We did not collect detailed data for infants with culture-negative sepsis who were treated with antibiotics in the first 24 hours of life.

Data for readmissions to hospitals other than the birth hospital were obtained through nhs.net correspondence. The NeoTRIPs network covered all London hospitals and frequent communications between members ensured that missing data were minimised.

Anonymised data were collated using Excel through nhs.net, stored on NHS computers and analysed using a centralised Excel spreadsheet through a secure nhs.net server. Monthly data were verified with contributors by three of the authors. Missing data were resolved as far as possible. Cases meeting definitions of missed and EOS were agreed by consensus. Compliance with data submission was supported through feedback at regular meetings throughout the study period. See Figure 1. Flowchart of methods.

**Expected incidence of missed cases**

The objective of this pragmatic study was to report the incidence of culture-proven and culture-negative missed EOS cases from all London hospitals over a 12 month period. Based on NHS Maternity Statistics,[16] we estimated ~95,000 livebirths at ≥34 weeks' gestation would be born during the study period. With a background EOS incidence of 0·8/1000 livebirths for Greater London,[17] we anticipated ~80 cases of culture-proven EOS and, based on the estimate defined in the original Kaiser Permanente study[10], we anticipated 5-6 missed culture-proven cases. Through consensus, we expected approximately 10 culture-negative for every 1 culture-proven case and thus around 60 culture-negative missed cases in this population.

**Statistical analysis**

Summary descriptive statistics are presented as medians with their corresponding interquartile ranges for continuous variables, and as percentages for categorical variables. All incidence rates are expressed as cases per 1000 or 100,000 livebirths ≥34 weeks' gestation, where appropriate, with denominator values based on available data.

Chi-squared tests were used for proportions, independent samples t test for comparison of means and Mann-Whitney U test for comparisons of medians. Non-parametric data were log transformed to preferentially conduct parametric testing where possible. Shapiro-Wilk test was used for assessing normality of original and log transformed data. GraphPad Prism was used for analyses. P values <0·05 were considered statistically significant. Odds ratio was chosen for events where the incidence was <10%. [18]

**Patient and Public Involvement**

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research

**RESULTS**

Blood culture data were not available for all months from all hospitals over the study period. Data were missing for 5 months from one SRC hospital and for 32 months from 7 NICE hospitals. The livebirth denominator corresponding with available data was 42952 for SRC hospitals and 56731 for NICE hospitals) (Table 1). Supplementary tables 2 and 3 present the livebirth denominator data by month for SRC and NICE hospitals.

*Blood culture screening and intravenous antibiotic use*

Overall, 11734 (12%) infants had a blood culture taken within 24 hours of birth, however, SRC hospitals obtained 50% fewer blood cultures than NICE hospitals (relative risk 0.5, 95%CI [0·47-0·51]) (Table 1). In both SRC and NICE hospitals, the majority of babies having a blood culture were treated with antibiotics (Table 1). Hospital-specific antibiotic use is presented in Supplementary tables 1 and 2. The proportions of infants receiving antibiotics at >24 to ≤72 hours, and >72 hours to ≤7 days were similar in both hospital types (odds ratio: 1.1, 95% CI (0.97 – 1.2) vs 1.0, 95% CI (0.81-1.3) with no shift towards later therapy in hospitals using SRC (Table 1).

Table 1. Outcomes of the participating hospitals.

All livebirths denote ≥34 weeks' gestation. Abbreviations: CI – confidence interval, EOS – early onset sepsis.

| | **SRC**<br>**10 hospitals** | **NICE**<br>**16 hospitals** |
|---|---|---|
| Livebirths denominator corresponding to available data | 42952 | 56731 |
| Infants screened with blood culture ≤24 hours of age, n (%) | 3297 (7·7) | 8437 (15) |
| Infants who started antibiotics ≤24 hours of age, n (%)† | 3111 (7·2) | 8428 (15) |
| Infants who started antibiotics >24 hours and ≤72 hours of age, n (%)† | 510 (1·3) | 620 (1·3) |

| | | |
|---|---|---|
| Infants who started antibiotics >72 hours and ≤7 days of age, n (%)† | 135 (0·3) | 176 (0·4) |
| Culture-proven EOS ≤7 days of age, n, incidence/1000 livebirths, [95%CI] | 21 (0·49/1000, [0·32- 0·75]) | 46 (0·81/1000, [0.61- 1·1]) |
| Missed culture-proven EOS (bacterial pathogen in blood culture), n (incidence/100,000 livebirths [95% CI]) | 2 (4·7/100,000, [1·2-19]) | 5 (8·8/100,000, [3·7-21]) |
| Missed culture-negative EOS (negative blood culture and receiving antibiotics >24 hours and ≤7 days for at least 5 days duration), n (incidence/1,000 livebirths, [95% CI]) | 187 (4·4/1000, [3·8-5]) | 158 (2·8/1000, [2·4-3·3]) |

† Timing of antibiotic administration was unavailable for 15 infants (SRC) and 2 infants (NICE).

*Incidence and characteristics of cases of EOS*

Across the entire study population, there were 67 infants with culture-proven EOS within the first 7 days of life, 65 within 72 hours (0·65/1000, 95% CI [0·51-0·83]) and 2 infants from >72 hours to 7 days. The most common pathogen was GBS (0·44/1000). The incidence of *Escherichia coli* was 0·07/1000, and other pathogens combined was 0·18/1000 (Supplementary table 4 and supplementary figure 1).

There was a higher number of culture-proven EOS within the first 7 days of life in the NICE hospitals (n=46; 0·81/1000) compared to SRC hospitals (n=21; 0·49/1000) (odds ratio 1·7, 95%CI [0·99-2·8]) (Table 1). Table 2 shows the clinical characteristics for infants with culture-proven EOS. Cases in the NICE hospitals were more likely to be asymptomatic at time of treatment (18 (42%) vs 3 (5%)). However, the timings of blood culture and initiation of antibiotics across the two groups were similar.

Table 2. Characteristics of 67 culture-proven EOS ≤7 days.

Abbreviations: CSF – cerebrospinal fluid, EOS – early onset sepsis, GBS – group B *Streptococcus*, IQR – interquartile range, SD - standard deviation.

| | **SRC (n=21)** | **NICE (n=46)** | **P value** |
|---|---|---|---|
| Gestational age, weeks, mean (SD) | 38·9 (1·7) | 39·1 (7·4) | 0·45 |

| | | | |
|---|---|---|---|
| Birthweight, g, mean (SD) | 3137 (553) | 3326 (458) | 0·47 |
| Male, n (%) | 9 (43) | 25 (54) | 0·41 |
| Vaginal delivery, n (%) | 4 (19) | 26 (56) | 0·005 |
| Highest maternal antepartum temperature, median (IQR)† | 37·2 (36·9-38·2) | 37·3 (36·9-37·6) | 0·4 |
| Maternal GBS status, n (%)‡ | | | |
| *-Unknown* | 10 (50) | 16 (36) | 0·29 |
| *-Positive* | 3 (15) | 17 (39) | 0·06 |
| *-Negative* | 7 (35) | 11 (25) | 0·41 |
| Rupture of membranes, h, median (IQR)± | 11 (5·5-22) | 15 (3-31) | 0·22 |
| Maternal antibiotics, n (%)* | | | |
| *-No antibiotics or any <2h prior to birth* | 17 (85) | 31 (76) | 0·42 |
| *-GBS specific antibiotics >2h prior to birth* | 0 | 3 (7·3) | 0·22 |
| *-Broad spectrum antibiotics 2-3.9h prior to birth* | 3 (15) | 4 (1) | 0·03 |
| *-Broad spectrum antibiotics >4h prior to birth* | 0 | 3 (7·3) | 0·22 |
| Initial hospital stay | | | |
| *-Assigned postnatal care and never admitted to neonatal unit, n (%)* | 7 (33) | 24 (52) | 0·15 |
| *-Assigned postnatal care and later admitted to neonatal unit, n (%)* | 5 (24) | 11 (24) | 1·0 |
| *-Admitted to neonatal unit from birth centre, n (%)* | 9 (43) | 12 (26) | 0·17 |
| Age at blood culture, hours, median (IQR) | 3·8 (2·2-10) | 2·7 (1·5-10) | 0·72 |
| Age at antibiotics, hours, median (IQR) | 3·8 (2·5-10) | 2·7 (1·5-10) | 0·86 |
| Clinical signs at birth, n (%)** | 10 (50) | 11 (26) | 0·06 |
| Developed signs before discharge, n (%)** | 7 (33) | 14 (33) | 1·0 |

| | | | |
|---|---|---|---|
| Never had clinical signs, n (%) | 3 (15) | 18 (42) | 0·04 |
| CSF culture positive, n (%)*** | 1 (5) | 2 (4·7) | 0·96 |
| CSF white cell count > 20, n (%)*** | 1 (5) | 3 (7) | 0·76 |
| Death, n (%) | 1 (4·7) | 1 (2·2) | 0·58 |
| EOS score at birth, median (IQR) | 2·0 (0·14-7·8) | - | - |

†Highest maternal antepartum temperature missing for SRC 4, NICE 26 infants

‡Maternal GBS status missing for SRC 1, NICE 2 infants

±Rupture of membrane timing missing for SRC 4, NICE 16 Infants

*Maternal antibiotics missing for SRC 1, NICE 5 infants

**Timing of clinical signs missing for SRC 1, NICE 3 infants

***CSF not obtained for SRC 1, NICE 3 infants

*Incidence of culture-proven missed EOS*

There were 7 culture-proven missed EOS cases (2, 4·7/100,000 for SRC versus 5, 8·8/100,000 for NICE (odds ratio 0·5, 95%CI [0·1; 2·7])) (Table 1). The maternal and infant characteristics are reported in Supplementary Table 5. Three infants had severe congenital abnormalities and were admitted to the neonatal unit directly (1 SRC, 2 NICE). Three infants were re-admissions from home following an initial asymptomatic course in hospital (all NICE). One infant developed symptoms whilst being observed on the postnatal ward (SRC). Detailed case histories are provided in Supplementary file 1.

*Incidence of culture-negative missed EOS*

There were 345 culture-negative missed EOS cases (187, 440/100,000 for SRC versus 158, 290/100000 for NICE (odds ratio 1·5, 95%CI [1·2; 1·9]) (Table 1). The maternal and infant characteristics are presented in Table 3. There were differences in maternal characteristics: length of rupture of membranes (limited interpretation due to missing data), GBS status and antibiotic therapy. Despite more cases in the SRC hospitals, there was no greater proportion of infants admitted to the neonatal unit from the postnatal ward, or re-admitted from home. Timing and duration of antibiotics were similar. There were no deaths in either group.

Table 3. Maternal and infant characteristics of 345 culture-negative missed cases.

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

## DISCUSSION

This large observational, pragmatic study was undertaken to assess and compare the outcomes of the routine use of two widely adopted neonatal sepsis management strategies, the Sepsis Risk Calculator and the NICE neonatal infection guideline. Decisions regarding which strategy to use were undertaken locally and therefore reflect a range of local factors, including perceived benefits and risks, caseloads and risk factors.

We found a high proportion of infants born at ≥ 34 weeks gestation who received antibiotics within 24 hours of birth – 15% in the NICE hospitals versus 7% in the SRC hospitals. This implies that 50% fewer infants received empiric antibiotics in the SRC hospitals. Despite this, there was no evidence of a resultant increase in missed cases of culture-proven EOS. Indeed, the absolute number of infants meeting the definition of a culture-proven missed case was small. Of the 7 missed cases, only 3 were re-admissions in the first 7 days of life following an asymptomatic course during the initial hospital stay. These 3 infants had been cared for in hospitals following NICE. Re-admission with bacteraemia, even across a population representing almost 100,000 livebirths, is therefore a rare event. The rarity is also reflected in other large studies following implementation of SRC: 3 cases across 56,261 livebirths (5·3/100,000) in Northern California[10] and 2 cases across 24,749 livebirths (8·1/100,000) in Wales.[6] All infants in these two studies were also asymptomatic during the initial postnatal stay and without clinical indicators for empiric antibiotics.[6,10] This indicates that neither approach will prevent all missed cases.

The proportion of infants receiving antibiotics ≤24 hours of age in SRC hospitals in our study is still higher than that reported at Kaiser Permanente hospitals (2·6%)[10] and other SRC centres in the USA (3·7%)[19]. This may be explained by the more conservative SRC approach generally adopted by UK hospitals, in which antibiotics are always started when obtaining a blood culture. Withholding antibiotics is one of the possible SRC recommendations for infants at intermediate risk. A Welsh study showed a similar reduction in antibiotic use to our study (45·5%), with SRC use resulting in 7·7% receiving antibiotics.[6] Another reason for the higher proportion treated with antibiotics in our study may be that the SRC was applied only to infants cared for on the postnatal ward, as opposed to those admitted to the neonatal unit. The high use of antibiotics in the hospitals in our study is highlighted further by an international study in high-income settings (with centres following a variety of approaches in managing risk of EOS) which reported that only 3% of infants were treated. [20] It is therefore clear that in our setting large numbers of infants are being exposed to antibiotics relative to the low incidence of EOS.

Although the overall incidence of culture-proven EOS (0·65/1000 livebirths ≥34 weeks gestation) is similar to that identified in other UK studies[21], as an observational pragmatic study there are inherent limitations in our ability to interpret the differences we found in outcomes between different hospitals. For example, differences in socioeconomic and ethnic backgrounds of the populations served and of obstetric practice regarding caesarean section rates and intrapartum antibiotic prophylaxis use may have a significant impact on the background risk of EOS.[22,23] The difference in the number of culture-proven missed cases in the groups (SRC=2, NICE=5) is small but could reflect the fact that fewer blood cultures were taken in the SRC hospitals meaning that some infants with transient bacteraemia[24] and minimal clinical signs were not captured; this has also been reported by the Kaiser Permanente group where the practice of taking a blood culture and awaiting the result is more common.[10]

The SRC was developed and validated using EOS confirmed by positive blood cultures.[7,8] Because infants can present with signs of sepsis with sterile blood or CSF cultures, we reported an additional 345 infants with culture-negative missed EOS who received ≥5 days of intravenous antibiotics after 24 hours of age. The incidence of culture-negative missed EOS was significantly higher in SRC units than in NICE units. Caution must be exercised when considering a definition of sepsis that includes duration of antibiotic therapy, as this may be influenced by a clinician decision to extend treatment following negative cultures, rather than by clinical indicators. Despite its limitations, a definition of 5 or more days of antibiotic therapy is used elsewhere. [1, 15] In the setting of a non-randomised study design, it is also possible that clinicians in SRC hospitals were more cautious following implementation of the SRC. However, there was no skew towards later antibiotic treatment suggesting delayed recognition or later manifestation of sepsis associated with the tool. Additionally, there was no increased adverse outcomes such as neonatal unit admission, re-admissions following discharge home or death. Whether (missed) culture-negative sepsis is associated with later sequelae, such as neurodevelopmental impairment, is not clear.[26]

A key strength of the study was the support provided by the network of London hospitals embarking on implementation of new practice, feedback at regular intervals and crucially, the trainee network to capture all re-admissions with presumed sepsis. This is the largest study of the outcomes of the SRC in the UK to date, with data representing 90% of the eligible birth population, and all hospitals in the network providing maternity care contributing data. Thus the results are generalisable to the wider population.

There are a number of potential limitations to consider: 1) This was a non-randomised study and therefore we cannot exclude differences in populations and clinical practices at hospitals that may explain (for example) the higher incidence of culture-negative missed cases in SRC units. 2) This was a pragmatic design with the capacity to obtain only a limited data-set. Broad coverage to capture rare events (missed cases) was prioritised over depth of clinical detail. We therefore did not collect laboratory data such as c-reactive protein levels. Data were only obtained for infants who had a blood culture received in a laboratory, and therefore it is possible to have missed a few infants who received antibiotics without a blood culture. There was also variation in the application of the SRC across

hospitals, with a modified approach used commonly (Supplementary table 1). Equally, without data on every eligible livebirth, uniformity of application of NICE guidance cannot be assessed. 3) The definition of culture-negative sepsis was the receipt of ≥5 days of antibiotics. Infants that died before the intention to complete ≥5 days would not have been captured. 4) Not all hospitals provided data for the entire study period, therefore we cannot assure all re-admissions following initial hospital discharge were captured. The possibility of re-admission to a hospital out-with Greater London remains, but this is likely to be rare. 5) The SRC was compared with NICE CG149,[3] which has since been replaced in 2021 by NICE CG195[27] with the removal of maternal broad spectrum antibiotics as a risk factor for neonatal EOS, and previous GBS colonisation mandating intrapartum antibiotic prophylaxis for the subsequent pregnancy, unless the woman has had a negative test in that subsequent pregnancy.[27] These new changes may bring about a reduction in neonatal antibiotic exposure and some of the missed cases observed in our study may have been avoided.

We propose that there is now a need to conduct a UK-wide randomised controlled trial to compare these two strategies. Findings from our study will help inform the design of such a study.

## CONCLUSION

The use of the SRC was associated with 50% fewer infants receiving empiric antibiotics compared to NICE CG149. Missed cases of culture-proven EOS were rare, with no difference between the two groups. These findings can help inform clinical guidelines as well as the design of definitive studies to compare outcomes of the SRC with the NICE CG195 introduced in 2021.[27]

## DECLARATIONS

### Consent for publication

Not applicable

### Data sharing statement

The data that support the findings of this study are available from the corresponding author CB, upon reasonable request.

### Competing interests

CB reports grants and personal awards funded by the National Institute for Health Research, personal fees from Chiesi Pharmaceuticals and Abbvie Pharmaceuticals; and is deputy chair of the NIHR Health Technology Assessment Prioritisation Committee for hospital-based care. PTH was a member of the NICE CG149 guideline committee and deputy chair of the NICE CG195 guideline committee. The other authors do not have any conflicts of interests to declare.

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**Author contributions and acknowledgements:**

CP wrote the first draft of the article with contributions from CB. CP, SG and RY carried out the analyses. All authors edited and approved the final version of the article. CP and CB conceived the study; CP, CB, GSK, KB, JR, CH, KN, JJ, AD, TL, PTH, KLD, SS contributed to the development and conduct of the study. CP, SG, RY, JO, DT, CL, KE were involved in data collection, along with the NeoTRIPs team, and supported by the wider multi-professional project team group (below). We thank Zeshan Rawn (London Neonatal Operational Delivery Network) for technical assistance and Katie Nichol (NHS England and NHS Improvement London). CB as guarantor accepts full responsibility for the conduct of the study and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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## Ethics and approvals

The study was deemed to be a service evaluation by the Chair and Approvals Officer of the London South East REC Committee and did not require ethical approval.

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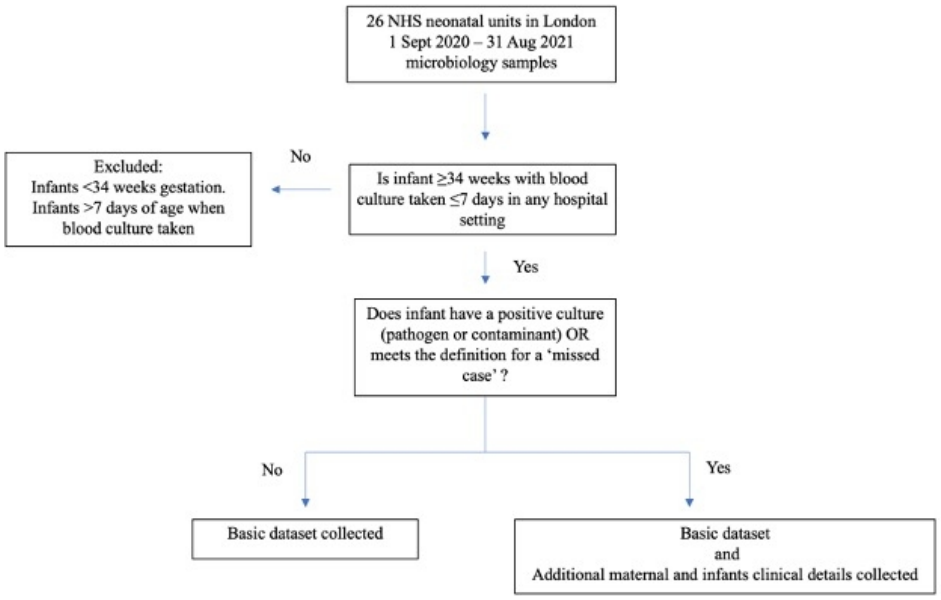



Data Collection flow chart

233x169mm (72 x 72 DPI)

# Supplementary material

## Contents

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

| Hospital | Groups of infants<br>(all eligible infants versus infants with risk factors as per NICE)<br>(postnatal versus postnatal and neonatal unit) | Management for infants at intermediate risk | Background incidence used during the study period |
|---|---|---|---|
| **1** | All eligible<br>Postnatal ward only | Take blood culture and give antibiotics | 0·8/1000 |
| **2** | All eligible<br>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)<br>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<br>Postnatal ward only | Take blood culture and give antibiotics | 0·6/1000 |
| **6** | Infants with risk factors<br>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<br>Postnatal ward only | Take blood culture and give antibiotics | 0·8/1000 |
| **8** | Infants with risk factors and meeting NICE criteria for antibiotics.<br>Postnatal ward only. | Take blood culture and give antibiotics | 0·8/1000 |
| **9** | Infants with risk factors<br>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<br>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 baumanii, Acinetobacter lwoffii, Bacillus cereus, 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. **≥34 weeks' gestation.

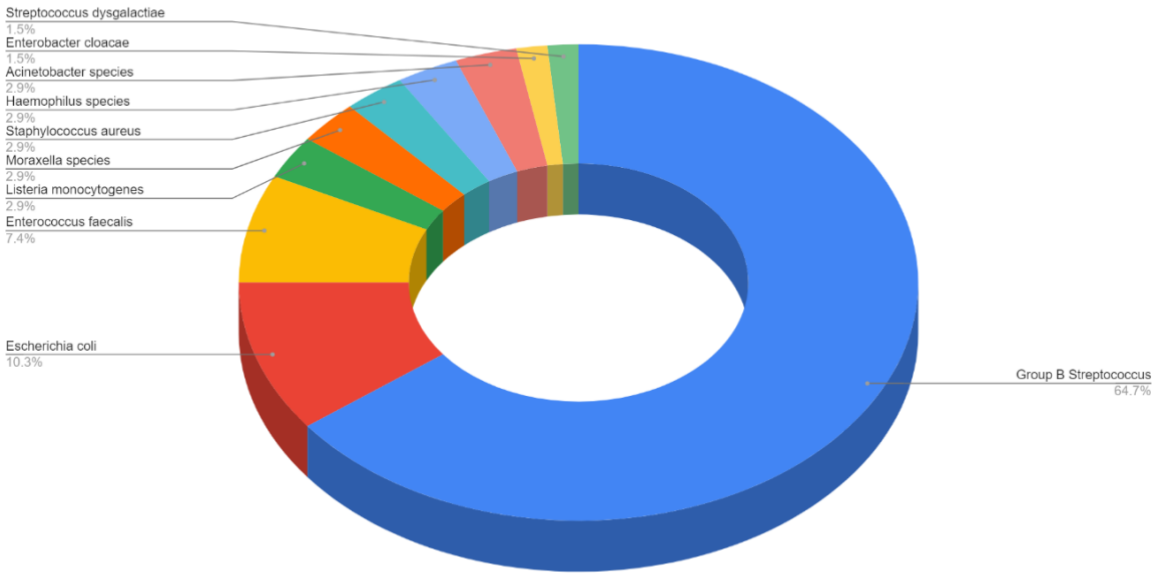
| Organism | SRC | NICE | Total | Incidence per 1000 livebirths ** (95%CI) |
|---|---|---|---|---|
| *Group B Streptococcus* | 15 | 29 | 44 | 0·44 [0·33-0·59] |
| *Escherichia coli* | 2 | 5 | 7 | 0·07 [0·03-0·15] |
| Other pathogens* | 4 | 14 | 18 | 0·18 [0·11-0·29] |
| Contaminants | 48 | 77 | 125 | 1·25 [1·05-1·49] |

**Supplementary table 5. Maternal and infant characteristics of 7 culture-proven missed cases**

*Coronial cause of death; blood culture not taken. **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 | *Bacillus cereus* and *Acinetobacter baumanii* | 39+4 | 2775 | 28:43 | No | Caesarean | 0 | 36.9 | Unknown | Harlequin icthyosis | 9 | Died |
| 2 | 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 |
| 3 | NICE | *Escherichia coli* and *Group B Streptococcus* | 36+4 | 2715 | 30:43 | No | Vaginal | Unknown | 37.5 | Positive | Severe hydronephrosis | 21 | Discharged home |
| 4 | NICE | *Staphylococcus aureus* | 37+4 | 2210 | 91:03 | No | Vaginal | 12 | Unknown | Unknown | Collodion baby | 7 | Discharged home |
| 5 | NICE | *Group B Streptococcus** | 38+2 | 2730 | - | Yes | Vaginal | 6 | 37.1 | Positive** | Cardiac arrest at home on day 3 | - | Died |
| 6 | NICE | *Haemophilus parainfluenzae* | 41+5 | 3570 | 65:09 | Yes | Vaginal | 4 | 36.8 | Positive | Presented with feeding difficulties | 7 | Discharged home |
| 7 | 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 figure 1. Proportions of bacterial pathogens causing early-onset sepsis.**



**Supplementary file 1. Detailed case histories of missed culture-proven early onset sepsis.**

Cases 1-3 were admitted directly to the neonatal unit after birth because of severe congenital abnormalities. Case 1: The EOS score at birth was 0·05. The blood culture was taken via an umbilical venous catheter (UVC). Antibiotics were given empirically due to harlequin icthyosis and the multiple attempts at inserting the UVC. Blood culture was taken on the second attempt at inserting UVC. The infant was transferred to a quaternary centre on day 2 for dermatology specialist care. The CSF was sterile. Certified causes of death were harlequin icthyosis, and sepsis. Case 2: This was a female infant with hydronephrosis diagnosed during the antenatal period. 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 is aimed at managing risk of EOS in healthy infants, and cannot extend to infants with rare anomalies. Case 4: 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 5 – 7 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 5: 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. The mother had GBS colonisation in her previous pregnancy. She was not tested during this pregnancy, and did not receive intrapartum antibiotic prophylaxis. Cases 6 and 7 presented with feeding difficulties and were discharged home. Case 6 – the mother had GBS colonisation in this pregnancy, but did not receive intrapartum antibiotic prophylaxis. The CSF was sterile in case 6, and not obtained in Case 7.

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract Y page 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Y page 2 |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported Y page 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses Y page 3 |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper Y page 3 and 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Y page 3 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Y page 4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Y page 4 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Y page 4 |
| Bias | 9 | Describe any efforts to address potential sources of bias Y page 5 |
| Study size | 10 | Explain how the study size was arrived at Y page 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Y page 5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding Y page 5 |
| | | (*b*) Describe any methods used to examine subgroups and interactions Y page 5 |
| | | (*c*) Explain how missing data were addressed Y page 5 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed Y page 5 |
| | | (*e*) Describe any sensitivity analyses N/A |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Y |
| | | (b) Give reasons for non-participation at each stage Y |
| | | (c) Consider use of a flow diagram Y |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Y page 6 |
| | | (b) Indicate number of participants with missing data for each variable of interest Y page 6 |
| | | (c) Summarise follow-up time (eg, average and total amount) Y page 6 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time Y page 6 and 7 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were |

| | | |
|---|---|---|
| | | adjusted for and why they were included Y page 6 and 7 |
| | | (*b*) Report category boundaries when continuous variables were categorized Y page 6 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Y page 7 |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives Y page 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Y page 14 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Y page 13 and 14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results Y page 15 |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Y page 15 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.

BMJ Open

# Comparison of diagnoses of early onset sepsis associated with use of Sepsis Risk Calculator versus NICE CG149: a prospective, population-wide cohort study in London, UK, 2020-21



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# Comparison of diagnoses of early onset sepsis associated with use of Sepsis Risk Calculator versus NICE CG149: a prospective, population-wide cohort study in London, UK, 2020-21

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## ABSTRACT

**Objective:** We sought to compare the incidence of early-onset sepsis (EOS) in infants ≥34 weeks' gestation identified > 24 hours after birth, in hospitals using the Kaiser Permanente sepsis risk calculator (SRC) with hospitals using the NICE guidance.

**Design and setting:** Prospective observational population-wide cohort study involving all 26 hospitals with neonatal units co-located with maternity services across London (10 using SRC, 16 using NICE).

**Participants**: All livebirths ≥34 weeks' gestation between September 2020 and August 2021.

**Outcome measures**: EOS was defined as isolation of *a bacterial pathogen in the blood or CSF culture from birth to 7 days of age*. We evaluated the incidence of EOS identified by culture obtained >24 hours to 7 days after birth. We also evaluated the rate empiric antibiotics were commenced >24 hours to 7 days after birth, for a duration of ≥5 days, with negative blood or CSF cultures.

**Results:** Of 99,683 livebirths, 42,952 (43%) were born in SRC hospitals and 56,731 (57%) in NICE hospitals. The overall incidence of EOS (<72 hours) was 0·64/1000 livebirths. The incidence of EOS identified >24 hours was 2.3/100,000 (n=1) for SRC versus 7.1/100,000 (n=4) for NICE (odds ratio 0·5, 95%CI [0·1; 2·7]). This corresponded to (1/20) 5% (SRC) versus (4/45) 8.9% (NICE) of EOS cases (chi=0.3, p=0.59). Empiric antibiotics were commenced >24 hours to 7 days after birth in 4·4/1000 (n=187) for SRC versus 2·9/1000 (n=158) for NICE (odds ratio 1·5, 95%CI [1·2; 1·9]). 3111 (7%) infants received antibiotics in the first 24 hours in SRC hospitals versus 8428 (15%) in NICE hospitals.

**Conclusion:** There was no significant difference in the incidence of EOS identified >24 hours after birth between SRC and NICE hospitals. SRC use was associated with 50% fewer infants receiving antibiotics in the first 24 hours of life.


## Strengths and limitations of this study

- Largest UK study with 99,683 livebirths comparing neonatal outcomes following the Kaiser Permanante Sepsis Risk Calculator (SRC) versus National Institute for Health and Care Excellence (NICE) guidance.
- Prospective one-year observational population-wide cohort study utilising a network approach to ensure capture of all re-admissions following discharge due to early-onset neonatal sepsis.
- Data were only obtained for infants who had a blood culture received in a laboratory, and therefore it is possible to have missed a few infants who received antibiotics without a blood culture.

## INTRODUCTION

Early-onset sepsis (EOS) can be defined as bacteraemia occurring within 72 hours of birth. EOS occurs in around 0·7/1000 livebirths in high income settings,[1] and remains a major cause of morbidity in neonates, particularly those born preterm.[2] As infants can initially be asymptomatic or present with non-specific symptoms, determining who should receive antibiotics can be a challenge, and is a balance between unnecessary use of antibiotics and avoiding harm from delayed antibiotic therapy. In the United Kingdom (UK), most hospitals follow the National Institute for Health and Care Excellence (NICE) guidance CG149 which uses maternal risk factors, clinical indicators and "red flags" [3] to guide decisions on investigations and antibiotics. However, concerns of associated antibiotic overuse[4] have prompted an increasing number of hospitals to adopt the Sepsis Risk Calculator (SRC)[5,6] for infants ≥34 weeks' gestation and within 12 hours of birth.[7]

The SRC was developed in the USA and estimates the risk of EOS based on background incidence, gestational age, highest maternal antepartum temperature, duration of membrane rupture, maternal GBS status, and type and timing of intrapartum antibiotics. The infant's evolving clinical presentation is factored into the second part of the model, which adjusts the prior risk of EOS. Depending on the estimated final risk, the SRC provides recommendations for clinical management (routine care/blood culture/empiric antibiotics) and monitoring of vital signs.[7,8] The SRC was endorsed by the American Academy of Pediatrics in 2018.[9] Whilst the SRC reduces antibiotic usage,[10,11,12] there have been concerns of the potential for missed or delayed identification of EOS compared to NICE.[13,14] Despite this, the SARS-CoV-2 pandemic accelerated its uptake in the UK; 10 out of 26 hospitals in London adopted the SRC to ration resources and facilitate earlier discharges. In this one-year prospective regional study we aimed to report the incidence of EOS cases, and compare the incidence at which it was identified >24 hours after birth in hospitals using SRC with hospitals using NICE guidance.

## METHODS

### Design

We applied a pragmatic study design, developed by a multi-professional project team (comprising doctors, nurses, midwives and network managers), supported by the London Neonatal Operational Delivery Network. A common minimum dataset was collected by a network of trainee and consultant paediatricians in the Neonatal Trainee Research and Improvement Projects (NeoTRIPS). The protocol is published on the NeoTRIPS website.[15]

### Setting

All 26 National Health Service (NHS) hospitals within Greater London providing newborn care and co-located with a maternity service participated in this study. These included 9 tertiary neonatal intensive care units (NICU), 13 local neonatal units (LNUs) and 4 special care baby units (SCBUs). 10 hospitals followed SRC and 16 followed NICE guidance. The decision regarding which approach to follow (SRC/NICE) was made by individual hospitals and was not influenced by participation in this study.

The background incidence of EOS used by the SRC hospitals during the study period ranged from 0.6-1/1000. There was variation in the application of SRC; in 9/10 units, it was applied only to subsets of

infants meeting specified risk thresholds, and there were differences in the management of infants deemed to be at intermediate risk (Supplementary table 1).

**Participants**

The eligible population was all livebirths ≥34 weeks' gestation during a 12-month period from 1 September 2020 to 31 August 2021.

**Main outcomes**

The primary outcome was the number of cases of EOS identified >24 hours to 7 days of age, as a proportion of livebirths. EOS was defined as isolation of a bacterial pathogen in the blood or CSF culture of an infant from 24 hours of age (up to 7 days of age). Bacterial pathogens were categorised as per the Vermont Oxford Network Manual of Operations.[16] The number of infants commenced empiric antibiotics in the first 24 hours and the number of infants with EOS in the first 72 hours were also assessed. We also evaluated the rate at which empiric antibiotics were commenced >24 hours up to 7 days of age, for a duration of ≥5 days, with negative blood or CSF cultures.

**Data collection**

The number of all livebirths ≥34 weeks' gestation per calendar month at each hospital site was obtained for the duration of the study. Patient-level data were collected for all infants who had a blood culture obtained during the first 7 postnatal days (Figure 1). These infants were identified by reviewing weekly lists of blood cultures from all microbiology laboratories serving these hospitals to ensure all screens for suspected EOS were captured from all settings (postnatal ward, neonatal unit, accident and emergency department). If an infant had more than one blood culture, the timing of the first sample was used.

For each infant who had a blood culture taken, a basic dataset was obtained: time of blood culture (hours of age), receipt of antibiotics and time of administration, admission to a neonatal unit, duration of antibiotics, length of initial hospital stay.

For all EOS cases, additional maternal and infant clinical details were collected (Figure 1): gestational age, birthweight, sex, mode of delivery, maternal risk factors (length of rupture of membrane, highest maternal antepartum temperature, GBS status in the current pregnancy, class and timing of intrapartum antibiotics), organisms isolated (blood culture, cerebrospinal fluid (CSF), or both), CSF white cell count, infant's clinical signs during initial hospital stay, whether the infant presented after discharge home, infant's symptoms upon re-admission from home, duration of antibiotics, and final clinical outcome. In addition, for SRC hospitals, we collected EOS scores at birth and after clinical examination. We did not collect detailed data for infants with culture-negative sepsis who were treated with antibiotics in the first 24 hours of life.

Data for readmissions to hospitals other than the birth hospital were obtained through nhs.net correspondence. The NeoTRIPs network covered all London hospitals and frequent communications between members ensured that missing data were minimised.

Anonymised data were collated using Excel through nhs.net, stored on NHS computers and analysed using a centralised Excel spreadsheet through a secure nhs.net server. Monthly data were verified with contributors by three of the authors. Missing data were resolved as far as possible. Cases meeting the definition of EOS was agreed by consensus. Compliance with data submission was supported through feedback at regular meetings throughout the study period. See Figure 1. Flowchart of methods.

**Expected incidence of EOS identified >24 hours after birth**

The objective of this pragmatic study was to report the incidence of EOS identified >24 hours after birth to 7 days of age from all London hospitals over a 12 month period. Based on NHS Maternity Statistics,[17] estimated ~95,000 livebirths at ≥34 weeks' gestation would be born during the study period. With a background EOS incidence of 0·8/1000 livebirths for Greater London,[18] we anticipated ~80 cases of EOS and, based on the estimate defined in the original Kaiser Permanente study[10], we anticipated 5-6 EOS cases identified >24 hours after birth to 7 days

**Statistical analysis**

Summary descriptive statistics are presented as medians with their corresponding interquartile ranges for continuous variables, and as percentages for categorical variables. All incidence rates are expressed as cases per 1000 or 100,000 livebirths ≥34 weeks' gestation, where appropriate, with denominator values based on available data.

Chi-squared tests were used for proportions, independent samples t test for comparison of means and Mann-Whitney U test for comparisons of medians. Non-parametric data were log transformed to preferentially conduct parametric testing where possible. Shapiro-Wilk test was used for assessing normality of original and log transformed data. GraphPad Prism was used for analyses. P values <0·05 were considered statistically significant. Odds ratio was chosen for events where the incidence was <10%.[19]

**Patient and public Involvement**

None.

**RESULTS**

Blood culture data were not available for all months from all hospitals over the study period. Data were missing for 5 months from one SRC hospital and for 32 months from 7 NICE hospitals. The livebirth denominator corresponding with available data was 42952 for SRC hospitals and 56731 for NICE hospitals (Table 1). Supplementary tables 2 and 3 present the livebirth denominator data by month for SRC and NICE hospitals.

*Blood culture screening and intravenous antibiotic use*

Overall, 11734 (12%) infants had a blood culture taken within 24 hours of birth, however, SRC hospitals obtained 50% fewer blood cultures than NICE hospitals (relative risk 0.5, 95%CI [0·47-0·51]) (Table 1). In both SRC and NICE hospitals, the majority of infants having a blood culture were treated with antibiotics (Table 1). Hospital-specific antibiotic use is presented in Supplementary tables 1 and 2. The

proportions of infants receiving antibiotics at >24 to ≤72 hours, and >72 hours to ≤7 days were similar in both hospital types (odds ratio: 1.1, 95% CI (0.97 – 1.2) vs 1.0, 95% CI (0.81-1.3) with no shift towards later therapy in hospitals using SRC (Table 1).

**Table 1.** Outcomes of the participating hospitals

| | **SRC**<br>**10 hospitals** | **NICE**<br>**16 hospitals** |
|---|---|---|
| Livebirths denominator corresponding to available data | 42952 | 56731 |
| Infants screened with blood culture ≤24 hours of age, n (%) | 3297 (7·7) | 8437 (15) |
| Infants who started antibiotics ≤24 hours of age, n (%)† | 3111 (7·2) | 8428 (15) |
| Infants who started antibiotics >24 hours and ≤72 hours of age, n (%)† | 510 (1·3) | 620 (1·3) |
| Infants who started antibiotics >72 hours and ≤7 days of age, n (%)† | 135 (0·3) | 176 (0·4) |
| EOS ≤7 days of age, n, incidence/1000 livebirths, [95%CI] | 20 (0·47/1000, [0·3- 0·72]) | 45 (0·79/1000, [0.6- 1·1]) |
| EOS identified >24 hours and ≤7 days, n (incidence/100,000 livebirths [95% CI]) | 1 (2.3/100,000, [0.3-16]) | 4 (7.1/100,000, [2·7-19]) |
| Negative blood culture and started antibiotics >24 hours and ≤7 days for at least 5 days duration, n (incidence/1,000 livebirths, [95% CI]) | 187 (4·4/1000, [3·8-5]) | 158 (2·8/1000, [2·4-3·3]) |

All livebirths denote ≥34 weeks' gestation. Abbreviations: CI – confidence interval, EOS – early onset sepsis.

† Timing of antibiotic administration was unavailable for 15 infants (SRC) and 2 infants (NICE).

*Incidence and characteristics of cases of EOS*

Across the entire study population, there were 65 infants with EOS within the first 7 days, 64 within 72 hours (0·64/1000, 95% CI [0·5-0·82]) and 1 infant from >72 hours to 7 days. The most common pathogen was GBS (0·44/1000). The incidence of *Escherichia coli* was 0·07/1000, and other pathogens combined was 0·16/1000 (Supplementary table 4).

There was a higher number of EOS cases within the first 7 days in the NICE hospitals (n=45; 0·0.79/1000) compared to SRC hospitals (n=20; 0·47/1000) (odds ratio 1·7, 95%CI [1.0-2·8]) (Table 1).

Table 2 shows the clinical characteristics for infants with EOS. Cases in the SRC hospitals were more likely to be symptomatic at time of treatment (10 (53%) vs 11 (26%)). However, the timings of blood culture and initiation of antibiotics across the two groups were similar.

**Table 2.** Characteristics of 65 cases of EOS ≤7 days

| | **SRC (n=20)** | **NICE (n=45)** | **P value** |
|---|---|---|---|
| Gestational age, weeks, mean (SD) | 38·9 (1·7) | 40·1 (7·4) | 0·43 |
| Birthweight, g, mean (SD) | 3156 (562) | 3255(436) | 0·45 |
| Male, n (%) | 8 (40) | 24 (53) | 0·33 |
| Vaginal delivery, n (%) | 4 (20) | 25 (56) | 0·008 |
| Highest maternal antepartum temperature, median (IQR)† | 37·6 (36·9-38·3) | 37·3 (36·8-37·6) | 0·32 |
| Maternal GBS status, n (%)‡ | | | |
| *-Unknown* | 9 (47) | 15 (35) | 0·38 |
| *-Positive* | 3 (16) | 17 (40) | 0·07 |
| *-Negative* | 7 (37) | 11 (26) | 0·39 |
| Rupture of membranes, h, median (IQR)± | 12 (8.3-24) | 16 (2.8-32) | 0·28 |
| Maternal antibiotics, n (%)* | | | |
| *-No antibiotics or any <2h prior to birth* | 16 (84) | 30 (75) | 0·44 |
| *-GBS specific antibiotics >2h prior to birth* | 0 | 3 (7.5) | 0·22 |
| *-Broad spectrum antibiotics 2-3.9h prior to birth* | 3 (16) | 4 (10) | 0·51 |
| *-Broad spectrum antibiotics >4h prior to birth* | 0 | 3 (7.5) | 0·22 |
| Initial hospital stay | | | |
| *-Assigned postnatal care and never admitted to neonatal unit, n (%)* | 7 (35) | 24 (53) | 0·18 |
| *-Assigned postnatal care and later admitted to* | 5 (25) | 11 (24) | 0.93 |

| | | | |
|---|---|---|---|
| *neonatal unit, n (%)* | | | |
| *-Admitted to neonatal unit from birth centre, n (%)* | 8 (40) | 11 (24) | 0·19 |
| Age at blood culture, hours, median (IQR) | 3·7 (2·1-9.2) | 2·6 (1·5-8.9) | 0·45 |
| Age at antibiotics, hours, median (IQR) | 3·7 (2·5-9.2) | 2·6 (1·5-8.7) | 0·76 |
| Clinical signs at birth, n (%)** | 10 (53) | 11 (26) | 0·04 |
| Developed signs before discharge, n (%)** | 6 (32) | 14 (33) | 0.94 |
| Never had clinical signs, n (%) | 3 (16) | 17 (40) | 0·07 |
| CSF culture positive, n (%)*** | 1 (5) | 2 (4·7) | 0·96 |
| CSF white cell count > 20, n (%)*** | 1 (5) | 3 (7) | 0·76 |
| Death, n (%) | 0 | 1 (2·2) | 0·50 |
| EOS score at birth, median (IQR) | 2·0 (0·14-7·8) | - | - |

Abbreviations: CSF – cerebrospinal fluid, EOS – early onset sepsis, GBS – group B *Streptococcus*, IQR – interquartile range, SD - standard deviation.

†Highest maternal antepartum temperature missing for SRC 4, NICE 25 infants
‡Maternal GBS status missing for SRC 1, NICE 2 infants
ǂRupture of membrane timing missing for SRC 4, NICE 16 Infants
*Maternal antibiotics missing for SRC 1, NICE 5 infants
**Timing of clinical signs missing for SRC 1, NICE 3 infants
***CSF not obtained for SRC 1, NICE 3 infants

*Incidence of EOS identified >24 hours from birth*

There were 5 cases of EOS identified by culture >24 hours to 7 days (n=1, 2.3/100,000 for SRC versus n=4, 7.1/100,000 for NICE) (Table 1). Owing to the difference in background incidence of EOS, the proportions of cases were compared; (1/20) 5% (SRC) versus (4/45) 8.9% (NICE) (chi=0.3, p=0.59). The maternal and infant characteristics are reported in Supplementary Table 5. One infant was born at a NICE hospital, had congenital hydronephrosis and was admitted to the neonatal unit directly. Three infants were re-admissions from home following an initial asymptomatic course in hospital (all NICE). One infant developed symptoms whilst being observed on the postnatal ward (SRC). Detailed case

histories are provided in Supplementary file 1. Two infants were excluded because of congenital anomalies predisposing to reduced skin integrity and the pathogenesis of invasive infection was probably postnatal rather than that of EOS. These were Bacillus cereus and Acinetobacter baumanii isolated at 28 hours in an infant with harlequin ichythosis (SRC), and Staphylococcus aureus isolated at 91 hours in a collodion infant (NICE).

*Rate of commencing empiric antibiotics >24 hours after birth for ≥5 days, with negative cultures*

There were 345 infants who were commenced empiric antibiotics >24 hours after birth for ≥5 days with negative cultures (187, 440/100,000 for SRC versus 158, 290/100000 for NICE (odds ratio 1·5, 95%CI [1·2; 1·9]) (Table 1). The maternal and infant characteristics are presented in Supplementary table 6. There were differences in maternal characteristics: length of rupture of membranes (limited interpretation due to missing data), GBS status and antibiotic therapy. Despite more cases in the SRC hospitals, there was no greater proportion of infants admitted to the neonatal unit from the postnatal ward, or re-admitted from home. Timing and duration of antibiotics were similar. There were no deaths in either group.

## DISCUSSION

This large observational, pragmatic study was undertaken to assess and compare the outcomes of the routine use of two widely adopted neonatal sepsis management strategies, the Sepsis Risk Calculator and the NICE neonatal infection guideline. Decisions regarding which strategy to use were undertaken locally and therefore reflect a range of local factors, including perceived benefits and risks, caseloads and risk factors.

We found a high proportion of infants born at ≥34 weeks gestation who received antibiotics within 24 hours of birth – 15% in the NICE hospitals versus 7% in the SRC hospitals. This implies that 50% fewer infants received empiric antibiotics in the SRC hospitals. Despite this, there was no evidence of a resultant increase in identification of EOS beyond 24 hours after birth. Indeed, the absolute number of infants meeting this definition of later identification was small. Of the 5 such cases, only 3 were re-admissions in the first 7 days of life following an asymptomatic course during the initial hospital stay. These 3 infants had been cared for in hospitals following NICE. Re-admission with bacteraemia, even across a population representing almost 100,000 livebirths, is therefore a rare event. The rarity is also reflected in other large studies following implementation of SRC: 3 cases across 56,261 livebirths (5·3/100,000) in Northern California[10] and 2 cases across 24,749 livebirths (8·1/100,000) in Wales.[6] All infants in these two studies were also asymptomatic during the initial postnatal stay and without clinical indicators for empiric antibiotics.[6,10] This indicates that neither approach will prevent all such cases.

The proportion of infants receiving antibiotics ≤24 hours of age in SRC hospitals in our study is still higher than that reported at Kaiser Permanente hospitals (2·6%)[10] and other SRC centres in the USA (3·7%)[20]. These centres reported on cohorts of infants born ≥35 and ≥36 weeks' gestation respectively, where our cohort included ≥34 weeks' gestation with overall higher incidence of infection. Nevertheless, contributions to higher antibiotic use may be explained by the more conservative SRC approach generally adopted by UK hospitals, in which antibiotics are always started when obtaining a blood culture (Supplementary table 1). Withholding antibiotics is one of the possible SRC recommendations for infants at intermediate risk. A Welsh study showed a similar reduction in antibiotic use to our study (45·5%), with SRC use resulting in 7·7% receiving antibiotics.[6] Another reason for the higher proportion treated with antibiotics in our study may be that the SRC was applied only to infants cared for on the postnatal ward, as opposed to those admitted to the neonatal unit. Almost all hospitals implemented a variation of the SRC with differences across hospitals (Supplementary table 1). The high use of antibiotics in the hospitals in our study is highlighted further by an international study in high-income settings (with centres following a variety of approaches in managing risk of EOS) which reported that only 3% of infants were treated.[21] It is therefore clear that in our setting large numbers of infants are being exposed to antibiotics relative to the low incidence of EOS.

Although the overall incidence of EOS (0·64/1000 livebirths ≥34 weeks gestation) is similar to that identified in other UK studies[22], as an observational pragmatic study there are inherent limitations in our ability to interpret the differences we found in outcomes between different hospitals. For example, differences in socioeconomic and ethnic backgrounds of the populations served and of obstetric practice regarding caesarean section rates and intrapartum antibiotic prophylaxis use may have a

significant impact on the background risk of EOS.[23,24] The difference in the number of EOS identified by culture >24 hours after birth in the groups (SRC=1, NICE=4) is small but could reflect the fact that fewer blood cultures were taken in the SRC hospitals meaning that some infants with transient bacteraemia[25] and minimal clinical signs were not captured; this has also been reported by the Kaiser Permanente group where the practice of taking a blood culture and awaiting the result is more common.[10]

The SRC was developed and validated using EOS confirmed by positive blood cultures.[7,8] Because infants can present with signs of sepsis with sterile blood or CSF cultures, we reported an additional 345 infants who commenced ≥5 days of intravenous antibiotics after 24 hours of age with negative cultures. The rate at which this occurred was significantly higher in SRC units than in NICE units. Caution must be exercised when considering a definition of presumed sepsis that includes duration of antibiotic therapy, as this may be influenced by a clinician decision to extend treatment following negative cultures, rather than by clinical indicators. Despite its limitations, a definition of 5 or more days of antibiotic therapy is used elsewhere. [1, 16] In the setting of a non-randomised study design, it is also possible that clinicians in SRC hospitals were more cautious following implementation of the SRC. However, there was no skew towards later antibiotic treatment suggesting delayed recognition or later manifestation of sepsis associated with the tool. Additionally, there was no increased adverse outcomes such as neonatal unit admission, re-admissions following discharge home or death. Whether later antibiotic therapy for presumed sepsis is associated with later sequelae, such as neurodevelopmental impairment, is not clear.[26]

A key strength of the study was the support provided by the network of London hospitals embarking on implementation of new practice, feedback at regular intervals and crucially, the trainee network to capture all re-admissions with presumed sepsis. This is the largest study of the outcomes of the SRC in the UK to date, with data representing 90% of the eligible birth population, and all hospitals in the network providing maternity care contributing data. Thus the results are generalisable to the wider population.

There are a number of potential limitations to consider: 1) This was a non-randomised study and therefore we cannot exclude differences in populations and clinical practices at hospitals that may explain (for example) the higher rate of empiric antibiotic therapy in the context of negative cultures in SRC hospitals. 2) This was a pragmatic design with the capacity to obtain only a limited data-set. Broad coverage to capture rare events (identification >24 hours after birth) was prioritised over depth of clinical detail. We therefore did not collect laboratory data such as c-reactive protein levels. Data were only obtained for infants who had a blood culture received in a laboratory, and therefore it is possible to have missed a few infants who received antibiotics without a blood culture. There was also variation in the application of the SRC across hospitals, with a modified approach used commonly (Supplementary table 1). Equally, without data on every eligible livebirth, uniformity of application of NICE guidance cannot be assessed. 3) We sought to determine the rate at which infants received ≥5 days of antibiotics commenced >24 hours after birth in the context of negative cultures. Infants that died before the

intention to complete ≥5 days would not have been captured. 4) Not all hospitals provided data for the entire study period, therefore we cannot assure all re-admissions following initial hospital discharge were captured. The possibility of re-admission to a hospital out-with Greater London remains, but this is likely to be rare. 5) The SRC was compared with NICE CG149,[3] which has since been replaced in 2021 by NICE CG195[27] with the removal of maternal broad spectrum antibiotics as a risk factor for neonatal EOS, and previous GBS colonisation mandating intrapartum antibiotic prophylaxis for the subsequent pregnancy, unless the woman has had a negative test in that subsequent pregnancy.[27] These new changes may bring about a reduction in neonatal antibiotic exposure and some of the cases identified later observed in our study may have been avoided.

We propose that there is now a need to conduct a UK-wide randomised controlled trial to compare these two strategies. Findings from our study will help inform the design of such a study.

## CONCLUSION

The use of the SRC was associated with 50% fewer infants receiving empiric antibiotics compared to NICE CG149. EOS identified by culture >24 hours after birth was rare, with no difference between the two groups. These findings can help inform clinical guidelines as well as the design of definitive studies to compare outcomes of the SRC with the NICE CG195 introduced in 2021.[27]

## DECLARATIONS

### Consent for publication

Not applicable.

### Data availability statement

The data that support the findings of this study are available from the corresponding author CB, upon reasonable request.

### Competing interests

CB reports grants and personal awards funded by the National Institute for Health Research, personal fees from Chiesi Pharmaceuticals and Abbvie Pharmaceuticals; and is deputy chair of the NIHR Health Technology Assessment Prioritisation Committee for hospital-based care. PTH was a member of the NICE CG149 guideline committee and deputy chair of the NICE CG195 guideline committee. The other authors do not have any conflicts of interests to declare.

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### Contributors

CP wrote the first draft of the article with contributions from CB. CP, SG and RY carried out the analyses. All authors edited and approved the final version of the article. CP and CB conceived the study; CP,

CB, GSK, KB, JR, CH, KN, JJ, AD, TL, PTH, KLD, SS contributed to the development and conduct of the study. CP, SG, RY, JO, DT, CL, KE were involved in data collection, along with the NeoTRIPs team, and supported by the wider multi-professional project team group (below). We thank Zeshan Rawn (London Neonatal Operational Delivery Network) for technical assistance and Katie Nichol (NHS England and NHS Improvement London). CB as guarantor accepts full responsibility for the conduct of the study and controlled the decision to publish. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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**Ethics approvals**

The present cohort study was based on anonymised data collected as part of a service evaluation. The study was deemed to be a service evaluation by the Chair and Approvals Officer of the London South East REC Committee and did not require ethical approval or participant consent.

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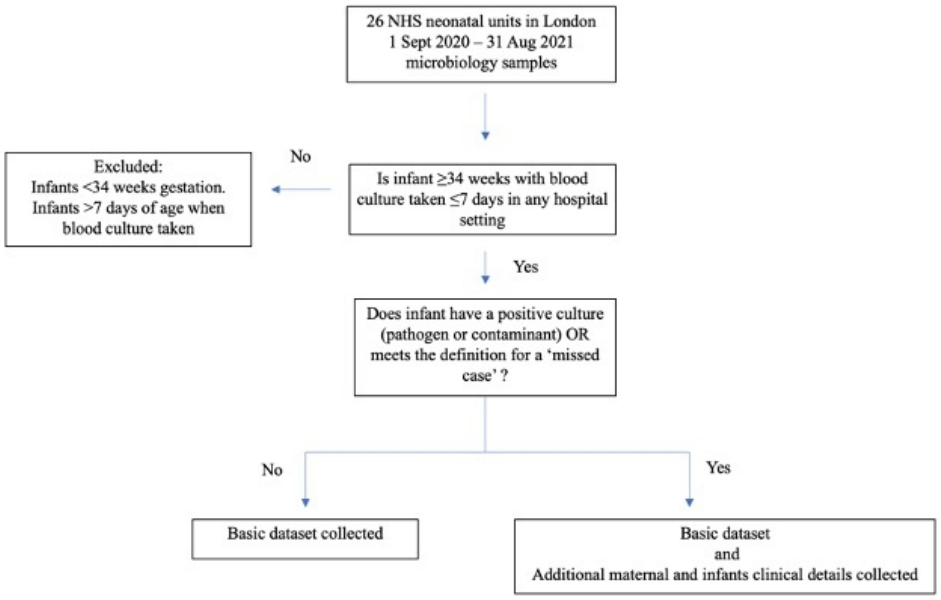


Data Collection flow chart

233x169mm (72 x 72 DPI)

# Supplementary material

## Contents

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

| Hospital | Groups of infants<br>(all eligible infants versus infants with risk factors as per NICE)<br>(postnatal versus postnatal and neonatal unit) | Management for infants at intermediate risk | Background incidence used during the study period |
|---|---|---|---|
| **1** | All eligible<br>Postnatal ward only | Take blood culture and give antibiotics | 0·8/1000 |
| **2** | All eligible<br>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)<br>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<br>Postnatal ward only | Take blood culture and give antibiotics | 0·6/1000 |
| **6** | Infants with risk factors<br>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<br>Postnatal ward only | Take blood culture and give antibiotics | 0·8/1000 |
| **8** | Infants with risk factors and meeting NICE criteria for antibiotics.<br>Postnatal ward only. | Take blood culture and give antibiotics | 0·8/1000 |
| **9** | Infants with risk factors<br>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<br>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

STROBE Statement—Checklist of items that should be included in reports of ***cohort studies***

| | Item No | Recommendation |
|---|---|---|
| **Title and abstract** | 1 | (*a*) Indicate the study's design with a commonly used term in the title or the abstract Y page 2 |
| | | (*b*) Provide in the abstract an informative and balanced summary of what was done and what was found Y page 2 |
| **Introduction** | | |
| Background/rationale | 2 | Explain the scientific background and rationale for the investigation being reported Y page 3 |
| Objectives | 3 | State specific objectives, including any prespecified hypotheses Y page 3 |
| **Methods** | | |
| Study design | 4 | Present key elements of study design early in the paper Y page 3 and 4 |
| Setting | 5 | Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection Y page 3 |
| Participants | 6 | (*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up Y page 4 |
| | | (*b*) For matched studies, give matching criteria and number of exposed and unexposed |
| Variables | 7 | Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable Y page 4 |
| Data sources/ measurement | 8* | For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group Y page 4 |
| Bias | 9 | Describe any efforts to address potential sources of bias Y page 5 |
| Study size | 10 | Explain how the study size was arrived at Y page 5 |
| Quantitative variables | 11 | Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why Y page 5 |
| Statistical methods | 12 | (*a*) Describe all statistical methods, including those used to control for confounding Y page 5 |
| | | (*b*) Describe any methods used to examine subgroups and interactions Y page 5 |
| | | (*c*) Explain how missing data were addressed Y page 5 |
| | | (*d*) If applicable, explain how loss to follow-up was addressed Y page 5 |
| | | (*e*) Describe any sensitivity analyses N/A |
| **Results** | | |
| Participants | 13* | (a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed Y |
| | | (b) Give reasons for non-participation at each stage Y |
| | | (c) Consider use of a flow diagram Y |
| Descriptive data | 14* | (a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders Y page 6 |
| | | (b) Indicate number of participants with missing data for each variable of interest Y page 6 |
| | | (c) Summarise follow-up time (eg, average and total amount) Y page 6 |
| Outcome data | 15* | Report numbers of outcome events or summary measures over time Y page 6 and 7 |
| Main results | 16 | (*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were |

| | | |
|---|---|---|
| | | adjusted for and why they were included Y page 6 and 7 |
| | | (*b*) Report category boundaries when continuous variables were categorized Y page 6 |
| | | (*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period |
| Other analyses | 17 | Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses Y page 7 |
| **Discussion** | | |
| Key results | 18 | Summarise key results with reference to study objectives Y page 13 |
| Limitations | 19 | Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias Y page 14 |
| Interpretation | 20 | Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence Y page 13 and 14 |
| Generalisability | 21 | Discuss the generalisability (external validity) of the study results Y page 15 |
| **Other information** | | |
| Funding | 22 | Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based Y page 15 |

*Give information separately for exposed and unexposed groups.

**Note:** An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at http://www.strobe-statement.org.